Contribution of Artificial Intelligence to the E-learning

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Abstract-Artificial intelligence (AI) is a property of machines which gives the ability to copy the human thought process. It is concerned with the design of intelligence in an artificial device. This term was defined by McCarthy in 1956.

There are two ideas in the definition.

1. Intelligence

2. Artificial device

This paper highlight to potential contribution of Artificial Intelligence (AI) to the e-learning environment. Artificial Intelligence enhances computer assist instruction systems by providing human like intelligence to the system. Here, we are focusing some AI techniques, which could be the main technology for e-learning. Also we discuss, how Intelligent Tutoring System (ITS) is proved as promising field to the training programmes and how AI could contribute to issues like Naural intelligence, learning from experience & intelligent interaction between human being & machine.

Keywords: *Artificial Intelligence, ITS, CAI, ML, NLP, e-learning, CA, ILE*

1. Introduction

If you ask to our respected senior citizen those who have retired from service or business, they all have very common thing that, the respect & memories of the educational institutions where they studied and old days traditional teaching. They shared their warm memories which are associated with institutes. In today modern time as the field of computer science and information technology has reformed day-to-day activities of entire human life. The computing field has provided us all that even we could not have dreamt.

The remarkable growth of this field has impacted educating in many ways.

Artificial Intelligence (AI) is the science & engineering of making intelligent machine, especially intelligent computer programs. It is related to the similar task of using computer to understand human intelligence. In fact, intelligence involves mechanism & AI research has discussed how to make computers to carry out some of them. AI makes traditional teaching more effective.

2. What is E- learning

E- Learning refers to learn that is to be delivered or enable via electronic technology. It encompasses learning delivered via a range of technologies such as the internet, television, videotape, intelligent tutoring systems, and computer-based training.

E-learning is subset of two large words, specifically, "information technology" and "education and training". It can be valuable when used as a part of well-planned and properly supported education and training environment. However, e-learning does not replace or render existing educational theories and approaches.

3. Intelligent Tutorial System (ITS)

An **intelligent tutoring system** (**ITS**) is a computer system that aims to provide immediate and customized instruction to learners, usually without requiring intervention from a human teacher like online teaching. It is difficult to provide a personal training assistant for each learner, however, a virtual training assistant that captures the subject matters and teaching expertise of experienced trainers provides a captivating new option. The concept, known as Intelligent Tutoring System (ITS) has been pursued by researchers in education, psychology and artificial intelligent. ITS can also be classified by model tracing tutor algorithm One of the objectives of Intelligent Tutorial System is to adopt hypermedia courses to each individual user by means of control of learning level, control of the course navigation, revision to available information, revision of the training methodology, explanation of errors, answers to the student's questions, advice, etc. In other words, intelligent tutoring system is a model which enables student to be evaluated and taught a subject and also for the education to be adapted to the students performance.

The traditional ITS model contains four components:

- Expert Module / Domain model / cognitive model / expert knowledge model
- Student Module / model tracing
- Curriculum Module / Tutoring model
- Interface Module.
- Expert Module contains information about the subject knowledge domain. Its contain the concepts, rules, and problem-solving strategies of the domain which is to be learned.
- Student Module can be thought of as an overlay on the domain model. It contains information about the student's understanding of the knowledge domain. It is considered as the core component of an ITS.
- Curriculum Module contains rules that allow it to judge how well the student's understanding of the subject domain matches actual knowledge structure.





It also accepts information from the domain and student models and makes choices about tutoring strategies and actions.

- Interface Module presents the user with a uniform environment within which instruction, analysis, remediation, and user driven learning may take place.

The user interface component integrates three types of information

- Knowledge about patterns of interpretation and action
- domain knowledge needed for communicating content; and
- knowledge needed for communicating intent

The Aim of ITS is to create a learning environment where the role of human teachers is replaced by the tutor module and domain knowledge module. A system plans and teaches individuals by maintaining its belief about each in the student module and acts according to the best teaching strategy

ITS can also be classified by model tracing tutor algorithm.

4. What AI present

Teaching and learning is not a simple process. Only train humans can teach effectively. Computer Assisted Instructions (CAI) could be useful in learning at an elementary level and even then can not compete with train humans in term of teaching quality. The creation of the ALGOL programming language in 1958 which was enabled in many schools and universities for beginning to develop Computer Assisted Instruction (CAI) programs and

Computer Aided Learning (CAL) which are lacking "the flexibility and learner- centered orientation of ITS" The complexity of the teaching task is the result of following main factors:

- Adaptive teaching strategies - Depending on the stage in the learning process, different subjects requires different instructional strategies at different levels.
- Continuous assessment of students - Human teachers do not rely on the test result for student's assessments, but they constantly assess the class and individual through various inputs like attention level, understanding level etc.
- Personalized teaching - Human teachers are flexible. To make their teaching effective, they deliver the content ranges from class level down to the individual student's level.

Artificial Intelligence enhances CAI systems by providing human like intelligence to the system. To enhance the efficiency of computer programs in handling the above mentioned factors, computer must be equipped with necessary sensors. They must be able to make sense out of their senses, and then they can act logically. They should be able to learn and be adaptable to new environment. We highlight the current developments in these issues and their applications in intelligent tutoring systems.

i) Aural Capability

Domains such as language and music require hearing ability in computers. The ability to here also implies to an understanding of what is being heard. Advances in speech recognition, speech processing and natural languages processing provides useful applications in many areas including ITS. At the current state-of-the-art, we have enquiry counters where clients can make the enquiries using interactive telephone dialogue. Clients talk to a computer as if they are talking to another human being.

ii) Visual Perception

Many recent works in education address the issues of affects and emotions. Information regarding students' affects could be useful in the adaptation of teaching strategies. This area is however still not mature.

The ability to visualize can be useful in teaching music performance as well. In many performing skills, the techniques are closely related to the poster (e.g. hand-shape, sequence of movements, etc.)

iii) Inference mechanisms

The talking which so far about perceives and acting (via speaking). Perhaps, the most important aspects of intelligent behaviors is about inference power. This is the area where most AI researchers have been investigating.

Logical inference is suitable for domains at a course grain abstraction. For example, the encoding of domain knowledge in a rule-based expert module. Probabilistic and statistical inferences are suitable in handing uncertainties in the domain. Bayesian networks, artificial neural networks are the most popular inference techniques.

iv) Machines that learn (ML)

One of the main secret ingredients for the success of any ITS system is the accuracy of its student model. Real students are dynamic. As such, ITS systems must possess the learning capability so that changes in students could be tracked. Learning is along standing research in AI and this is one of the areas where AI could make a useful contribution to ITS in e-learning environments.

v) Interactive learning environment(ILE)

Finally, we would like to comment on the interaction between human and machine. The interaction between learner and computer in the main ingredient in the success of an ITS. Information from the interactions serves three purposes:

(i) to perceive useful information from the environment,

(ii) to model an accurate student model, and

(iii) to actuate the environment (e.g., feedback) with useful information.

5. Application in E-learning

Here we highlight AI application in ITS which a part of the e-learning environment. . Let us look one application of language teaching

5.1 Language Teaching

Teaching language involves the teaching of reading and writing skills. The whole scene involves content development, the delivering of content and an assessment of the delivering process. Here, we highlight the assessment dimension in language teaching.

Speech recognition is a hard problem. Same words or phrase contribute two different meaning in two different contexts. However, with a supplied context, this is not too hard problem. Given a word, a phrase, or a sentence, assessment of pronunciations could be automated using speech technology. This opens up a whole new approach for language teaching and learning. An ITS could be very useful in enhancing essay writing. Students have a constant need for tutors to give feedbacks on errors or mistake as well as meritorious use of language. Highlighting errors and mistakes could be easily automated using the spelling check and grammar check utilities. One of the major restrictions in most spelling check and grammar check utilities is the lack of context analysis(CA). To handle context dependency, sophisticated Natural Language Processing (NLP) techniques could be employed then the promise of an ITS which could benefits writing skills is not far away.

6. Conclusion

Many traditional instructional methods presents learners with facts and concepts followed by test questions, but artificial intelligence involves in capturing domain knowledge, providing intelligent assessment power and providing intelligent feedback etc. Thus as compare to old days of our citizens, use of information technology in general and Artificial Intelligence in particular area makes the education highly interactive, highly accessible, and highly individualized.

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INNOVATIVE TECHNIQUES IN HIGHER EDUCATION THROUGH E-LEARNING

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Abstract- The term E-learning refers to a novel teaching and learning in education. This educational high technology is an important part of today's world, which delivers supports and enhances the quality of learning. E-learning involves the participation of educator, and students who are use this technology to update their work. E-learning is the technique for how to understand and how to memorize the topic for long time. The E-learning is the use of technologies to improve knowledge and performance, and gives the advantage of 24x7 and 365 days a year. E-learning technologies offer learners control over content, learning sequence, pace of learning, time and often media, allowing them to adapt their experiences with to collect their personal learning objectives. Innovation in e-learning technologies point toward a revolution in education, especially higher education allowing learning to be individualized, enhancing learner's interaction with others and transforming the role of educator / teacher in higher education.

Keyword: *ALT, ITS, ICT, VLE, MIS, VRT*

1. Introduction

The brisk growth of the information age has made a big impact on the educational process in the last few years. The growth of information together with recent technological achievements has led to Computer Assisted Learning (e-learning) is enabling wider access to education to an increasing variety of people, independent of time or location.

E–learning is defined as acquisition of knowledge and skill using electronic technologies such as computer and Internet-based courseware at local and wide area networks. Electronic learning or e-learning is general term used for to refer to computer enhanced learning. It is commonly associated with the field of advanced learning technology (ALT), which deals with learning using network and/or multimedia technologies, it uses various technological tools that may be web based, web distributed or web capable for solving the purpose of education. E-learning facilities, such as 3D models and animations which are elements of Virtual Reality Technology, used for acquiring new knowledge.

The main objective of e-learning is to improve the quality of the learning experience for students who are in higher education.

2. What is E- learning

Learning system based on formalized teaching but with the help of electronic resources is known as E-learning. While teaching can be based in or out of the classrooms, the use of computers and the Internet forms the major component of E-learning. E-learning can also be termed as a network enabled transfer of skills and knowledge, and the delivery of education is made to a large number of recipients at the same or different times.

E- Learning refers to learn that is to be delivered or enable via electronic technology. It encompasses learning delivered via a range of technologies such as the internet, television, videotape, intelligent tutoring systems, and computer-based training.

E-learning is subset of two large words, specifically, "information technology" and "education and training". It can be valuable when used as a part of well-planned and properly supported education and training environment. However, e-learning does not replace or render existing educational theories and approaches.

3. Importance of E-learning in Higher Education

A student who is learning in higher education is a way that uses information and communication technologies (ICTs) by using e-learning. Following are different types of capability:

- Internet access to digital versions of materials unavailable locally.
- Internet access to search, and transactional services.
- Interactive diagnostic or adaptive tutorials.
- Interactive educational games
- Remote control access to local physical devices.
- Personalized information and guidance for learning support.
- Simulations or models of scientific systems.
- Communications tools for collaboration with other students and teachers.
- Tools for creativity and design.





- Virtual reality environments for development and manipulation.
- Data analysis, modeling or organization tools and applications.
- Tele-Medicine

For each of these, there is a learning application that could be exploited within higher education. Each one encompasses a wide range of different types of interaction – internet access to services, for example, includes news services, blogs, online auctions, self-testing sites, etc. Imagine, for example, a remotely controlled observatory web cam embedded in an on line conference environment for astronomy students, or computer aided design (CAD) device embedded in role play environment for students of urban planning.

The range and scale of possible applications of new technologies in Higher Education is almost beyond imagination because, while we are trying to cope with what is possible now, another technological application is becoming available that will extend those possibilities even further. Everything will need updating again when 3G/4G or even advance generations in mobile phones begin to have an impact on our behavior.

4. Intelligent Tutorial System (ITS)

An **intelligent tutoring system** (**ITS**) is a computer system that aims to provide immediate and customized instruction to learners, usually without requiring intervention from a human teacher like online teaching. It is difficult to provide a personal training assistant for each learner, however, a virtual training assistant that captures the subject matters and teaching expertise of experienced trainers provides a captivating new option. The concept, known as Intelligent Tutoring System (ITS) has been pursued by researchers in education, psychology and artificial intelligent. ITS can also be classified by model tracing tutor algorithm One of the objectives of Intelligent Tutorial System is to adopt hypermedia courses to each individual user by means of control of learning level, control of the course navigation, revision to available information, revision of the training methodology, explanation of errors, answers to the student's questions, advice, etc. In other words, intelligent tutoring system is a model which enables student to be evaluated and taught a subject and also for the education to be adapted to the students performance.

The traditional ITS model contains four components:

- Expert Module / Domain model / cognitive model / expert knowledge model
- Student Module / model tracing
- Curriculum Module / Tutoring model
- Interface Module.

5. Advantages of ITS:-

Intelligent Tutoring systems (ITS) are effectively used for teaching the course of the specified domain with following features and benefits:

- Increases student / instructor ratio from around 1:1 so that it reduce training costs extremely, and still deliver close to a one on - one learning experience.
- Shortens training time and / or improve skill level.
- Automatically optimizes individual learning.
- Builds "student module" for each student that includes: Performance on training exercises.
- Details of information / remediation received
- Details of knowledge mastered / failed / unknown / misunderstood.
- Performance on remediation activities.
- Student preferred learning style.

It is important because e-learning can make a significant difference: to how learners learn, how quickly they master a skill, how easy it is to study, and equally important, how much they enjoy learning. Such a complex set of technologies will make different kinds of impact on the experience of learning:

- Cultural: - Students are comfortable with e-learning methods, as they are similar to the forms of information search and communications methods they use in other parts of their lives.
- Intellectual: - Interactive technology offers a new mode of engagement with ideas via both material and social interactivity online.
- Social: - The reduction in social difference affordable by online networking fits with the idea that students should take greater responsibility for their own learning.
- Practical :- e-learning offers the ability to manage quality at scale, and share resources across networks; its greater flexibility of provision in time and place makes it good for widening participation.
- Financial :- Networks and access to online materials offer an alternative to place-based education which reduces the requirement for expensive buildings, and the cost of delivery of distance learning materials

6. Technology used in E-learning

Many technologies can be, and are used in E-learning, including:

- Blogs
- Classroom Response System.
- Collaborative Software.

- Computer Aided Assessment.
- Discussion Boards.
- E-mail.
- Educational animation.
- Electronic Performance Support System.
- ePortfolios
- Games.
- Hypermedia in general.
- Learning Management Systems(LMS)
- PDA's
- MP3 players with multimedia capabilities.
- Interactive Board
- Virtual Classrooms
- Web-based teaching materials

In higher education especially, the increasing tendency is to create Virtual learning Environment (VLE) which is sometimes combined with a Management Information System (MIS) to create a Managed Learning Environment. in which all aspects of a course handled through a consistent user interface standard throughout the institution. While some programs require students to attend some campus classes or orientations, many are delivered completely online. In addition, several universities offer online student support services, such as online advising and registration, e-counseling, online textbook purchase, student governments and student newspapers. E-learning can also refer to education web site such as those offering learning scenarios, worksheets and interactive exercise for children. The term also used extensively in the business sector where it generally refers to cost effective on line training.

7. Advantages of E-Learning

- More active learning class
- Diversified teaching method
- Better student attention and realization
- Effective time management for lecturers
- Visual stimulation
- Convenient for students
- Lower cost
- Up-to-date learning materials
- Flexible way of learning
- World-wide learning society
- Scalable e-learning systems
- Higher degree of freedom for students
- Better maintenance

8. Objectives:

E-learning represents an innovative shift in the field of learning, providing a rapid access to specific knowledge and information. It offers online instruction that can be delivered anytime and anywhere through a wide range of electronic learning solution such as web based courseware, online discussion groups, live virtual classes, video and audio streaming, web chat, online simulations, and virtual mentoring.

E-learning enables organizations to transcend distance and other organizational gaps by providing a cohesive virtual learning environment. Companies must educate and train their employees, partners, and clients to stay competitive, and elearning can provide such just in time training in a cost-effective way.

Following are main objectives of E-Learning:-

- Computer based learning.
- Computer based training.
- To reduce learning costs.
- To motivate employees.
- To improve flexibility of course delivery.
- To expand the capabilities of the business.

9. Methodology

The implementation of e-learning into contact teaching allows elimination of number of hours of contact teaching and giving space to individual work with student. The implementation of e-learning into distance learning allows simulating classical forms and methods of education by creating a virtual environment, which imitates classical classroom with whiteboard and the possibility of visual communication.

The following methods are used for the implementation of e-learning.

- Survey of existing tools for creation of information infrastructure.
- Comparison of individual programs for creation of electronic teaching materials and selection of the most appropriate ones.
- Distance learning project team training.
- CASE tool method for the creation of databases.

10. Conclusion

E-learning refers to the use of Internet technologies (IT) to deliver overseas array of learning modes that enhance learner's knowledge and performance. E-learning for higher education is designed, implemented and delivered. For students, e-learning can provide an educationally- superior alternative to traditional lectures, in which learning can take place outside the lecture hall/Class room. E-learning is also providing a model for students on how to become self directed independent learners, which may support them to lifelong learners. They also used for easily and useful understanding of subject by using Graphical / Pictorial form and can be remembered for long times.

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Big Data Storage Technologies and Challenges of Big Data Storage and Management

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Abstract - Big data is a term to refer to huge data sets, have high Velocity, high Volume and high Variety and complex structure with difficulties of management, analyzing storing and processing. Due to characteristics of big data it becomes very difficult to management, analysis, storage, Transport and processing the data using the existing traditional techniques. This paper introduces Big Data Analysis and Storage Technologies, Challenges of Big Data Storage and Management and Suggestions for Big Data Storage and Management. Storage and Management are major concern in this era of big data. The ability for storage devices to scale to meet the rate of data growth, enhance access time and data transfer rate is equally challenging. These factors, to a considerable extent, determine the overall performance of data storage and management.

Keywords: *Big Data Definition, Characteristics, Data Storage Technologies, Challenges Of Big Data Storage And Management, Suggestion For A Big Data Storage And Management.*

Big Data Definition

"Big Data is at the foundation of all the megatrends that are happing."

Chris Lynch, Vertica Systems

Data is everywhere, in fact the amount of digital data that is growing at a rapid rate, and changing the way. This is the field that didn't even exist 20years back. Now data is growing faster than ever faster before and by the year 2020; about 1.7megabytes of new information will be created every second for every human being on the planet.

Data is essentially just raw bits of information science.

Big data is basically a term that describes large amount of data. Big data sets those are so big and complex that traditional data-processing application software is in adequate to deal with them. Big data challenges include capturing data, data storage, data analysis, search, sharing, transfer, visualization, querying, updating, information privacy and data source. There are number of concepts associated with big data: originally there were 3 concepts volume, variety, and velocity. Other concepts later attributed with big data are veracity (i.e., how much noise is in the data) and value.

The position of big data storage within the overall big data value chain can be seen in **figure 1.** Big data storage systems typically address the volume challenges by making use of distributed shared nothing architectures. This allows addressing increased storage requirements by scaling out new nodes providing computational power and storage. New machines can seamlessly be added to a storage cluster and storage system takes care of distributing the data between individual nodes transparently. Storage solutions also need to cope with the velocity and variety of data.

Velocity is important in the sense of query latencies, i.e. how long does it take to get a reply for a query? This is particularly important in the face of high rate of incoming data. For instance, random write access to a database can slow down query performance considerably if it needs to provide transactional guarantees. In contrast, variety relates to the level of effort that is required to integrate the work with the data that originates from a large number of different sources. For instance graph databases are suitable storage systems to address these challenges.

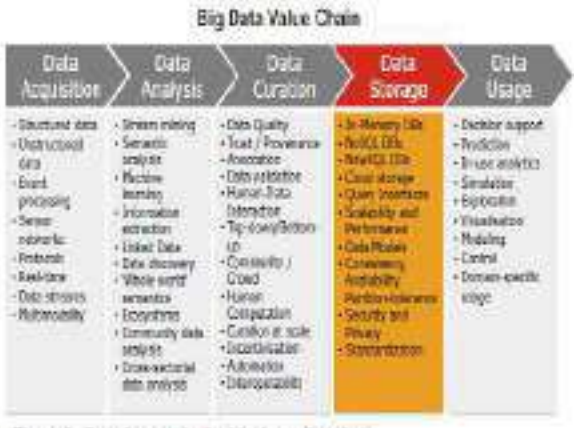


Figure 1: Data Storage in the big data value chain

Big Data Characteristics

The three Vs (volume, velocity and variety) are known as the main characteristics of big data. The characteristics are described in **figure 2** below.

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AMRAVATI

Volume: refers to amount of data and there are many factors that can contribute to the volume increase in data it could amount to hundreds of terabytes or even pet bytes of information generated for everywhere. The number of sources of data for an organization is growing.



Figure 2: 3 Vs of big data

Figure 2 shows that the data volume is growing from megabytes (106) to petabytes(1015) and beyond.

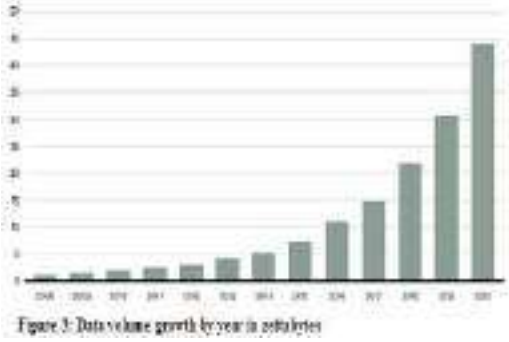


Figure 3: Data volume growth by year in petabytes

Figure 3 indicates that the volume of data stored in the world would be more than 40 zettabytes(1021) by 2020 .

Velocity: refers to data speed measures the velocity of information creation, gushing and collection, velocity is the most misunderstood big data characteristic. The data velocity is also about the rate changes, and about combining datasets that are coming with different speeds. The velocity of data also describes bursts of activities, rather than the usual steady tempo where velocity frequency equated to only real-time analytics.



Figure 4: Examples of big data velocity

Figure 4 shows few examples of the pace of data. Data speed administration is significantly more than a bandwidth issue; Figure 2 also reflect velocity as characteristics of big data, showing how it requires near real-time and/or real-time analytics.

Variety: Other than typical structured data, big data contains text, audio, images, videos, and many more unstructured and semi-structured data, which are available in many analog and digital formats. From an analytic perspective, variety of data is the biggest challenge to effectively use it. Some researchers believe that, taming the data variety and volatility is the key of big data analytics.

Figure 5 shows the comparison between increment of unstructured, semi-structured data and structured data by years.

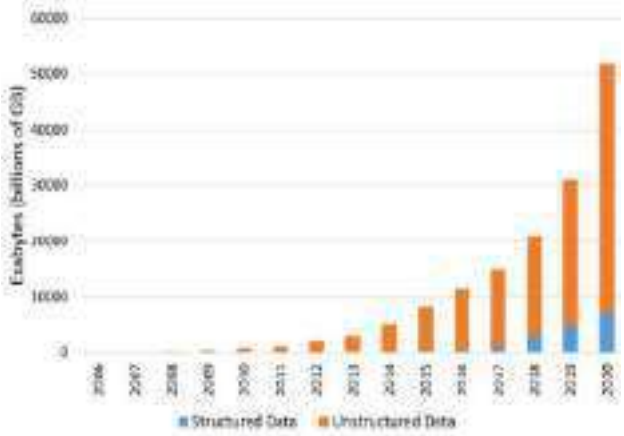


Figure 5: Growth of data variety by years

This paper investigates and analyzes big data storage technology from the following four aspects: distributed file system, NoSQL database, new-type data storage technology of MPP architecture and database all-in-one machine.

- **Distributed File Systems:** File system such as Hadoop file system(HDFS)

HDFS is an integral part of the Hadoop framework and has already reached the level of de-facto standard. It has been designed for large data files and is well suited for quickly ingesting data and bulk processing Data Storage Technologies

- **Big Data Querying Platforms:** Technologies that provide query facades in front of big data stores such as distributed file systems or NoSQL databases. The main concern is providing a high-level interface, e.g. via SQL like query languages and achieving low query latencies.

- **NoSQL Databases:** Probably the most important family of big data storage technologies are NoSQL database management systems. NoSQL databases use data models from outside the relational world that do not necessarily adhere to transactional properties of atomicity, consistency, isolation, and durability (ACID).

- **NewSQL Databases:** A modern form of relational databases that aim for comparable scalability as NoSQL

databases while maintaining the transactional guarantees made by transactional database systems.

- **Big Data Querying Platforms:** Technologies that provide query facades in front of big data stores such as distributed file systems or NoSQL databases. The main concern is providing a high level interface, e.g. via SQL like query languages and achieving low query latencies.

1. NoSQL Databases :

NoSQL databases are design for scalability, often by sacrificing consistency. Compared to relational databases they often use low-level, non-standardized query interfaces, which make them more difficult to integrate in existing applications that expect an SQL interfaces. The lack of standard interfaces makes it harder to switch vendors. NoSQL databases can be distinguished by the data models they use.

- Key-Value Stores: Key-value stores allow storage of data a schema-less way. Data objects can be completely unstructured or structured and are accessed by a single key. As no schema is used, it is not even necessary that data objects share the same structure.
- **Columnar Stores:** "A column-oriented DBMS is a database management system(DBMS) that stores data table as sections of columns of data rather than as rows of data, like most relational DBMSs". Such databases are typically sparse, distributed, and persistent multi-dimentional sorted maps in which data is indexed by a triple of a row key, column key, and a timestamp.
- **Document Databases:** In contrast to the values in a key- value store, documents are structured. However, there is no requirement of common schema that all document are must adhere to as in the case for records in a relational databases. Thus document databases are referred as a storing semi-structured data similar to key-value stores, documents can be querying their internal structure, such as requesting all documents that contain a field with a specified value.
- Graph Databases: Graph databases store in graph structured making them suitable for storing highly associative data such as social networking graphs.

2. NewSQL Databases :

NewSQL databases are modern form of relational databases that aim for comparable scalability with NoSQL databases while maintaining the transactional guarantees made by transactional database systems. The expectation is that NewSQL systems are about 50 times faster than traditional OLTP RDBMS.

3. Big Data Query Platforms :

Big data query platform provide query facades on top of underlying data stores. They typically offer an SQL like query interface for accessing the data, but differ in their approach and performance.

4. Cloud Storage :

As cloud computing grows in popularity, its influence on big data grows as well. While Amazon, Microsoft, and Google build on their own cloud platforms, other companies including IBM, HP, Dell, Cisco etc., build their proposal around Open Stack, an open source platform for building cloud systems, Cloud in general, and particularly cloud storage, can be used by both enterprises and end users. For end users, storing their data in the cloud enable access from everywhere and from every device in a reliable way. As cloud storage is a service, applications using this storage have less control and may experience decreased performance as a result of networking. These performance differences need to be taken into account during design and implementation stages.

Challenges of big data storage and management

With the rate of data explosion, storage system of organizations and enterprises are facing major challenges from huge quantities of data, and ever increasing of generated data. Data irrespective of its size play a vital role in the industry. Value can be created from large data set. For example, Facebook increases its ad revenue by mining its user personal preferences and creating profiles, showcasing advertisers which products they are most interested in. Google also uses data from Google search, Google hangouts, YouTube, and Gmail accounts to profile user's behavior.

In spite of numerous benefits that can be gained in large data set, big data demand for storage and processing poses a major challenge. The total size of data that will be generated by the end of 2015 is estimated at 7.9 zettabytes(ZB), and by 2020, is expected to reach 35 ZB. It is clear that big data has outgrown its current infrastructure, and pushes the limit on storage capacity and storage network. Existing traditional techniques cannot support and perform effective analysis, due to large scale of data.

Big Data Storage Management

Due to massive increase, and the heterogeneous nature of application data, one main challenge of big data is effectively, manage the petabyte (PB) of data being generated daily. Storage management encompasses technologies and process organization to improve data storage performance. Big data require more efficient technologies in processing large quantities of data within an acceptable time frame. A wide range of techniques and technologies have been developed and adopted to manipulate, analyze and visualize big data. Technologies such as massive parallel processing (MPP) database, data mining grids, distributed file system, cloud computing platforms, and scalable storage systems are highly desirable. The development of Map-Reduce, with Yahoo's Pig, alongside Facebook's Cassandra applications, has gotten the attention of the industry. Google file system, GFS, is designed to meet the increasing demands of big data, such as scalability, reliability and availability. GFS is composed of clusters, which is made up of hundreds of storage servers that support several terabytes of disk space. This meets the scalability issue of big data. Hadoop is free version of Map-reduce implementation by Apache Foundation. Hadoop distributed file system(HDFS), is a distributed file system designed to run on commodity hardware. HDFS can store data across thousands of servers. All data in HDFS is reduced into block size chunk, and distributed across different nodes and are managed by the Hadoop cluster

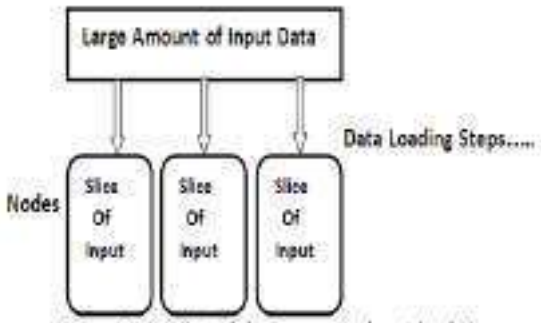


Figure 6: Distributed data across nodes at load time

Figure 6 shows the distribution of data across different data nodes to enhance performance of the entire Hadoop system. Storage vendors such as NetApp, EMC, Hitachi Data Systems, and many more are offering storage management solutions to big data inclined companies. EMC VPLEX enables manageability of storage area network, through a vital storage infrastructure that consolidates heterogeneous storage devices.

Suggestion for a Big Data Storage and Management

System Big data storage and management has been challenge in the face of the increasing volume of organizational data. This paper suggests approaches that we think in our opinion efficiently mitigate challenges of big data storage and management.

1. **Big Data Storage Mediums**: All storage management solutions have at their end, storage devices. The qualities of these storage devices can have significant impact on the entire storage effectiveness; can be critical in the big data environment. We suggest the use of a hybrid storage device, which is an aggregate of hard disk drive (HDDs), and solid state drives (SSDs). HDDs provide huge storage capacity, at a relatively cheap price. This characteristic of the HDDs allows storage system to scale to meet the rate of growth of data. The disadvantage here is that, HDDs has a slow data transfer rate becoming a bottleneck for performance. On the other hand, SSDs provides avenue for high performance and reliability. They have low latency, thus providing a much faster, random access. SSDs are very expensive for the storage capacity they provide. The combination of these storage devices into a logical unit in an array should solve the storage demands posed by large datasets.

2. **Backup Strategies:** Recovery is the main objective for backup. The ability of production system to recover, and in a timely manner is very crucial in the era of big data. From this prospective, this paper recommend full back as a favorable choice over the others. Full backup ensures speedy recovery, through it takes a considerable amount of time to back up a large dataset. Applying full backup to large datasets may increase the data block repetition. Data reduplication technology, significantly reduce the volume of stored data block for every single full backup, and allow users to backup, and recover data within relatively short period of time. Rather than directly from the production system. Replication keeps copy of production data in real time.

3. **Business Continuity and Disaster Recovery:** An optimal business continuity solution, takes into account, two parameters, to a negligible level – Recovery Point Objective (RPO), which is the point in time that a production system, and data must be recovered after a disaster. Recovery Time Objective (RTO) is the time frame within which production system, and data must be recovered after a disaster. In a large dataset, the complexity of business continuity increases, with the influx of a variety of data, which must be maintained in their formats. Business continuity planning requires, saving a copy, or multiple copies of production data, through backups, local or remote replication. The use of enterprise software such as EMC Power path can be beneficial. EMC Power path provides features such as cluster support, dynamic load balancing, configuration and management, automatic path failover.

Conclusion

In the recent years, a academia pays more attention to cloud computing. Big data focuses on “data”, like data service, data acquisition, analysis and data mining which pays more attention on ability on data storage. Cloud computing focuses on computing architecture and practices. Big data and cloud computing are two sides of same issue.

Big data era has brought about an explosive growth of data. The increase of mobile applications, social media, and big data analytic initiatives has cause big data storage challenges to become even greater. Choosing the right storage devices, management tool, and efficient techniques is relevant and determines the rate of growth.

The approaches to big data storage and management can significantly, affect the entire organization. This paper examines and summarizes existing current storage technologies for big data applications. Variables such as capacity, scalability, data transfer rate, access time, and cost of storage devices, are also highlighted. Finally some suggestions are made to curb the problems posed by big data storage.

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Leap Protocol in Wireless Sensor Network

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ABSTRACT- Wireless sensor network are becoming significantly vital to many applications, and they were initially used by the military for surveillance purpose. One of the biggest concerns of WNS is that they are very defenseless to security threats. Due to the fact that these networks are susceptible to hackers, it is possible for one to enter and

render a network. For Example, such network may be hacked into the military, using the system to attack friendly forces, for this a key management protocol for sensor network i.e. LEAP (Localized Encryption and Authentication Protocol) is designed to support in-network processing. The design of protocol is motivated by the observation of different types of messages exchanged between sensor nodes have different security requirements and that single keying mechanism is not suitable for meeting these different security requirements , and LEAP uses four types of key for each sensor node. The prototype implementation of LEAP in sensor network is also reported.

Keywords*: Key Management (four key used by LEAP) , Sensor Network , Designing Goal of LEAP, Working of LEAP, TDMA-slot, TDMA-cycle, NS2Platform.*

INTRODUCTON

Wireless Sensor Network spatially consist of distributed autonomous sensors to monitor physical and environmental conditions such as temperature, sound, vibration, pressure motion and pollutants and to cooperatively pass their data through network to main location with the help of protocol.

Protocol: It specifies the standard for communication and provides detail information on processes involve in data transmission. A single process can handle by more than one protocol simultaneously.

LEAP (Localized Encryption and Authentication Protocol) is a proprietary wireless LAN (Local Area Network) authentication method developed by Cisco System. Important feature of LEAP is dynamic WEP (Wired Equivalent Privacy) Keys and mutual authentication between a wireless client and RADIUS (Remote Authentication Dial In User Service) Server.

LEAP (Localized Encryption and Authentication Protocol) , sometimes called EAP(Extensible Authentication Protocol)-Cisco Wireless, is interesting in that it was really the first commercial use of IEEE 802.1X and EAP(Extensible Authentication Protocol) for wireless LAN(Local Area Network)

LEAP (Localized Encryption and Authentication Protocol) PROTOCOL:

LEAP (Localized Encryption and Authentication Protocol) is the authentication protocol used in wireless network and point-to-point connection. LEAP is designed to provide more secured authentication for 802.11 WLANs (wireless local area networks) that support 802.1X port access control. It is a key management protocol for sensor network that is designed to support in-network processing, while providing security properties similar to those provided by pair wise key sharing schemes. LEAP includes support for multiple keying mechanisms. The design of this mechanism is motivated by the observation that different types of messages exchange between sensor nodes have different security requirements.

DESIGN GOAL

LEAP is designed to support secure communication in sensor network, therefore it provide the basic security services such as confidentiality and authentication. In addition LEAP is to meet several security and performance requirement that are considering more challenging to sensor network.

- Supporting Various Communication Patterns :

There are typically three types of communication pattern in sensor network : unicast (addressing a message to single node) , local broadcast (addressing a message to all the nodes in the neighborhood) , and global broadcast (addressing a message to all the nodes in the network).

- Supporting In-network Processing: Security mechanism should permit in network processing operation such as data aggregation and passive participation. In network processing could significantly reduce energy consumption in sensor network.

- Survivability: Due to the unattended nature of sensor network an attacker could launch various security attacks and even compromise sensor node without being detected. Therefore , a sensor network should be robust against security attacks, and if an attack succeed , its impact should be minimized .

- Energy Efficiency: Due to the limited battery life time, security mechanism for sensor network must be energy efficient. Especially, the no of message transmission and the number of expensive computation should be as few as possible. Moreover size of sensor should not be limited by the pre-node storage and energy resources.

- Avoiding Message Fragmentation: A unique challenge in sensor network is due to small packet size. The default supported packet size is only 36 bytes for increasing the reliability of packet delivery. Thus the message in security





protocol has to be small enough to fit in one packet to avoid message fragmentation.

Key Management Scheme:

LEAP supports the establishment of four types of keys for each sensor node :

An individual key shared with the base station. Every key has unique key that it shares with the base station. This Key is used with secure communication between nodes and the base station. Individual key is used to compute message authentication code for its sensed reading by node, if it is verified by base station.

A pair wise key shared with another sensor nod:

Every node shares pair-wise key with each of its neighboring node. In LEAP pair wise key is used for securing communication that requires privacy and source authentication. Each node can used its pair-wise key to secure the distribution of cluster key to its neighbor or to secure the transmission of its sensor reading to an aggregation node.

A cluster key shared with multiple neighboring nodes:

A cluster key is key shared by node and its neighbors and it is mainly used for securing locally broadcast message i. e. routing control information or securing sensor messages which can benefit from passive participation.

A group key shared by all nodes in the network:

This is globally shared key used that is used by base station for encrypting message that are broadcast to the whole group. For Ex: The base station issues missions , send queries and interests.

Security Requirements for Key Management

To provide secured communication in WSN, sensor node first need to setup pair-wise with each other. There are some majors:

Data Confidentiality: In sensor network data flows from many intermediate nodes and chances of data leak is more hence only encrypted data is used so that only recipient decrypts the data to its original form.

Data Integrity: Data receive by receiver should not be altered or modified is data integrity.

Data Authentication: It is the procedure for confirmation that the communicating nodes is the one that it claims to be. It is important for receiver to do verification that the data is receive from authenticate node.

Data Availability: This means the services are available all the time even in case of some attacks such as Denial of service.

Source Localization: For Data transmission some application use location information of the sink node. It is important to give security to the location information. Non-secured data can be controlled by the malicious node by sending false signal strength or replaying signals.

Self-Organization: In WNS no fixed infrastructure exists , hence every node is independent having properties of adaption to the different situation and maintain self organizing and self healing properties. This is the great challenge for security in WNS.

Working of LEAP

The process is summarized as:

1. The authentication server challenges the device by sending a random string. The device must prove it knows the key by sending response derived from challenge.
2. The device sends a challenge to the authentication server, which must also respond correctly.
3. The authentication server generates and sends a session key to access point with the EAP (Extensible Authentication Protocol) success notification in RADIUS (Remote Authentication Dial In User Service) message.
4. The access point notifies the device of authentication using the EAPOL (Extensible Authentication Protocol Over LAN)-Success message. At this point the client computes the matching session key.
5. The access point sends an EAPOL(Extensible Authentication Protocol Over LAN) key to activate encryption.
6. The device and access point communicate using WEP encryption.



Figure 1: EAP-LEAP

Hardware Technologies

A sensor network is an embedded system, or rather a digital system committed to specific duties. Each node consist of sensor board and a programming board. The sensor board could be differentiating by specific kind of sensor. Light, temperature, humidity but also distance tracking or GPS receiver. The programming board supplies wireless between a

node and a base station. A node is equipped with a microcontroller and low storage memories.

NS2 Platform : It is an open source simulation tool that runs on LINUX . It is a node platform for low power and high data rate sensor network applications designed with dual goal of fault tolerance and development ease. The low power operation of the module is due to the low power T1 MSP430 microcontroller. This 16-bit RISC processor features low active and sleep current consumption. In order to minimize power consumption, the processor in sleep during majority of the time , wakes up s fast as possible to process , then return to sleep mode again.

Software Technologies

It follows the demand of specific ad hoc software technologies. Hence, operating system for WSN nodes are typically less complex than general-purpose operating system. In general operating system in WSN should fulfill requirements like:

1. Robustness: once deployed, a sensor network must work unattended for months and years.
2. Low resource usage: sensor network node includes very small RAM, and run off batteries.
3. Multiple service implementations: application should be able to choose between various implementations.
4. Adaptability to evaluations: mote hardware is in constant evaluation, application and most system service must be portable across hardware generation.
5. Adaptability to application requirements: applications have very different requirements in terms of life time, communication, sensing etc.

Leap implement token passing procedure that:

- Ensures synchronization between nodes and clusters.
- Allows initializing and self configuring to the optimal working point
- Allows for the addition of new nodes

A token is a particular message that carries the information on the duration of TDMA-slot and a TDMA-cycle, the transmitting and receiving schedule of TDMA-cycle, a synchronization message carrying the current execution state of the TDMA-cycle. The controller has all the information to calculate the optimal set of parameters, consequently, it is able to generate a token before the network starts operating. The network initialization algorithm works as :

1. When the network starts all nodes are awake and listening.
2. The controller multi cast the token to all nodes of one of the connected cluster.
3. Nodes of the selected cluster read the information on scheduling and duration of TDMA-slot and TDMA-cycle. Moreover each node acquires the information about the global time and launches periodic timer for CSMA and TDMA slot. In the midtime, a random back-off timer starts for each node before sending an acknowledgement.
4. The first node that expires the back-off time sends the acknowledgement to the controller and become the token forwarder. Then all nodes in the cluster go to sleep.
5. At the beginning of the second TDMA-slot the token forwarder wake up and immediately multi-casts the token to all nodes in the next cluster.
6. With the same random acknowledgement-based scheme, a node is elected token forwarder for nodes in following cluster.
7. Information about routing and TDMA-slot duration needs also to be updated during network operation. Hence, the Controller periodically performs a token refreshing procedure.

Conclusion

The LEAP protocol was implemented and simulated using one base station and fifty sensor nodes situated randomly. Initially, an individual key was generated for each node from a randomly generated master key. Then a cluster key was generated by each node and published to their neighboring nodes using the pair –wise keys. Finally the global key was generated in order to enable public broadcasts.

The whole idea behind LEAP was to implement a system whereby multiple base station have been employed for the soul purpose of improving tha data transmission amongst node and to come up with a solution for base station , should it be compromised.

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8. Internet of Things Security Architecture: Challenges and Issues

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Abstract

Wireless communication networks are highly prone to security threats. The major applications of wireless communication networks are in military, business, healthcare, retail, and transportations. These systems use wired, cellular, or adhoc networks. Wireless sensor networks, actuator networks, and vehicular networks have received a great attention in society and industry. In recent years, the Internet of Things (IoT) has received considerable research attention. The IoT is considered as future of the internet. In future, IoT will play a vital role and will change our living styles, standards, as well as business models. The usage of IoT in different applications is expected to rise rapidly in the coming years. The IoT allows billions of devices, peoples, and services to connect with others and exchange information. Due to the increased usage of IoT devices, the IoT networks are prone to various security attacks. The deployment of efficient security and privacy protocols in IoT networks is extremely needed to ensure confidentiality, authentication, access control, and integrity, among others. In this paper, an extensive comprehensive study on security and privacy issues in IoT networks is provided. In this paper, the in-depth meaning of Internet of Things (IoT) was explained. The role it contributes to our daily lives was described. The reason why security and privacy are the biggest challenges facing Internet of Things was given. Confidentiality, integrity and availability of IoT were analyzed.

Keywords : Internet of Things (IOT), Security issues in IoT, privacy, IoTAttacks, Confidentiality, Availability, Integrity.

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1. Introduction

In a digital world, everything is being connected to the internet, from humans to electronic devices, objects and animals. The connections of those objects to the internet, which exchange and monitor data each other without the intervention of human being, is call as Internet of Things. The number of those connected objects will reach 80 billion in 2025[1]. IoT has helped companies to deliver outstanding Customer services, to enter a new market, and even to develop new business models. However, privacy and security are the biggest challenges facing IoT. Many IoT devices have vulnerabilities such as lack of strong encryption or no encryption at all. Few years ago, some companies implemented IoT in their systems, later they discovered that data were being send in clear text. That means an attacker could capture data and analyses them. That might be the bad news for the entire organization because attackers will have access to all data being sent in clear text, hence the lack of confidentiality. There is no doubt that the raise of IoT has lent a hand to the increase number of security-attacks [2]. Before IoT, there were some few security attacks, but observe how security attacks are growing faster, it grows exponentially with respect to that increase is almost at the same rate of IoT. All those factors made IoT to experience a rapid growth and popularity. How the number of connected devices is increasing exponentially in the following Figure 1 [3].

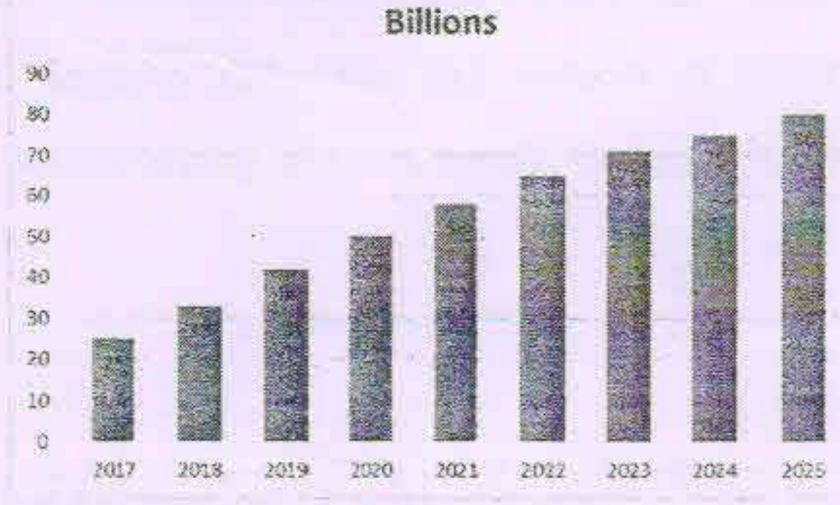


Figure 1: Connected devices in billion from the year 2017 to 2025.

2. Current Background Overview of IOT

A. From manufacturers to consumers

From manufacturers to consumers, IoT has played a tremendous role. Healthcare devices are nowadays being implemented with IoT capabilities that enable medical doctors to remotely

application installed on a smartphone or any computer. That helps the owners to control their entire home remotely whenever they want wherever they are [4].

B. Security and Privacy challenges in IoT

IoT has contributed a lot in different areas such Business infrastructure, industrial control systems where the entire factory can be connected to the internet be controlled via smartphone. Despite all mentioned achievements, security and privacy remain a big challenge in IoT. IoT is exposed to larger attack surface [4].

• Many IoT systems have both hardware and

Software vulnerability that remain unpatched. If a hacker exploits those vulnerabilities, there will be zero-day attacks. That could be a disaster for the entire organization, it will be hard to mitigate those attacks because the manufacturers were not aware of vulnerabilities [5].

• IoT is exposed to larger attack surface. Because devices are connected each other, many attacks are possible not to one device but to the entire network [6].

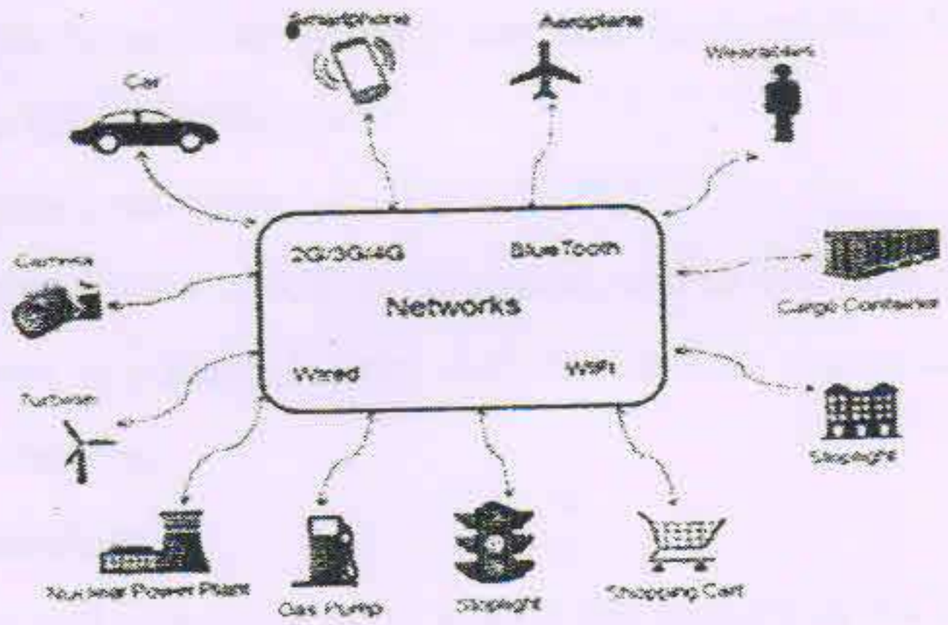


Figure 2: Example of IoT System [3].

3. SECURITY and PRIVACY CHALLENGES

The era of IoT has changed our living styles although the IoT provides huge benefits, it is prone to various security threats in our daily life. The majority of the security threats are related to leakage of information and loss of services. In IoT, the security threats straight forwardly are affecting the physical security risk. The IoT consist of different devices and platform with different credentials, where every system needs the security requirement depending upon its characteristics [4, 5].

The privacy of a user is also most important part because a lot of personal information is being shared among various types of devices [4, 5]. Hence a secure mechanism is needed to protect the personal information. Moreover, for IoT services, there are multiple types of devices that perform communication using different networks. It means there are a lot of security issues on user privacy and network layer. User privacy can also be uncovered from different routes. Some security threats in the IoT are as follows:

1) E2E Data life cycle protection:

To ensure the security of data in IoT environment, end-to-end data protection is provided in a complete network. Data is collected from different devices connected to each other and instantly shared with other devices.

2) Secure thing planning:

The interconnection and communication among the devices in the IoT vary according to the situation. Therefore, the devices must be capable of maintaining security level. For example, when local devices and sensors used in the home-based network to communicate with each other safely, their communication with external devices should also work on same security policy [6].

3) Visible/usable security and privacy:

Most of the security and privacy concerns are invoke by misconfiguration of users. It is very difficult and unrealistic for users to execute such privacy policies and complex security mechanism. It is needed to select security and privacy policies that may apply automatically [7].

4. CIA Triad in IOT

IoT will reach its full potential and full popularity only if interactions between connected devices fulfils the fundamental security model which is known as CIA triad (Confidentiality, Integrity, and Availability)

A. Confidentiality

IoT manufacturers and vendors must make sure that data being transmitted in connected devices will be accessed only by authorized people, i.e. consumers. But confidentiality has remained a challenge to IoT because so many devices were discovered exchanging data in clear text in IoT system [8].

B. Integrity

Data being transmitted among IoT systems must remain unchanged during the entire life cycle.

C. Availability

Availability in critical devices must be 99.999%, i.e. the downtime will be as minimal as possible.

D.IoT Challenges

The IoT improve the communication between devices but still, there are issues related to the scalability, availability and response time. Security is a concern where the data is securely transmitted over the internet. While transporting the data across international border, safety measure. Among different security challenges, the most important challenges relevant to IoT are discussed.

1) Data Privacy: Some manufacturers of smart TVs collect data about their customers to analyse their viewing habits so the data collected by the smart TVs may have a challenge for data privacy during transmission [9].

2) Data Security: Data security is also a great challenge. While transmitting data seamlessly, it is important to hide from observing devices on the internet.

3) Insurance Concerns: The insurance companies installing IoT devices on vehicles collect data about health and driving status in order to take decisions about insurance.

4) Lack of Common Standard: Since there are many standards for IoT devices and IoT manufacturing industries. Therefore, it is a big challenge to distinguish between permitted and non-permitted devices connected to the internet [10].

5) Technical Concerns: Due to the increased usage of IoT devices, the traffic generated by these devices is also increasing.

6) Security Attacks and System Vulnerabilities: There has been a lot of work done in the scenario of IoT security up till now. The related work can be divided into system security, application security, and network security [11].

a) System Security: System security mainly focuses on overall IoT system to identify different security challenges, to design different security frameworks and to provide proper security guidelines in order to maintain the security of a network [12].

b) Application security: Application Security works for IoT application to handle security issues according to scenario requirements [13].

c) Network security: Network security deals with securing the IoT communication network for communication of different IoT devices. In the next section, the security concerns regarding IoT are discussed. The security attacks are categorized into four broad classes [13].

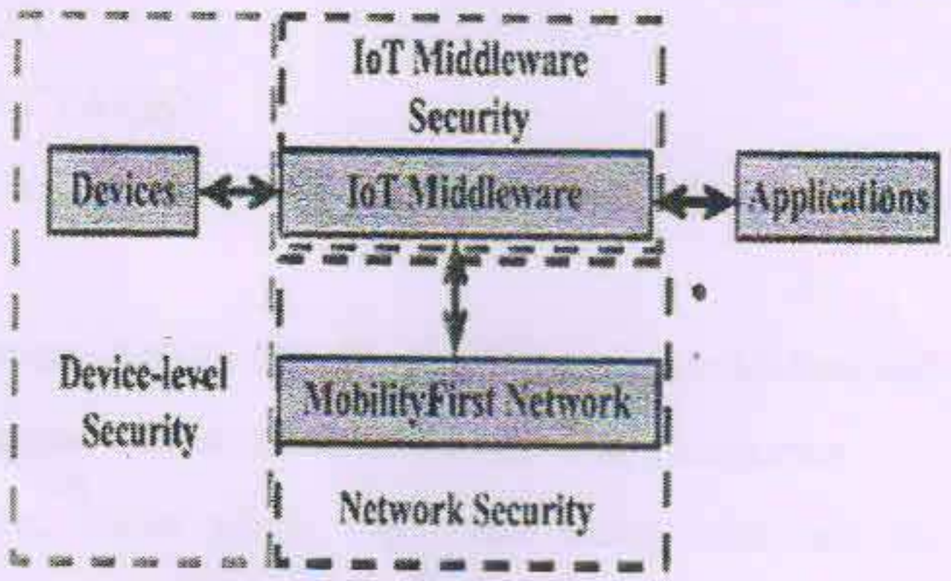


Figure 3: IoT Security Architecture.

5. Analysis of Different Types of Attacks and Possible Solutions

In IoT, all the devices and people are connected with each other to provide services at any time and at any place. Most of the devices connected to the internet are not equipped with efficient security mechanisms and are vulnerable to various privacy and security issues e.g., confidentiality, integrity, and authenticity, etc. For the IoT, some security requirements must be fulfilled to prevent the network from malicious attacks [14]. Here, some of the most required capabilities of a secure network are briefly discussed.

1. Resilience to attacks

The system should be capable enough to recover itself in case if it crashes during data transmission.

2. Data Authentication

The data and the associated information must be authenticated. An authentication mechanism is used to allow data transmission from only authentic devices.

3. Access control

Only authorized persons are provided access control.

4. Client privacy

The data and information should be in safe hands. Personal data should only be accessed by authorized person to maintain the client privacy. Different levels of attacks are categorized into four types according to their behaviour and propose possible solutions to threats/attacks [15].

1) Low-level attack

If an attacker tries to attack a network and his attack is not successful.

2) Medium-level attack

If an attacker/intruder or an eavesdropper is just listening to the medium but don't alter the integrity of data.

3) High-level attack

If an attack is carried on a network and it alters the integrity of data or modifies the data.

4) Extremely High-level attack

If an intruder/attacker attacks on a network by gaining unauthorized access and performing an illegal operation, making the network unavailable, sending bulk messages, or jamming network.

6. Classification of IOT

SECURITY ATTACKS

An action that compromises the security of data. The security attacks can be divided in to two types [16, 17].

1. Active Attacks: Active attacks involve some modification of the data stream or the creation of false stream and can be subdivided into four categories:

a) Masquerade: Takes place when one entity pretends to be a different entity. A masquerade attack usually includes one of the forms of active attack.

b) Replay: Replay involves the passive capture of a data unit and its subsequent retransmission to produce an unauthorized effect.

c) Modification of Messages: Simply means that some portion of a legitimate message is altered, or that message are delayed or reordered, to produce an unauthorized effect.

d) Denial of Service: The denial of service prevents or inhibits the normal use or management of communications facilities. This attack have a specific target; for example, an entity may suppress all messages directed to a particular destination.

2. Passive Attacks: Passive attacks are in the nature of eavesdropping or monitoring of transmission. This attack is divided into following categories:

a) Release of message content: For a release of message content, a telephonic conversation E-mail message or a transferred file may contain confidential data. A passive attack

monitors the contents of the transmitted data. When the message are exchanged neither the sender nor the receiver is aware that a third party may capture the messages.

b) Traffic analysis: Traffic analysis is a special type of inference attack technique that looks at communication patterns between entities in a system. Traffic analysis is the process of intercepting and examining messages in order to deduce information from patterns in communication.

7. Analysis and Discussion

An Active attack attempts to alter system resources or affect their operation. Active attack involve some modification of the data stream or creation of false statement. Ensure both confidentiality and integrity of data. To maintain data confidentiality, symmetric encryption can be applied. The attacker intercepts the connection and modifies the information. Effects confidentiality and integrity of data. Always causes damages to the system. A Passive attack attempts to learn or make use of information from the system but does not affect system resources. The goal of the opponent is to obtain information is being transmitted. Ensure confidentiality of data do not allow an attacker to fetch information using symmetric encryption techniques. In which an intruder attempts to alter data on the target system or data en-route for the target system. Usually breach data confidentiality and involves probing for network information [18].

"Active "in which an intruder initiates commands to disrupt the network's normal operation. While "Passive" when a network intruder intercepts data traveling through the network.

On the other hand, it is quite difficult to prevent active attacks absolutely, because of the wide variety of potential physical, software, and network vulnerabilities. Instead, the goal it is to detect active attacks and to recover from any disruption or delays by them. The detection has a deterrent effect; it may also contribute to prevention. So, the threat level of Active attacks is high and modification of stream / data or its false creation, difficult to prevent, focus is on detection and recovery. While Passive attacks is low and difficult to detect, no alteration of data, focus on prevention.

Summary of Different Types of IOT Attacks

Table1: Comprehensive Study of IOT Attacks Along With Their Level, Nature, Detection technique, Prevention method, limitations and Experiment derived [18,19].

Category of Attacks	Attacks Type	Layer	Threat Level	Behavior	Detection Technique	Prevention Method	Parameter used	Limitations	Experiment derived
Active Attacks	Masquerade	Network	High	Is a disguise.	Profiling-based detection approach	To create innovative algorithms that can efficiently detect the suspicious action	1.Stolen passwords and logons 2.Steal sensitive data	To gain greater privileges than they are authorized for.	The attacker pretends to be an authorized user of a system.
	Replay	Network	Medium	In which a valid data transmission is maliciously or fraudulently repeated or delayed	1 Strong digital signatures with timestamps. 2 Random session keys with time bound and process bound.	1.One-time password 2. Generating a Session-ID and a component number.	1 Login Authentication 2 IP Packet Substitution.	A valid data transmission is maliciously.	Can be prevented by tagging each encrypted component with a session ID and a component number.
	Modification of messages	Application	Extremely high	Data en route to the target	It cause duplication of logon procedure and capture the user password	1. Alters packet header addresses	Intrusion Detection techniques	Modify the numbers in an electronic bank transfer.	Communication delay occurred between sender and receiver.
	Denial of service	Application	Extremely High	Malicious user may modify the packet or resend a packet again on	1. Activity Monitoring.	Some or all legitimate requests from being fulfilled	1. Real time response detection mechanism	Flood a target system or resource.	Apply cryptographic techniques to ensure security of network.

				network.						
Category of Attacks	**Attacks Type**	**Layer**	**Threat Level**	**Behavior**	**Detection Technique**	**Prevention Method**	**Parameter used**	**Limitations**	**Experimental derived**
Passive Attacks	**Release of message content**	Multi-Layer	Low to Medium	Alteration and eavesdropping are the example of this attack.	1 Tamper detection.	1. Using a mutually trusted certificate authority. 2. Mutual-Authentication	1 DSL Modems. 2 WiFi base stations. 3 Router	1 Newly generated server key. 2 Generate trusted authority certificate.	Apply data confidentiality and proper integration on data to ensure integrity.
	Traffic analysis	Physical	Low to Medium	The information content may be lost by an eavesdropper that silently senses the medium	Network Monitoring software(a Sniffer)	Using personal firewales,updated antivirus software, and virtual private networks	1Authentication tokens. 2.Sending Sensitive data 3 .Power splitting and jamming	Unsecured network communications. Public wiFi networks	Apply encryption on all the devices that perform communication.

7. Conclusion

In this paper, IoT was explained considering its contributions to the people all over the world.IoT has been proven to be a beneficial technology to both manufacturers and consumers. Challenges facing IoT were demonstrated. Confidentiality, Availability and Integrity of IoT were analyzed as the fundamental of security model that need to be followed to minimize attacks in IoT. The main emphasis of this paper was to highlight major security issues of IoT particularly, focusing the security attacks and their countermeasures. Due to lack of security mechanism in IoT devices, many IoT devices become soft targets and even this is not in the victim's knowledge of being infected. In this paper, the security requirements are discussed such as confidentiality, integrity, and authentication. In this Survey, six different types of attacks are categorized as low-level attacks, medium-level attacks, high-level attacks, and extremely high-level attacks along with their nature or behavior as well as suggested solutions to encounter these

attacks are discussed. Considering the importance of security in IoT applications, it is really important to install security mechanism in IoT devices and communication networks. Moreover, to protect from any intruders or security threat, it is also recommended not to use default passwords for the devices and read the security requirements for the devices before using it for the first time. Disabling the features that are not used may decrease the chances of security attacks. Moreover, it is important to study different security protocols used in IoT devices and networks.

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Factors Affecting Segmentation of Web Pages Using Web Content Mining

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Abstract—

Web is a treasure of information and data, where large amount of data is available in different formats and structures. Finding the useful data from the web is a complex task, the above problem has given rize to the development of web content mining. Extraction of Information has become an important task for discovering useful knowledge or information from the Web Pages. But On the Internet web pages contain several items that cannot be classified as the informative content. Maximum clients and end users search for the informative content, and don't interest in non-informative content. With the informative content, web pages commonly have blocks that are not the main content blocks and are called the non-informative blocks or noise. For getting the informative content, first we do the segmentation of web pages into differ blocks such as main content, title, heading header footer etc. Various factors are to be considering in segmentation of web pages for content extraction from web pages using web content mining. The main objective of this paper is to eliminate the non-informative content blocks by doing segmentation of web pages using web content mining techniques. In the paper we proposed techniques, factors for segmentation for content extraction.

Keywords-content extraction, information extraction, web content mining, web segmentation, Informative blocks

Introduction:

Use of internet and World Wide Web (WWW) has become as first source of information for everyone, but the World Wide Web has been exponentially increases [1, 2]. It resulted in difficulties for individual user to process all these information. With the increasing of web usage, the content available on web becoming more mature, and its presentation even more sophisticated. In Presentation, creators placing different pieces of information on web pages for different purpose to the end-user. The information must appear coherent to users who browse the web page. These pieces have carefully-placed visual and other clues that cause most users to sub consciously segment the browser-rendered page into semantic regions, each with a different purpose, functionality, and content. From the web, it is difficult task to find, retrieve and identify dissimilar information elements. In addition with the main content present web pages contains a bunch of textual elements such as text ads, snippet previews of related documents, legal disclaimers, navigation menus, user comments etc. Separating these different elements and classifying them into relevant and non-relevant parts is important for high-class results.web page segments are left navigation menu bar, site-specific banner that might be at the top, navigation footer, links and abstracts of related web pages, banner and other forms of advertisement scattered

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throughout a page, copyright notices, terms of service, and contact information, and last but not the least, the actual content itself. It also depends on how the creator of the web page chose to organize it, the content might itself be represented by multiple segments. Method to divide a Web page into visually and semantically cohesive pieces is called web page segmentation. There is a huge no. of benefits and potential for web applications using web page segmentation. Web Page segmentation is of extreme importance when information is to be extracted omitting the noise from web pages [4]. Web page segmentation distinguishes informative and non-informative content on a web page; they can also differentiate between different types of information. Consider a multiword query whose terms match across different segments in a page; this information can clearly be useful in adjusting the relevance of the page to the query. Identification of segments also plays an essential role in displaying web pages on screen-space constrained devices such as smart phones, PDAs etc [5]. We consider three input application areas for web page segmentation. (1) De-duplication. Matching content information may be presented using different web page layouts. (2) Content Extraction. Besides the obvious Benefits for Web-based news clipping etc., removing template noise might also increase classifier performance. (3) Keyword-based Web search. A page should be regarded less relevant to the query if the matched term only occurs in a template segment. Different types of segmentation consist of DOM-based segmentation and vision based segmentation. The page segmentation problem has been addressed from many different perspectives. Many methods and techniques used different approaches such as DOM based, Vision Based, Text based, and Hybrid etc. [12].

Literature Review:

Today, the most frequently used segmentation algorithm is Vision-based Page Segmentation (VIPS), proposed by [3] from Microsoft Research. The vision-based method utilizes visual clues in a Web page. VIPS utilizes many visual cues such as element size, background color, font size and etc. to build a visual partition tree of a web page. Each node in the tree is a visual block of the web page. Yang proposed the VIPS (Vision-based Page Segmentation) algorithm by considering vision information and heuristic rules to identify blocks [6]. VIPS approach focus on segmentations of web pages and informative block detection algorithms [3]. Row column splitting indicator helps us provide an easy to use partition granularity value which solves the difficulty of choosing an appropriate Degree of coherence value in VIPS algorithm. Manjusha Annam et al [7] state Entropy based Informative Content Density approach for efficient web content Extraction. This paper proposed a web content extraction technique build on Entropy based information content Density algorithm. The proposed EICD algorithms mutually analyses higher text density content. The Page information density (PID), Tag information density (TID) and content ratio (CR) calculated. EICD is to utilize the information entropy for representing the knowledge that correlates to the amount of informative content in a page. Dr.Anna saravijeanream et al [5] provides a simple but effective approach named layout based detachment approach (LBDA). Using this approach we removes the irrelevant information like header, footer content, navigation bars and other noisy image and extract the main content from the web page. It can eliminate noise and extract the main content blocks from web. Ranking the Relevance and Evaluation of Search Results through Web Content Mining is stated by G. Poonkuzhali, [1]. Correlation algorithm is studied for web content mining and correlation method for relevance ranking and normalized discounted cumulative gain for useful

evaluating this ranking method. The search results obtained through this approach is accurate and time consuming. V. Bharanipriya et al [2] presented a paper web content mining tools a comparative study. It was mainly focused on one of the categories of Web mining namely Web Content Mining and its various tasks. After studying of different techniques of WCM it observed that Screen scraper is not user friendly and some of these tools seem to be applicable for email data mining. Rajkumar et al. [13] presents a new method that segments web pages based on either reappearance based scheme, by recognizing reappearance tag pattern from the DOM tree structure of a web page.Ruijie et al. [14] proposed a method that analyzes semantically the content of web page in order to extract the textual contents.

Factors For Segmentation

DOM-based and layout-based is the accepted web page segmentation algorithms. Web page based on the Document Object Model is considered for tag information used to divide a web page using DOM-based segmentation. The DOM has a tree structure in which each node contains one of the components from an HTML tag. Web pages split using some relatively simple DOM nodes such as the <P>, <TABLE>, and <UL> nodes for further conversion or summarization. The <TABLE> node and its offspring to be a content block and use entropy-based approach to determine the informative ones. Nodes such as <TABLE> and <P> are not only used for content organization but also for layout presentation. The layout-based segmentation method uses layout information after rendering, assuming that similar content blocks are located close to each other and have similar shapes. This Web page segmentation method is comprised of three steps: (1) dividing a Web page into minimum blocks, (2) classifying the blocks into title blocks or non-title blocks, and (3) combining the blocks into Web content chunks based on title blocks. In DOM based segmentation main factor that affect the segmentation is tag and its structure. Depending on tag we calculate precision and recall for result consideration.

In EICD technique we used factors like No. of characters of node, No. of informative pages and No. of informative tags. The Text Density and Entropy factors are considered. Others factors considering for EICD approach are page information density (PID) and tag information density (TID). Page information density is the number of web page classified as informative in a given set of pages. These metrics are calculated using the following equations:

PID= (No of informative pages)/ (Total number of pages in dataset)

TID= (No of informative tags)/ (Total number of text content tags)

The content ratio is a measure to define the count of nodes which are high text content threshold condition for different values of α.

Content Ratio= (No of nodes satisfied threshold)/ (Total number of nodes)

In LBDA (Layout based detachment approach) No. of Relevant terms and precision Factors are used. The Time and memory factors are considered. As per the LBDA Based segmentation perform operation through the system and collected the results. Number of relevant and irrelevant pages related to the given keyword is the key issues for segmentation. Others parameter like f-Measure, Precision and recall, F-measure, Goodness are consider for segmentation that affect segmentation.

Conclusion

To conclude, paper discusses various segmentation methods for web content extraction with the factors affecting segmentation of web pages. In the future more research will be needed for efficiency and accuracy of information extraction for better results using segmentation.

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Discrimination at work place

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Abtract- Women are enjoying more freedom today and have joined the work as doctors, lawyers, teachers, designers, truck drivers and in many other professions. But discrimination against women still exists in various forms, particularly at the workplace. Women should know their rights as a worker and take responsibility to stop rights violations at the workplace.

Keywords Discrimination, Legislation, Sexual harassment

According to Hindu mythology, the Manusmriti is the word of Brahma. In Manu's set of laws, women were treated on par with slaves or Shudras. It means from the ancient time, our society is male dominating or supremacy of the men over the women. Another sign of the lower status of women was the practice of monogamy for the wife while the husband was free to have several wives. They were targeted of various types of violence and discriminatory practices done by men.

Now the time is changing. From the last five decades, the women are actively participating at the workplace with the role of housewife, mother, and care taker. Many women are making her career in the field of interest. They want to become self- independent. She shows aptness and assiduity in her work whether she may at home or at workplace. One thing is cleared that women are striving to gain equality in the work.

But even today, women are not treated the same as men. One area where this oppression shows is the 'equal pay for equal jobs'. Another area in which women are inconvenient at the workplace is though discrimination. Discrimination can be an uncomfortable situation for the women concerned. There are two types of discrimination- indirect and direct. Indirect discrimination may contain a woman being neglected for the promotion or an employee displaying improper sexual matter or allotment of more work at the workplace. On the other hand, direct discrimination may include a women being took out from her employment during pregnancy, or being excluded from after work group events.

Another major area where being the women have been suffered at the workplace is sexual harassment. Sexual harassment is the direct sign of sex discrimination and mostly the sexual discrimination is occurred where the women having lower paying jobs. The sexual harassment or sexual discrimination at workplace creates tensions that make the women doing job more difficult. Thus the condition of working women is particularly vulnerable. They need equal treatment and special protection under the laws. To protect the working women, many legislative provisions have been provided in almost all labour statutes which address the problems of women labour in their employment situation. The Second National Commission on labour, 2002 has also justified the protective discriminatory legislation by recommending that all such legislations are necessary for women workers.

There are a provision for protection of women under labour laws such as- The Factories Act- 1948, The Employees' State Insurance Act- 1948, The Maternity Benefit Act-1961, The Equal Remuneration Act- 1976, The Workmen Compensation Act- 1923, The Minimum Wages Act- 1948, National Rural Employment Guarantee Act- 2005, The Contract Labour (Regulation and Abolition) Act-1970 and Sexual Harassment of Women at Workplace (Prevention, Prohibition and Redressal) Act, 2013.

These legislations in the Indian labour laws regulates the employment in dangerous occupations, prohibition of night work, restriction on carriage of heavy loads, wages, health, gratuity, maternity relief, equal pay for equal work, social security, provision of creches and other welfare facilities etc. These labour laws for women have been classified into three categories such as (1) Measures in regard to health, safety and welfare (2) Social security measures (3) Wage protection. Everyone should know

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about these laws. Our constitution provides all women workers health, safety and welfare.

Conclusion- India presents an inimitable set of challenges that are deep-rooted in diverse cultural, religious and social. Thus collective action must be taken towards establishing the equality in gender roles and women in the workplace. By the way, gender inequality is a genuine issue that limits the progress of modern India and our mission is to establish spontaneous and natural workplace for members of all genders. Women's in India has the potential to be powerful community leaders and the responsibility of change lies on every one of us.

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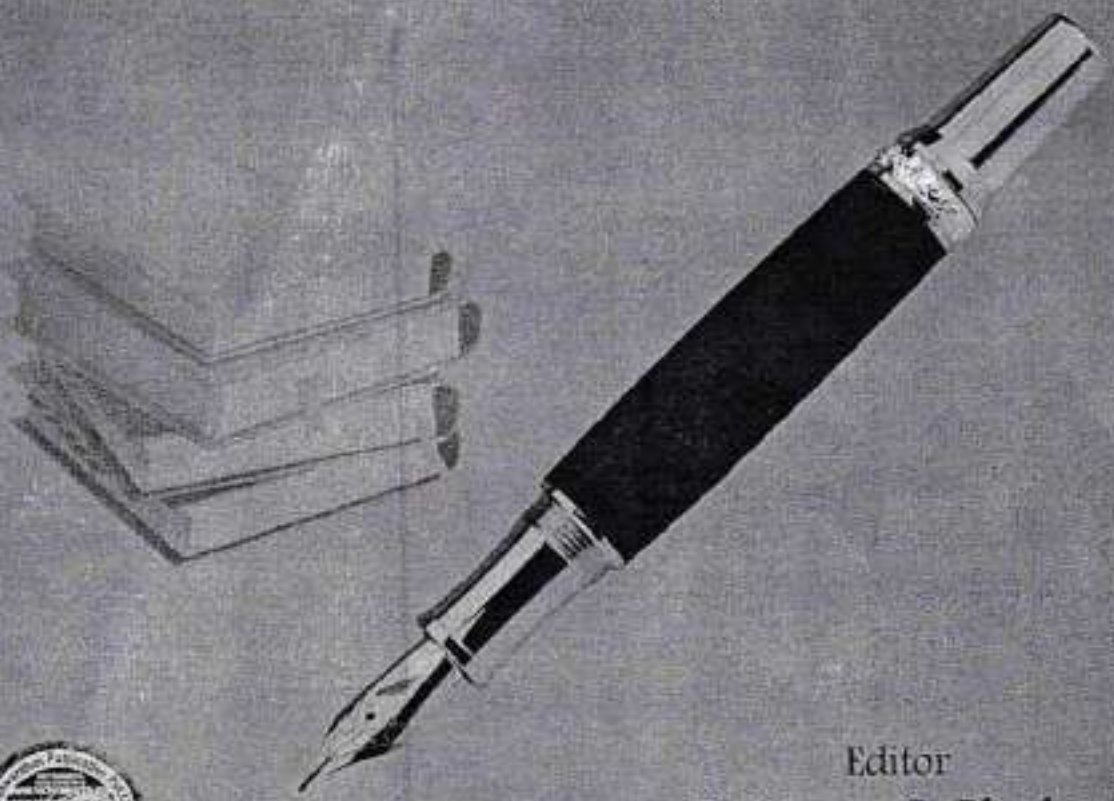
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slowly in Bangladesh the hawk eyed super powers will try to fish in troubled waters which will be suicidal for India in particular and the entire subcontinent in general. It is thus the geographic factor that has played a determining role in shaping the bi- lateral relations.

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11

Socialite Evenings: A Chronicle of Karuna's journey towards emancipation as a new woman

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Abstract:

Women have always been given a subordinate role in the family system of India. They have been fighting a perennial battle against their counterparts for their dominance and to avail equal status. But women can carve a niche for themselves if they are strong in mind and body, and bold enough in their outlook to put their traditional identity and nature of submissiveness aside.

This paper discusses the journey of Karuna from assertion to emancipation in the maiden novel **Socialite Evenings** by Shobha De. A middle class girl, Karuna dreams of being a part of the upper class society, who rebels against her family and tries to create an independent world of her own. The novel is about the journey of a prominent Bombay socialite Karuna from a middle class girl to a self-sufficient woman. Making a feminist approach, the novel gives us the picture of the marginalization of the Indian women at the hands of their husbands. Many a times Karuna adopts a militant attitude towards her husband as she does not want to be marginalized in a patriarchal society. The portrayal is authentic, being an inside story as the narrator herself

belongs to this class. The novel is a romantic tale, suffused with feminist traits.

Keywords: - Society, patriarchal, emancipation, perennial, submissiveness, militant.

The journey from assertion to emancip ation is symbolic of the winds of social change blowing across the world and intends to focus on "women who are today in a fair way to dethrone the myth of femininity, they are beginning to affirm their independence in concrete ways; but they do not easily succeed in living completely the life of a human being." (Beauvoir,Sex)'.The battle to come out of the shadow of male dominance has been going on for centuries. The fight for autonomy in a male dominated and traditional society is a tough one "but women can find a respectable place for themselves in the society only if they have an intellectually strong mind to put aside all traditional factors and come out of the Sita-Savitri image and the tradition of submissive ness." (Shirwadkar, Image of Woman...p.55)

Shobha De's first novel - **Socialite Evenings** deals with the story of a middle class girl Karuna who wants to rise above her ranks. She is not ashamed of her sexuality and does not miss any opportunity to cut down to size her male counterparts. But the tug of war between her role as a house maker and her desire for individual freedom and happiness creates a problem for her. The novel describes her journey where she reaches the cross- roads. Her dilemma is to go back to her old life or to be a part of the elite world. Though they have discarded the old order, but have not been able to carve out any new concrete niche for themselves. Finally, the realization is there that individual freedom is just a myth and not a reality.

Indian fiction in English has been enriched by several talented women novelists including Kamala Markandaya, Anita Desai, Nayanatara Sahyagal, Attai Hosain, Santhara marau, Shashi Deshpande and Shobha De. They have a women perspective on the world. They have written about Indian women, their struggle, their suffering and their awkward position, keeping in view their image and role which the society has created. Their chief contribution consists of their exploring the moral strength of women characters and their struggle with challenges in creating their own identity.

Shobha De is a prolific writer born in Maharashtrian Brahmin Family in Mumbai,she writes about the high-flying upperclass society of India. She has dealt with issues related to woman.To project urban culture, she has changed traditional picture of enduring, submissive and self-sacrificing women with a new picture of bold and liberated urban women. Shobha De is renowned for bold and frank style of writing. She explored the lives of bored housewives and their loveless rich husbands and family. Her novels mirror the life styles of the elite and the middle classes of urban world.

Socialite Evenings is Shobha De's first novel published in 1988. The novel portrays Mumbai high society and explores the lives of bored rich housewives trapped in loveless marriages and engaging in ill-fated, extra-marital affairs, smug selfish husbands, fashionable parties, false spiritual leaders, and a portrait of general moral, spiritual and intellectual bankruptcy and decadence of the elite who have traded their traditional culture for westernization and modernization. In the novel, Karuna the main protagonist and narrator caught up in a drab, boring life that she seeks to escape by writing memoirs. Her memoirs are successful and she achieves a measure of fame and pride in herself as she becomes an active socialite and eventually uses her new found prominence as celebrity to get herself a position as an advertising copy writer and creator of a television series.

In the novel **Socialite Evenings** Karuna is the main protagonist. She is all agog to break-out of such thralldom which compels her to

assume the status of the other. A problem child both at home and at school, she declines a dog the traditional path of etiquette and manners. At home, she refused to cower before elders and at school she wore her sash hipster style. As she grows in age there develops in her the emotional urge to identity with the outside world, the modern crowd, the bewitching and fascinating world of affluent girls who had the lewd and clandestine world of modeling with her secret assignment as the Terkosa Girl. Throughout the novel Karuna figures as a woman who asserts her feminine psyche through protest and defiance. She figures as a woman, not victim. Shobha De deals with the sullenly skewed of art. We do not have here the stereotypes associated with male artistic representations of women. Karuna's initiation into the fashionable world of modern life begins at Anjali's fancy place in Malabar Hill. But Anjali accuses Karuna of bitchiness and lechery, her insatiable appetite for sex. This is borneout when Karuna dates with the New Delhi ad film-maker in London. Further her stay in the United States gives her a feeling of superiority and makes her assertive. Karuna, with all her attempts at ego assertion, refuses subscription to stereotypes, to succumb to the hegemony of the malist culture.

Socialite Evenings gives us the image of new women at the hands of their husbands. ShobhaDe's is the picture of women not only as protagonists but also as motivating factors in society, initiating and regulating their own lives as well as the lives of others in the voluptuously fascinating world of Bombayites, its enticing glitter and glamour enamoring many a Karuna to its ensnaring and captivating gossamer. Karuna's marriage is a failure since it is loveless, joyless and bridgeless. There is no under standing between the husband and the wife. She feels that she has married "the wrong man for the wrong reasons at the wrong time. Her husband is just the average Indian husband, unexciting, uninspiring, untutored. He was not made for introspection. The average Indian woman's conjugal life is to her an exhausted generation of wives with no dreams left and marriage is like a skin allergy, an irritant. But she is not afraid to face this irritant, this allergy. She boldly and defiantly encounters it, for she realizes "marriage is nothing to get excited or worried about. It is just something to get used to" (De, Socialite, p.68) and she gets used to this stereotyped social institution in the course of time. She detests the stand-offish and callous attitude of the husbands who often kept themselves busy in drab monotonous activities – like reading and business pages of The Times of India. But despite these laxities, a husband was above all, a sheltering tree, a rock to the wife. They were not wholly bad or evil and the wife as a woman was only peripheral being, Karuna says:

> We were reduced to being marginal people. Everything that mattered to us was trivialized. ...roof over our head and four square meals a day. (De, Socialite, p.69)

The subordination of women as housewives stems from a castration-panic on the part of the husband. The Indian male is presented by Shobha De as a person "terribly threatened by self-sufficient women."(De, Socialite, p.69) He is inadequate and incomplete as a husband since he lacks the traits of an ideal husband. Fear of the loss of domination and control over the self-affirming wife makes him resort to several defense mechanisms. One of these strategies is his male chauvinism and power-assertion ventilating in bullying and committing atrocities upon his wife. But his stupid self-conceit and ego restricts a free exchange of views among sexes. Karuna inquisitively wonders: "how could he communicate anything at all to men who perpetually sat reading pages of The Times of India while concentratedly picking their noses ?" (p.69)

Karuna learns from Ritu, whom she

chances upon at a finance director's party that "men like dogs could be conditioned through reward and punishment." (p.87). But could she condition her husband in the like manner. But she was fed up with her husband's compulsive socializing, his horrible safari suits and the gum he constantly chewed. She could not turn to anything in such a boring milieu save her books and her fantasies. Crosswords and newspaper chess were other alternatives to utter boredom. She realizes that despite her little acts of protest, she is "a well-trained Indian wife" (p.54) but she shares the same rational human nature as men do. Karuna is not "the toy of man, his rattle," which "must jingle in his ears whenever, dismissing reason, he chooses to be amused."(Surendran, Another De..., p.12)

The subordination of women in the malist culture is symptomatic of hierarchization of socio-moral values between the sexes. It symbolizes the polarity between activity and passivity, between meek obedience and defiance. Helene Cixous observes: "A male privilege can be seen in the opposition between activity and passivity. Traditionally, the question of sexual difference is coupled with the same opposition: activity/passivity." Women are often the symbols of passivity.Helene Cixous further maintains: "Either the woman is passive; or she doesn't exist. What is left is unthinkable, unthought of. She does not enter into the opposition, she is not coupled with the father who is coupled with the son." (p.288)

Woman is thus reduced to matter, a mere object. This reduction of woman to matter or a commodity is in the main a phallocentric pattern. Karuna's husband treats her as matter, a mere object subjected to his own will. Karuna's humorously sarcastic approach to her problems in the patriarchal male culture apparently deconstructs the traditional gender hostility used to elaborate the polarities of connubial ties. Karuna undermines male superiority. She loathes her husband's dwelling in "post-mortems." (p.186) She makes an ingenuous declaration about her inner urge to express herself through love:

"I love this friend of yours, and I want to be with him in Venice. There is a good chance ...It's the Taurean in me that's surfacing these days. Treat this as a short-term mania that will wear itself out." (p.186)

It is clear that Karuna has just a formal relationship with her husband. Intimacy between the husband and wife is lacking for Karuna who never calls her husband by his name but derogatorily as 'Black Label.' Shobha De resorts to the technique of manipulating language in order to deconstruct the male ego: "the fact that his wife had taken a lover excited him. resisting – it would have only consumed more time." (p.188)

Shoba De in her long narration depicts the pathetic story of Karuna and her incessant struggle tobe free from the dominance of her husband and her journey towards emancipation; she also has added the other female character such as Anjali, Ritu and Gul. They faced a dilemma which is the outcome of their own undoing, their blind urge to emulate the elites and in this process they are uprooted and wandered aimlessly in the jungle fully of female devourers. In the beginning, these women discard the social norms and march ahead on the path of emancipation and liberation and once they achieved their desire, they find themselves all alone and feel lost. With no support and no clear path outlined for them, disillusionment sets in and plunges them into dilemma, now they have two choices to make- either to come back to their roots or to continue suffering.

Women in Shobha De's novels symbolize the overpowering materialism and the lack of spirituality that characterizes modern age. With the crumbling of moral and ethical values there is an inner conflict which drives the modern Indian women to seek shelter in different identities for momentary solace. One of the most

notable features of these women is they lack an identity. But the whole blame cannot be laid on women only because in ShobhaDe's novels there are type of men who use and abuse women and then discard them. In **Socialite Evenings** one encounters a liberal Indian husband who allows his Indian wife to go abroad and get herself screwed once for all as the last gesture of good will. From the individual, it comes to the family. It is the family which is the centre of deviance. Subhash Chandra regards family's disintegration is the instrument of degeneration of Socialite Evenings.

Thus ShobhaDe's novel **Socialite Evenings** shows the image of new woman against predatory male-dominated society. But her vamp ideology of feminism provides no redemption for the deviant and fallen women who in their frantic struggle to escape male-domination and attain individuality, meet with failure and are victimized in one way or the other. In enacting the drama of seduction and betrayal in her foray against patriarchal structures, the glamorous vamp in De's novels, may end up being as seductively treacherous to women as to men. A woman in Indian society marries not just the man but also his family and subsequently loses her identity in marriage, relinquishes her freedom and sets about pleasing everybody. But the new generation of women with their new-found release from matrimonial bondage adopts different perspectives, and revolt against the old order. De's women are such liberated individuals in search of a niche in their lives.

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BABY HALDER'S "A LIFE LESS ORDINARY": AN EXTRAORDINARY AUTOBIOGRAPHY

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ABSTRACT

Baby Halder, formerly a domestic worker and now a writer, is the author of three memoirs. Her first book, Aalo Aandhare (2002), written in Bengali, is the first account of a domestic help from India. It has been translated into 25 languages. Baby Halder's story is extraordinary precisely because domestic workers' realities are so invisible in middle and upper-class peoples' everyday consciousness. Halder battled enormous odds, a single mother of three, at the age of 25. Her autobiography, written alongside her job as a domestic worker, is a bestseller and has been translated into twenty-one languages. Written without a trace of self-pity, A Life Less Ordinary is a shocking look deep inside a world of poverty and subjugation that few outsiders know about—and an inspiring true story of one remarkable woman's strength, courage, and determination to soar above her circumstances. The present paper reveals the courageous character of Baby Halder, the champion who comes out with triumph.

INTRODUCTION

Article 2 of the universal declaration of Human rights states: " Everyone is entitled to all the rights and freedom set forth in this declaration, without distinction of any kind, such as race, color, sex, language, religion, political or other opinion, national or social origin, birth or other status"

India, as an ancient country has seen many upheavals both natural and man- made. In early Vedic era, equal opportunities s of education for women is mentioned. But later on Manu openly played a degenerating role in lowering women's status. In addition to this, frequent invasions from the other parts of the world also kept changing the position of women in Indian society. They were considered as a commodity or a prize of war. They were deprived of the changes in the society. On the emergence of women like Meerabai from Bhakti Movement, general position of women's education was restricted only to listening to Kathas and kirtans.

During the Mughal empire, nothing much has been done in this field except to provide access to education to women of elite class. Whenever the society was in flux, the most affected and suppressed class was the women. The social norms and prejudices became more tenacious against the women. But with the advent of British people, some changes were being brought from the West. Some literate Englishmen and enlightened Indians like Raja Rammohan Roy, Ishwarchand Vidyasagar, Mahtma Jotiba Fule worked very hard to start educational institutions for girls. Mahatma Jyotiba Fule an ardent lover of humanity started first girls school in the house of Mr. Bhide in 1848 in Pune. This school was meant for girls from the poor as well as rich classes. Girls from untouchable classes were also admitted and education was imparted to them. This rumor of girls school spread all over Pune and some parts of the country too. In the later half of the 19th century the efforts of these philanthropists resulted in the realization by the emergent Bengali " Bhadralok" to impart a certain measure to educate their women folk. The heroine of this article Baby Halder is the outcome of such a long lasted strife against the existing social systems.

The story of Baby Halder's life is an extraordinary lesson in courage and survival. It is a story of a young domestic worker who has battled poverty, hardship and violence. A strenuous life story with storms and woos. She only used to sob and go ahead with courage and strength. Nobody, even her father, step mothers, brothers and relatives helped her to come out of the miseries and agony in her life. The sufferings which are found in her story are beyond imaginations and tolerance.

A small girl of hardly eleven years leaves her home with her small brother from Dhanbad to Durgapur to her Jetha (Brother of her father). Stayed there and joined school. She wants to learn. She joins school. No books and other aids for learning but an utter desire and urge for education

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pushed her upto higher class in school. Her father was in army once upon a time, after his retirement came back and joined some other jobs. He could not provide financial support to family. He did not take care of his wife and children. Finally his wife along with his younger son, a child of 3 years leaves his house without telling anyone around her. In this situation Baby's elder sister (Didi), Baby and one younger brother Bunny became like orphans.

Baby's story is a story of hardships and acute poverty. Story begins from her childhood. Her father got her elder sister (Didi) married with a person who was a bad man. He used to beat her often. Her Didi could not resist much and finally one fine morning committed suicide. Being a paternal society nobody in the family could oppose him. Baby was left alone with her brother for further suffering. After going through a lot of hardships with two steps mothers who ill treated Baby. No good food and sufficient clothes were served to her. But still baby continued to learn.

One day Baby was in her Mashi's house she found her bed and clothes wet with blood. She started weeping. She didn't understand what was happening to her. She was very much frightened and started weeping. Pishi Mashi convinced her and added one more burden that now she was no more a small girl. But as Baby was very courageous she used to play with boys. She loved to play all the boys games. She used to run very fast, swim very swiftly and so on.

The tragic story of her life has taken a second bad turn when she was eleven and half years. Her father got her married to a man of twenty six years. As her father and other relatives were negotiating her marriage, Baby was unable to understand the situation. She anyhow was not prepared for the marriage. Her marriage was settled with a man named Shankar, a son of a potter.

Shankar who was a mere worker having a small house of mud. He spoke lie while fixing the marriage that he has no father or mother and he is all alone. But he has a family at a small village. As per nature's law Baby became pregnant and conceived a son in the hospital. Despite pains and labor for three to four days her husband did not turn up to see her or did not care for her at all. He used to come from work, used to eat and go to sleep. He was very cruel and selfish. For him a woman was only a means of enjoyment. He never used to give her money for home expenses. On top of it he was very much suspicious about his wife and never allowed her to speak to neighbors like Bhasti and her sisters who were kind enough to her. Actually Baby liked to see cinemas, jatras and participate in the pooja of Kali but Shankar always forbidden her from all these activities. If she failed to obey him, he would beat her like animal. He never pitied her. Once when she was carrying four months child in her womb, Shankar beat her so brutally that she got aborted. She went to her father's house with the determination of not going back to Shankar's house ever but she was helpless. As her stepmother didn't like her staying in the house. So her father insisted her to go back to her house.

Baby comes to her husband's house to live together, but her husband was very much reserved type of a man. They did not have any cordial relations. He never used to give her money. She was totally dependent on him. This dependency and despondency made her a slave of Shankar. She remained pregnant again and gave birth to a son. Still she had to survive in the same hopeless conditions. There was no improvement in the relations of husband and wife.

Baby, as a woman, a wife and as a mother had tried to resist and revolt against the situation many times. Her struggle for searching her identity, for her freedom and liberty was going on relentlessly. But Shankar had no sympathy for her. When she quarreled for justice, he used to beat her cruelly. She became desperate and left all hopes of cordial relations with her husband. She conceived one more daughter in such a tense relations. Living with such an inhuman and callous man was getting critical day by day. One day Shankar fought with her very badly and beat her horribly before her children. Children were terribly frightened to see this. Baby decided to stop the farce.

On the next morning, with an air of finality, Baby went to her father's house along with her children and declared that she will never go back to her husband's house. Her father didn't like this. He tried to explain to her that her husband's house is the only destination for her. She demanded few money to her father and address of her brother and got the railway tickets. With all sorts trouble she reached Faridabad to her brother's house. Baby's sister-in-law didn't like this addition to her family. She along with her three children had her dinner and next morning went in search of another room which was near her brother's house. She requested him to search for some work for her so that she can pull on her expenses. Moreover she wanted her children to learn. It had been her dream that

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the children should go to a school. After two days she found a work. She requested a small place to live with her children. Memsab was very unsympathetic with her all the times. She used to keep her busy for the whole day. Baby hardly got any time to spare with her children. Memsab used to love her dog' more than maid servant. Baby felt very bad and left her job.

Baby Halder started working in the house of Dr. Prabodhkumar Shrivastav. He used to give her Rs. 500 per month. He was very kind hearted man. He used to give her fatherly and brotherly treatment in the house. He never treated her like a servant. He asked her to bring her children there in his house only. He gave one room for them. As her school going children were small he used to ask Baby to take milk for her children. He was living there with his sons. One day she went up-stairs which happened to be a study room of Dr. Prabodhkumar. She started cleaning the bookshelves and books very carefully and neatly. Her busy hands would go slow as she dusted the books. During this she picked up one book and started reading it. She didn't know Dr. Prabodhkumar was also present in the study room at that time. He was very much surprised to see her reading a book. He asked, "Do you read?" and she kept quiet for a while. She looked so guilty as if he had caught her hand in the biscuit tin. Thereafter Dr. Prabodhkumar encouraged her to read and write at her leisure time. One day he asked her to show what she wrote. She handed over the papers to him. He read all those papers and sent to his friend to go through. His friend liked the story very much and asked Dr. Prabodhkumar to publish it. Dr. Prabodhkumar belonged to a literary family. His grandfather Munshi Premchand was one of India's best known writers whose novels and short stories brought out a social reform in the early 20th century.

Here Dr. Prabodhkumar, her dada, worked as a source of inspiration in Baby Halder's life. He encouraged her to read and write. As a servant Baby entered his house, he treated her sympathetically like his daughter and behaved like a good human being, a true Samaritan. As the days passed the result came out in the form of a book, "A life less Ordinary" (Published in Hindi and Bengali as 'Aalo Andhari', from which means 'darkness to light')

During an interview 'If You will.....U Can.....Baby Halder proved it' which was telecasted on Delhi Doordarshan in a programme called 'Stree Shakti', Baby Halder shared one incident in which she said when she used to clean the bookshelf at her dada's house she came across a book written by Mahashweta Devi which depicted a pathetic story of a suppressed woman who undergoes the ordeal of life, wins in life by creating her own identity. Baby was overwhelmed to read this experience. She was also highly inspired by these words of encouragement. Coincidentally Mahashweta Devi, the great Champion of Women's Freedom Movement in India read Baby Halder's Autobiography and wrote her comment," A story of courage and grace.....a book worth waiting for."

Our Former Prime Minister, Pandit Jawaharlal Nehru said that until and unless our male and female are suppressed under the dominance of some power they cannot find themselves independent and free by any law or rule. Economic dependence is the main reason of backwardness of Indian women. They are never free as long as they are not economically self- reliant.

CONCLUSION

Baby Halder's book is miraculous and an inspiration to all of us. It gives the message to the reader's that Education brings rays of happiness and prosperity in one's life. She is a woman with perseverance, self respect and resilience. She showed the courage to fight against all odds in life and worked as a torch bearer, bringing light of hopes and spirit not only for herself but also for all the women folk in India who are fighting the battles of life, searching for their own identity in the darkness. She underwent the ordeal of life only to prove herself. Of course in this rigorous journey of adversity Mr. Prabodhkumar, her dada, played the role of a lighthouse which stands firm to show light and gives right direction to the ship that loses path during the voyage.

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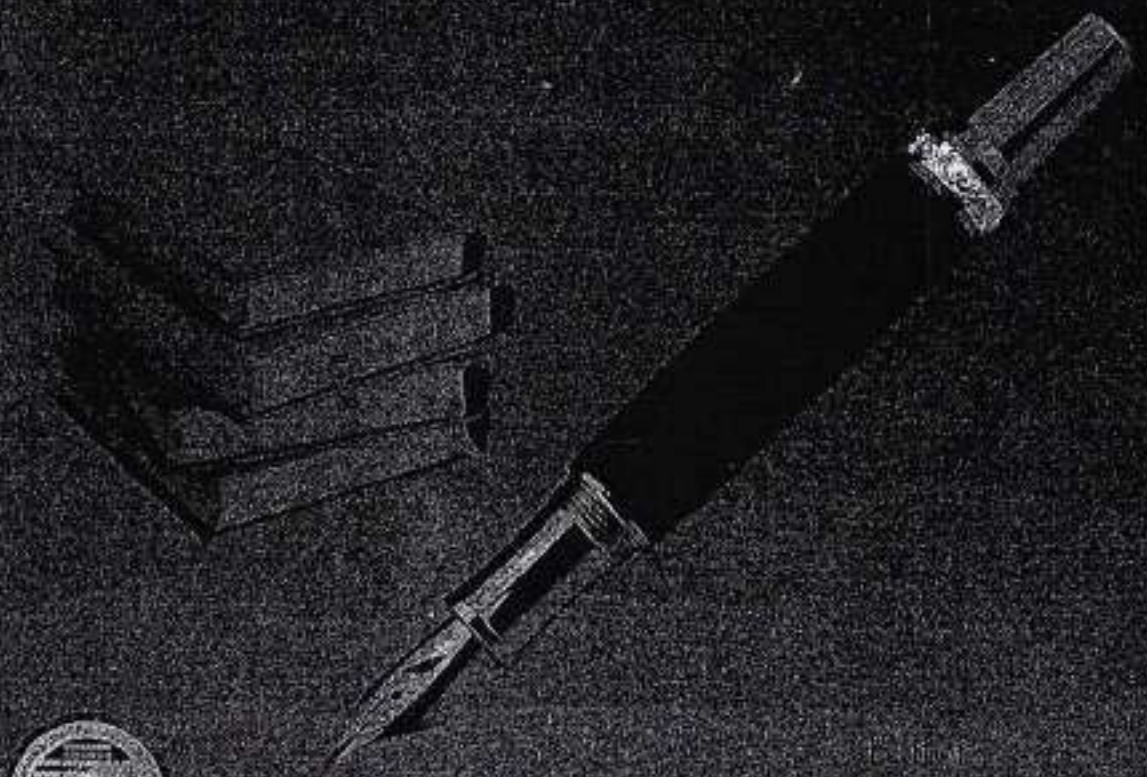
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There have been many disputes about whether it should be accepted or not without solid decisions of its acceptance or not. The question of evaluating the act of death in the variety of methods prevalent is often intricate, thus contemporary debate on euthanasia being morally valid is continual throughout the world. It has been studied that, all over the world that philosophies and religion plays a central character in determining ethical standing of euthanasia. While active euthanasia is not easy to be implemented, it is not impossible to secure passive euthanasia. It appears to be ethically acceptable.

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A Married Woman: an analysis in Feminist Perspective

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Abstract: Manju Kapur, an internationally famous Indian woman novelist has written five novels. She reveals the life of women, their oppression as well as their struggle for rights, survival and quest for identity. In this paper, efforts have made to analyze Manju Kapur's novel **A Married Woman**, from the feminist point of view. Indian writers have made a significant contribution in enriching the novel as a genre. Despite all challenges and problems Indian English novel has carved a niche of its own. Many of the female writers during post independent era have used their pens to delineate Indian women in new perspective. They have mainly focused on the issues related to woman such as self-reliance, financial independence, self-respect and above all their emancipation from the male dominance.

Feminism is rational movement that advocates for seeking equal political, economic and social rights for women. It focuses on women's woes and sufferings all over the world, and struggle for eradicating gender inequality prevailing in the society. The major component of the feminist theory is to challenge the patriarchal beliefs for attaining independence and individuality. The first feminist movement started from Britain and gradually, it took the shape of a global association. Anita Desai, Nayantara Sahgal, Manju Kapur ,Shashi

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Despande, Shobha De and others are writers who observed the gender issues which marginalize and oppress women in the patriarchal society. These writers protest the repression and suppression of women. This paper discusses issues related to women's identity, self-respect, their role in decision making and above all spirit of gender equality from feminist point of view as reflected in A **Married Woman,** a novel by Manju Kapur.

Key word: Feminist, Feminism, independence, movement

Manju Kapur like that of her contemporary female writers described human psyche and the plight of female world. **A Married Woman** is the story of an artist whose canvas challenges the constraints of middle class existence. The story is simple-a married woman struggles to keep her identity. The novel centers round a middle class Delhi-based Hindu family. Hemant, an America-returned Delhi business man, married Astha Bhadra, a middle-class educated Hindu girl. Initially their married life runs smooth and they have two children, a daughter Anuradha and a son Himanshu. Their traditional marriage is soft, sound and healthy till Astha meets Aijaz Khan. The death of the Aijaz Khan scattered her world. Then Astha is encountered with Pipeelika, the widow of Aijaz. Pipeelika is a qualified Hindu girl. She is an M.A. in Economics and Sociology. Astha and Pipeelika is probably a lesbian couple. Their love relationship reaches a climax when Pipeelika flies to the US for her Ph.D. Manju Kapur is determined that the new, educated Indian woman has the ability to decide her priorities for self-discovery. She has visualized the emerging image of the educated Indian woman symbolically represented by Astha.

The novel is the story of well educated woman, Astha. She is traditionally well brought daughter by her parents. But, in an Indian conventional family, a girl is a liability to the parents. It is a middle class family who struggle in their life for children and everything. Astha gets admitted in the college. Her father was in favor of her higher education. During her college days she was attracted towards Bunty. Her first love disappears when she received the letter from Bunty which reveals that he is not able to meet her further. In fact, she never spoke openly about her love. With this letter everything comes to an end in her life. It is very hard to imagine the condition of Astha's heart that aches inside. In the process she dates with a couple of young men of her own choice like her western counter parts, marries a man of her parents' choice and discovers the joys of intimacy with her husband, begets children, yet grows distant from him ,and struggles to become a painter. Much against her husband and her other family members she becomes a social activist, and falls in love with a woman, and finds herself –sort of, more. She reflects the middle class values and seems to enjoy her mental bliss for a long time but gradually experiences that there is something certainly lacking in her life. She suffers from a sense of incompleteness, suppression and agony which is further provoked by her involvement into the outer world of upheaval and protest.

This novel can be read at the feministic level as it has dealt with many issues related to the female world. Manju Kapur is in one of her interviews reveals her views: "I am a feminist. And what is a feminist? I mean I believe in the rights of women to express themselves in the rights of women to work. I believe in equality, you know domestic equality, legal equality. I believe in all that. And the thing is that women don't really have that-you know even educated women, working women. There is a trapping of equality but you scratch the surface and it is not really equal (Unheard Melodies, p.4).

The female protagonist Astha who is the daughter of a cultured father and an orthodox mother, has an earnest desire for passive co-existence in the family. But she is dominated

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against and discriminated at her-in-law's house. There, she is made-up to have a willing body at night, a willing pair of hands and feet in the day and a submissive mouth. Her marriage with Hemant, does not show to be based on mutual co-operation and appreciative. She is duty-bound to be a stable wife and sacrificing mother, like a sacred cow in the position of married woman. It traps to her bodily exploitation and emotional hunger. Being depressed of her emotional discharge, she recklessly seeks for it and drives to a "substitute-husband" (Rationale, p.110), lesbianism. Astha, has stamped out a self-governing life of the woman for self-fulfillment and advocated for inter-religious marriage and female-female relationship divergent to the patriarchal norms of traditional society. Astha had the passions or infatuations of a teenager like any other girl. But those infatuations are turned into oblivion. She has to set up a diverse life after her marriage with Hemant. She is cynical with her husband's love for her family relationships are not right with her. Her mother-in-law likes her to be a stable and sacrificing woman like customary wives and mothers. She is constantly under stress of work and suffocating with her responsibilities to meet everybody's need. She is "always adjusting to everybody's need" (AMW, p.227). She senses that a married woman's status in the family is always dependent on her husband. She is torn between her responsibility and socio-religious perception. She has no emotional free will from the domestic relationships. She is exhausted of her responsibility and thinks "A tired woman cannot make wife good" (AMW, p. 154). She is feeling under the pressure and dejection of a married woman who is no better than an unpaid servant. She has to give pleasure to her husband and for pleasing him; she must be "A willing body at night, a willing pair of hands and feet in the day and an obedient mouth" (AMW, p. 231). She is marginalized in her own family by sadistic social atmosphere. She thinks of freedom from stress and depression. She thinks of a fine job thinking that "with good job comes independence" (AMW, p. 4) so, she joins as a teacher but this job also does not keep her free from distress and trauma of discrimination.

Indian Society prefers a baby-boy rather than a baby-girl. "Manju Kapur gently digs at the Indian attitude of preferring a baby-boy to a baby-girl in the novel" (Rationale, p. 107). Astha s family proves that their need of baby-boy by their superstitional belief, "When her daughter Anuradha was four, Astha conceived again. Her mother brought in a poojari to perform special pooja to propitiate the gods to grant them a boy for Astha" (Rationale, p. 107). Having given birth to Himanshu a son, she does not feel substandard to anyone in the society and the family members are thankful to her because they feel "the family is complete at last" (AMW, p. 68). Astha also feels happy about her motherhood like a married woman but she does not like the gender discrimination. She is much traumatized at the uninterested response of members of the family and society at her daughter, Anuuradha's birthday. But she obtains an appraisal and sanction of motherhood after the birth of her son—Himanshu. She abhors such a false notion and discrimination between a daughter and a son, such an outlook of Indian traditional society is injurious to equal status of women who "feel caught up in the web of daily life"(AMW, p.84) and fall a victim to tension and depression that is "the disease of modern life"(AMW, p.76). The narrow-minded socio-cultural tradition is responsible for such a dilemma of women in our society "Where we must recognize the critical role played by popular culture in reinforcing prejudices against women". It gives women to be broadminded like earth instead of conveying them equal status like men. Manju Kapur has responded harshly against unequal treatment of women in our family and society. The perception of male dominant patriarchal society that women should

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Only economic freedom is not enough for them. Socio-religious culture has to accept their individuality. The researchers have to permit her to let her be what she decides and let her have the integrity which has been ignored to her for ages. They can no longer remain submissive, subjugated and discriminated. In Astha-Aijaz-Pipee episode, religion has been decreased. Aijaz himself is a secular and open-minded Muslim. He is connected with a theatre group which works for the awakening of society. Pipee also runs an N.G.O. and Astha is also shown connected with a Manch. Her paintings also help in carrying out a new type of political consciousness. There are no embarrassments for matters such as lesbianism, extra marital relationship etc. A post–modernistic trend has been seen by the novelist through this novel. In short, Manju Kapur is a feminist by vocationand by practice. Her female protagonist, Astha has represented her all ideas lurking in her mind to exhibit her ideology as far as the emancipation of female world is concerned.

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14

Relationship Between Economics and Sociology

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Lokseva education society's Arts and Commerce College Garkheda Parisar, Aurangabad

Abstract:

There is a relationship between economics and sociology. These are long established, as is the interest in sociology shown by some economists. We need only recall the role played in both disciplines by Vilfredo Pareto at the turn of the last century. We will not attempt to summarize the history of these relations, however, which are often presented as conflicted, or even define the frontier between economics and sociology. It is well known that the two disciplines are distinguished as much by their methods as their focus of study; it is easy to think of points of contact between them, such as social reference points in motives for economic behavior or intervention of "non-market," social relationships in business, government, and sometimes even in the market itself. In this article, an attempt is made to discuss the relationship between economics and sociology in general and the major difference between both sociology and economics.

Keywords: Economic sociology, social conse quences of economic exchanges, social associations, economic welfare, etc.

Introduction:

The drive to understand the evolution of human society in all its dimensions is one that comes naturally; it has always been and remains a deeply-rooted motivation for historians,

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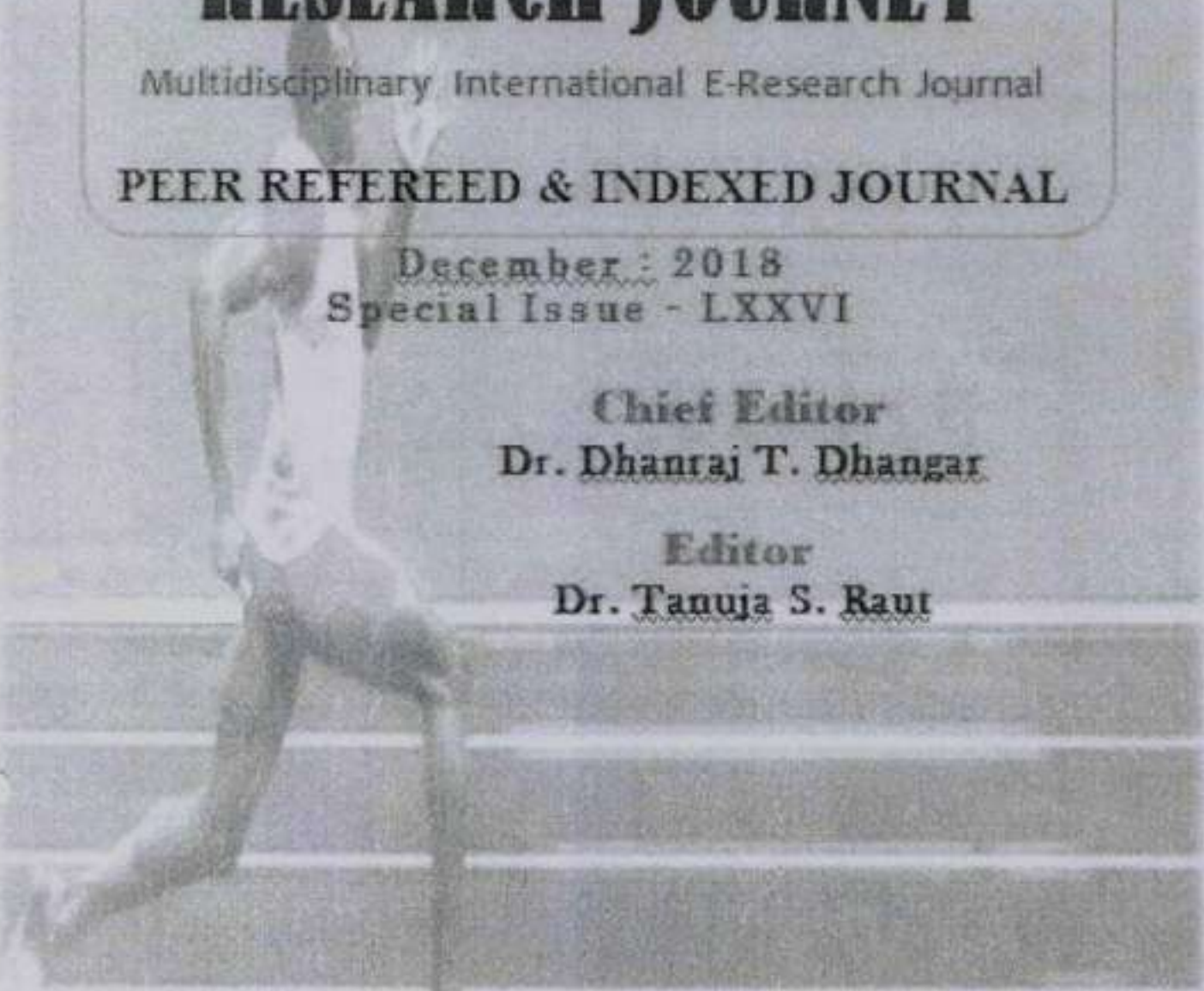
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blissful experiences. On the other hand neglect of any of the three aspects (i.e. body, mind & spirit) of health result in imbalance and disharmony in the being and the person carries negative health.A good deal of studies have been done to indicate the short and long term effects of the yogic practices on psycho physiological functioning and their role in the prevention and management of different health problems. The selected yogic practices have a favorable conditioning effect on various physiological systems. The different meditational practices have relaxing and rejuvenating effects on the respiratory, circulatory and nervous system. As a result yogic practices have been found useful in preventing and managing disorders related to the body systems.

Meaning of Yoga

The word "Yoga" comes from "Yuj" root in Sanskrit which means union or joining together. When a man develops a relationship with another that relationship is also known as yoga. According to general language, three meanings of Yoga are Jodna, Samadhi and sanyama. So it is clear that Yoga word is multi meaning.

Definitions of Yoga

*Oxford Dictionary defined it "a Hindu system of Philosophic meditation and asceticism designed to affect the reunion of the developed soul with the Universal sprit"

*According to swami Vivekananda "Each soul is potentially divine. The goal is to manifest this divinity within, by controlling Nature- external and internal. Do it either by work or worship, psychic control or philosophy, by one, or more, or all of these and be free"

*According to Bhagvad Gita. "This Yoga must be followed with faith, with a strong and courageous heart"

The stages of Yoga

The right means are just as important as the ends in view. Patanjali enumerates these means as the eight limbs or stages of Yoga for the quest of the soul. They are

1. Yama (Universal morall commandments)
2. Niyama (Self-purification by discipline)
3. Asana (Physical Posture)
4. Pranayam (rhythmic control of the breath)
5. Pratyahara (with drawl of sense organs)
6. Dharana (Concentration)
7. Dhyana (Meditation) -
8. Samadhi (a state of super consciousness)

Yoga as a Science:

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Yoga is a complete science of life and although ancient one, has become popular only in recent past. It is a scientific method for exercising and relaxing to ease the tensions and stress of modern day living. Yoga is one of the techniques which help the development of physical and mental health of a person. The science of Yoga has a very wide spectrum as regards its application. In India and any other developed countries yoga is included as a discipline in the curriculum of education.

Yoga is a science which combines body movements that coordinates with mind, posture and breathing techniques which produces the best results for healthy living. Today Yoga is gaining popularity due to its possible application to various fields of human interest i.e., health cure and prevention of sports injuries, sports performance, development of physical fitness. Yoga is recognized as a system which promotes an integral development of body and mind. Yoga and Physical Fitness

Problems of Modern Life Style

Uncountable problems are created by present day's life style. The following are the three main problems which are the root cause for others problems and risk

- Stress.
- Cardiac problems
- Obesity

The problems accumulated at the body level as stiffness of joints and spasms of muscles can be released by the practice of yogasanas which are congenial posterns of the body. Yoga in itself is a science of health management rather than a method of treatment. When yoga is combined with certain healing and therapeutic modalities, it increases health, general wellbeing and longevity. It does this by removing tension, calming the mind and improving vitality. Yoga generally enhances our lives on all levels.

Today's life style stress, Cardiac Problems and obesity is the burning problems and risk.

Stress.

Stress (roughly the opposite of relaxation) is a medical term for a wide range of strong external stimuli, both physiological and psychological, which can cause a physiological response called the general adaptation syndrome, first described in 1963 by Hansselye in the journal "Nature". It can be understood as tension: (Psychology) a state of mental or emotional strain or suspense.

Stress is the body's physical, mental and chemical reactions to circumstance that frighten,

excite, confuse, challenge, surprise, anger, endanger or irritate. The events that cause stress may be good or bad.

While many people have always thought of yoga as some mystic Hindu practice, that image is rapidly disappearing-almost as fast as the stressed of our modern lives are increasing. The American Academy of Family physicians has noted that stress related symptoms promptheart decease and 60 millions have hypertension.

Obesity

It may be defined as excess Wight or deposition of excess fat on body, which leads various diseases like diabetes, heart diseases, hypertension, lowered pulmonary function, lowers life expectancy.

Obesity, obviously, is a curse and a serious disease by itself. If you donot modify your life style and choose the right food on a regular basis, the weight you lose on any diet will come right back. Almost 70 per cent of those who diet, regain their lost weight within a year, and have to diet all over again. Constant losing and gaining of weight in the battle of bulge is fur sting and demoralizing. It often leaves serious psychological sears. You can help yourself to be fit and not fat.

Yoga a way to Balanced Life

Health is the foundation on which rests the happiness of the people and the strength of nation. Yoga is *a* science that regulates the physical and physiological behavior of an individual. Regular practice of Yoga will develop physical fitness and keep the ailments away and also it gives the mental power. Some of the advantages of Yoga are:

- It's a traditional system of practice, coordination, both mind and body, which is ultimately needed for the today's modernized society.Yoga plays a vital role determining the individual's physical and mental fitness.
- Unlike some allopathic medicines, Yoga practice has no side effects.
- Regular practice of yoga prevents occurrence of many diseases of modernized life style.

two-third of the office visits to family Physicians Exercise and alternative therapies are now commonly prescribed for stress-related complaints and illness. Even a recent issue of consumer Reports suggests Yoga for stress relief.

Practicing Yoga can alter your *brain* chemistry. Some yoga positions in particular are effective in stimulating the pituitary gland to release endorphins and to reduce the level of cortisol (the stress hormone.)

Asanas greatly influence the functioning of the endocrine system. We know the important role the endocrine glands play during stress adaptation, by secreting the stress hormones. There is such an intaricate. relationship between the glands that one malfunctioning gland can cause the disruption of the whole system.

Cardiac Problems

Heart is said to be most sensitive to emotional stress. During stress period, the vessels of the visceral organs are tightened and amount of blood flow to the muscles is increased. By restricting the tiny vessels to visceral organs, the heart is pressed to work harder, when heart beats faster, the blood pressure rises. If the emotional stress persists blood pressure remains consistently high leading to stroke and other cardiovascular disease.

Yogic practice help to prepare a healthy body and mind trained in such a way that a necessary equilibrium is established in over all functions. It is short of recondition of physiological mechanism of body as a whole. The effectiveness of Yoga in controlling hypertension by removing stress related disorders.

Conclusion:

1. Yogic Science fruitful field for fundamental and applied research and teaching at higher levels by behavioural scientist, particularly psychologistic.

2. It is important that indigenous knowledge of yoga and yoga psychology is suitably incorporated as an integrated aspect of life in our routine.

3. Yoga is good for everyone so people of all professions, cultures, religions and socio-economic strata adopt yogic lifestyle and attain an inspired vision for future.

4. Yogic life style has the potential to harmonize the emotional life of the individual and helps one to gear up for the inner journey of the everlasting contentment. Yoga is a complete science of life and although ancient one, has become popular only in the recent past. It is a scientific methods for exercising and relaxing to ease the tension and stresses of modern day living. To conclude this, I would strongly recommend suggest yoga as one of the preventive & social medicines of westernized society.

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विद्याभारती महाविद्यालय,कॅम्प, अमरावती

प्रस्तावना :

हिंदुस्थानचा स्वातंत्र्य लढा चालू असतानाच हिंदुस्थानच्या आर्थिक परिस्थितीविषयी नेते मंडळी व अर्थतज्ज्ञ विचार करत होते. देशाच्या अर्थव्यवस्थेसंबंधी सखोल विचार करण्यात दादाभाई नौराजी, न्यायमूर्ती रानडे, नामदार गोखले, रोमेशचंद्र दत्त आघाडीवर होते. तर्खडकर, जोशी आदी प्रभुतीनीही देशाच्या आर्थिक दुरावस्थेविषयी विचार व्यक्त केले जाते. परंतु हे सर्व थोर विचारवंत नेते मवाळ होते. सरकारच्या चांगुलपणावर त्यांचा भरवसा होता. सनदशीर लढ्यावर त्यांचा विश्वास होता. अशा परिस्थितीत हिंदुस्थानला आक्रमक खंबीर नेतृत्वाची गरज होती अन ती लोकमान्य टिळकांच्या रुपाने पुरी झाली. आपल्या जहाल नेतृत्वाने त्यांनी भारतीयांना आकर्षित केले. संपूर्ण स्वराज्याची मागणी करत असतानाच त्यांनी ब्रिटीशांच्या आर्थिक धोरणाचे वाभाडे काढले. त्यांचे केसरीमधील लेख, त्यांची काँग्रेसच्या व्यासपिठावरील भाषणे व इतर लेखन हे टिळक उत्तम अर्थतज्ज्ञ असल्याचे सुचित करतात. हिंदुस्थानच्या प्रगतीसाठी पाश्चात्य आर्थिक धोरण उपयोगी नसून, या देशाच्या धार्मिक, आध्यात्मिक विचारणामधूनच त्यासाठी उपाय शोधला पाहिजे या विचारांवरच त्यांची आर्थिक राजकीय नीती उभारलेली होती. लोकमान्यांनी वेळोवेळी व्यक्त केलेल्या अर्थविषयक विचारांची ही एक झलक.

हिंदुस्थानच्या दारिद्र्याची कारणे :

अर्थव्यवस्थेविषयी विचार करताना आपल्या दारिद्र्याची कारणे कोणती हे आपणास समजले तरच त्यावर योग्य उपाय करता येतील. या मूलभूत समस्येबद्दल विचार करताना टिळक लिहीतात 'देशाची विपन्नावस्था होण्यास मुख्य तीन कारणे असतांत.'

१) देशातले लोक सुस्त, निरुद्योगी व अज्ञान असल्यामुळे त्यांच्याकडून मुळीच किंवा व्हावी तितकी संपत्ती उत्पन्न होत नाही.

२) कदाचित ते उत्पन्न करत असतील, पण ते दुसरेच कोणीतरी काढून नेत असेल.

३) ते जितके उत्पन्न करतात तिच्यापेक्षा व्यय करणारे अधिक निपजत असतील. आमच्या भाग्यशाली भरतखंडात तिन्ही कारणे पूर्ण वास करत आहेत. आम्हाकडून व्हावे तितके उत्पन्न होत नाही. झालेल्याचा बराच भाग बाहेर जातो आणि प्रतिवर्षी उत्पन्न करणाऱ्या संख्येपेक्षा ती सटकावणाऱ्यांची संख्या झपाटयाने वाढत आहे. (भारताच्या लोकसंख्या वाढीच्या गंभीर प्रश्नाकडे लक्ष वेधणारे टिळक हे पहिले पुढारी असावेत) दुर्दैवाने आज शे-सव्वाशे वर्षानंतरही लोकसंख्येच्या या समस्येमुळे देशाची प्रगती अपेक्षित वेगाने होत नाही.

दारिद्र्य दुर करण्याचे उपाय :

१) मुलद्रव्ये पुष्कळ उत्पन्न केली पाहिजेत. मुलद्रव्यांची उत्पत्ती अधिक होण्यास खाणीचा शोध व शेतकी सुधारणा हे उपाय केले पाहिजेत. म्हणजेच नैसर्गिक संपत्तीचा शोध घेऊन तिचा उपयोग करणे (भारताला स्वातंत्र्य मिळून ६७ वर्षे झाली असून सुद्धा आजही आपण देशाच्या नैसर्गिक साधनसंपत्तीचा संपूर्ण शोध घेऊ शकलेलो नाही)

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२) या सामग्रीचा उपयोग करण्यासाठी लागणारे ज्ञान, कौशल्य, यांत्रिक कलेतील निष्णातता (कुशल इंजिनियर्स, तंत्रज्ञ) प्राप्त करण्यासाठी आपल्या विद्यार्थ्यांना युरोप, अमेरिका, जपान येथे पाठवावे.

३) यासाठी लागणाऱ्या पैशाची तजवीज करण्यासाठी संस्थानिकांनी पुढाकार घ्यावा. विद्यार्थ्यांना शिक्षणासाठी अल्प दराने पैसे देऊन नंतर तो विद्यार्थी कमावता झाल्यानंतर त्याने हप्त्याने कर्जाची परतफेड करावी.

४) मजुरी व कच्चामाल या आपणास अनुकूल असलेल्या घटकांचा योग्य उपयोग.

औद्योगिक पारतंत्र्य :

परकीय राज्य हे आपल्या देशाच्या सर्व समस्यांचे मूळ होते. राजकीय, धार्मिक व सामाजिक पारतंत्र्याबद्दलल समाजामध्ये खल होत आहे. परंतु या पारतंत्र्यांचा अविभाज्य भाग असलेल्या औद्योगिक पारतंत्र्याबद्दल मात्र पाहिजे तितकी चर्चा होत नाही. याबद्दल टिळकांनी खंत व्यक्त केली होती. औद्योगिक पारतंत्र्याबद्दल जनता पुरेशी जागरुक नसल्यामुळे आपल्या देशाची आर्थिक अवनती वेगाने होत आहे याकडे टिळकांनी लक्ष वेधले होते. युरोपातही औद्योगिक क्रांती होण्यापूर्वी सर्व कामे हातानेच केली जात. परंतु तेथे झालेल्या औद्योगिक क्रांतिमुळे अगदी थोड्या अवधीत मालाचे प्रचंड प्रमाणात उत्पादन होऊ लागले. युरोपातील या क्रांतीचा लाभ आपल्यातील उठवता आला नाही. आपल्या या अपयशाची कारणमीमांसा टिळकांनी येणेप्रमाणे केली.

१) आपला देश अतिविस्तीर्ण व अतिसुपीक आहे

२) सर्वसाधारण भारतीयांची निवृत्ती मार्गाकडील प्रवृत्ती

३) शेकडो वर्षांची परकीय सत्ता

४) या देशाचे हवापाणी

५) सर्वसामान्य लोक ठेविले अनंते तैसेची रहावे अशा अल्पसंतुष्ट वृत्तीचे आहेत (म्हणूनच टिळकांनी गीतारहस्याद्वारे भारतीयांना कार्यप्रवृत्त करण्याचा प्रयत्न केला.

आपल्या आजारी अर्थव्यवस्थेचे निदान करतांना लोकमान्य म्हणतात, युरोपात मोठ्या प्रमाणावर मालाची निर्मिती होत आहे. यंत्राच्या या राक्षसी सामर्थ्यामुळे आपला हस्तव्यवसाय हतबल झाला आहे. तशातच आपल्याकडील भांडवलाची कमरता, तंत्रज्ञानाची वानवा यामुळे आपण उद्योगधंद्यात प्रगती करु शकत नाही. आपल्याकडे उद्योगधंदे नसल्याकारणाने नफारुपी भांडवल जमा होत नाही, तसेच उद्योगधंदे नसल्यामुळे तंत्रशिक्षणाकडे लोकांचे दुर्लक्ष होत आहे. याउलट ही दोन्हीही साधने नसल्यामुळे उद्योगधंद्यांत वाढ होत नाही. अशा तऱ्हेने आपली अर्थ व्यवस्था एका दुष्टचक्रात (Viscious Circle) सापडली आहे. परंतु हताश न होता या समस्येवर मात केली पाहिजे. टिळकांनी यावर सूचवलेली उपाययोजना ही एखाद्या कसलेल्या अर्थतज्ज्ञाला साजेशी आहे.

टिळकांचे उपाय

१) छोट्या उद्योगांना प्रोत्साहन देणे

२) औद्योगिक शिक्षणाची कास धरणे

३) आवश्यकता असेल तेथे परदेशी तंत्रज्ञास नोकरीस ठेवणे.

४) परदेशांतून व्याजाने पैसे घेणे

टिळक म्हणत भांडवल उभारणीचे काम श्रमसंयोगाने किंवा सहकारी तत्वावर (को.ऑपरेशन आणि को ऑपरेटिव्ह सोसायटया) होऊ शकते. वैयक्तिक स्तरावर उद्योग सुरु करणाऱ्यास त्या व्यवसायासंबंधी मन:पूर्वक प्रेम पाहिजे तसेच ती व्यक्ती शिक्षणामुळे सुसंस्कृत असून, प्रामाणिक पाहिजे हे त्यांनी आग्रहपूर्वक सांगितले. (आजच्या कर्ज पुरवठा करणाऱ्या आधुनिक संस्थानही नेमक्या वाच गोष्टींचा म्हणजे कर्जदाराच्या चारित्र्य, सामर्थ्य आणि क्षमता यांचा अग्रक्रमाने विचार करतात हे येथे मुद्दाम लक्षात घेतले पाहिजे).

ब्रिटीशाची आर्थिक नीती :

व्यापाराच्या सहाय्याने हिंदुस्थानात आलेल्या ब्रिटीशांनी येथील अनागोंदीचा पुरेपूर फायदा उठवत संपूर्ण हिंदुस्थान आपल्या ताब्यात घेतला. तत्कालिन आधुनिक शस्त्रास्त्रांनी युक्त असे शिस्तबध्द सैन्य व व्यापारी धूर्तता यांच्या जोरावर त्यांनी आपले राज्य स्थिर केले. येथे इंग्रजी शिक्षणाची सुरुवात करुन त्यांनी आपल्या सैन्यांच्या व मालाच्या सुलभ वाहतुकीसाठी रेल्वेचे जाळे पसरवण्यास सुरुवात केली. पोस्ट खाते व तारायंत्रे यांच्या साह्याने जलद संपर्क सोय केली. इंग्रजांनी केलेल्या विविध सुधारणांमुळे आणि निर्माण झालेल्या राजकीय स्थैर्यमुळे अनेक लोक इंग्रजांचे गुणगान करु लागले. परंतु इंग्रज राज्यकर्ते अत्यंत कावेबाजपणे आपल्या देशाची पध्दतशीर लूट करत आहेत हे टिळकांनी वेळोवेळी दाखवून दिले. उदा. स्वत:च्या देशातील कापड धंद्याला ऊर्जितावस्था यावी यासाठी त्यांनी या देशात तयार होणाऱ्या जाड कापडावर शेकडा साडेतीन टक्के कर बसवला, तर इंग्लंडमधून आयात केल्या जाणाऱ्या तलम कपड्यावरील कर पाच टक्क्यावरुन साडेतीन टक्क्यांवर आणला. परिणामस्वरुप ब्रिटीश माल वापरणाऱ्या श्रीमंत लोकांचा फायदा झाला तर जाडेभरडे सुती कपडे वापरणाऱ्या गरीब जनतेचा तोटा झाला.

संदर्भग्रंथ :

१) लोकमान्य टिळक आणि क्रांतीकारक, य.दि. फडके
२) लोकमान्य ते महात्मा, डॉ. सदानंद मोरे, राजहंस प्रकाशन, पुणे.
३) लोकमान्य टिळक यांचे चरित्र, नरसिंह चि.केळकर, रिया पब्लीकेशन, कोल्हापूर.

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INTERNATIONAL RESEARCH FELLOWS ASSOCIATION

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PRINCIPAL
VIDYA BHARATI MAHAVIDYALAYA
AMRAVATI

Indian Art and Architecture

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India is well-known in the world due to its cultural heritage, art and architecture. Ancient Indian civilization is remarkable in various felid like language, literature, science, technology, art and architecture.

Following is the area of Art and Architecture achievement in India.

Indus valley civilization-

Urban civilization having the knowledge of urban structure.

Indian art contains various form such as plastic, visual art, textile etc. Indian arts exposed the symbol of religion like Hinduism, Buddhism, Jainism and Islam.

Indus valley civilization consisting different type of arts like dancing girl in Mohenjo-Daro seals, yoga pose, idol of Pashupati, figure of Lord Shiva etc.

Mauryan art (340 BCE – 232 BCE)-

Monumental art is famous related to Mauryan art. Indian rock architecture, Ashoka pillars, Emblem of India etc are remarkable achievements in the area of art.

Buddhist art –

There are many sites scattered in India which explorer the art in Buddhism. Sanchi, Bharut, Amravati, and Ajanta, caves are the main example.

Gupta Art-

Jain religion art found in northern part of India.

Dynastic of South Asia

is full of Badami caves, shore temples, Shiva and Nataraj sculpture, Temple of Khajuraho is considered as a world heritage.

Akabarnama, Jama Masjid, Taj Mahal, etc art and painting is the part of Mogul art. Charminar, Golkumbha are the symbol of Deccan art of south. Central India Later on in British Kingdom also has great impact on Indian art. Super wall painting, natural maintaining, jewelry, temple art, folk and tribal art etc are the various types of Indian art.

The Indian Art has many aspects to explore the various chapter of Indian culture.

Following are some of Indian art forms-

Visual Arts

1. Lalit Kala Akadami (National Academy of Fine Arts established 1954 in New Delhi. Basically it promotes painting, sculpture, print making and ceramics. It also organizes the exhibitions on contemporary Indian Arts.

Performing Art

Types of performing art.

1. Music
2. Dance

3. Theatre
4. Literature

Institution of Arts -

1. Sahitya Academy
2. National School of Drama
3. Lalit Kala Academy
4. Sangit Natak Academy

There is a provision to award and sponsor the various fellowship, scholarship and grants for promotion of Indian Art. Archeological survey of India (ASI) also plays an important role to present the Indian art. Department of culture and ministry of tourism maintain conservation and perseverance of centrally protected monuments and museums, libraries, etc.

Indian art is most traditional and has the oldest history in the world with highly realistic approach.

Literature and architecture, philosophy are the main components of Indian art. Sacred and holiness is the main immortal part of Indian art.



Following are some of the feathers of Indian art-

1. Earth, water, fire, air, sky are the main symbols in Indian art
2. Cuisine, trip, rangoli fresco, mosaic, sketch etc are the various medium of Indian art
3. Oldest, spiritual and uniqueness are different than other culture.
4. Remarkable about food, language, festivals, religion, epic, sculpture, painting, agriculture, clothing, music, dance etc expose **'unity in diversity'**.
5. Performing dance, sports, literature, and films along with recreation, education are inserted as Indian Art,
6. Heritage of Ayurveda, yoga, culture, folkdances, handcrafts and artefacts are universal things related to Indian art.
7. Indian culture is 5000 years old culture having richness of an ancient heritage and contemporary art.
8. Beliefs, purans, costumes, traditions also reflect in Indian art.

Indian Architecture

The architecture of India is deeply inserted in history, culture, religion, and civilization. Indian architecture explores the various feathers of the stages.

In the early middle era, Vijayanagar kingdom was well-known in south India. Chankya, Hoyasala, Pandya and Chola styles provided best, simplest, and attractive art of India. Qutub Minar, Red fort, Fatepur Sikri, Taj Mahal are the achievement of Islamic architecture and Mogul era around (1526 AD-1857 AD)

Ellora in Western India, Khajuraho in central India, Konark in South India are remarkable achievement in the architecture of India. Indian architecture represents the diversity of Indian culture.

Following are the some of the fantastic evidence of Indian architecture-

1. Lingraja Temple – 100 A.D.
2. Mukteshwar Temple
3. Jagnath Temple- Puri
4. Sun Temple- Pattadakkal
5. Parasnath Temple- Konark
6. Somnathpur Temple
7. Shore Temple Mahabalipuram
8. Brihadishwara Temple- Tanjore
9. Meenakshi Temple- Madurai
10. Hampi-Karnataka

Conclusion-

Indian architecture is a symbol of pluralistic and unique approaches. Temples, building, paintings in this duration has special and unique attraction in the world. It also explores the culture and living standard of the region. Different types of Indian architecture styles express the space and time in history. Glaciers of Hindus and Islam's, ancient, cave rock and temple etc are the main examples of Indian architecture.

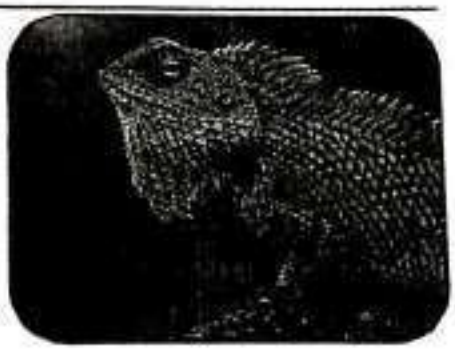
Indian architecture preserves and creates varicdness, beautifully and blended monumental scripts architecture style.

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HEMATOLOGICAL RESPONSES TO ENDOSULFAN TOXICITY IN THE INDIAN GARDEN LIZARD, *CALOTES VERSICOLOR*



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ABSTRACT

The organochlorine insecticide, endosulfan is widely used in crop field as well as for garden plants to control insects. The Calotes, common habitant of garden, is unknowingly affected by such insecticides. Hematological parameters vary in response to different toxicants in different animals. Considering this the present study was undertaken to evaluate the effect of endosulfan on some hematological parameters of Indian garden lizard, Calotes versicolor. Endosulfan (2.5 µl) was introduced orally to it at 24, 48, 72 and 96 hrs. It was observed that hemoglobin declined gradually throughout the experimental period than that of control. The lymphocytes decreased suddenly at early phase of 24 hours and then increased after 48 hrs. in experimental lizards, but could not increase beyond the lymphocyte count of control throughout the experimental period. Eosinophils, red blood cells and total leucocytes decreased gradually upto 96 hours than that of control after exposure to endosulfan.

KEYWORDS: *Hematological indices, Endosulfan, Calotes versicolor.*

INTRODUCTION:

The pesticides developed for human welfare are being considered as the most disastrous factors in producing harmful effect in environment and have become the serious sources of pollutant (Rameshwarsing, 2004). The regular utilization of large quantities of these pesticides into environment creates a pesticide pollution which constitutes the most dangerous health hazards on non-target organism. Reptiles have been reported to be more sensitive to the effects of these pesticides than are birds and mammals (Davidson *et al.*, 2002). Some studies established that the reptiles face many impact from human activities (Khan and Law, 2005). Hall (1980) reviewed several studies showing deaths of lizards and other reptiles following use of organochlorine pesticides, especially DDT, Dieldrin, Endrin, and Heptachlor and reported widespread mortality in two lizard populations following application of Heptachlor. Alterations in hematological parameters due to water pollutants are well established (Radha *et al.*, 2005; Sah *et al.*, 2006; Gupta *et al.*, 2007). Reduction in erythrocytes is reported in *Labeo rohita* exposed to sub lethal concentration of Nuvan and it became anemic (Wedemeyer *et al.*, 1984). The hematology of fingerlings of *L. rohita* exposed to two sublethal concentrations i.e. 10.3 ppm and 2.06 ppm of Nuvan was studied by Das and Mukhaerjee (2001), and it was found that there was reduction in total erythrocytes count and hemoglobin percentage. Total counts of erythrocytes and hemoglobin were decreased and leucocytes were increased in endosulfan treated group of rats and differential counts of leucocytes showed significant increase in basophils and monocytes (Das *et al.*, 2010). Possible impacts on lizards include direct poisoning from eating (or licking) poisoned bait and secondary poisoning from eating dead, dying, or disorientated insects contaminated with insecticides. The impact of pesticides on reptiles exposed to it is by many routes but perhaps the most common route is agricultural practices which affect natural habitat in several ways. As endosulfan is a worldwide used synthetic insecticide that has an important role on management of pests in agriculture, the present work was undertaken to determine the effect of endosulfan on the hematological parameters of *Calotes versicolor* which can be a promising procedure for use in biomonitoring programmes to diagnose pesticide exposure of wild populations.

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The pressure on land in India is constantly mounting due to rapidly increasing need of providing food to the ever increasing population. Owing, the limited scope for exploitation of unused land for agriculture, the solution lies in intensive and extensive cultivation to increase production and productivity. Pesticides may continue to play an essential role to ensure an adequate supply of food to meet the need of human beings.

Keeping the above references in mind, it is evident that, despite the pesticide poisoning incidents all over the world, no effective protective and preventive steps are implied. The no. of deaths has kept arising. Although many physiological causes for poisoning have been reviewed by scientists, root cause for the poisoning is still not evident. This is our small attempt to search to farmers in rural areas for finding the root causes of pesticide poisoning.

METHOD AND MATERIALS

Yavatmal district has a population of 2,07,7144, from this population 53% are directly involved with agriculture. The survey was conducted in different villages of district Yavatmal. The survey included villages from tehsil Ner, Mahagaon, Pusad, Darwha, Arni and Umarkhed. The villages undertaken our survey are Kali (Tq. Mahagaon), Shilona (Tq. Pusad), Sarkinhi (Tq. Mahagaon), Malkinhi (Tq. Mahagaon), Kapshi (Tq. Ner).

The survey was conducted from 25th September 2017 to 15th February 2018. Primary data were collected by cross sectional guided questionnaire and observations on spot. The survey included 30 to 40 farmers that were engaged in pesticide application practices and also includes visits to family member of farmer which were died due to pesticide poisoning. The questionnaire consists of closed and open ended questions. Secondary data were collected by the Shri Vasantrao Naik Government College and Hospital Yavatmal.

When poisoning were assessed, the interviewed person was asked if he had fallen ill during the past months or years and if he answered yes, then he was asked to specify the systems in details.

OBSERVATION AND RESULT

In our survey Separate questionnaire was asked to the farmers of different villages of Yavatmal district. As Maharashtra is famous for its traditional crops like Cotton, Tur, Soya bean, most no. of pests are attacked on these crops which requires pesticides as a pest control. On the basis of answers given and interactions with the farmers in selected areas, list of pesticides is prepared which are mostly used. The table below indicates the list of most used pesticides.

Pesticides	Chemical group
Polo	Diafenthiuran
Profex super	Profenofos + Cypermethrin
Police	Imidacloprid + Fipronil.
Monocil	Monocrotophos.

Table:- Different pesticides used by farmers and their chemical groups.

All the farmers usually use mixture of two to four pesticides in one spray. During the interviews, majority of the farmers stated that using mixture of pesticides makes the dose even stronger and effective while some believed that single dose proves less effective. It was also noted down that the person who sprays pesticide prefers making the formulations on his own or as told by experienced farmers. Farmers stated that the doses depend on the amount of attack of pests but usually the whole bottle of pesticides is used at once. There was no standard method preferred for making formulations.

All the farmers of cotton field usually sprays on cotton once a week in one field. But they undertake hired spraying work in other farmer's field. Farmers stated that on an average, they spray 8 hours per day. It

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was observed that the farmers who spray pesticides usually spray whole day i.e. in hot and humid conditions.

When we asked about time from which they apply pesticides, they responded that all of them spray pesticide from about 8-9 years and had poisoning after prolonged use of pesticides. They also stated that the symptoms of pesticide poisoning didn't arrive early.

It was noted that while applying pesticides, there were lot of difficulties faced by the farmers, among these difficulties common answers were increased height of cotton crop which is the probable cause of inhalation poisoning, also direction of wind played important role for entering the human route through nasal track. It was also noted that most of the farmers don't use any protective equipments while applying the pesticides in the fields.

According to answers given by the farmers general symptoms observed and their extent is given in table below

S.N	Symptoms	Prevalence (%)
1.	Headache	88%
2.	Dizziness	70%
3.	Blurred vision	73%
4.	Difficulty in Breathing	89.4%
5.	Skin rashes	67%
6.	Vomiting	55%
7.	Irregular heart beat	47%
8.	Excessive Sweating	84.6%
9.	Eye rashes	47 %

Table 2: Occurrence of symptoms with their prevalence

From the survey it was evident that there are very few farmers who use protective equipments. It was observed that there is direct relationship between no. of protective equipments used and occurrence of symptoms. The graph below shows relationship as no. of symptoms are more when there is less use of protective equipments.

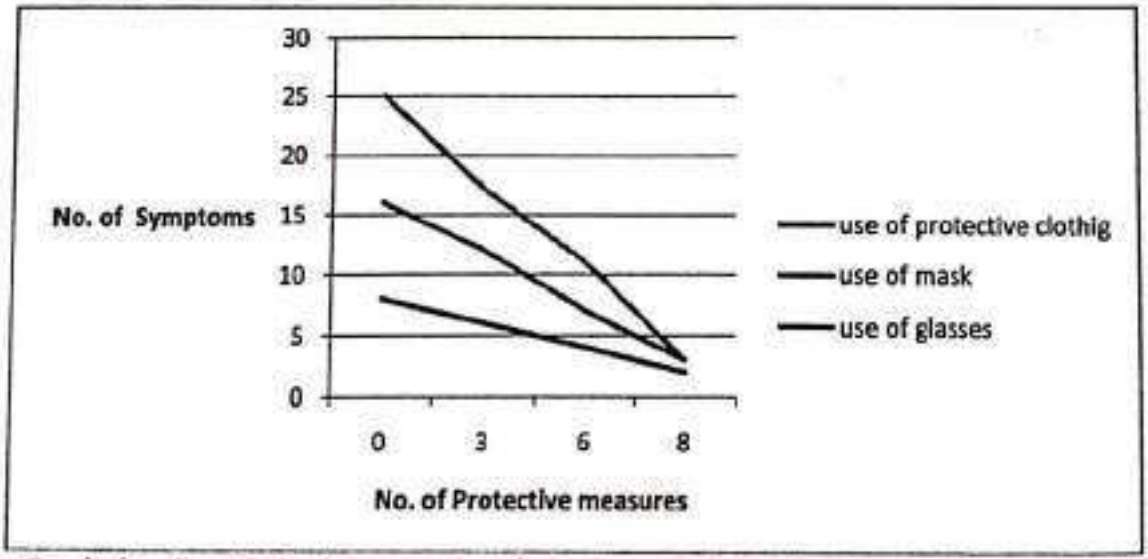


Fig: Graph showing relation between No. of symptoms and No. of protective equipments used.

It was observed that due to lack of education and awareness, most of the farmers had very little knowledge about the toxicity and safe handling of pesticide. This was thought to be one of the important

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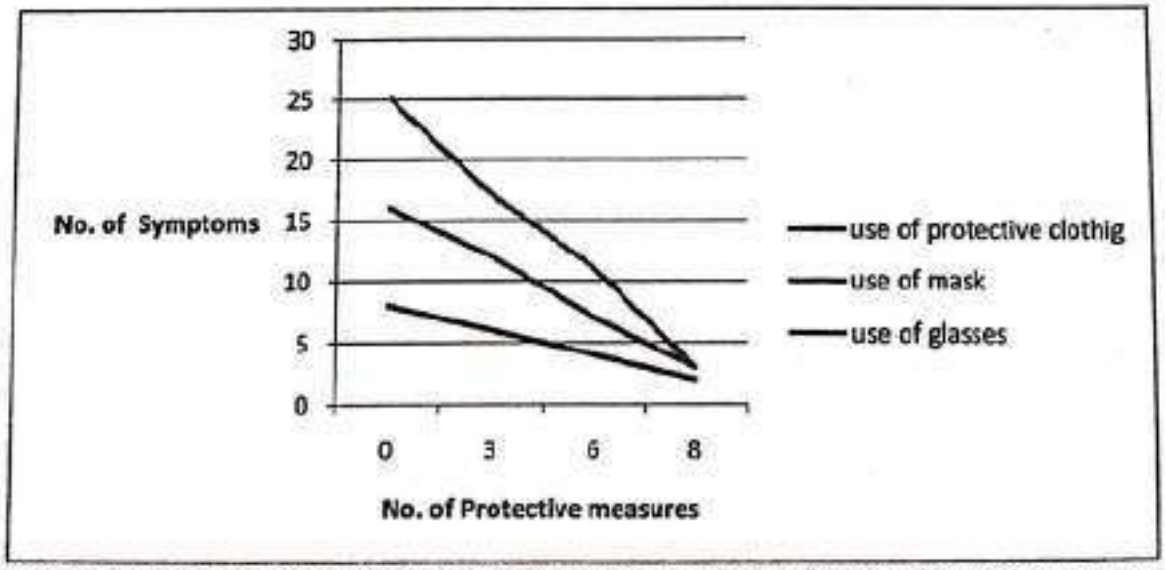


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It was observed that due to lack of education and awareness, most of the farmers had very little knowledge about the toxicity and safe handling of pesticide. This was thought to be one of the important

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reason for increasing cases of poisoning as 95% of the farmers who spray pesticides stated that they didn't even knew how to read the instruction on user manual.

DISSCUSSION

The approach of face to face questionnaire and direct interaction with the affected as well as the daily sprayers was made to assess the common reasons behind this much extent of pesticide poisoning.

Despite the fact that most of the farmers were aware about the health hazards associated with pesticide spraying, they avoided the use of personal protective equipments. A higher percentage of farmers said that they received instructions from agriculture shop or neighbor but the dilemma is that there was no training or workshop regarding the safe practices. With regarding to no. of hours spent for application of pesticide, the study found that most of the farmers used to spray about 7-8 hours/day according to the answers provided by them. The finding of this study was quite similar to the study conducted by Jensen *et al.*, (2011) who concluded that symptoms of pesticide poisoning were related to no. of hours spraying and no. of personal protective equipments used.

From this survey it was also reported that Organophosphate was the most impactful pesticide leading to increasing no. of affected persons. Similar study was conducted by Antonijevic (2007), who concluded that Organophosphates are deterious to target as well as non target organisms.

CONCLUSION

From this survey based analysis of the extent of pesticide poisoning amongst pesticide spraying people in different villages of Yavatmal district, it is evident that most of the reported health effects were observed due to lack of knowledge about safe handling of pesticides. Although farmers had awareness about the danger of pesticides, but no protective measure were used by them, which proved to be the main reason behind inhalation and contact poisoning.

Most of the farmers were uneducated and reading the instruction manual was not possible. Spraying the pesticides without knowing the proper dose proved to be one of the main reasons for poisoning. The first priority for reducing the no. of pesticide poisoning cases must be to effectively phase out the most hazardous pesticides from the market. Proper knowledge and Education amongst pesticide sprayers for the proper use of pesticides is the need of hour. This can be achieved by awareness among farmers towards proper use of pesticides by conducting seminars and workshops by the agriculture department of that particular area.

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ENDOSULFAN AND PARATHION INDUCED EFFECT ON LIVER AND KIDNEY OF GARDEN LIZARD *CALOTES VERSICOLOR* IN RESPECT OF METABOLITE: GLUCOSE AND PROTEIN

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ABSTRACT:

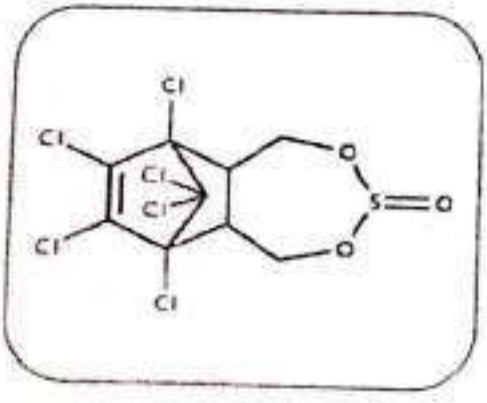
The present study highlights the effect of endosulfan (2.5µl) and parathion (3µl) on kidney and liver of Calotes versicolor. A moderate decrease in kidney protein was found in Calotes versicolor treated with endosulfan and parathion. A significant decrease were noted in liver protein in endosulfan treated Calotes for 24 and 48 hours but statistically non significant changes were found in rest of the exposure periods under the treatment of both pesticides. A significant decrease were noted in liver glucose except 24 & 48 hours whereas non significant decrease was noted in kidney glucose.

KEYWORDS – *Induced effect, endosulfan and parathion, Calotes versicolor.*

INTRODUCTION

Pesticide and related chemical destroy the delicate balance between species that characterizes a functioning ecosystem. Fish, bird and wildlife that live in direct contact with environment subject to pesticide exposure are sentinel species (Kegley *et al.*, 1999) A number of wildlife species can be affected by pesticides used in a agricultural field because of their effect on physiological functions of all kind of animals. Due to human activities and involvement in an effort to increase agricultural product and the use of indiscriminate pesticides, approximately 25% of reptiles and 20% of amphibians are listed as threatened (Hilton-taylor, 2000).Organophosphate and Carbamate are widely used and have a variety of lethal and sublethal effect on non target wild life (Parson *et al.*, 2000). A lot of work has been done on the effect of pesticides on amphibians and reptiles by Antony and Ramalingham (1990); Balasundaram and Selvarajan (1990); Alvarz *et al.*,(1995); Pauli and Money (2002). There has been great deal on interest in reptiles and amphibians ecotoxicology. Some work has been reported by Khan *et al.*, (2003) about the reduction of cholinesterase activity and protein content in *Calotes versicolor* due to pesticides. In present study the effect of endosulfan and parathion on glucose and protein content of liver and kidney of *Calotes versicolor* is observed.

MATERIAL AND METHODS



Local *Calotes* were collected from the field irrespective of sex. They were kept in a aquarium for seven days before the experiment. During captivity food and water were provided in the aquarium. Two groups of six experimental animals were exposed to the predetermined dose of (LC50 for 96 Hrs.) endosulfan (2.5µl) and parathion (3µl) separately was introduced orally to the *Calotes* (single pesticide per 6 animals).A batch of unexposed lizard were also maintained in same laboratory condition. After 24, 48, 72 and 96 hours animals were

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rificed and glucose and protein content was estimated from liver and kidney of these animals.

OBSERVATIONS

Table No. 1.

Effect of sub lethal concentration of endosulfan (2.5µl) and parathion (3µl) on kidney and liver protein (gm/dl) level of *Calotes versicolor*

Exposure periods	Tissue	Control	Experimental	
			Endosulfan	Parathion
24 Hrs.	Liver	4.1+0.260	2.8 + 0.219 ** (-31.7)	2.5+0.089** (-39.00)
	Kidney	3.8+0.089	2.6+0.148** (-31.57)	2.7+0.141** (-28.94)
48 Hrs.	Liver	4.2+0.173	2.1+0.219** (-50)	2.0+0.167** (-52.3)
	Kidney	3.7+0.14	2.1+0.118** (-43.24)	1.8+0.089** (-51.35)
72 Hrs.	Liver	3.7+0.194	3.3+0.757NS (-10.87)	2.6+1.007 NS (-3.18)
	Kidney	3.8+0.089	1.7+0.178** (-55.26)	1.5+0.089** (-60.52)
96 Hrs.	Liver	3.8+0.2)	3.4+0.118 NS (-10.52)	2.8+0.963 NS (-26.3)
	Kidney	3.9+0.141	1.10+0.148** (-71.79)	1.2+0.077** (-69.23)

Table No:-2

Effect of sub lethal concentration of endosulfan (2.5µl) and parathion (3µl) on kidney and liver Glucose (gm/dl) level of *Calotes versicolor.*

Exposure periods	Tissue	Control	Experimental	
			Endosulfan	Parathion
24 Hrs.	Liver	125.6±1.368	121.5 ± 4.037** (-3.26)	123.5±2.58* (-1.67)
	Kidney	116.5±1.378	114.3±2.277^{NS} (-1.89)	113.1±2.927^{NS} (-2.91)
48 Hrs.	Liver	124.3±4.71	119.3±1.81** (-4.02)	122.6±2.58** (-1.36)
	Kidney	116.3±1.033	115.5±0.84^{NS} (-0.68)	112.8±2.00^{NS} (-3.00)
72 Hrs.	Liver	125.3±5.988	117.8±4.490* (-5.98)	122.0±2.607* (-3.18)
	Kidney	116.0±1.095	113.8±1.169* (-1.89)	112.3±2.339* (-3.18)
96 Hrs.	Liver	125.5±6.12	116.3±4.63 ** (-7.33)	121.8±2.92** (-26.3)
	Kidney	116±0.984	113.6±2.066* (-2.06)	113.1±2.92** (-2.5)

ues are mean ± SD of six observations
Non Significant,
ues are significant at *P<0.05, **P<0.01

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RESULT AND DISCUSSION

Under the effect of endosulfan and parathion kidney protein was found to decrease moderately. Liver protein was found to decrease moderately in 24 and 48 hours of exposure periods but later no significant decrease were noted in protein content due to the same treatment for 72 and 96 hrs. Liver glucose was found to decrease significantly in most of the exposure periods except 24 & 48 hrs. Whereas there was non significant decrease noted in kidney glucose under the treatment of both pesticides. The result of present investigation indicate that the influence of both pesticides on the liver and kidney of *Calotes versicolor* reduce the level of protein. Similar results were also observed by Khan et al., (2002) in kidney and liver protein of *Calotes versicolor* and frog *Rana tigrina* due to the treatment of cypermethrine. Khan, (2005) noted inhibition in the activity of cholinesterase in liver and kidney of *Calotes versicolor* due to the treatment of cypermethrine and Malathion. Deli and Kiss, (1988) observed a muscle damaging effect in Chicken embryo when treated with parathion and methyl parathion. They suggested that this muscle damaging effect of organophosphate insecticide may be related to the decrease of tissue content of certain cytoskeletal protein. Age dependant toxic effect of endosulfan was observed by Kiran and Verma (1988) in different age groups of rat. They observed a maximum depletion of liver glycogen and maximum inhibition of brain cholinesterase activity in 365 days old animal. Kaur and Dhanju (2005) studied toxic effect of three oraganophosphate: Monocritophus, Dimethote and methyl parathion on the ovaries of albino rat, they noted significant decrease in the concentration of cytoplasmic as well as membrane bound protein cholesterol.

Tilak *et al.*, (1999) suggested that the decrease in protein content in the kidney and liver of fish, *Labeo rohita* due to the interference of pesticides in protein metabolism and according to them when the fish exposed to pesticides stress the tissue were actively involved in deamination leading to protein depletion. A significant decrease in kidney carbohydrate was noted by Kumari and Kumar (1997) in the fish *Channa punctatus* and they augmented that this decreased kidney glucose may be due to increased glycogenolysis under the pollutant stress. Decreased liver glucose of endosulfan treated *Heteropneustes fossilis* was observed by Shrivastava and Singh (1997) and according to them this decrease was probably due to acceleration of TCA cycle, along with elevated glycogenolysis and gluconeogenesis to meet the excessive energy demand during pesticide stress condition. Shrivastsva and Singh (1997) also observed consistent depletion in the amount of glucose in liver of *Heteropneustes fossilis* under the treatment of endosulfan. Sharma (1999) noted a reduced protein level in the liver of fish *Clarius batracus* when treated with pesticide Carbaryl. Dhapate *et al.*, (2006) noted a reduction in kidney and muscle protein of the fish *Clarius batrachus* due to the treatment of endosulfan. Rajyashree (1996) also observed decline in protein level in liver during Carbamide exposure to *Labeo rohita* and augmented that this decrease due to the physiological adaptability of fish to compensate to pesticide stress.

In the present investigation the exposure of *Calotes* to endosulfan and parathion toxicity resulted into moderate decrease in kidney and liver protein which is similar to the findings of other investigators cited above. Thus we can argue that the exposure of toxicity of both pesticides brings hepatocellular damages and inhibition of protein synthesis in liver, which finally resulted into decreased in liver protein level, Secondly this reduced protein content of liver may be attributed to stress mediated mobilization of this compound to fulfill the increased demand for energy to cope with the detrimental condition imposed by the pesticides. Because to overcome the stress, animal required high amount of energy and this energy demand might have led to the stimulation of protein catabolism which finally resulted in to decline in liver protein level. The resulted decrease in protein content of kidney may be due to increased proteolytic enzymes activity for the breakdown of tissue protein into amino acid in this condition of endosulfan and parathion stress.

Glucose is the major fuel of most organisms and it can be mobilized from glycogen in the time of demand to meet day to day energy requirement. Thus we can conclude that the resulted significant decrease in kidney glucose may be due to its high utilization to meet the energy demand during stress of both pesticides endosulfan and parathion. Decreased liver glucose may be due to elevated glycogenolysis and gluconeogenesis to meet the excessive demand of energy to compensate the stress of both pesticides.

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RESULT AND DISCUSSION

Under the effect of endosulfan and parathion kidney protein was found to decrease moderately. Liver protein was found to decrease moderately in 24 and 48 hours of exposure periods but later no significant decrease were noted in protein content due to the same treatment for 72 and 96 hrs. Liver glucose was found to decrease significantly in most of the exposure periods except 24 & 48 hrs. Whereas there was non significant decrease noted in kidney glucose under the treatment of both pesticides. The result of present investigation indicate that the influence of both pesticides on the liver and kidney of *Calotes versicolor* reduce the level of protein. Similar results were also observed by Khan *et al.*, (2002) in kidney and liver protein of *Calotes versicolor* and frog *Rana tigrina* due to the treatment of cypermethrine. Khan, (2005) noted inhibition in the activity of cholinesterase in liver and kidney of *Calotes versicolor* due to the treatment of cypermethrine and Malathion. Deli and Kiss, (1988) observed a muscle damaging effect in Chicken embryo when treated with parathion and methyl parathion. They suggested that this muscle damaging effect of organophosphate insecticide may be related to the decrease of tissue content of certain cytoskeletal protein. Age dependant toxic effect of endosulfan was observed by Kiran and Verma (1988) in different age groups of rat. They observed a maximum depletion of liver glycogen and maximum inhibition of brain cholinesterase activity in 365 days old animal. Kaur and Dhanju (2005) studied toxic effect of three oraganophosphate: Monocritophus, Dimethote and methyl parathion on the ovaries of albino rat, they noted significant decrease in the concentration of cytoplasmic as well as membrane bound protein cholesterol.

Tilak *et al.*, (1999) suggested that the decrease in protein content in the kidney and liver of fish, *Labeo rohita* due to the interference of pesticides in protein metabolism and according to them when the fish exposed to pesticides stress the tissue were actively involved in deamination leading to protein depletion. A significant decrease in kidney carbohydrate was noted by Kumari and Kumar (1997) in the fish *Channa punctatus* and they augmented that this decreased kidney glucose may be due to increased glycogenolysis under the pollutant stress. Decreased liver glucose of endosulfan treated *Heteropneustes fossilis* was observed by Shrivastava and Singh (1997) and according to them this decrease was probably due to acceleration of TCA cycle, along with elevated glycogenolysis and gluconeogenesis to meet the excessive energy demand during pesticide stress condition. Shrivastsva and Singh (1997) also observed consistent depletion in the amount of glucose in liver of *Heteropneustes fossilis* under the treatment of endosulfan. Sharma (1999) noted a reduced protein level in the liver of fish *Clarius batracus* when treated with pesticide Carbaryl. Dhapate *et al.*, (2006) noted a reduction in kidney and muscle protein of the fish *Clarius batrachus* due to the treatment of endosulfan. Rajyashree (1996) also observed decline in protein level in liver during Carbamide exposure to *Labeo rohita* and augmented that this decrease due to the physiological adaptability of fish to compensate to pesticide stress.

In the present investigation the exposure of *Calotes* to endosulfan and parathion toxicity resulted into moderate decrease in kidney and liver protein which is similar to the findings of other investigators cited above. Thus we can argue that the exposure of toxicity of both pesticides brings hepatocellular damages and inhibition of protein synthesis in liver, which finally resulted into decreased in liver protein level, Secondly this reduced protein content of liver may be attributed to stress mediated mobilization of this compound to fulfill the increased demand for energy to cope with the detrimental condition imposed by the pesticides. Because to overcome the stress, animal required high amount of energy and this energy demand might have led to the stimulation of protein catabolism which finally resulted in to decline in liver protein level. The resulted decrease in protein content of kidney may be due to increased proteolytic enzymes activity for the breakdown of tissue protein into amino acid in this condition of endosulfan and parathion stress.

Glucose is the major fuel of most organisms and it can be mobilized from glycogen in the time of demand to meet day to day energy requirement. Thus we can conclude that the resulted significant decrease in kidney glucose may be due to its high utilization to meet the energy demand during stress of both pesticides endosulfan and parathion. Decreased liver glucose may be due to elevated glycogenolysis and gluconeogenesis to meet the excessive demand of energy to compensate the stress of both pesticides.

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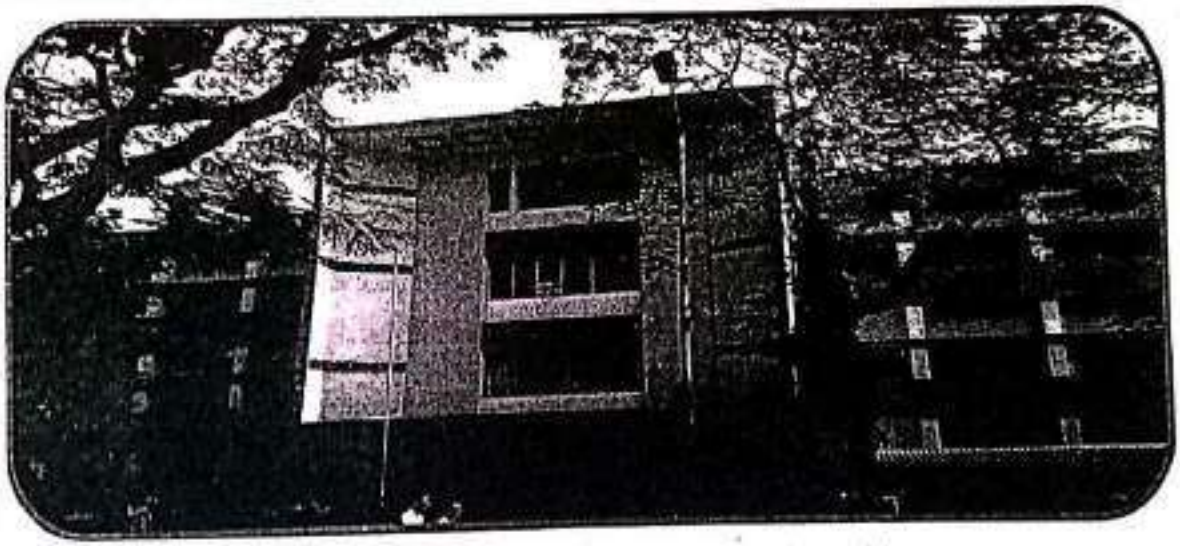
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आधुनिक काळातील : भारतीय स्त्री

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आधुनिक काळातील भारतीय स्त्रीचा विचार करण्यापूर्वी निरनिराळ्या कालखंडातील भारतीय स्त्री चा अभ्यास प्रथमतः करणे आवश्यक आहे. स्त्रीयांना स्वातंत्र देवूनही स्त्री म्हणजे पापाची खाण आहे. अशी जुनी समजूत होती. वैदिक काळापासून स्त्रीयांचा इतिहास पाहता, स्त्री स्वातंत्र व स्त्री शिक्षण हा बराच वादग्रस्त असा विषय राहिला आहे. स्वतः स्त्री जागृत नसल्यामुळे व पुरुषी वर्चस्वामुळे स्त्री ही स्वातंत्र व शिक्षणापासून बरीच दुर राहिलेली दिसते. पुरुषप्रधान संस्कृतीत स्त्रीचे स्थान पुरुषांच्या बरोबरीचे आहे ही कल्पनाच पुरुष वर्गाला मान्य होण्यासारखी नव्हती. आजही आधुनिक काळाचा विचार करता मुलांसाठी वेगळी वागणूक व मुलींसाठी वेगळे नियम मोठ्या प्रमाणात दिसून येतात. त्याला काही अपवाद सुद्धा आहे. परंतू त्यामुळे सामाजिक जिवनात फार मोठे परिवर्तन झाले असे म्हणता येत नाही.

निरनिराळ्या कालखंडातील स्त्रियांची स्थिती :

भारतीय इतिहासाचा विचार करता, स्त्रियांच्या कालखंड खालीलप्रमाणे अभ्यासिले जावू शकतात.

अ) वैदिक कालखंड, ब) उत्तर वैदिक कालखंड, क) स्मृती युग, ड) 19 वे शतक, इ) वर्तमानातील भारतीय स्त्री या कालखंडाच्या थोडक्यात गोषवारा खालील प्रमाणे करता येईल.

अ) वैदिक कालखंड : वैदिक साहित्यावरुन असे दिसुन येते की, या कालखंडामध्ये स्त्री–पुरुष समानता असल्याचे दिसून येते. शिक्षण, विकास, संपत्ती याबाबतीत स्त्रीयांना पुरुषा इतकाच दर्जा होता. वैदिक कालखंडातील समाज पुरुषप्रधान असला तरी या कालखंडात स्त्रियांना महत्वाचे व मानाचे स्थान होते.

ब) उत्तर वैदिक कालखंड : इ.स. पुर्व 600 ते इ.स. 300 या उत्तर वैदिक कालखंड म्हणुन इतिहासात समजला जातो. या कालखंडामध्ये स्त्रियांचा दर्जा खालावलेला दिसुन येतो. तसेच स्त्रियांना लिहिण्या वाचनाची योग्य संधी मिळालेली दिसत नसुन शिक्षणाचा स्तर घसरुन 'चुल व मूल' ही संकल्पना प्रकर्षाने उदयास आलेली दिसून येते. याच कालखंडामध्ये 'बालविवाह' प्रथेचा उदय झाल्याचे प्रकर्षाने दिसून येते.

क) स्मृती युग : हा कालखंड प्रामुख्याने रामायण, महाभारताचा कालखंड या नावाने प्रचलित आहे. त्या काळात स्त्रियांची परिस्थिती अधिकच हिन झालेली दिसून येते. विवाहाचे वय हे दहा ते बारा वर्ष असे

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या कालखंडातील साहित्यावरुन दिसून येते. पत्नीने पतीधर्म पाळावा, पतीसेवा हेच स्त्रिचे कर्तव्य आहे. स्त्री ही मानसिकदृष्टया पुरुषापैकी कमकुवत आहे. ही धारणा बनली.

ड) एकोणविसावे शतक : एकोणविसावे ते शतक हे स्त्रियांच्या उत्थानाकरीता महत्वाचे ठरले. कारण एकोणविसावे व्या शतकात इंग्रजी राजवट अस्तित्वात होती. इंग्रजी राजवटीने बालविवाह, सतीप्रथा, केशवपन, या विरोधात कडक कायद्यांची तरतुद केल्यामुळे या कालखंडात स्त्रीयांवर होणा–या अत्याचाराला कायद्याचे बळ मिळाले. तसेच या काळात ईश्वरचंद विद्यासागर, ॲनी बेझंट, राजा राममोहन रॉय, महर्षी कर्वे इत्यादी समाजसुधारकांनी स्त्रियांच्या स्थितीत सुधारणा करण्याचा प्रयत्न केला. त्यामुळे भारतीय स्त्रियांच्या बाबतीत भविष्यात अनुकुल वातावरण निर्मिती होण्यास मदत झाली.

एकोणविसाव्या शतकानंतर स्त्री सुधारणाच्या दृष्टीने वातावरण निर्माण झाल्यामुळे छत्रपती शिवाजी महाराज, शाहु महाराज, महात्मा फुले, सावित्रीबाई फुले, डॉ. बाबासाहेब आंबेडकर अशा अनेक समाजसुधारकांनी आधुनिक काळातील स्त्रियांना गतिमान करण्याचे कार्य केले. डॉ. बाबासाहेब आंबेडकरांनी तर स्त्रियांवर अन्याय करणारे, स्त्रि पुरुषामंध्ये असमानता दर्शविणारे, स्त्रियांना जनावरांप्रमाणे वागणूक देणारे, स्त्रियांच्या प्रगतीला गालबोट लावणारे अशा 'मनुस्मृती' चे दहन करुन स्त्री उच्चाटनाचा मार्ग मोकळा केला. डॉ. बाबासाहेब आंबेडकरांनी घटनेमध्ये स्त्रियांच्या बाबतीत अनेक महत्वाचे कायदे केल्यामुळे आधुनिक भारतातील स्त्री ख–या अर्थाने स्वातंत्र्याचा आनंद घेत असल्याचे दिसून येते. आज आधुनिक भारतातील स्त्री ही सर्वच क्षेत्रामध्ये प्रगती करतांना दिसून येते. शिपाई ते राष्ट्रपती, ॲटोचालक ते पायलट अशी विविध क्षेत्रे पादांकांत करीत आहे. त्यामुळे आधुनिक भारतीय स्त्रीचं जीवनमान उंचावण्यास मदत होत आहे. आज भारतीय स्त्रीची, कौटूंबिक व वैवाहिक स्थिती, शैक्षणिक क्षेत्र, आर्थिक क्षेत्र, सामाजिक क्षेत्र, राजकीय क्षेत्रात आपली बुद्धिमत्ता व कार्यकौशल्य प्रगट करुन आपली योग्यता सिद्ध केलेली दिसुन येते.

एकंदरीत भारतीय स्त्रीची प्रगती ही विकसित दिसत असली तरी, स्त्रियांच्या बाबतीत तीन प्रमुख अडथळे दिसून येतात. ते म्हणजे शहरी – ग्रामीण भेदभाव, वर्णभेद, लिंगभेद इत्यादी. आज भारतीय स्त्रीया पुरुषांच्या बरोबरीने त्यांच्या खांद्याला खांदा लावून सर्वच क्षेत्रामध्ये वाटचाल करीत असतांना स्त्रीला आजही लैगिंक अत्याचारापासून पाहिजे तशी मुक्ती मिळालेली नाही. कामाच्या ठिकाणी लैगिंक अत्याचाराचे प्रमाण वाढलेले दिसुन येते, आजही भारतीय स्त्री कामानिमित्त बाहेर जात असतांना तिला असुरक्षिततेची जाणीव होते. तिच्याकडे आजही उपभोगाचे साधन या दृष्टीने पाहिले जाते.

स्त्री–पुरुष समानता ही तत्वे नुसते मान्य करुन चालणार नाही. तर त्या तत्वांची सामाजीकरण करणे गरजेचे आहे. त्यासाठी कुटूंब, शाळा, समाज या सर्वांचे सहकार्य मिळून त्यांचा प्रचार व प्रसार करुन समाजात जनजागृती करणे स्त्रीयांना अपेक्षीत आहे. या सर्वातून सहकार्य, स्वातंत्र, व सुरक्षेची हमी मिळाल्यास तरच भारत एक प्रगतीशिल राष्ट्र म्हणून आपली ख्याती संपुर्ण विश्वात मिळविल्याशिवाय राहणार नाही.

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"ROOT CAUSES OF PESTICIDE POISONING AMONG FARMERS IN DIFFERENT VILLAGES OF YAVATMAL REGION"



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ABSTRACT

India is currently the largest manufacturer of pesticides and the second largest producers of agrochemicals in Asia, out of 145 pesticides registered in India, 85 are of technical grade and are locally produced. Multiple cases of pesticide poisoning were reported in India causing Deaths mostly among farmers. This cross sectional study was conducted among the farmers of different villages in Yavatmal district during the period of 25th September 2017 to 15th February 2018 to know the root cause of pesticide poisoning. From this survey based analysis it was evident that most of the reported health effects were observed due to lack of knowledge about safe handling of pesticides. Although farmers had awareness about the danger of pesticides, but no protective measure were used by them, which proved to be the main reason behind inhalation and contact poisoning.

KEYWORDS: *Pesticides, Poisoning, Knowledge, Survey, Yavatmal.*

INTRODUCTION

Many farmers in India have an impression and belief that if pesticides are used in excess, pests can be controlled quickly to get more protection from pests and high yields. In India, the sale, dosages and uses of many of these pesticides is not very well regulated. According to official estimates, Pesticide poisoning is directly responsible for the death of at least 10,000 people every year and these deaths are mostly of poor people, who are not reported or are under- reported (Gupta, 2004). Pesticides are the chemicals that are designed to kill member of one species i.e. insect's pests, but it is often found that members of different species are also affected including humans. Pesticides come under the category of economic poisons, a general term to describe chemical agents the use of which is acknowledged to confer benefits that outweigh the harmful consequences that may be associated with their use (Aiyar, 2003).

The world health organization stated that there are 3 million cases of pesticide poisoning each year and up to 2, 20,000 deaths, primarily in developing countries (W.H.O. 2016). Gupta (2017) analyzed the pesticides exposure scenario in India and concluded increasing cases of pesticide exposure were found.

Jeyaratnam *et al.*, (1987) investigated the extent of acute pesticide poisoning amongst agricultural communities in Indonesia, Malaysia, Sri Lanka and Thailand and confirmed that the existence of the problem was due to the inadequate knowledge of safe practices in the use of pesticides and the lack of personal protective equipments use by farmers in hot and humid conditions.

India is currently the largest manufacturer of pesticides and the second largest producers of agrochemicals in Asia, out of 145 pesticides registered in India, 85 are of technical grade and are locally produced from which, Insecticides (73%) dominate the market.

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MATERIALS AND METHODS

Calotes were collected from the nearest agricultural field without regard of sex. They were kept in cages, acclimatized for two weeks in laboratory conditions before the experiment and fed with insects during and before the experiment. The Endosulfan (2.5µl) was introduced orally to the *Calotes*. A batch of untreated lizard was also kept for comparison as control without administration of endosulfan. At 24, 48, 72, and 96 hrs. the blood was drawn from both control and experimental groups from the orbital sinus with the help of glass capillary tube for analysis of eosinophils, lymphocytes, monocytes, neutrophils, RBC and hemoglobin percentage.

RESULTS

Alterations in hematological parameters of *Calotes versicolor* after exposure to Endosulfan

Parameters	Groups	Periods of Exposure			
		24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.
Hemoglobin (gm/dl)	Control	7.7±0.374	7.6±0.316	7.5±0.489	7.4±0.435
	Experimental	5.4±0.352** (-29.8)	5.1±0.556** (-32.8)	4.3±0.624** (-42.6)	4.2±0.331** (-76.1)
Eosinophil %	Control	10.6±1.213	9.5±1.048	10.3±1.633	10.8±0.983
	Experimental	7.8±1.189* (-26.41)	5.6±0.819** (-41.05)	3.5±1.048** (-66.01)	2.3±0.9** (-78.70)
Lymphocytes%	Control	6.0±2.0	5.1±1.69	5.5±2.345	5.6±1.833
	Experimental	2.6±2.18** (-56.66)	3.8±1.685 NS (-25.49)	4.1±1.691 NS (-25.45)	3.6±1.833** (-35.71)
Monocytes %	Control	1.6±0.521	1.8±0.409	1.5±0.547	1.5±0.707
	Experimental	0.83±0.752* (-48.1)	0.66±0.515** (-63.3)	0.5±0.836** (-66.6)	0.33±0.505** (-78)
Neutrophils %	Control	3.8±1.685	3.3±1.319	3.6±1.166	3.5±1.870
	Experimental	2.1±1.691** (-44.73)	2.8±1.68 NS (-15.15)	2.6±1.833 NS (-27.77)	2.5±1.224 NS (-28.57)
Red Blood Cells (Million/mm3)	Control	1.20±0.044	1.21±0.051	1.21±0.037	1.19±0.037
	Experimental	1.37±0.052* (14.16)	1.17±0.037 NS (-3.30)	1.13±0.046 NS (-6.61)	1.10±0.04 NS (-7.56)
Total Leucocytes count(cu.mm. In thousands)	Control	5.69±0.043	5.68±0.151	5.67±0.309	5.68±0.122
	Experimental	5.63±0.130 NS (-1.05)	5.59±0.026 NS (-1.58)	5.53±0.137 NS (-2.46)	5.50±0.167** (-316)

Values are mean ± SD of six observation NS- Not Significant Values are significant at *P<0.05, ** P<0.01
Values in parenthesis expresses percentage difference.

DISCUSSION

The toxicity of endosulfan varies depending upon the route of administration, vehicle, species and sex of animal. (Dikshith *et al.*, 1988). The experiments conducted on sexually matured male rats to determine the effect of endosulfan on the hematological and haemochemical parameters of albino rats fed with 5 mg/kg body weight endosulfan in mixed food stuff for 42 days revealed decreased total counts of erythrocytes and hemoglobin, whereas leucocytes were increased in treated group (Das *et al.*, 2010). In our experiment significant decrease was found in hemoglobin percent in *Calotes* in all the exposure periods treated with endosulfan. The percent changes in hemoglobin over the control were 29.8, 32.8, 42.6 and 76%. The decrease in hemoglobin percent may be due to the disruptive action of the pesticide on the erythropoetic tissue. Solanke and Singh (2000) also reported declination in hemoglobin percent in Rat, *Rattus rattus* when exposed to thidon 53EC and postulated that this decrease may be due to haemolysis, hemorrhage and reduced erythropoiesis resulted due to the stress of endosulfan. In our investigation a reduction in R.B.Cs. number was observed but statistically it was nonsignificant. Compared to control, decrease was noted in R.B.Cs. count at 48, 72 and 96 hrs., but a slight increase was observed at 24 hrs. Thus it can be concluded that the decreased hemoglobin percent may be due to

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the reduced number of R.B.Cs. Sayim *et al.*, (2005), also reported decrease in mean corpuscle volume, hemoglobin, RBCs count and mean corpuscular hemoglobin, whereas no statistically significant increase in WBCs count, but significant increase in number of lymphocytes and monocytes in hematological analysis of rats when orally administered with synthetic pyrethroid insecticide, cypermethrine (150 and 300 mg/kg for 28 consecutive days). This decrease in R.B.Cs. count was suggested due to disrupted erythropoiesis due to pesticidal stress. Johal and Garwal (2004) studied toxicity of Carbaryl on *Channa punctatus* and recorded a general decrease in R.B.Cs count suggesting metabolic stress. Thus it may concluded that decrease in R.B.Cs due to disrupted erythropoiesis caused by stress of Endosulfan and slight increase in initial exposure periods may be justified for increased demand of energy during the experimental period.

Statistically no significant changes were noted in total leukocytes count in all the exposure periods but slight decrease in all the exposure periods may be due to the leucocytopenia exerted by endosulfan stress. A significant decrease was noted in neutrophil percent of treated *Calotes* in our study. Dikshith *et al.*, (1982) noted a reduction in neutrophil percent after repeated oral administration of Quinalphos to male goat. Similar result was also recorded by Rajini *et al.*, (1987) in Albino rat after the treatment of Primiphos which causes an adverse effect on normal functioning of the bone marrow or changes in the varied factors responsible for normal leucocyte balance. Thus, it can be concluded that the endosulfan interfere in the normal physiology of neutrophils. Mandal and Lahiri (1985) noted a significant decrease in lymphocyte number in blue rock pigeon after the treatment of Sumithion.

In our studies, also a significant decrease was noted in Lymphocyte percent in *Calotes*. Lymphocyte percent was decreased sharply at early period of 24 hours and later increased steadily in endosulfan administered lizards but could not increase than that of control group. Thus the resulted lymphocyte count may be justified due to immunosupression caused by endosulfan toxicity. The assessment of the acute toxicity (96-h LC50 median value of 2.6 µgl.) and physiological parameters after exposure to 0; 0.25; 1; 2; 3; 4 and 16 µgl. endosulfan for 96 h under semi-static conditions in a freshwater perciform fish, *Cichlasoma dimerus* was done by Da Cuña *et al.*, (2011) and found decrease in erythrocyte mean corpuscular volume and mean corpuscular hemoglobin concentration in exposed fish suggesting a state of anemia. Rehaman (2006) observed decrease in lymphocyte count in Endosulfan treated fish *Cyprinus carpio* where the red blood cell population was observed to be declined by 20% at 120 hr. and by 45.2% at 240 hr. of endosulfan exposure. The hemoglobin levels were also depressed by 32.2 % at 120 hr. and 64.3 % at 240 hr exposure. The decrease of 24.6 % of counts of small lymphocytes was noted at120 hr. which further declined 52.6%, at 240 hr. The counts of large lymphocytes were found to be lowered in endosulfan-affected fish by 19.5 at 120 hr, and 65.9% at 240 hr. Suppression of the basophil numbers was observed at 120 hr and by 37.9% at 240 hr of endosulfan treatment. Attenuation of neutrophils was 9.4%; not significant at 120 hr. and 12.5% at 240 hr. of the pesticide exposure. The eosinophils were diminished by 30.4% at 240 hr. The thrombocyte was the only blood parameter studied showing elevated counts (9.5%) a 120 hr. The monocytes were depressed by 11.7% at 120hr and by 29.5% at 240 hr in endosulfan-exposed fish.

In our findings a moderate decrease was noted in eosinophil percent in *Calotes* and notable changes were recorded in monocyte count after the treatment of endosulfan in all the exposure period. Dikshith, *et al.*, (1982) observed a decreased monocyte count after oral treatment of Quinalphos to male goat. Nath and Banarjee (1999) also recorded a low count of monocyte in *Heteropneustes fossilis* due to toxicity of Rogor. Omoyakhi *et al.*, (2008) observed a progressive decrease in monocyte percent in growing rabbit due to the treatment of Acetellic dust. Mandal and Lahiri (1985) also observed a gradual decrease monocyte percent in pigeon *Columbia livia* exposed to Sumithion. According to them this decreased eosinophilic count may be due to splenic immunosupression caused by pesticidal stress. The above findings support our investigation and can be concluded that Endosulfan exert stress on eosinophils and moncytes count via suppressed leucocytes.

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EXPLORATION, ASSESSMENT AND ETHNOBOTANICAL STUDIES OF TRIBE KORKU INHABITED IN MELGHAT FOREST AREA OF AMRAVATI, MAHARASHTRA, INDIA

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ABSTRACT: Melghat forest is rich in biodiversity of medicinal plants and this area is inhabited by scheduled tribe Korku. The purpose of the present study was to record the ethnobotanical knowledge of korku tribe using these wildly growing medicinal plants and the survey was conducted during the years 2014-2017. Forty eight plant species belonging to thirty four families which are extensively being used as medicinal plants as well as for food were collected and their traditional usage by korku tribe were studied. The botanical name, family, vernacular name, Flowering periods, Voucher specimen, date of collection, Precise GPS Location, Height above Sea level, Life form, Abundance, Frequency Citation, Relative Frequency Citation index, parts used, Drug formulation & dosage to cure various ailments are discussed in this study. The indigenous extraction and drug formation practices recorded in the present study can be tested and standardized on scientific scale. This study will be helpful in providing awareness about harvesting these medicinally important plants in a conservative manner.

KEYWORDS: Melghat Forest, Korku, Indigenous knowledge, Statistical methods.

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1.INTRODUCTION

Forest structure and floristics knowledge are necessary for the study of forest dynamics, animal – plant interactions and cycling of nutrients. As life support system forests are the most important component on the earth. These days Biodiversity has always remained the topic of hot debate and discussion. Biodiversity conservation strategy needs strong basis of Biodiversity Assessment. Until and unless we know what is our biodiversity, we can't decide what is to be conserved and how. As far as plants are concerned most of the region of the country are floristically explored – are continuously being explored - and to good extent we have idea about our species wealth [1]. Besides the detailed assessment of floristic diversity of area of conservation, whether they are endemic, endangered or medicinally important plant species, the causes of forest destruction are also equally important in assigning conservation values. Plants have now been used as traditional medicines from about more than five thousand years for curing, suppressing, and prevention of diseases of humans [2]. Ancient methods of using plants for various diseases is known as herbal medicine which refers to the use of different parts of the plant for medicinal purposes [3]. The herbal medicines are considered to be of great importance among different indigenous and rural communities in many developing countries [4]. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparations for therapy [5]. According to WHO, traditional medicines is therapeutic practices which have an existence from more than hundreds of years [6]. Analyses of published information on medicinal plants used by the six major systems of medicine in India are as; 1250-1400 plants in Ayurveda [7]; 342 plants in Unani; and 328 plants in Siddha; 4671 in Folk; 482 in Homoepathy; 1106-3600 plants in Tibetan Medicine [8]. Even most world population belonging to developing countries are still dependent on these traditionally used medicinal plants for their health care [9]. The information about the usage and importance of these medicinal plants was discovered by local tribal communities. Due to the rich biodiversity of Melghat forest certain scheduled tribes are inhabited in this area which includes ‘Korku’, ‘Gond’, ‘Nihal’, ‘Balai’ and ‘Gaoli’ etc but majority of population and area is covered by Korku tribe while as percentage of other tribes is limited [10]. According to official website of Melghat Tiger Reserve, Korku’s had been drawing their sustenance from a period of almost one century from the forests of this area and are mainly engaging themselves in forest produce harvesting. This tribe has very important role in providing laborers for development works and forest conservation. They have acquired skills which are required for harvesting these forest products which are later processed and send to markets as forest products. The main purpose of this survey is that it can be very important for research students dealing with medicinal plants. Some already studied plants of this area have shown that nutritional value of those plant foods is quite high, as they contain greater amounts of vitamins, minerals, carbohydrates, protein, and fat than cultivated plant foods. Taking these perspectives in consideration, the exploratory study for the study of plants with medicinal use was carried out within

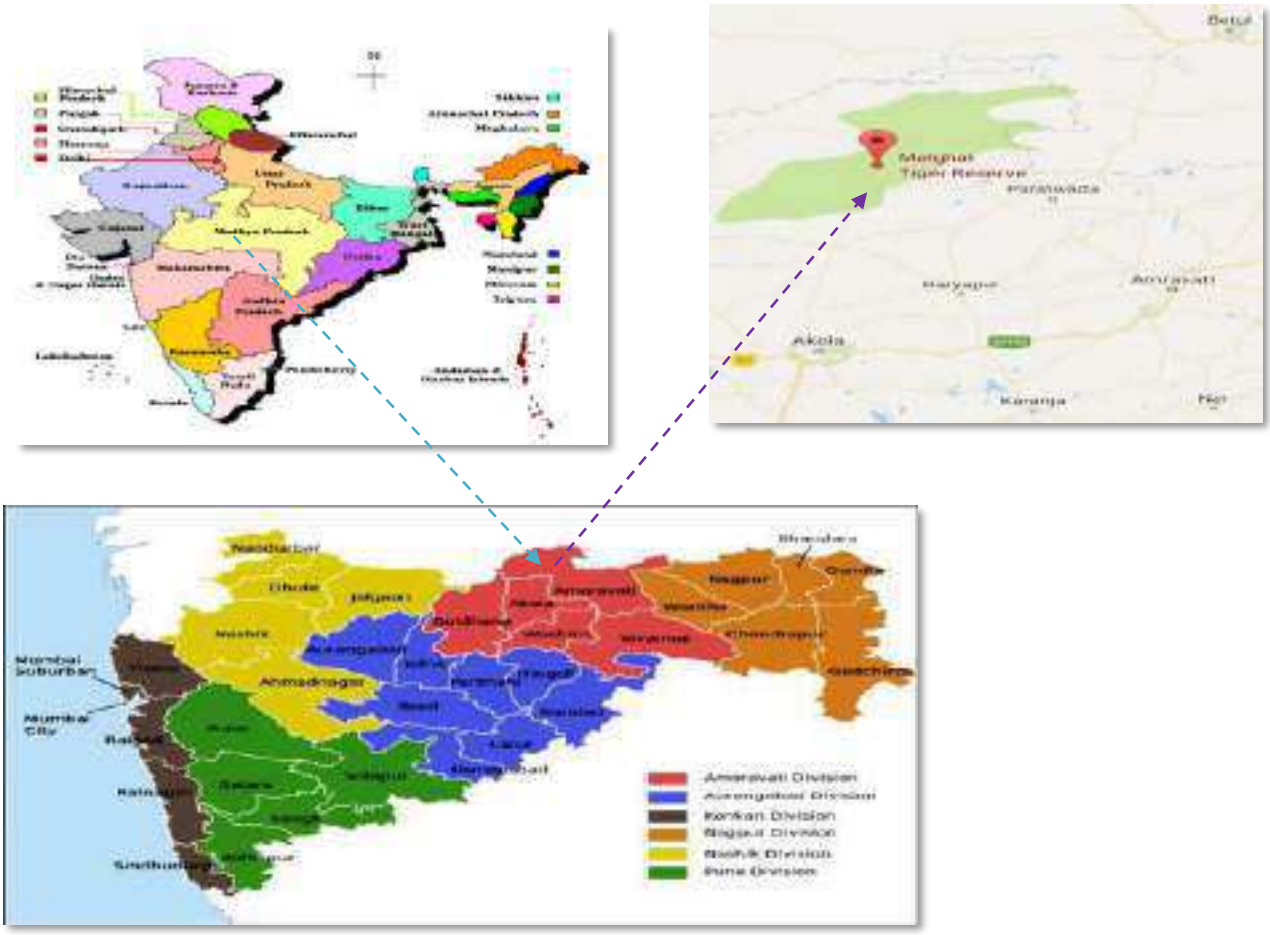
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korku tribe inhabiting in the Melghat forest. This area being hilly in character, tribal people are mostly relying on the plants or plant derived products for the basic health care and foods. Most of the human ailments and veterinary diseases are cured by prescriptions of local bhagat (vaidoo) and elderly people with the help of herbal products.

2. MATERIALS AND METHODS

Demography

The Melghat area is in the Northern part of Amravati District of Maharashtra State and was declared a tiger reserve in 1974. The total area of the biosphere reserve is around 1677 km^2. The forest vegetation is tropical dry deciduous in nature. The study was done in the Korku tribe which reside in Melghat area at coordinates 21˚ 26′45″N and 77˚11′50″E which is also shown by map in "Figures 1, 2, &3".



Figures 1, 2, & 3: Map of India showing Maharashtra State in which study area Melghat Forest Area has been shown

Methodology

The study was planned in the beginning of the May 2014 - January 2017 to investigate and enumerate the flowering plant which are used by people of korku tribe in their routine health care system to cure various ailments. Nature of ailments was identified with the help of elderly tribal healers of the particular area. Seven trips were done to the understudy area during investigating time

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period (May & September, 2014; March & November, 2015; November & December, 2016; January, 2017) by all the authors from time to time in order to record the diversity and ethnic knowledge of the plant diversity found in the understudy area. For collection of data questionnaire, semi-structured interviews and direct observations were done [11]. Before each interview, researchers and the informants signed a Prior informed consent (PIC) according to Kyoto protocol concerning the intellectual property rights (IPR) of local inhabitants and plant resources of the area. The sole purpose of this study was designed for unveiling the precious wealth of indigenous knowledge. The information about local name, part used and methodology of usage from the korku tribe was noted during the survey [12]. During observation field notes were recorded in field notebooks and voucher specimens of these species were collected. The collected specimens were processed using usual taxonomic methods of drying and mounting [13] and herbarium were prepared by standard methods [14]. The specimens were identified with the help of existing literature [15],[16],[17],[18],[19] and authorized taxonomist of the area. These collected specimens have been preserved in the herbarium of Department of Botany, Vidyabharati Mahavidyalaya College, Amravati (M.S.). The plants were classified according to the classification of Bentham and Hooker (1862-1883) [20] and their botanical name, local name, family, flowering phonology, altitudinal range, life form representation, part used and methodology of using these parts (wherever necessary) and most frequently treated diseases. The plants in this survey were classified into herbs, shrubs, trees and climbers using the Raunkiar's (1934) [21] life form classification system. Data documented during the ethnobotanical survey was entered on a Microsoft excel database and analyzed to determine the proportions of different variables. Relative Frequency of Citation (RFC) of reported species was also determined by using formula;

$$RFC=FC / N \ (0<RFC<1)$$

This index shows the local importance of each species and it is given by the frequency of citation (FC, the number of informants mentioning the use of the species) divided by the total number of informants participating in the survey (N), without considering the use-categories [22], [23],[24].

3. RESULTS AND DISCUSSION

The local inhabitants have learnt to utilize plants for treating various diseases. Thus there is a vast list of plants used by this tribe but some important wildly growing forty eight plant species belonging to thirty four families which are extensively being used to cure various ailments are given in "Table 1". In the present study, a total of 51 persons were interviewed among which 20 were males and 31 were females. The informants were divided into four age groups; (1) 12-20 years; (2) 20-35 years; (3) 35-65 years and (4) above 65 years old. Age group of 35-65 years old comprised the most informants. 6 drug formulations practices or recipes formulations were harvested from 1st age group, 29 from 2nd age group, 23 from 3rd age group and 43 from 4th age group. Present study was unique in comparison to the previous ethnobotanical studies all around the world as we interviewed first

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time the female community of the korku tribe residing in Melghat tiger reserve of Amravati, Maharashtra. In this area, the females of the said community are traditional and very conservative in talking to males (strangers or outsiders) except their close relatives within the community. Authors were assisted by an elderly woman of the same community for interviewing these females within their houses. This strategy was adopted for the purpose of the data collection from female informants and also to compare their indigenous knowledge with male members of the same community. Other purpose was to know their interest regarding the use of medicinal plants to treat different ailments. The aim of the data collection was explained to the local inhabitants and then semi-structured questionnaire based interviews were carried out. The inhabitants of the korku community were requested to share the knowledge of utilizing these medicinal plants in their local language in order to collect the detailed information which was converted to common tongue by a member (*Mama*) of the same community. It can be assumed from this study, that most members of the community generally rely on traditional herbal medicines due to easy availability and rich diversity of medicinal plants in the area. It is noted during the survey, that the female informants in comparison to male members have a significant knowledge about the preparation and administration of herbal drugs which reflect their role in house hold management and disease treatment in order to keep the family healthy. However, the technique for diagnosis of the various ailments is very primitive in the tribe. Different diseases are being diagnosed on the external characters of the patient by these elder men and women of the tribe. Color of the tongue, eyes, cold and hot conditions of the body are common indicators which are being used to understand the patient's problem. The specimens studied, their assessment and ethnobotanical usage are given in the Table 1. The study was undertaken for the first time in the understudy tribe and the results revealed that Korku tribe is good in plant based ethno-medicine. The gender, related age group from which the knowledge was harvested and number of recipes has been presented in "Figure 4". During the field work of the present study, 48 plant species belonging to 44 genera and thirty four families were collected. The complete inventory of ethnoflora consisting of taxon name, with their family, Local name / vernacular name, flowering period, voucher specimen number, date of collection, life form, abundance, Frequency citation, Relative frequency of Citation, part used, mode of administration and dosage has been recorded in the present study shown in "Table 1". The best represented families are Ceasalpinaceae (four species), Euphorbiaceae (3 species) while as Liliaceae, Anacardiaceae, Papilionaceae, Zingiberaceae, Lamiaceae, Moraceae, Lythraceae, Myrtaceae, Rhamnaceae each represented by two species and other 23 families with one species each. Some of the species were commonly found in the study area while as some the species showed different abundance patterns. However, we can also state that, more commonly a plant taxon found in an area, the greater will be the probability of its popular use. In accordance with the life form, tree species (26) were the highest followed by herbs (17), shrubs (4) and climbers (1) as shown in "Figure 6". This is not surprising as the area is deciduous

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forest type in which dominant vegetation is Trees followed by the growth of herbs in rainy monsoons. The findings of this study indicate that aerial parts (67.54%) were mostly used, followed by the usage of underground parts (29.87%) and whole plants (2.59%) for the formulations of recipes shown in "Figure 8". The present study also shows that the area has vast medicinal flora with major potential to cure many diseases. Both fresh and dried parts are used for making drugs in crude form. Mostly, the drugs are prepared in the form of paste, tablets, powder, latex, decoction, and even as extracts shown in "Figure 7". The dosage and mode of administration against different ailments is subject to approximation during treatment procedure. The ailments which were cured by these under study plants are anti-emetic, skin diseases, cough, menstruation disorders, stomach pains, cholera, indigestion, muscle pains, rheumatic pains, Diabetes, anti-fertility, breast ulcers, gastric disorders, ophthalmic disorders, Blisters, jaundice, headache, paralysis, etc. The study also gives the approximate GPS location where these medicinal plants can be collected and harvested as well as can be protected from unsustainable harvesting or over harvesting in that area. The photographs taken during the data collection (interviewing the informants and collection of plant specimens) are presented in Photoplate 1 and Photoplate 2 & 3 show the digitalized pictures of some important species of the area.

Some plant species of this study area are widely distributed in other parts of country as they have wide adaptability for different ecological zones. Among all medicinal plants reported in present study *Syzygium cumini, Ficus religiosa, Euphorbia hirta, Butea monosperma, Sterculia urens, Hemidesmus indicus, Emblica officinalis, Cassia fistula* and *Aegle marmelos* have high RFC values which indicates that these are well-known plants of the korku tribe. Findings of the present study are in contrast to most of the previous ethnobotanical studies where different plant species are being reported with respect to their preference use [13, 25, 26, 27]. The other most cited medicinal plants based on RFC data includes *Acalypha indica L., Cayratia auriculata, Chlorophytum tuberosum, Costus speciosus, Dendrocalamus strictus, Colebrookea oppositifolia, Lagerstroemia parviflora, Madhuca indica, Miliusa tomentosa, Wrightia tinctoria, Zizipus xylopyra, Anisochilus carnosus.*

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Table 1: Exploration, Assessment and Ethnobotanical Usage

Botanical name / Family/ Vernacular name / Fls & frts./ Voucher specimen No./ Date of Collection	Location / Height above Sea level	Life Form	Abundance	FC	RFC	Part/s Used	Methodology of Usage/ Formulation of Recipes and Disease Treated
Acalypha indica L. / Euphorbiaceae/ Khajoti/ Throughout the year. (NAW-1361)/ 07-05-14	N-21^0.28.234_ E-077^{0}23.326 897m	S	1	17	0.33	Roots Leaves	Roots ground with black peper (*Piper nigrum*) and the extract orally administered as an anti-emetic. Leaves with turmeric (*Curcuma longa*) ground in to fine paste applied for skin diseases.
Achyranthes aspera L. / Amaranthaceae/ Agahada / Throughout the year. (NAW-1362) 03-09-14	N-21^0.28.273_ E-077^{0}24.267 667m	H	1	14	0.27	Roots	Root ash with honey used medicinally to relieve cough. Root extract used for normal delivery.
Aegle marmelos (L.) Correa / Rutaceae Bela / Fls.: May June; Frts: Oct.–Nov. (NAW-1363) 22-03-15	N-21^0.28.296_ E-077^{0}24.291 667m	T	3	20	0.39	Stem Leaves Fruits	Stem bark ground with black pepper (*Piper nigrum*) and the filtered extract administered for cholera (2 spoonful s thrice a day for 3 days) Extract from stem bark ground with *Saccharum officinarum* administered for chest pain (5 spoonfuls thrice a day for 2 days). Leaf juice poured in to paste and applied on head and also taken internally for cooling the body. Fruits edible use medicinally in gastric disorder.
Asparagus racemosus Willd. / Liliaceae/ Shatavari. / Fls, & frts. : Oct .- Dec./ (VBMV-1739) 03-09-14	N-21^0.28.815_ E-077^{0}23.931 634m	H	3	15	0.29	Tuber	Tuber crush with turmeric (*Curcuma longa*) and the filtrate administered for chest pain and stomach pain (2 spoonfuls twice for three days). Also tuber chewed to stop dehydration.

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Bauhinia racemosa Lam. / Caesalpinaceae /Bhusa / Fls .: Apr – June ; Frts, : Nov - Jan. (NAW-1364) 22-03-15	N-21^0.28.827_ E-077^{0}23.034 628m	T	3	12	0.23	Roots Stem Leaf	Root bark crushed and the filtrate administered for diarrhea by 5 spoonfuls twice a day for 5 days. Stem bark crushed and filter mixed with goats milk administered orally for epilepsy by kurku. Tender leaf juice poured in to eyes (2drops) for ophthalmic infections and tender leaves and fruits used as vegetable.
Bauhinia vahlii Wight & Arn. / Caesalpinaceae Mahul / Fls: June - Aug ; Frts: Dec - Jan./ (NAW-1365) 11-12-16	N-21^0.28.300_ E-077^{0}24.195 699m	T	2	16	0.31	Stem Fruits	Decoction of bark is used to treat jaundice. Fruits are used as vegetable or eaten raw and used to cure infertility.
Bombax ceiba L. / Bombacaceae Katasavar / Fls: Feb; Frts: Mar. (NAW-1366) 11-12-16	N-21^0.28.447_ E-077^{0}23.954 685m	T	4	13	0.25	Root Stem bark	Root bark crushed with garlic (*Allium sativum*) and the extract administered (Spoonfuls once a day for 5 days after menstruation) for menstrual disorders. Stem bark ground with urine of infant and paste mildly heated and applied on blisters and ulcers.
Buchanania lanzan Spreng./ Anacardiaceae Charodi / Fls: Jan - Feb; Frts.: Apr- May (NAW-1367) 24-03-15	N-21^0.28.423_ E-077^{0}23.848 677m	T	4	8	0.15	Stem bark	Stem bark ground with soaked rice (*Oryza sativa*) and the filtrate administered for chest pain by kurku 2 spoonful twice a days for 5 days. Stem bark paste mixed with castor oil (*Ricinus communis*) and applied on boils and ulcers.
*Butea monosperma (*Lam.) Taub. / Papilionaceae Palas / Fls & Frts.: Feb - Mar./ (NAW-1368) 24-12-16	N-21^0.28.818_ E-077^{0}23.996 629m	T	1	24	0.47	Stem bark	Stem bark crushed with oil (*Sesamum indicum*) and the filtrate administered for antifertility (One spoonful twice a day for 7 days after menstruation).

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Cayratia auriculata (Roxb.) Gamble / Vitaceae Kumbli / Fls.& Frts.: Sep-Nov./ (VBMV-1740) 24-11-16	N-21^0.28.837_ E-077^{0}23.082 624m	H	2	16	0.31	Leaves	Leaves ground with turmeric (*Curcuma longa*) and the paste applied externally for chicken pox and is also used to feed domestic cattle.
Chlorophytum tuberosum (Roxb.) Baker Liliaceae/ Musli / Fls.: June & frts.: Sep (VBMV-1523) 03-09-14	N-21^0.28.900_ E-077^{0}23.187 622m	H	4	16	0.31	Tubers Leaves	Tubers collected by tribal people and are good demand from traders as they are sweet in taste and also used against indigestion. Leaves used as vegetable.
Cissampelos pareira L./ Menispermaceae Pahadmul / Fls.: Aug-Oct; Frts.: Oct. Nov. (VBMV-1488) 20-11-16	N-21^0.28.455_ E-077^{0}23.848 685m	C	3	12	0.23	Tubers Leaves	Tuber extract mixed with a pinch of salt administered for chest pain and stomach pain. 2 spoonfuls thrice a day till cure. Leaves crushed with that of *Andrographis paniculata* and *Pongamia pinnata* and the extract given orally to kill intestinal worms (3 spoonfuls thrice a day for 3days).
Costus speciosus (J. Koenig) Sm. / Zingiberaceae/Jangli adrak / Fls: Aug; Frts: Nov./ (VBMV-1742) 04-09-14	N-21^0.28.489_ E-077^{0}23.824 685m	H	3	15	0.29	Rhizome	Rhizome ground with *Pennisetum americanum* (bajra) and formulated as tablets (eaten continuously for almost 21 days) for muscular rheumatism (waat).
Curcuma pseudomontana J. Graham / Zingiberaceae Kuksuma root / Fls & Frts. July-Aug. (VBMV-1028) 22-05-14	N-21^0.28.507_ E-077^{0}23.811 685m	H	3	10	0.19	Roots Tubers	Root powder one spoonful twice a day with milk use in tuberculosis (T.B). Tuber extract administered for jaundice (2 spoonfuls twice a day till cure). Warm tuber paste applied on body swelling and on head for cooling effect. Boiled tubers ground with a pinch of salt and given orally for increased lactation.
Dendrocalamus strictus (Roxb.) Nees / Poaceae/ Katbans / Flower not seen. (VBMV-1034) 04-05-14	N-21^0.28.893_ E-077^{0}23.152 627m	T	1	18	0.35	Leaves Grains	Tender leaves boiled, cooled and tied over the eyes for sores. Tender sprouts used as vegetable. Grains boiled and eaten.

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Desmodium gangeticum (L.) DC. / Papilionaceae Chikum ghass / Fls & Frts: Oct- Nov./ (VBMV-1746) 24-11-16	N-21^0.28.886_ E-077^{0}23.286 632m	H	3	12	0.23	Roots	Roots ground with garlic (*Allium sativum*) and made in to pills and administered for epilepsy by korku 2-3 pills twice a day till cure.
Dioscorea hispida Dennst. / Dioscoreaceae/ Baichan / Fls & Frts.: Sep. Nov. (NAW-1296) 20-11-16	N-21^0.28.892_ E-077^{0}23.247 630m	H	2	14	0.27	Tubers	Tubers kept in running water for a day and boiled with the leaves of tamarind and water filtered then cooked and eaten.
Cassia fistula L. / Caesalpinaceae Amaltas / Fls.: May – Aug; Frts.: Oct - Feb. (VBMV-1366) 20-11-16	N-21^0.28.524_ E-077^{0}23.785 659m	T	1	22	0.43	Stem Leaves	Tender leaves cooked with juice of tamarind eaten as vegetable and also used as a purgative. Stem bark pieces tied together and worn as necklace for malarial fever. Tender leaves ground with turmeric and this paste is applied for skin diseases.
Cassia obtusifolia L. / Caesalpinaceae/ Tarota / Fls, & Frts. : Aug.- Nov. (VBMV-1365) 22-11-16	N-21^0.28.497_ E-077^{0}23.661 654m	S	3	8	0.15	Whole Leaves	Whole plants crushed and the extract administered for epilepsy (two spoonfuls once a day for 15 days). The leaf paste applied for cuts, wounds and scorpion stings. Tender leaves used as vegetable.
Clerodendrum serratum (L.) Moon / Verbenaceae Bharanga / Fls-Frts.: Sep.- Dec (NAW-1531) 09-05-14	N-21^0.28.902_ E-077^{0}23.352 648m	S	2	9	0.17	Roots	Roots crushed with that of *Rauwolfia serpentina* and the filtrate administered for fever stomach pain and menstrual disorders (3 spoonfuls once a days for 5 days).
Colebrookea oppositifolia Sm./ Lamiaceae Bhaman / Fls. & Frts.: Dec.- Mar. (NAW-1369) 22-12-16	N-21^0.28.898_ E-077^{0}23.415 657m	S	2	18	0.35	Stem bark Infloresence	Stem bark crushed and the filtrate administered for giddiness (2 spoonfuls twice a day for 3 days). The dried inflorescence used in sorcery.

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Curculigo orchioides Gaertn. / Amaryllidaceae Kali musli / Fls. & Frts: June – Sep (VBMV-1750) 22-05-14	N-21^0.28.898_ E-077^{0}23.415 657m	H	3	8	0.15	Tuber	Tuber extract administered for asthma and piles and extract administered for asthma and piles (2 spoonfuls twice a day till cure) and the paste applied on cuts. Raw tuber eaten for dysentery.
Euphorbia hirta L. / Euphorbiaceae/ Dhodhi / Fls. & Frts: Throughout Year/ (NAW-1370) 09-11-15	N-21^0.28.596_ E-077^{0}23.593 646m	H	1	26	0.50	Leaves Latex	Tender leaf extract mixed with sugar administered for dysentery (2 -3 spoonfuls thrice a day). Latex applied on cuts by kurku.
Ficus benghalensis L./ Moraceae/ Wad / Fls.: Feb - June; Frts: Nov.- Jan. (NAW-1107) 08-11-15	N-21^0.28.574_ E-077^{0}23.588 675m	T	2	6	0.11	Latex	Latex applied for breast ulcer.
Ficus religiosa L./ Moraceae/ Piple / Receptacle: Feb –May. (NAW-1108) 08-11-15	N-21^0.28.447_ E-077^{0}23.954 685m	T	2	27	0.52	Stem bark	Stem bark extract mixed with buttermilk administered for paralysis (3 spoonfuls twice a day for 30 days). Branches used in festivals and religious ceremonies.
Adina cordifolia (Roxb.) Hook. f. / Rubiaceae/Haldu / Fls : June-July; Frts. : Feb.-May. (NAW-1373) 22-12-16	N-21^0.28.895_ E-077^{0}23.462 655m	T	2	15	0.29	Root Stem	Root and Stem bark extract mixed with oil of *Sesasum indicum* administered for antifertility (2 spoonfuls thrice a day for 9 days after menstruation).
Hemidesmus indicus (L.) R. Br. Ex Schult. / Periplocaceae Dhodhkadi / Fls . & Frts.: Sep.-Jan. (VBMV-1120) 09-05-14	N-21^0.28.846_ E-077^{0}23.641 675m	H	2	24	0.47	Roots	Roots crushed with garlic (*Allium sativum*) and the extract administered for menstrual disorders (2 spoonfuls twice a day for 5 days). Root powder along with goat milk given orally for impotency and also to tone the health (3-4 spoonfuls once a day for 30 days). Root powder with garlic administered orally as lactagogue.

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Holarrhena antidysenterica (Roth) Wall. ex. A. DC. / Apocynaceae Kudda. / Fls.: Apr - July; Frts.: Nov. - Feb. (NAW-1564) 04-05-14	N-21^0.28.888_ E-077^{0}23.573 660m	T	3	12	0.23	Root Stem Latex	Root bark ground with the roots of *Hemidesmus indicus* and the paste made twice a day till cure. Stem bark ground with black pepper and the paste made into pills administered for cough (1-2 pills twice a day for 3 days). Latex applied on cuts.
Lagerstroemia parviflora Roxb. / Lythraceae Landiya / Fls . : Apr.-May; Frts. : Dec.- Jan. (NAW-1142) 08-11-15	N-21^0.28.617_ E-077^{0}23.561 637m	T	2	18	0.35	Leaves	Leaves crushed with that of *Magnifera indica* and *Syzygium cumini* and the filtrate administered for stomach pain. Wood also used for making agricultural implements and house construction.
Lannea coromandelica (Houtt.) Merr. / Anacardiaceae Moin / Fls . : Feb. – Apr.; Frts. : May. - June. (VBMV-1330) 07-01-17	N-21^0.28.607_ E-077^{0}23.459 645m	T	3	16	0.31	Stem bark	Stem bark decoction administered for chest pain gastric trouble and muscle pain (1 spoonful twice a day till cure). Stem bark paste or gum applied on cuts and wounds also used for head ache.
Leea macrophylla Roxb. ex Hornem. / Leeaceae Hattikand / Fls. & Frts. : Oct.-Dec. (VBMV-1156) 09-05-14	N-21^0.28.820_ E-077^{0}23.687 683m	H	3	14	0.27	Root bark Ste	Root bark extract administered orally for stiff joint and rheumatic pains by 2 spoonfuls once a day till cure. Stem bark paste mixed with castor oil mildly heated and applied on cuts and wounds.
Madhuca indica J.F. Gmel. / Sapotaceae Moha / Fls. : Feb.-Mar ; Frts. : June-July. (VBMV-1226) 09-05-14	N-21^0.28.742_ E-077^{0}23.752 707m	T	2	18	0.35	Roots	Root paste applied on abscess boils. Seed cooked and eaten.
Martynia annua L. / Martyniaceae Moha / Fls. & Frts. : Sep.-Nov. (VBMV-1199) 11-12-16	N-21^0.28.710_ E-077^{0}23.797 711m	H	2	12	0.23	Roots Leaves	Roots decoction administered orally for bronchitis by Chenchus. Leaf paste applied over head for cooling effect and headache.

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Miliusa tomentosa (Roxb.) J. Sinclair / Annonaceae Humba / Fls. : May-June; Frts. : June - July. (VBMV-1200) 22-11-16	N-21^0.28.497_ E-077^{0}23.661 659m	T	3	16	0.31	Fruits	Fruits edible and Wood also used for making agricultural implements and for house construction.
Mitragyna parviflora (Roxb.) Korth. / Rubiaceae Kalam / Fls . :May.- June; Frts. : Mar.-Apr. (NAW-1203) 07-01-17	N-21^0.28.902_ E-077^{0}23.352 648m	T	2	14	0.27	Stem Leaves	Stem bark crushed with that of *Haldina cordifolia* and the extract administered for peptic ulcers (2 spoonfuls twice a day for 3 days). Stem bark extract missed with jaggery given orally for dysentery (2 spoonfuls twice a day, till cure). Leaf juice poured into eyes for jaundice.
Sida cordata (Burm. f.) Borss. Waalk. / Malvaceae Bhumi / Fls . & Frts. : Aug.- Jan. (VBMV-1146) 24-11-16	N-21^0.28.617_ E-077^{0}23.561 637m	H	2	13	0.25	Leaves	Leaf juice mixed with goats milk administered for paralysis (2 spoonful twice a day till cure). Leaf paste applied for scorpion sting.
Sterculia urens Roxb. / Sterculiaceae Sardol / Fls.: Dec. - Feb; Frts.: Mar. - Apr. (NAW-1376) 03-09-14	N-21^0.28.693_ E-077^{0}23.810 700m	T	3	24	0.47	Stem Gum	Stem bark ground with turmeric, the filtrate mildly heated, and administered for rheumatic pains and peptic ulcers (2 spoonfuls twice a day for 5 days). Gum dissolved in water given orally for cooling the body and also to cure dysentery.
Syzygium cumini (L.) Skeels / Myrtaceae Jamun / Fls . : Apr. – June;Frts. : July.- Aug. (VBMV-1108) 04-05-14	N-21^0.28.632_ E-077^{0}23.867 697m	T	2	34	0.66	Stem Fruits	Stem bark extract administered for leucorrhoea and also for cough (2 spoonfuls twice a day for 5 days). Stem bark ash mixed with niger oil and applied over burns and wounds. Crushed stem bark used as fish-poison. Fruits edible.
Syzygium heyneanum (Duthie) Gamble / Myrtaceae/ Jamon / Fls. : Apr. – June & Frts. : July.-Aug/ (NAW-1344) 04-05-14	N-21^0.28.898_ E-077^{0}23.415 657m	T	3	13	0.25	Fruits	Fruits powder used to control diabetes.

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Terminalia chebula Retz. / Combretaceae Hirda / Fls. :Mar. – May Frts.: May.-June. (NAW-1377) 07-01-17	N-21^0.28.895_ E-077^{0}23.462 655m	T	3	14	0.27	Stem Fruits	Fruits ground with the latex of *Ficus racemosa* and the paste applied over for muscle pain and rheumatic pain. Fruit paste mixed with breast milk, administered orally to infants for cough, and also applied on wounds. Crushed stem bark and fruits used as fish-poison.
Wrightia tinctoria R. Br. / Apocynaceae Dodhi / Fls . :Mar.-May; Frts : Oct.-Feb. (NAW-1124) 07-05-14	N-21^0.28.908_ E-077^{0}23.513 655m	T	2	16	0.31	Latex	Latex applied on cuts and also 3-5 drops for preparing instant curd. Bark fiber used for making cordage.
Woodfordia fruticosa (L.) Kurz / Lythraceae Dhin / Fls. : Jan.-Apr & Frts. : Apr.- May (NAW-1378) 07-11-15	N-21^0.28.593_ E-077^{0}23.897 701m	T	3	12	0.23	Stem Leaves	Dried stem bark added to toddy to enhance taste and intoxication. Leaves crushed and mildly heated, gently massaged for rheumatic pain. Leaves boiled in water and taken bath for body pains.
Zizipus xylopyrus (Retz.) Willd. / Rhamnaceae Gorgot / Fls.: Apr. - June & Frts.: Dec. - Jan. (NAW-1286) 07-01-17	N-21^0.28.508_ E-077^{0}23.891 697m	T	2	18	0.35	Stem Fruits	Stem bark paste made into pills and administered orally for cholera by taking 2 pills thrice a day for 2 days. Fruits edible.
Ensete superbum (Roxb.) Cheesman / Musaceae Jangli kela / Fls . & Frts. : Oct. - Jan. (NAW-1287) 04-05-14	N-21^0.28.428_ E-077^{0}23.926 689m	H	3	12	0.23	Roots Fruits	Root powder mix with curd and crystal sugar (1 glass daily) for menstruation problems. Fruits and pithy inner part of stem eaten by local people.
Anisochilus carnosus (L.f.) Wall. / Lamiaceae Chikhal ghass / Fls . & Frts. : Sep.-Nov (NAW-1690) 07-01-17	N-21^0.28.466_ E-077^{0}23.691 692m	H	2	16	0.31	Inflorescence	Inflorescences burnt in a plate and the ash mixed with coconut oil is applied to boils and pimples.
Zizyphus mauritiana Lam. / Rhamnaceae Bor / Fls.: Dec. - Feb & Frts. : Feb. - Apr.	N-21^0.28.632_ E-077^{0}23.513	T	2	14	0.27	Fruits	Tender fruits crushed and the extract administered for diarrhea (2 spoonfuls twice a day for 5 days) and fruit paste applied on head

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(NAW-1379) 07-01-17							for cooling effect. Fruits edible.
Emblica officinalis Gaertn. / Euphorbiaceae Aola / Fls.: Feb. - Mar & Frts.: Oct. - Dec. (VBMV-1092) 22-11-15	N-21^0.28.461_ E-077^{0}23.958 691m	T	2	22	0.43	Leaves Fruits	Fruits pickled by korku tribals. Leaf ash mixed with oil applied to burnt skin which prevents black scar formation.
Cyathocline lutea law ex Wight / Asteraceae Piwali Gangawan / Fls &Frts: Feb. – April (NAW/-1380) 04-05-14	N-21^0.28.818_ E-077^{0}23.996 629m	H	4	9	0.17	Roots Whole	Root decoctions are used to relieve stomach pains. Crushed plant is applied on wounds as antimicrobial. Decoctions of whole plant are used as anti-helminthic.

Life Form (Habit of plant): H= Herb; S= Shrub; T= Tree; C= Climber

Abundance: 1 = very common; 2 = common; 3 = uncommon; 4 = rare; 5 = very rare

FC: Frequency Citation

RFC: Relative Frequency Citation

Table No. 2: Definitions of Abundance categories

Value	Category	Definition
1	Very common	Easy to find close to all houses
2	Common	Close to houses, but not always all houses
3	Uncommon	Close to few houses, but very scarce in the natural environment
4	Rare	Hard to find in valleys (inhabited area)
5	Very rare	Hard to find at the scale of the valley

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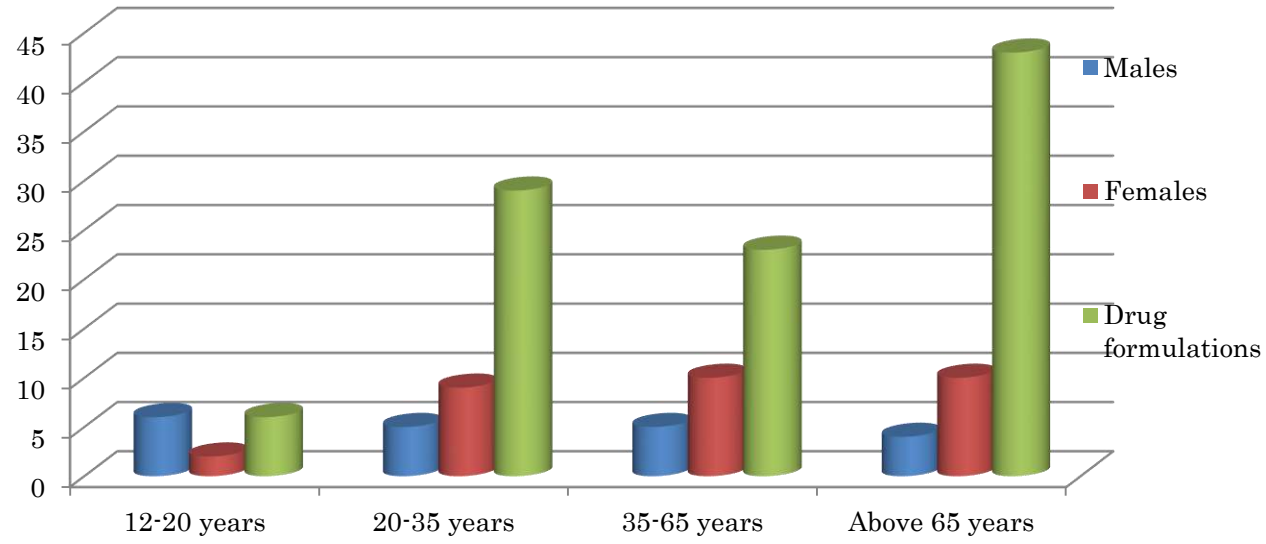


Figure 4: Distribution of gender, age groups and drug formulations of the interviewed informants

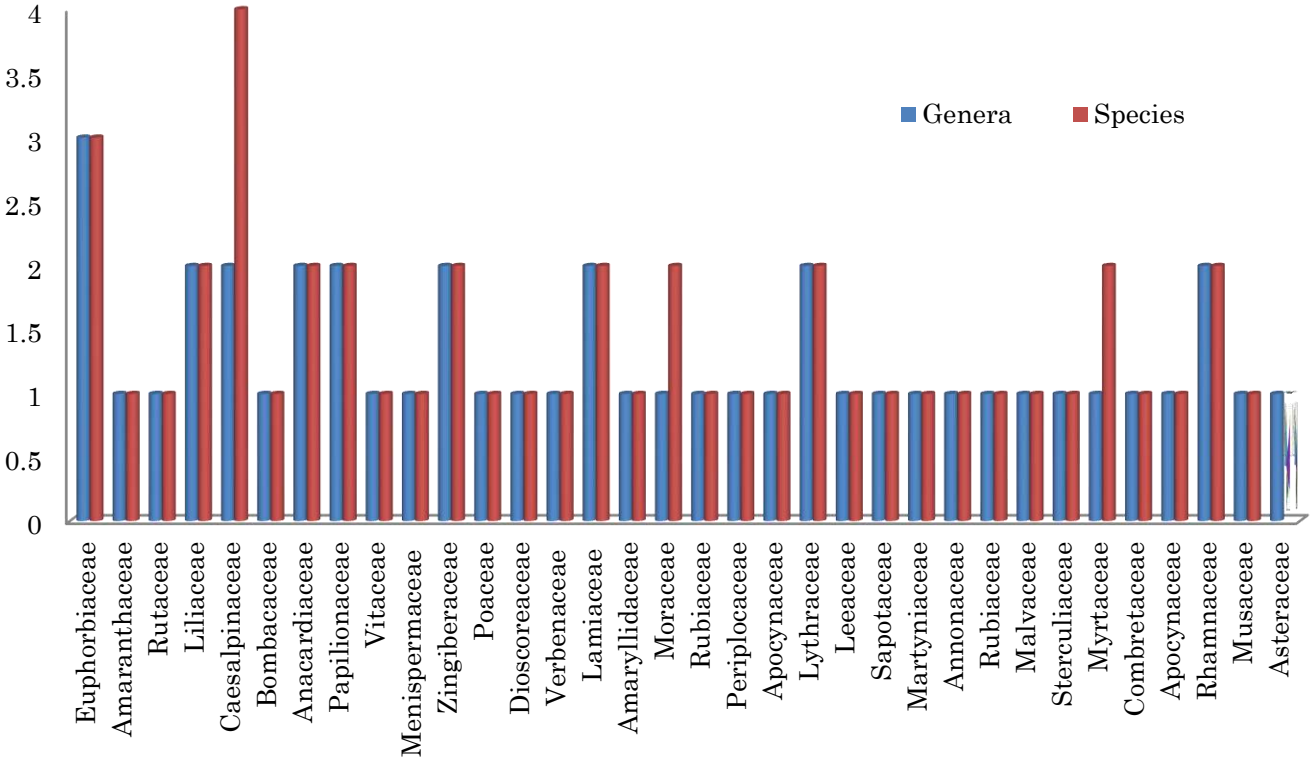


Figure 5 : Familes with their respective genera and species studied

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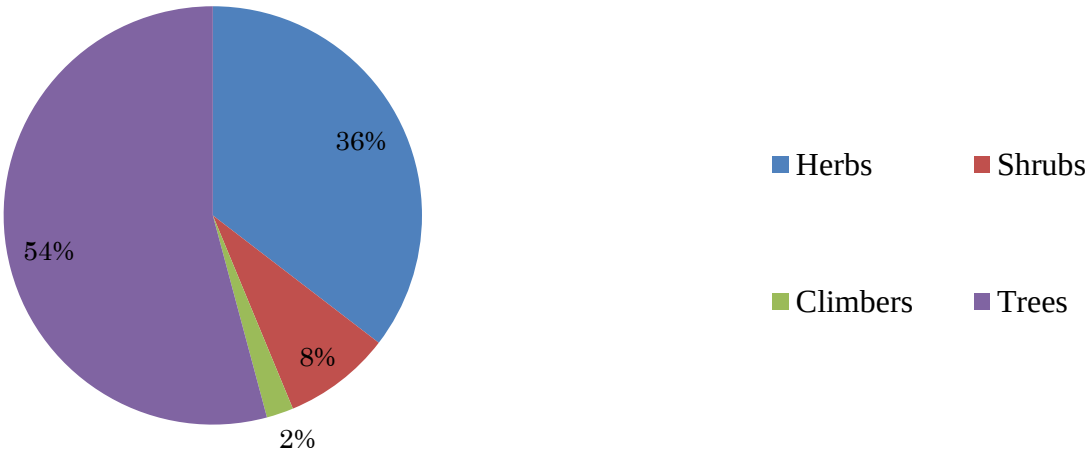


Figure 6 : Life form representation of medicinal plants

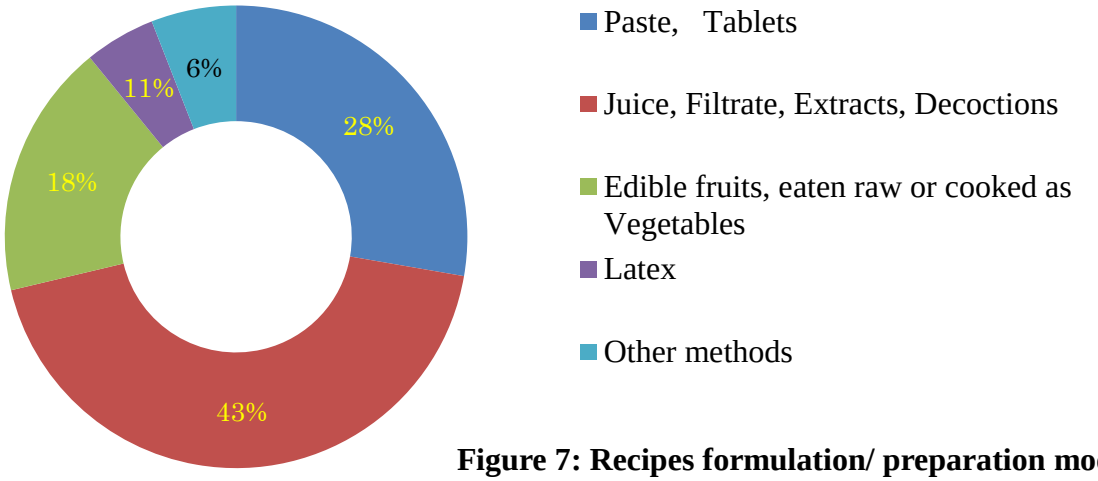


Figure 7: Recipes formulation/ preparation mode

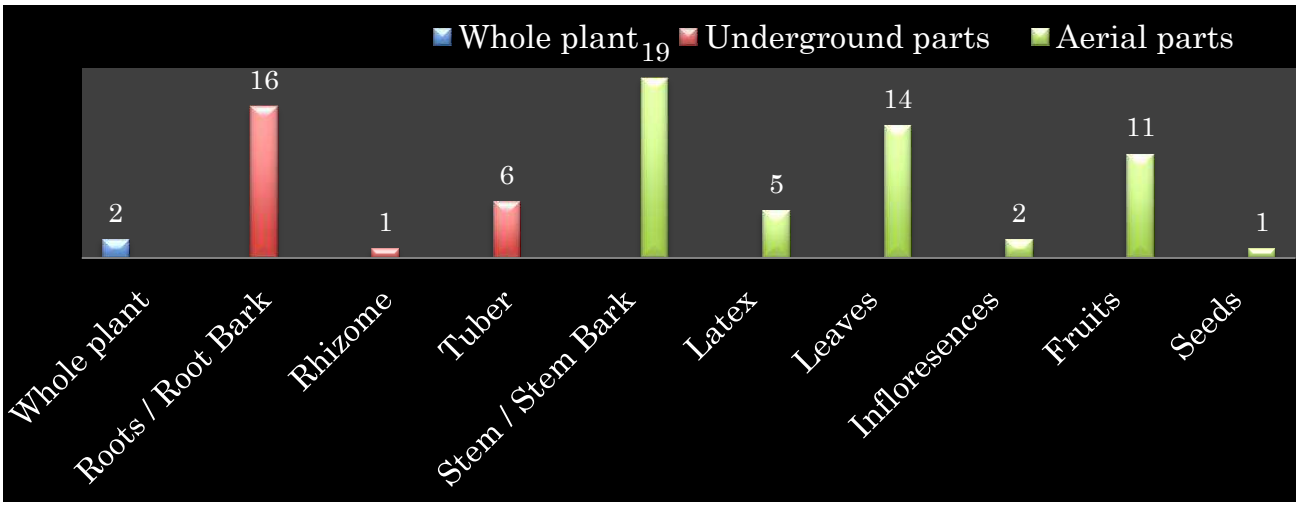


Figure 8: Plant parts used for Herbal drug preparation and Utilization

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Photoplate 1



Photoplate 1 showing various pictures of authors taken during the collection and interviewing of the persons of the korku tribe.

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Photoplate 2



Bahaunia vahilli



Chlorophytum tuberosum



Clerodendrum serratum



Costus speciosus



Curcilago orchoides



Curcuma pseudomontana

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Photoplate 3



Leae microphylla



Dioscorea bulbifera



Sterculi urens



Wrightia tinctoria



Cyathocline lutea



Butea monosperma

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4. CONCLUSION

This study contributed to the establishment of an inventory of plant based medicines used by korku tribe inhabited in Chikhaldara of Melghat Tiger Reserve, Amravati, Maharashtra, India. A total of 51 inhabitants were interviewed during the survey to document the indigenous knowledge about the use of wildly growing medicinal plants. The paper summarizes a adata of 48 plant species used to treat 101 common ailments. RFC values ranked *Syzygium cumini; Ficus religiosa, Euphorbia hirta, Butea monosperma* as top most cited and well known species in the area. A vast number of ailments were cured by this community with the help of these locally growing medicinal plants. The data provided by informants of the korku tribe clearly shows that they are still dependent on the indigenous knowledge of medicinal plants. This novel information has provided rich ethnopharmacological knowledge that will provide basis for new avenues in future for the pharmacological screening of novel natural compounds which can be used to improve healthcare systems. However, detailed pharmacological investigations must be carried out to improve the use of these medicinal plants globally. The study has also provided good information regarding the used plant parts, formulation and dosage which can be used as medicine. It will also provide various socioeconomic dimensions associated with the common people.

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Authors are sincerely thankful to the knowledgeable and experienced persons of korku tribe (especially Mama) of the study area whom we consulted most during the course of field observations and as well as his cooperative help in interviewing different persons within the tribe. Authors are also thankful to Retired Professor S.P. Rothe (Ex-Head, Department of Botany, Shri Shivaji Science College, Akola) for his help in identification and authentication of several plant species. Authors are also thankful to Dr. V.R. Deshmukh (Ex-Head Department of Botany, Vidyabharati Mahavidyalya College, Amravati) for providing lab facilities and library facilities during this study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests with any author, agency or institution. And no funding was provided by any agency, institution or any individual.

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Cytotoxic Properties of *Curcuma inodora* Blatt. Leaf Against (Miapaca-2) Human Pancreatic Carcinoma Cell Line

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Abstract:

In the present study cytotoxic effect of Curcuma inodora Blatt. aqueous extract of leaf was evaluated on human pancreatic carcinoma cell lines (MiaPaca-2). MiaPaca-2cells were cultured in a DMEM medium and incubated with different concentrations (10, 20, 30, 40 and 50µg/ml)of aqueous extract of Curcuma inodora leaf for 48 hrs. with standard positive control chemotherapeutic agent viz. 5-Flurouracil.Cell viability was assessed by MTT assay.Cell proliferation was measured using a calorimetric method based on the ability of metabolic active cells to cleave the yellow tetrazolium salt MTT to an insoluble purple formazan crystal. The soluble formazan dye was directly quantified using ELISA plate reader. The aqueous extract of Curcuma inodora leaf decreases the viability in malignant cells in a dose dependent manner. The IC_{50} value in MiaPaca-2 cells was determined as 115.29 ± 17.01µg/ml. It may be concluded that Curcuma inodora can cause cell death inMiaPaca-2 cells which can be considered as a promising chemotherapeutic agent in pancreatic cancer treatment.

Keywords: *Curcuma inodora*, leaf, Cytotoxicity, Pancreatic cancer cells, MTT assay, 5-Flurouracil.

Introduction:

In the modern world it has been realized the herbal drugs strengthen the body system specifically and selectively without side effects. The importance of traditional herbal medicinal system has now gained vital importance in developed and underdeveloped countries. India is blessed with rich and diverse heritage of cultural traditions. These traditions are associated with use of wild plants as medicinal herbs.The wild plants offer a good material for studying the phytochemical compounds responsible for curative properties of the plants. In the developing nations, numerous types of wild plants are exploited as a source of food and hence provide an adequate level of nutrition to the inhabitants (Borkataky *et al*., 2013).

Cancer has been thought to be a preventable disease due to its slow development and progression, taking many years to become invasive in a step by- step manner (Yao *et al*., 2011). Such property provides a great opportunity not only for early detection but also for prevention of the disease progression. Over the past several decades, there has been a particular interest in the role of medicinal plant extracts in cancer prevention. Plants are rich sources of chemically diverse compounds, many with beneficial properties to human health. Consequently, about 50% of the anticancer therapeutic agents known are derived from plants (Balunas and Kinghorn, 2005). Chemical compounds were extracted from plant origin such as Taxol and Vinca alkaloids acts to destabilize the microtubules of cancer cells, preventing the rapid proliferation of tumors (Prasain and Barnus, 2007).

Pancreatic cancer (PC) is a highly aggressive human malignancy worldwide with an extremely poor prognosis (Siegel *et al*., 2016). For the majority of the PC patients, the only therapeutic promise is cytostatic treatment using standard chemotherapeutic drugs such as gemcitabine and 5-FU (5-fluorouracil) or their combination (Michl and Gress, 2013). However, the median survival time of PC patients is only about six months mostly due to an almost

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complete chemotherapy resistance, and the dismal 5-year survival is currently approximately 2% (Ramfidis *et al*.,2014) Therefore, there is a dire need for both new biomarkers with prognostic and predictive value and newer therapeutic options for this disease. MIA PaCa-2 cell line is a primary tumor currently used in vitro models to study pancreatic carcinogenesis. Natural compounds provided many effective anticancer agents in current use.

Curcuma inodora Blatt. belongs to family-Zingiberaceae, commonly known as scentless turmeric. Traditionally, it is used in the treatment of muscular pain, psychosomatic disorders and constipation. Scentless turmeric is used by the tribal as a hair tonic and to cure wound. Curcuma is the widely used Rasayana in the field of Ayurvedic medicine. Curcumin (diferuloylmethane) is a polyphenol derived from the *Curcuma longa* plant, has several pharmacologic properties under both pre-clinical and clinical conditions (Prasad *et al*., 2014).Tribal uses of *Curcuma inodora* gives an importance to this plant to scientific community and no scientific literature is available to explore the use of anticancer effect of *Curcuma inodora*. Hence, present study was attempted to evaluate the cytotoxic properties of aqueous extract of *Curcuma inodora* leaf in the inhibition of cell proliferation by using MTT assay.

Materials And Methods

Materials

Selection and Collection of Plant: The leaves of *Curcuma inodora* were collected from Melghat region of Amravati District in the month of June to September.



Curcuma inodora Habitat

Identification and Authentication of plants:

The plant was identified with the help of standard floras (Sharma et al., 1996; Dhore, 2002) and authenticated by Taxonomist Dr. S.P.Rothe Professor and Head Department of Botany, Shri. Shivaji Science College, Akola.

Preparation of test solution:

1 gm powder of leaf part was crushed in mortar and pestle by adding 10 ml. DW, then centrifuge at 4000 rpm for 10 min. Concentrations (10-50 µg/ml) were prepared by using supernatant accordingly.

In-vitro Cytotoxic Activity Assay

Cell Line and Culture Medium:

The Human Pancreatic Carcinoma cell (MiaPaCa-2) was procured from the National Centre for Cell Sciences (NCCS), Pune, and Maharashtra. These cells were grown in Dulbecco's Minimum Essential Medium (DMEM) (GIBCO by Life Technologies) which contained, 1.5 g/L sodium bicarbonate,10% fetal bovine serum (GIBCO by Life Technologies) and 1X Antibiotic-Antimycotic solutions (Invitrogen). All cells were maintained at 37°C, 5% CO_2, in a 90% humidified atmosphere in CO_2 incubator (Galaxy Make) Cells were passed after every 5th days. Cells were used in experiments during the linear phase of growth (fig.3.1) and all experiments were carried out in 96 well tissue culture plates. The cytotoxic activity was measured using MTT

(3-(4,5dimethylthiazol- 2-yl)-2,5-diphenyltetrazolium bromide) assay [Berridge MV]. Briefly, 2 X 10^4cells/well were seeded in 96-well microliter plates.

Cell Treatment Procedure

Cells were treated with various working concentrations (10-50 µg/ml) of aqueous extract of leaf and standard anticancer drug i.e. 5-Fluorouracil (5-FU) (10-50 µg/ml) for 48 hours. At the end of incubation period, the medium was replaced by 150µl fresh medium and 50 µl MTT (1mg/mL) was added to each well, followed by an incubation period for a further 4 hours at 37°C. Later, 150 µl of DMSO was added to each well for solubilization of the formazan products. Absorbance was taken at 630 nm using a Bio-Tek microplate reader. The percent cell cytotoxicity was calculated by using the following formula.

$$\% \text{ Cytotoxity} = \frac{(\text{Absorbance of control sample} - \text{Absorbance of treated sample})}{\text{Absorbance of control sample}} X\,100$$

Statistical Analysis

The results are presented as means ± SD of three independent experiments. Statistical differences among means were determined by one way ANOVA. Differences were considered significant at $P<0.05$. The IC_{50} values were calculated using Graph Pad Prism 5.0 (Graph Pad Software Inc., San Diego, CA). Every experiment included a set of negative controls (untreated cultures) and positive control treated with 5-Flurouracil (Standard anticancer drug).

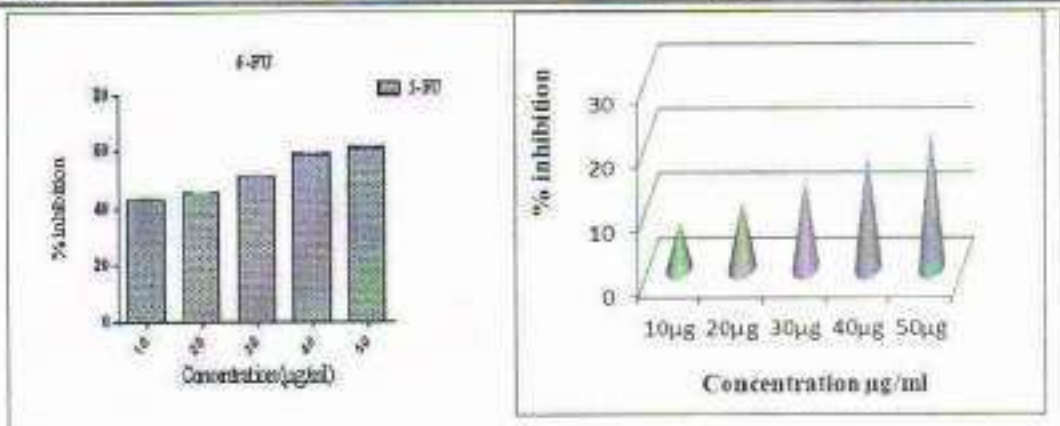
Results And Discussions:

The results for cell growth inhibition by aqueous extracts of the leaf against MIAPaCa-2 cell lines at 10-50µg/ml concentrations is shown in Table 1 and graphically represented in Fig. 1. The aqueous extract of Curcuma inodora leaf was tested in vitro for its potential human cancer cell growth inhibitory effect on MIAPaCa-2 cancer cell line using MTT assay, a non radioactive, fast and economical assay widely used to quantify cell viability and proliferation. In the present study MIA paca-2 cells showed growth inhibition in a dose dependent manner when treated with aqueous extract at concentrations ranging from 10-50µg/ml (Table 1 & Fig.1). The percentage of dead cells for each concentration was found to be 7.14, 10.23, 13.80, 17.85 and 21.66. The 50% cytotoxic effect (IC_{50}) of aqueous extract of Curcuma inodora leaf was found to be 115.29± 17.01µg/ml. The IC_{50} for the 5-FU standard control was found to be 25.9 ±0.68µg/ml.

Table 1: Effect of aqueous extract of Curcuma inodora leaf on growth of MIAPaCa-2 cell line after the incubation for 48 hrs.

*Results are represented as an average of three± replicates[**AQ**-Aqueous extract; 5-FU- 5-Flurouracil]

Conc. (µg/ml)	% inhibition	
	AQ	5-FU
Control	0	0
10	7.14 ± 0.71	43.02 ±1.00
20	10.23 ± 1.79	45.78 ± 0.10
30	13.80 ± 1.09	51.02 ± 0.36
40	17.85 ± 1.88	59.37 ± 0.72
50	21.66 ± 0.82	61.07 ± 0.52
IC_{50}	**115.29 ± 17.01**	**25.9 ± 0.68**



A B

Fig. 1: Cytotoxic effect of aqueous extracts of *Curcuma inodora* leaf on growth of MIAPaCa-2 cells after the incubation for 48 hrs. using MTT assay. (A) 5-FU as standard (positive control) and (B) % inhibition of CU-L extract. Data are represented by mean ± SD (n=3). Statistical significance between untreated and treated cells was determined using one-way ANOVA where $p < 0.05$ verses untreated control cells.[AQ-Aqueous extract; 5-FU- 5-Flurouracil]

The cytotoxicity assay is based on the capacity of mitochondria succinate dehydrogenase enzymes in living cells to reduce the yellow water soluble substrate tetrazolium salt 3-(4,5 dimethyl thiazol-2-yl)-2-5-diphenyl tetrazolium bromide (MTT) into a blue colored i.e. formazan crystals which is measured spectrophotometrically (Masters, 2000; Mosmann, 1983). Since reduction of MTT can only occur in metabolically active cells, the level of activity is a measure of the viability of the cells. The number of cells was found to be proportional to the extent of formazan production by the cells used (Francis and Rita, 1986).In the last few decades, human cancer cell lines have aggregated an accessible, easily usable set of biological model to examine cancer biology (Green, 2003). The utility of cell lines acquired from tumor allows the investigation of tumor cells in a simplified and controlled environment (Arya *et al.*, 2011).

MTT proliferation assay was carried out to determine the growth rate of cells. In this study, the aqueous extract of *Curcuma inodora* leaf has indicated significant growth inhibition on Miapaca-2 cell line. The aqueous extract treatment on Miapaca-2 cells lines showed significant decrease in growth rate compared with control. The qualitative phytochemical analysis of aqueous extract of *Curcuma inodora* leaf detected the presence of carbohydrate and glycosides, protein and amino acids, alkaloids, phenolic compounds & flavonoids, phytosterols, saponins and terpenoids (Ghurde, 2018) which could be responsible for this activity. Flavonoids have been found to possess antimutagenic and anti-malignant effects (Masmaan, 1983). Moreover it has protective effect against cancer by their effect on signal transduction in cell proliferation and angiogenesis.

Conclusion:

The present study revealed that the aqueous extract of *Curcuma inodora* Blatt. leaf was found to be cytotoxic towards human pancreatic cancer cell line in MTT assay. The 50% cytotoxic effect (IC_{50}) of aqueous extract of Curcuma inodora leaf was found to be 115.29 ± 17.01µg/mlmay be due to thebioactive compounds. Hence present study shows the positive

efficacy of Curcuma inodora leaf for cytotoxicity towards MIA PaCa-2 cells thus suggesting the potentialtherapeutic agent in pancreatic cancer treatment in future after animal experimentation.

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Research Article

METAPHORICAL EFFECTS OF ORGANOPESTICIDES CARBENDEZIM AND MALATHION ON THE GROWTH AND PHYSIOLOGICAL ACTIVITIES OF CYANOBACTERIA *NOSTOC COMMUNE*, VAUCHER INHABITING THE RICE FIELD OF BHANDARA DISTRICT (M.S.)

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A B S T R A C T

The effect of pesticides on Cyanobacteria (*Nostoc* ***commune*** vaucher) has been analyzed in vitro in the laboratory, for which the pure culture of *Nostoc commune* (Voucher) was treated with various concentrations of two pesticides i.e. carbendazim and malathion and its metabolic effect was analyzed using parameters like concentration of proline and protein along with change in biomass production. The result obtained in the study indicates that amount of biomass and extracellular protein was increased with enhancing incubation time as well as with increase in concentrations of pesticides but decline after certain limit. The present data obtained cleared a way that the use of high concentrations and continuous use of organophosphorus pesticide causes detrimental effect on rice field cyanobacteria.

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INTRODUCTION

Several unique features of cyanobacteria such as cosmopolitan, pioneer, oxygenic photosynthesis, high biomass yield, growth on non-arable lands and on a wide variety of polluted water sources, generation of useful by-products and bio-fuels by them, enhancing the soil fertility, reducing green house gas emissions, have collectively offered these bio-agents as the precious bio-resource for sustainable development (Thajuddin and Subramanian, 2005). They are phototrophic, and naturally occur in several agro-ecosystems like paddy fields and from Antarctica to Arctic poles (Pandey et. al., 2002). Cyanobacterial biomass is the effective bio-fertilizer source to improve soil health and physico-chemical characteristics such as water-holding capacity and mineral nutrient status of the degraded lands (Nanjappan et. al, 2007.) As a beneficial microbe, cyanobacteria could play a potential role in the enhancement of agriculture productivity and mitigation of GHG emissions (Prasad et. al., 2005). It has been proposed that cyanobacteria could be the vital bio-agents in ecological restoration of degraded land (Singh et al. 1988). Cyanobacteria are the group of photosynthetic organisms which can easily survive on bare minimum requirement of light, carbon dioxide (CO_2) and water (Brouwer et. al. 1999).

The term pesticide covers a wide range of compounds including insecticide, fungicides, herbicides, rodenticides, molluscicides, nematicide, plant growth regulator (PGR) and others. There has been steady growth in the production of technical grade pesticide in India, from 5000 metric tons in 1958 to 102,240 metric tons in 1998. India ranks 10th in the world in pesticide consumption, as its total consumption amounts to about 500 million tons (Lari et. al. 2014). The Indian pesticides market is the 12th largest in the world with a value of US$ 0.6 bn. which is 1.6% of the global market (Hundal B. S., 2006; Lari et. al. 2014,) Despite increasing research efforts toward crop improvement by methods obviating the use of pesticides, agriculture remains heavily dependent on these chemicals (Gadkari, 1988). Cyanobacterial photosynthesis, growth and heterocysts differentiation is reduced or inhibited by herbicides and pesticides, such as, 2,4-D, atrazine, metsulfuron methyl (Berard *and* Benninghoff, *2001*). The biochemical constituents of cyanobactreia depend on the nature of strains, physiological state of the culture & the environment (Mounika et. al. 2018). In correlation with these studies the present analysis was carried out to evaluate the effect of two pesticides i.e. carbendazim and malathion (diethyl (dimethoxy phosphinothioyl) thiobutanedioate) on the growth and physiological activities of cyanobacteria *Nostoc commune* Voucher.

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MATERIAL AND METHOD

Sample collection, isolation and identification

The culture of Nostoc commune was isolated from rice field of Lakhandur (Bhandara), then it was sub-cultured and pure culture of *Nostoc commune* Voucher in vitro was obtained. Microscopic observation and identification was done by spreading isolated culture on glass slide and observing it under high power microscope. Pure forms of cyanobacteria were identified on the basis of morphological characteristics mentioned in Bergey's Manual of Determinative Bacteriology and Bergey's Manual of Systematic Bacteriology, 2nd ed. Vol. 1 (Buchanan and Gibbons, 1994) and Desikachary (1959).

Estimation of proline

Proline is a basic amino acid found in high percentage in basic protein. Free intracellular proline is said to play a role in plants under stress conditions. Though the molecular mechanism has not yet been established for the increased level of proline, one of the hypotheses refers to breakdown of protein into amino acids and conversion to proline for storage. Many workers have reported a several-fold increase in the proline content under physiological and pathological stress conditions. Hence, the analysis of proline in plants has become routine in pathology and physiology division of agricultural sciences (Bates, 1973).

Optimization of Biomass Production

Pure culture of *Nostoc commune* was inoculated in conical flask containing 100 ml BG-11(Andersen, 2005) broth and incubated at 30ºC for 15 days in continuously illuminated chamber at 4000 lux. The best growth medium was selected to carry out further experiments. At the stationary phase, *Nostoc commune* was harvested using centrifugation at 2000 rpm. Biomass was obtained by filtration using Whatman No. 1 filter paper and dried in hot air oven at 50ºC for 2 hrs to remove extra moisture then total biomass was weighed. Same process was followed by control test and pesticide different gradient concentration.

Protein estimation

The Lowry method (Lowry et al., 1951) was used to measure the protein content of the pretreated culture of *Nostoc commune,* The cells were pretreated with aluminum oxide for 5-min to release all the cellular protein followed by crushing. It resulted into total disruption of algal cells and longer periods of milling did not further increase the concentration of protein in the cell homogenates for liquid suspension**.** The obtained extract then analyzed for protein estimation.





Figure 1 Filtration and optimization of Biomass culture of *Nostoc commune*

RESULT

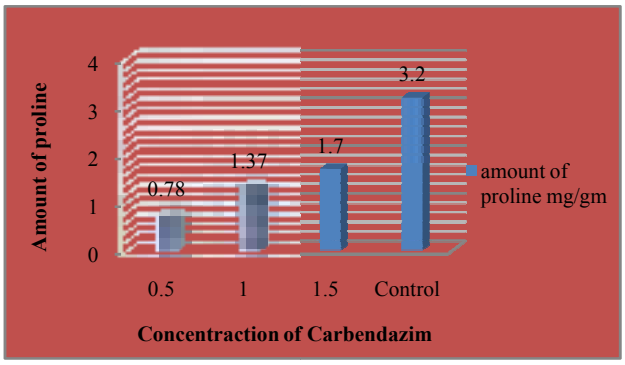


Fig 2 Amount of proline in culture extract of *Nostoc commune* in different concentrations of pesticide Carbendazim, after 15 days incubation

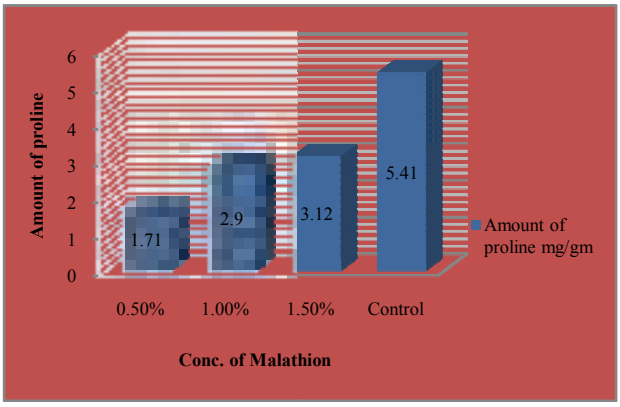


Fig 3 Amount of proline in extract of *Nostoc commune* in different con .of pesticide Malathion after 15 days incubation

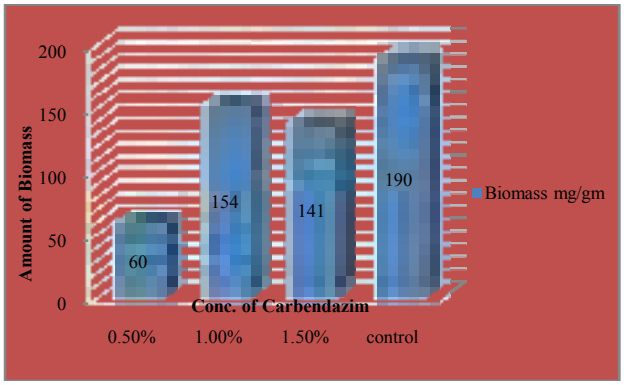


Fig 4 Total biomass estimation of Nostoc commune in different concentrations of pesticide Carbendazim after 15 days incubation

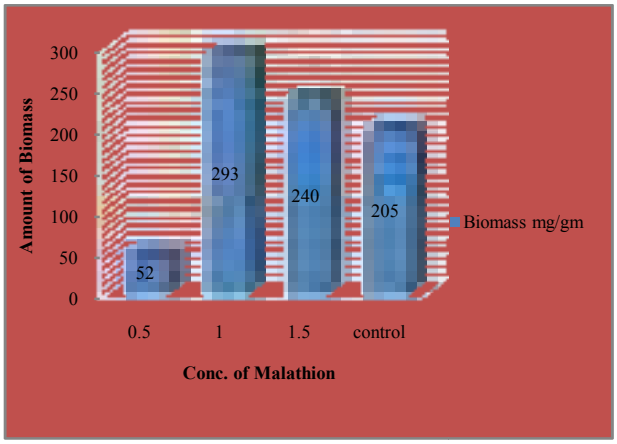


Fig 5 Biomass estimation of Nostoc commune in different concentration of pesticide Malathion after 15 days incubation

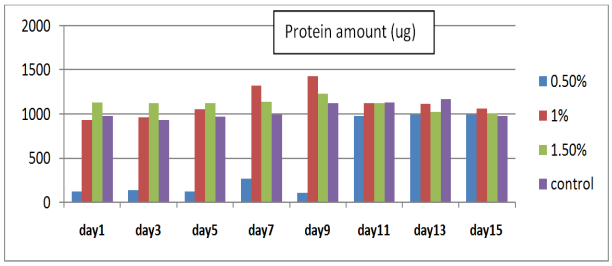


Fig 5 Total proteins in culture of Nostoc commune in different concentration of pesticide Carbendazim during15 days incubation

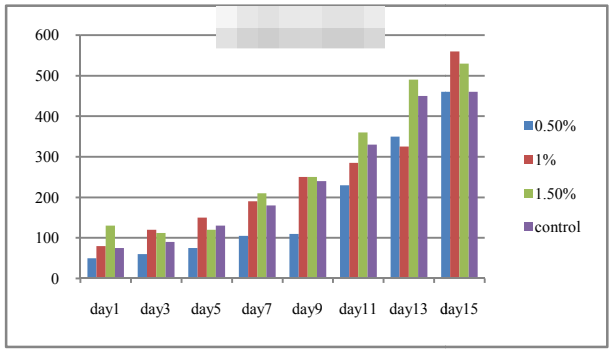


Fig 6 Total proteins in culture of Nostoc commune in different concentration of pesticide Malathion during15 days incubation

The data obtained in the present study reveals that proline content was increased as the concentrations of pesticide enhances but it remains lowered as compare to control of both the insecticides. Proline is a basic amino acid found in high percentage in basic protein. Free proline is said to play a role in plants under stress conditions. Though the molecular mechanism has not yet been established for the increased level of proline, one of the hypotheses refers to breakdown of protein into amino acids and conversion to proline for storage. Many workers have reported a several-fold increase in the proline content under physiological and pathological stress conditions.

The biomass and metabolite estimation of various incubation extract was evaluated using standard protocols and results obtained showed that biomass was increased as incubation period augmented as well as it depends on the concentrations of pesticide. It has been found that minimum biomass i.e. 52 mg was produced in 0.5% concentration of pesticide malathion after 15 days incubation in Nostoc commune. The biomass was maximum i.e. 293 mg at 1.0 conccentration of pesticide during 15 day incubation. Results indicates that amount of proteins was increased up to 15 days incubation time but not significantly. Amount of protein was maximum i.e. 1430 ug at 9th day in carbendazim and 560 ug in malathion treated group respectively.

The biochemical constituents of cyanobactreia depend on the nature of strains, physiological state of the culture & the environment. Rosaleset al.2005, observed significant variation in protein content among the isolated of Nostoc sp. Due to this biochemical variation he could enabled to distinguished between the sub species in several cyanobacterial genera. There are certain factors including pesticide stress, which also influence the protein synthesis (Borbely et al. 1985).

cyanbacteria are nurtured by soil and in spite that most reverend providing health, fertility and microflora to the soil. Because of it exhibit novel properties such as bio indicator and bio-remediator in contaminated agriculture field due to pollutant stress at moderately. But Nosoc commune in general do not resist to a very high concentration of insecticides carbendazim and malathion as it is revealed in present analysis. However the effect of pesticide on the population of nitrogen fixing cyanobacteria in rice fields also depends on other insecticide concentration and flooding of water associated with paddy fields. More detailed field studies are needed, avoiding the use of high application rates more than recommended will likely increase the more tolerant cyanobacteria.

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Arbuscular Mycorrhizal biodiversity associated with *Citrus aurentifolia* from Amravati region

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ABSTRACT

Arbuscular Mychorrhizai fungus is a key component of soil, which associate with root and rhizosphere of soil and create symbiotic association. In the present work, five soil samples were collected from five different sites of Amravati region (Maharashtra) for isolation and identification of AM spores, for this sieves and decanting method were used and observed that all the collected sample were infected by AM fungi but there population varied according to the soil sample, the Chandur Railway and Mardi site having maximum population of Am fungi but the Malkhed site contain very less population. The isolated spore belongs to five Genera which are *Acaulospora, Entrophosphora, Gigospora, Glomus and Scutelospora*. *Glomus* species was observed high amount.

Key words: Citrus plant, Rhizosphere soil, AM spore, AM species.

INTRODUCTION

Arbuscular Mycorrhiza is fungus-root symbiosis that occurs in the vast majority of plants have existed since the Devonian period and might have been essential for the evolution of land plants. Fungal species involved in the formation of arbuscular mychorhiza (AM) with higher plants are worldwide distributed in all terrestrial ecosystems. During the past decade, it has been established that AMF influences soil fertility and thus the growth and development of plant and therefore, these can be an alternative to rising agriculture and fertilizer costs. AMF form a key functional group of soil biota that can contribute towards the ecosystem sustainability and plant productivity (Urcoviche *et al.* 2014). AMF, which belong to phylum Glomeromycota (Schubler *et al*., 2001), Arbuscular mycorrizal fungi (AMF) propagule composition has an important effect on root colonization *(*Klironomos and Hart, 2002*)*. The occurrence of AMF at four soil depths i.e. 8, 15, 23 and 30cm. were studied by and registered more species at 15cm. depth. (Charles *et al*., 2008). The ability of soil to

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support AMF population decreased significantly with increased soil depth and the involvement of factor other than soil P^H and moisture content in AMF distribution (Shukla *et al*., 2013).

Arbuscular Mycorrhiza are associate with the root of majority of the land plants, the most important role of Arbuscular Mycorrhiza is that they uptake phosphorus, which is a limiting nutrient in most of the soils (Yao *et al*., 2001; Koide and Schreiner, 1992) and nitrogen (N) and also water from the soil and transport them to the plant root. AM fungi not only uptake the nutrient from the soil but also it enhance the productivity of plant by suppressing plant disease *(*Khaosaad *et al*., 2007*)*, controlling nematode infection *(Elsen et al., 2008)*, stimulation of phytohormones production (Martínez-Medina *et al*., 2011), improve soil texture (Wu *et al*.,2008) and plant tolerance to stress conditions including drought (Pinior *et al*., 2005) and salinity (Hajiboland *et al*., 2010*).* The Biotic and Abiotic factor are greatly affected the diversity and distribution of Arbuscular mycorrhiza *(Mohammad et al. 2003).* The recent experimental study showing that AMF can grow and form spores in vitro, if provided with a carbon source and stimulated by particular bacterial strains (Hildebrandt *et al*., 2006). On global basis, Mycorrhiza occurs in 83% dicot and 79% monocot, whereas all gymnosperms are having Mycorrhizal colonization (Wilcox, 1991). Am fungi are fatty acid heterotrophs(Wewer, 2014) that depend on host deliverd organic carbon (C) in the form of fatty acids (Bravo, 2017, Keymer *et al.* 2017) in order to complete their life cycle.

MATERIALS AND METHODS

Sampling:

The Rhizosphere soil samples of *Citrus aurentifolia* were collected in sterile polythene bags. The collection was carried out in the month of February 2013 from Mardi, Amravati, Chandur Railway, Malkhed and Phora. All soil samples were dried and stored at 4^0C.

Quantitative and Qualitative Estimation of AM fungi:

Different methods are used for counting AM fungal spores. The procedure describe by *(Gaur and Adholeya, 1994)* was used for counting Am spores as it is a simplified method for counting Am fungal spores. In the present study, the wet sieving and decanting technique was used (Gerdemann and Nicolson, 1963) for isolation of AM fungi. Isolated fungi were scanned and mounted on slide in Polyvinyl Lactic Acid as mounting medium. The AM fungi were identified by using standard manual of *(*Schenck and perez, 1990*)* keys of (Morton and Benny, 1990*)* and of (Mehrotra and Baijal, 1994). The Isolated AM fungi were identified by morphology of spores especially on the basis on their wall layer.

Observation:

Qualitative Analysis of AM fungi:

Root and rhizosphere soil sample of *Citrus aurentifolia* from five different sites of Amravati were collected in sterile polythene bags during the month of February 2013.

Quantification Analysis:

The isolated AM fungi from each soil samples were varied according to the soil sample. Soil PH, soil moisture, micronutrients and soil depth all are major factor which effect on AM fungi population. In the present study, found that *Glomus* species in high amount in all the five samples total 18 species, out of 18 species *Glomus aggregatum and Glomus fasciculatum* observed in maximum site then after *Glomus albidum, Glomus arborense, Glomus fecundisporum, Glomus flavisporum, Glomus fulvum, Glomus geosporum, Glomus globiferum, Glomus glomerulatum,* Glomus halon, *Glomus leptotichum, Glomus manihot, Glomus maculosum, Glomus microaggregatum, Glomus verseforme and Glomus pulvinatum* also isolated and identified then *Acaulospora* with 8 species and *Enthrophosphora* and *Gigospora* found very less in number, *Enthrophosphora* Am fungi observed only at site number 1, 3, 5 and *Gigaspora* found in site 1 and 4. The total numbers of AM fungi were recorded during the study in soil sample showing in the Table2.

Quantification analysis show the number of species found in all the sites, one the basis of the above observation following graph is formed, it show the number of spore in each 100g of soil sample.

Table-1. Showing the site number of collected samples and identifies species.

Sr. no.	Site no.	Genera	Species identified
1	S1, S2, S3, S4, S5	*Acaulospora*	*Acaulospora appendicular*
2	S1, S4, S5	*Acaulospora*	*Acaulospora delicate*
3	S2, S4,S5	*Acaulospora*	*Acaulospora bireticulata*
4	S1,S2,S3,S4,S5	*Acaulospora*	*Acaulospora denticulate*
5	S3	*Acaulospora*	*Acaulospora foveta*
6	S2, S4	*Acaulospora*	*Acaulospora lacunose*
7	S1, S3	*Acaulospora*	*Acaulospora laevis*
8	S3	*Acaulospora*	*Acaulospora tuberculata*
9	S5	*Entrophosphora*	*Entrophosphora colombiana*
10	S1, S3	*Entrophosphora*	*Entrophosphora infrequens*
11	S1, S4	*Gigaspora*	*Gigaspora decipiens*
12	S1, S2 ,S4,S3	*Glomus*	*Glomus aggregatum*
13	S1,S2, S4	*Glomus*	*Glomus albidum*
14	S1	*Glomus*	*Glomus arborense*
15	S1, S2, S3, S4, S5	*Glomus*	*Glomus fasciculatum*
16	S1, S3	*Glomus*	*Glomus fecundisporum*
17	S1, S4,S5	*Glomus*	*Glomus flavisporum*
18	S2,S4,S5	*Glomus*	*Glomus fulvum*
19	S2,S4,S5	*Glomus*	*Glomus geosporum*
20	S3,S2	*Glomus*	*Glomus globiferum*
21	S5	*Glomus*	*Glomus citriculata*
22	S3	*Glomus*	*Glomus glomerulatum*
23	S2,S4,S5	Glomus	Glomus halon
24	S1,S3	*Glomus*	*Glomus hoi*
25	S3	*Glomus*	*Glomus leptotichum*
26	S1,S4,S5	*Glomus*	*Glomus manihot*
27	S5	*Glomus*	*Glomus maculosum*
28	S3,S2	*Glomus*	*Glomus microaggregatum*
29	S5	*Glomus*	*Glomus verseforme*
30	S3	*Glomus*	*Glomus pulvinatum*
31	S1,S2,S3,S4,S5	*Scutelospora*	*Scutelospora nigra*
32	S5	*Scutelospora*	*Scutelospora clavispora*

{S1-Chandur railway, S2- Malkhed, S3-Mardi, S4-Amravati, S5- Pohra}

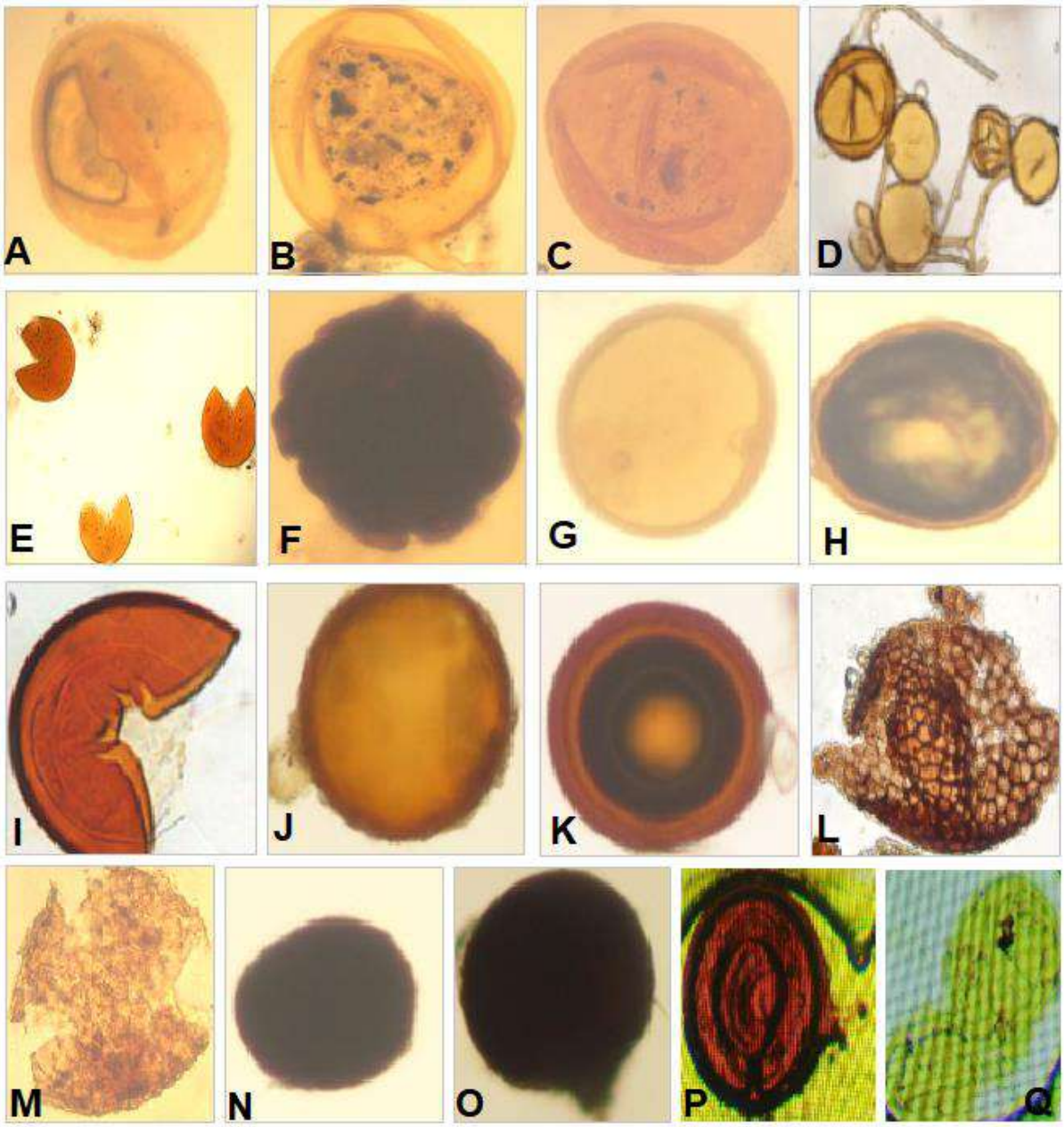


Figure 1 : A, B *Glomus fasciculatum;* **C,D,E:** *G.aggregatum;* **F***: Glomus citriculata;* **G:** *G. dominikii;* **H**- *G.glomerulatum;* **I**- *G.tuberculatum;* **J**: *G.albidum;* **K :**- *A.foveata;* **L, M:** *A. bireticulata;* **N**: *A.sporocarpa;* **O:** *Scutellospora nigra.;* **P :***E.infraquens;* **Q**: *E.colombiane*

Table-2. Total number of AM fungi species as follow

Serial No.	Name of AM Genra	No. of spores found in each Sites Number					No. of Species
		S.1	S.2	S.3	S.4	S.5	
1	*Acaulospora*	4	4	5	5	4	8
2	*Glomus*	8	8	9	8	9	19
3	*Gigospora*	1	-	-	1	-	1
4	*Enthrophosphora*	1	-	1	-	1	2
5	*Scutelospora*	1	1	1	1	2	2

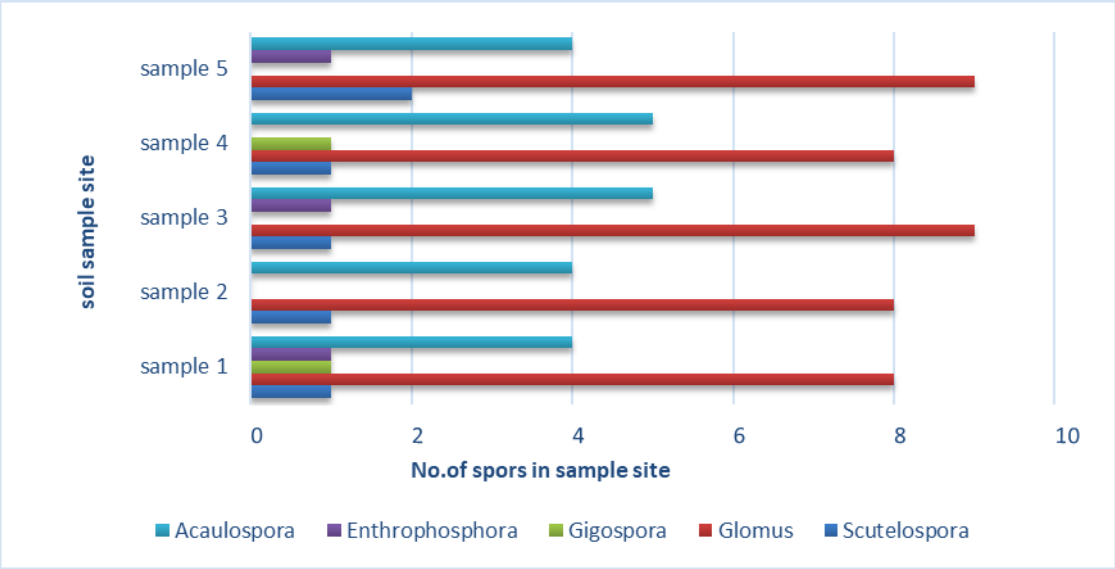


Fig:2. Showing the number of spores found in each soil sample and identified spores in each sample.

Result and Discussion:

An extensive field investigation was carried out in Amravati region, Maharashtra (India), on a *Citrus* plant which belongs to Rutaceae family. The association of AM fungi with *Citrus aurentifolia* plant and their colonization and population in the Rhizosphere is presented in (Table 1). All the sites having low to moderate AM population but in site1 (Chandur railway) maximum population were observed with maximum AMF colonization. More than 102 AM species have so far been reported from India (Manoharachary,C. ,2005). AMF colonization is about 20 % of the fine root segments in *Citrus volkameriana*. A total of 32 AMF species were isolated from rhizospheric soil. Maximum species belongs to *Glomus* (Fig 1-10) and *Acaulospora* (Fig 11-14) isolated species were 19 & 8 in numbers, remaining belongs to *Enthrophosphora, Gigospora* and *Scutelospora* which were 2, 1 & 2 in numbers they were isolated and identified on the basis of their morphological characteristics. Seasonal variation is a major factor in biodiversity of AM fungus was quite evident from the fluctuations of spores in soils (Sampath Kumar, 2001). *Glomus* species were the most commonly found in all type of different soil (Panneerselvam and Thamizhiniyan, 2011; Camprubí and Calvet,1996; Beena *et al.*, 2000; Bhuvaneswari, 2010; Unegbu *et al.*, 2016) and in present work also the major isolated species was belongs to Glomus. *Acaulospora appendicula* and *A. denticulata* were also observed in all five sites. *Gigaspora* spore was frequently observed in the two soils sites (Chandur railway, Amravati), but they were apparently from only one species. The soil sample of village Malkhed (s-2)contains least number of AM spores, the possible reason behind these variation season, age of plant, soil P^H, salinity etc. (Abbott and Robson, 1991; Johnson *et al.*, 1992), whereas Mardi(S3) and Amravati sites (S4)contain the widest variety of AM species. All the five sites of soils exhibit different physico-chemical and microbiological characteristics. Citrus plant mostly contain *Glomus* and *Acaulospora* species in major quantity but absence of other genera or they may be present in low rate is not surprising because sometimes they are not detected at the time of survey of Am fungi, in present survey also found that *Glomus* and *Acaulospora* were present in high rate, (Singh *et al.*,2008). A total 32 species were isolated from all the sites. 19 species belonging to *Glomus*, 8 species from *Acaulospora*, *Enthrophosphora* and *Scutelospora* both were having 2 species and only one species i*n Gigospora. G. fasciculatum* was found in all the five site and *G. aggregatum* found in four site. Similarly *A. appendicula* and *A. denticulate* were found in all the sites.

CONCLUSION

Arbuscular Mycorrhiza is associate with the soil and root of major land plants. AMF is an ecofriendly it increase the soil fertility by up taking phosphorus from the soil and improve plant productivity. AMF is a natural tool so, it is necessary to retain the AM population in soil. In the present study, only few site

having high AM population and that site productivity was good the only reason that site uptake phosphorus compound from the soil, these compound concentration in soil is low but it is soluble phosphorus.

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Embedded System Security

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Abstract:

Security is an important aspect of embedded system design. The characteristics of embedded systems give rise to a number of novel vulnerabilities. A variety of different Solutions are being developed to address these security problems. In this paper, we provide a brief overview of important research topics in this domain.

With the increasing use of embedded devices in our daily life, security threats have also been increasing in a proportional rate. However, ensuring security in the embedded systems has become a great challenge not only for the embedded device experts but also for the manufacturers. The problem especially arises because of the limited hardware and software implementation options for the designers. At the same time, companies are trying to keep the vulnerabilities of the operating system of those embedded devices in secret and they are not relieving any necessary security updates quickly. It has become very urgent to ensure proper security of the embedded systems to save it from any major technological disaster near future. In this paper, we have broadly discussed the structures, characteristics and applications of different embedded devices in our daily life. Beside this, we have also discussed about the different causes of security threats and some of our suggested solutions to protect the systems from the attackers as well that we have found in our research.

Keywords: cryptography, firmware, hackers, microcontroller, real-time constraints, Vulnerabilities

Introduction

An embedded system can be defined as a special type of computer system that performs some specific pre-defined programs which is generally used within a larger scale of electrical or mechanical system. Generally, it is started from small MP3 players to largely complex hybrid vehicle systems. Some other examples of frequently used embedded systems in our daily life are keyboard, mouse, ATM, TV, PDA, cell phone, printer, elevator, smoke detector, DVD player, refrigerator, camera, GPS navigator, radio, TV remote, telephone, game controller, monitor, digital image processor, bar code reader, SD card, washing machine, anti-lock breaking system, blender etc. We use embedded systems especially because of its dependability, efficiency and it meets the real-time constrains

Characteristics Of Embedded Systems:

In general, embedded systems are designed to perform any particular pre-defined task that must meet any real time constraint. The main difference between a computer and an embedded system is a computer is used to perform multiple tasks defined by the user. On the other hand, an embedded system is used to perform a specific task that is pre-defined by the manufacturers. Here, meeting all the real-time constraints is a very

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embedded system. A real-time constraint is divided into two parts. One is hard real-time system and the other is soft real-time system. Hard real-time system means it must meet all its deadlines with a zero degree of flexibility and it is acceptable to be little flexible in the soft real-time system. It is not necessary to be standalone always for the embedded devices. Actually most of the embedded systems are integrated within a large computerized device. Devices such as MP3s, cameras and TV remotes are the example of standalone embedded devices. For the example of integrated embedded devices car and nuclear power plant are some good examples. GPS, fuel injection controller, anti-locking brake system, transmission controller, cruise control, active suspension, air- bag system, air-conditioner, display monitor-all the devices are integrated in a modern car system. The term 'firmware' is used to refer the program instructions written for embedded systems. It is stored in ROM (Read Only Memory) or in a flash memory chip. Resources like computer hardware do not need much to run. Another important characteristic of embedded systems is the dedicated user interface. It may range from no user interface to complex graphical user interface. For simple button and LED system, no user interface is needed. User interface means the task of button can change with the on-screen display and the selection depends on the user.

The specialization of embedded system often comes with one or more drawbacks of the following type:

- **Limited processing power** implies that an embedded system typically cannot run applicationsthat are used for defenses against attacks in conventional computer systems (e.g.,virus scanner, intrusion detection system).
- **Limited available power** is one of the key constraints in embedded systems. Many such systems operate on batteries and increased power consumption reduces system lifetime(or increases maintenance frequency). Therefore embedded system can dedicate only limited power resources to providing system security.
- **Physical exposure** is typical of embedded systems that are deployed outside the immediate control of the owner or operator (e.g., public location, customer premise). Thus, embedded systems are inherently vulnerable to attacks that exploit physical proximity of the attacker.
- **Remoteness and unmanned operation** is necessary for embedded system that are deployed in inaccessible locations (e.g., harsh environment, remote field location). This limitation implies that deploying updates and patches as done with conventional workstations is difficult and has to be automated. Such automated mechanisms provide potential targets for attacks.
- **Network connectivity** via wireless or wired access is increasingly common for embedded systems. Such access is necessary for remote control, data collection, updates. In cases where the embedded system is connected to the Internet, vulnerabilities can be exploited remotely from anywhere.

These characteristics lead to a unique set of vulnerabilities that need to be considered in embedded systems.

Vulnerabilities

Embedded system are vulnerable to a range of abuses that can aim at stealing private information, draining the power supply, destroying the system, or hijacking the system for other than its intended purpose. Examples of vulnerabilities in embedded systems are:

- **Energy drainage (exhaustion attack):** Limited battery power in embedded systems makes them vulnerable to attacks that drain this resource. Energy drainage can be achieved by increasing the computational load, reducing sleep cycles, or increasing the use of sensors or other peripherals.
- **Physical intrusion (tampering):** The proximity of embedded systems to a potential attacker create vulnerabilities to attacks where physical access to the system is necessary. Examples are power analysis attacks or snooping attacks on the system bus.

Applications Of Embedded Systems:

As we describes earlier, embedded systems have become parts and parcels of our daily life in term of use. From the following table we can easily understand our daily use of embedded systems.

Home Applications	Dishwasher, Washing Machine, Microwave Oven, Top-set Box, Home Security Systems, HVAC system, DVD player, Answering Machine, Garden Sprinkler Systems, Lighting Systems, Remote Controls, Air Conditioners, Sprinklers.
Consumer Electronic Products	Cell phones, Cordless Phones, Digital Cameras, Video recorders, DVD players, TV set, Calculators, MP3 Players, Stereo Systems, Cable TV tuners, Digital watches, Personal PDA, iPhone.
Industrial applications	Personal Smart Phone, Fax Machines, Photo Copy Machines, Printers, Scanners, Assembly Line, Data Collection System, Monitoring Systems on Pressure, Voltage, Current, Temperature, Hazard Detecting System, Industrial Robot.
Business Equipment	ATM, Cash Registers, Alarm Systems, Card Readers, Finger Print Detectors, Automatic Toll Systems, Voice recognizers, Smart Vendor Machine, Cash Register, Bar Code Reader.
Automobile	GPS, Fuel Injection Controller, Anti-locking Brake System, Transmission Controller, Cruise Control, Active Suspension, Air- bag System, Air-Conditioner.
Communication Systems	Router, Hub, Cell Phone, Web Camera, Modem, Network Cards, Tele-conferencing System.
Aerospace	GPS system, Automatic Landing System, Flight Attitude Controller Inertial Guidance System, Space Robotics, RADAR.
Medical Technology	CT scanner, ECG, EEG, EMG, MRI, Glucose Monitor, Blood Pressure Monitor, Diagnostic Device, X-ray machines, Digital Pulse Monitor.
Security Systems	Face Recognition System, Finger Recognition, Irish Recognition, Building Security System, Airport Security System, Alarm System, Digital Access Card, Fingerprint based Smart Card.

Classroom applications	Smart Board, Smart Room, OCR, Calculator, Smart Cord, Stereo Systems, Projector.
Game and Entertainment	Video games

Causes Of Security Threats Of Embedded Systems

In this age of advanced technology, almost all of the embedded systems are connected to different network systems such as internet. At one side, these embedded devices are being more connected to our life day by day whereas on the other hand its security threats are also increasing as a proportional rate. Security threats in the embedded systems are not a new concept at all.. Some major causes of embedded system security threats are explained below: One of the major limitations of embedded systems are they are very cost sensitive. A little change in cost can make a big difference in the case of heavy manufacture devices. This cost sensitivity leads manufactures to use4-bit processor or 8-bit processor. Bigger cryptographic key cannot be stored by many of these 8-bit microcontrollers. Embedded devices have to perform same task again and again usually by using loop. Here, speed can easily reach to 100 loops in every 5 seconds with strong real-time constraints. Therefore, a single delay of even 0.01 second can cause a loss of control loop stability which means the system can be vulnerable to attack that is designed to destroy the system timing. In the most of the time, embedded systems have no real administrator by which an internet connected device can be easily launched by distributed denial-of-service (DoS) attacks by the hackers. Many embedded systems are designed and developed by the small development teams even by the single engineer sometime. Organizations that write few kilobytes of code per year usually cannot afford any embedded system security specialist even they do not understand the importance the necessity of the security specialists as well. There are many embedded systems that have significant battery constraints and powered by battery as well such as PDAs or cell phones. Some embedded systems can get fresh battery charge daily but other must last months or years depending on a single battery only. An attacker can create system failure by seeking to drain the battery especially when the security of the system is very high or almost impossible to break the security system of that particular device. This vulnerability is very much critical and worsens the security of the device. As an example, ensuring enough security in the battery-powered device is not easy at all that uses the power-hungry wireless communication system. Firmware is being completed day by day and will be more completed in near future. This will increase more bugs and other security problems. One reason may be the use of more popular programming languages such as C and C++ as they are very efficient for embedded systems. However they cannot protect against the simple kinds of attacks such as buffer overflows. Although small programs can be theoretically prove as safe but it is about impossible against complex programs.

Solutions Of Security Threats In Embedded Systems

Security requirements of embedded devices can vary from different aspects. As an example of a cell phone system, end user may be concerned about his private data protection while content provider may be concerned about copy protection of the multimedia contents delivered to the cell phone and manufacturers may be concerned about the proprietary firmware that has been used in that cell phone. Here the system of attack may also vary for users, content providers, manufacturers etc. We have already described different challenges of embedded

systems in term of security and in this section we will describe some probable solutions also to get rid of those problems also. Modern cryptography techniques provide strong defiance against the conventional attacks. However, much more effort and care is still required in the software design to make the system more protected from bugs and design flaws. Designers should be emphasizing more on Software Development Life Cycle (SDLC). Different secure level practices should be applied which can be classified into three. They are the design level, the implementation level and the testing level. Tamper-resistance techniques should be strengthening more to protect the system against different software and hardware attacks. These techniques can be used for attack detection, recovery and prevention as well. To prevent side-channel attacks, different hardware and software level approaches have been proposed to identify symptoms that allow the leak of the system's side-channel information like power dissipation, timing and electromagnetic radiations. Software based countermeasures include randomization instruction sequence, introducing dummy instructions, bit splitting and balancing hamming weights of internal data. Randomization can also be applied on the clock signal or the power consumption. It has been experimented that software based countermeasures are most efficient although they slightly

Conclusions

Embedded devices have made our life more easy and comfortable by meeting almost all the real-time constraints. Although it is very popular among the mass people but they are quite unconscious about the probable security threats till now even the manufactures and the engineers associated with embedded devices. Expert hackers from the different parts of the world have already found many security pitfalls of the embedded devices and they are further working on it. So, it is very clear that it could create a huge blow in near future for the technological industry if the engineers and the manufactures do not take the necessary security solutions as proposed in this paper to protect the unauthorized access from the unsecured third party. We heartily believe that more concentration on cryptography, tamper-resistance techniques, advanced microcontroller and algorithms can mostly make the embedded devices secure enough. At the same time, it is also important for the manufacturer companies to design and implement the whole embedded system with much more security concern.

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Study of Advances in Artificial Intelligence and Deep Learning

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Abstract –

Artificial Intelligence (AI) is a multidisciplinary field whose goal is to automate activities that presently require human intelligence. Reasoning is concerned with higher level cognitive functions such as planning, drawing inferential conclusions from a world model, diagnosing, designing, etc. In this paper we have observed the extended goals of Artificial Intelligence including logical reasoning, knowledge representation, planning and navigation, natural language processing, perception and emergent intelligence.

Machine learning is an integral part of artificial intelligence, which is used to design algorithms based on the data trends and historical relationships between data. Also, Deep learning is an emerging area of machine learning (ML) research. It comprises multiple hidden layers of artificial neural networks.

This paper elaborates some basic machine learning tasks adopted by researchers in their common applications of AI. The recent machine learning techniques accomplished by the researchers has also been presented in this paper. It has been noted that, in recent years, machine learning has achieved great success in many fields, such as computer vision and natural language processing. Compared to traditional computer based learning methods, machine learning has a strong learning ability and can make better use of datasets for feature extraction. The study concludes that, we need to provide a machine learning framework to construct and implement models for general purpose tasks useful for common people for successful delivery of AI-based systems.

Keywords – Artificial Intelligence, Machine Learning, AI Assistants, Supervised Learning, Unsupervised Learning, Chatbots

Introduction

Artificial Intelligence is a method of making a computer, a computer-controlled robot or a software think intelligently in a manner similar to the human mind. AI is accomplished by studying the patterns of the human brain and by analyzing the cognitive process. The outcome of these studies develops intelligent software's and systems. Researchers extend the goals of AI to the following:

Logical Reasoning: AI programs enable computers to perform sophisticated tasks. On February 10, 1996, a computer called Deep Blue, designed by IBM, won a game of chess against the former world champion, Garry Kasparov.

Knowledge Representation: Smalltalk is an object-oriented, dynamically typed, reflective programming language that was created as the language to underpin the "new world" of computing demonstrated by "human-computer symbiosis."

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Planning and Navigation: The process enabling a computer to get from point A to point B. A prime example of this is Google's self-driving Toyota Prius.

Natural Language Processing: Set up computers that can understand and process language.

Perception: Use computers to interact with the world through sight, hearing, touch, and smell.

Emergent Intelligence: An intelligence that is not explicitly programmed, but emerges from the rest of the explicit AI features. The vision for this goal is to have machines exhibit emotional intelligence, moral reasoning and more.

Some of the Artificial Intelligence based applications used today are given below: Top companies are constantly rolling out revolutionary changes to how there should be an interaction with machine-learning technology. For Example, DeepMind Technologies, a British artificial intelligence company created a Neural Turing Machine, allowing computers to mimic the short-term memory of the human brain. Google's driverless cars and Tesla's Autopilot features are the introductions of AI into the automotive sector. It uses vast amounts of data from image and audio recognition systems, along with new ML called Deep Learning and Deep Nets, to build systems that can drive autonomously. The technology teaches the cars about the nature of objects on the road and understand how they would react, the audio recognition technology using audio sensors based ML systems to teach the vehicle to diagnose cars problem themselves whereas, the Deep nets are used for everything from prediction to planning to mapping and simulation.

Common applications of AI utilized by most of the people is virtual personal assistants in the smartphones. These applications collect information, interpret what is being asked and then supply the answer via fetched data and each one gradually improves based on user preferences.

Machine Learning –

Machine Learning is a form of artificial intelligence that automate data analysis to enable computers to learn and adopt through experience to do specific tasks without explicit programming.

Machine learning, as a key subset of artificial intelligence (AI), Machine Learning has come a long way and with its numerous algorithms, can accomplish a great deal of impressive tasks. Machine Learning concepts and techniques includes supervised and unsupervised learning, mathematical and heuristic aspects to develop algorithms.

Netflix recommendations and virtual personal or AI assistants like Siri, Cortana, Alexa and Google Assistant are some of AI's best-known applications which uses machine learning techniques and are found in iOS, Windows and Android phones. AI assistants emulates human interaction using the voice enabled technology to perform particular tasks like personal assistance. It has the capacity for learning, reasoning and understanding which the three key elements are required to emulate the ability to solve the problems. The trouble is that collecting, analyzing and utilizing all this data has grown beyond what is humanly possible, even using traditional data analytics.

The solution to process this ore of data into material that's suitable for construction lies in using machine learning to automate the creation of data analysis models. Humans can typically create one or two good models a week; machine learning can create thousands of models a week. Machine learning not only handles vast amount of raw, unlabeled data, it craves it. The more you feed it, the smarter it gets. Machine learning algorithms can determine clusters, patterns and

relations among data and then predict outcomes and even recommend actions. With the power of machine learning and other applications of AI, the users can make the data useful for the growth to business and the customers.

Armed with this huge volume and wide variety of data, machine learning algorithms can be "trained" based on past experience, then exposed to new data and unleashed to hunt for patterns, learn from what they find and even build predictive models on their own.Machine learning is now useful to organizations of any type andany size, for processes ranging from theroutine to the revolutionary.

The two most widely adopted machine learning methods involved supervised learning andunsupervised learning.

1. Supervised learning uses structured data, stored in relational databases, this is the type of data that's most familiar to businesses, but it was noted that, only comprises about 20 percent of all data. Structured data comes in from human input, mechanical sensors, website or other automated logs, point of sale devices and similar sources. Supervised learning algorithms are useful when the desired output is known, or if you have a specific question you want to ask such as finding new data points that match a specific target value. This is useful for functions like inventory control, recommendation engines and predictive maintenance.

2. Unsupervised learning uses data that is unstructured, contains no historical labelsand doesn't fit neatly into a database. Such data includes customer transactions, social media, document text, graphics, video and other content. It was observed that, approximately 80 to 90 percent of the data in most organizations is unstructured. With unsupervised learning, the algorithm must draw its own inferences to figureout what it's looking at. It does this by finding clusters and hidden patterns, such as similarities between behaviors and customers. This type of learning is especially useful for market segmentation (marketing campaigns), fraud detection and hardware fault diagnostics.

Some of the top roles of AI and ML includes

AI/machine learning researcher make its use to Research and identify improvements to machine learning algorithms. AI software development, program management, and testing: Develop systems and infrastructure that can apply machine learning to an input data set.

Data mining and analysis: Investigate large data sources, often creating and training systems to recognize patterns.

Basic Machine Learning Tasks

ML techniques provides a set of tools that can automatically detect patterns in data which can be utilized for predictions and for developing models. Developments in ML algorithms and computational capabilities have now made it possible to scale engineering analysis, decision making and design rapidly. Following ML tasks are prominently done,

- Performance Measures
- Classification
- Regression
- Clustering

Some of the live projects on which researcher are working recently that can be found on the internet are

Project 1: Build a Predictive Model for Housing Prices

Project 2: Build a Phishing Website Detector Using LR Algorithms
Project 3: Build a Phishing Website Detector Using KNN Algorithms
Project 4: Build an MNIST Classifier

Machine learning applications:

Apply machine learning or AI framework to a specific problem in a different domain. For example, applying machine learning to gesture recognition, ad analysis or fraud detection.

The researchers used supervised or unsupervised machine learning, or a combination of the two (known as semi-supervised learning), these are the three ways for any business, regardless of industry, can utilize such algorithms to help build a competitive advantage.

1. Automating Business Processes
2. Marketing - AI and machine learning are commonplace tools for digital marketers.
3. Improving Customer Experience–Some of the ways of utilizing machine learning used today to optimize the marketing and advertising, both online and offline are:

- Demand forecasting and sales projection
- Determining customer lifetime value
- Streamlining lead sourcing
- Customer churn risk modeling
- Product pricing and dynamic pricing (based on real-time demand)
- Dynamic and personalized product ranking (website)
- Visual merchandising placement (retail)
- Augmented reality (AR) integration (retail)
- Purchase recommendations
- Micro-segmentation
- Personalized headline and ad/email copy
- Optimized message targeting
- Automated and real-time media buying/ ad insertion
- Customer qualifying/lead scoring using web data
- Content research and creation
- Automatic translations
- Plagiarism detection
- Social monitoring (for issues, affinity and competition)
- Social media posting and advertising
- Text-to-video creation

To get the most out of machine learning, all this diverse data is usually stored in a type of repository known as a "data lake". A term coined in 2010 by James Dixon, the founder and CTO of Pentaho, data lakes differ from traditional data warehouses in that they store all their data in its raw, natural state, regardless of whether it is structured, semi-structured, or unstructured. A data warehouse only keeps data in a very structured format.

While this makes data easier to find specific things, its inflexibility makes it difficult to perform innovative analyses. "Structured data enables us to answer certain questions, but the structure may not accommodate questions that arise at some point in the future," explains Jared

Crapo, Senior Vice-President at Health Catalyst. "The data lake concept allows for unstructured data—and more flexibility to answer new questions.

Machine learning not only automates this intelligence gathering from familiar sources and internal databases; the algorithms actually go into the outside world to collect, analyze, learn and predict.

A form of artificial intelligence, machine learning is revolutionizing the world of computing as well as all people's digital interactions. By making it possible to quickly, cheaply and automatically process and analyze huge volumes of complex data, machine learning is critical to countless new and future applications. Machine learning powers such innovative automated technologies as recommendation engines, facial recognition, fraud protection and even self-driving cars.

The Machine Learning techniques are used to accomplish the following:

- Master the concepts of supervised, unsupervised and reinforcement learning concepts and modeling.
- Gain practical mastery over principles, algorithms, and applications of machine learning through a hands-on approach which includes working on various projects.
- Acquire thorough knowledge of the mathematical and heuristic aspects of machine learning.
- Understand the concepts and operation of support vector machines, kernel SVM, naive Bayes, decision tree classifier, random forest classifier, logistic regression, K-nearest neighbours, K-means clustering and more.
- Comprehend the theoretical concepts and how they relate to the practical aspects of machine learning.
- Be able to model a wide variety of robust machine learning algorithms including deep learning, clustering, and recommendation systems

Chatbots and other applications of machine learning can handle a number of routine, repetitive HR tasks, including:

- Screening and shortlisting job applicants from hundreds of résumés
- Scheduling interviews, performance reviews and other group meetings
- Measuring and managing employee engagement
- Streamlining office workflows
- Tracking and enhancing employee rewards and recognition programs
- Identifying knowledge gaps or opportunities for employee development
- Answering questions about company policies, benefits, office procedures and even basic conflict resolution
- Attracting and reaching out to top talent (through such sites as Glassdoor, LinkedIn or Indeed)

Machine learning is also excellent at examining vast amounts of historical sensor, logistics and failure data from appliances, machinery or vehicles. The models' predictions could then recommend preventive maintenance, mitigate transportation or supply chain risks or even detect anomalies in real time that would indicate a failure is imminent.

Future Scope

Machine learning is set to redefine the world of software and IT in the near future. Machine Learning supports the technologies such as Data Science, Big Data and Data Analytics which are increasingly shaping future of work and jobs.

Data Science:

Dealing with unstructured and structured data, Data Science is a field that comprises of everything that related to data cleansing, preparation, and analysis. Data Science is the combination of statistics, mathematics, programming, problem-solving, capturing data in ingenious ways, the ability to look at things differently, and the activity of cleansing, preparing and aligning the data.

Applications of Data Science

Internet search: Search engines make use of data science algorithms to deliver best results for search queries in a fraction of seconds.

Digital Advertisements: The entire digital marketing spectrum uses the data science algorithms - from display banners to digital billboards. This is the mean reason for digital ads getting higher Click Through Rate (CTR) than traditional advertisements.

Recommender systems: The recommender systems not only make it easy to find relevant products from billions of products available but also adds a lot to user-experience. A lot of companies use this system to promote their products and suggestions in accordance with the user's demands and relevance of information. The recommendations are based on the user's previous search results.

Big Data:

Big Data refers to humongous volumes of data that cannot be processed effectively with the traditional applications that exist. The processing of Big Data begins with the raw data that isn't aggregated and is most often impossible to store in the memory of a single computer. A buzzword that is used to describe immense volumes of data, both unstructured and structured, Big Data inundates a business on a day-to-day basis. Big Data is something that can be used to analyze insights which can lead to better decisions and strategic business moves.

The definition of Big Data, given by Gartner is, "Big data is high-volume, and high-velocity and/or high-variety information assets that demand cost-effective, innovative forms of information processing that enable enhanced insight, decision making, and process automation".

Applications of Big Data

Big Data for financial services: Credit card companies, retail banks, private wealth management advisories, insurance firms, venture funds, and institutional investment banks use big data for their financial services. The common problem among them all is the massive amounts of multi-structured data living in multiple disparate systems which can be solved by big data. Thus big data is used in a number of ways like:

- Customer analytics
- Compliance analytics
- Fraud analytics
- Operational analytics

Big Data in communications: Gaining new subscribers, retaining customers, and expanding within current subscriber bases are top priorities for telecommunication service providers. The solutions to these challenges lie in the ability to combine and analyze the masses of customer-generated data and machine-generated data that is being created every day.

Big Data for Retail: Brick and Mortar or an online e-tailer, the answer to staying the game and being competitive is understanding the customer better to serve them. This requires the ability to analyze all the disparate data sources that companies deal with every day, including the weblogs, customer transaction data, social media, store-branded credit card data, and loyalty program data.

Data Analytics:

Data Analytics the science of examining raw data with the purpose of drawing conclusions about that information. Data Analytics involves applying an algorithmic or mechanical process to derive insights. For example, running through a number of data sets to look for meaningful correlations between each other.

It is used in a number of industries to allow the organizations and companies to make better decisions as well as verify and disprove existing theories or models. The focus of Data Analytics lies in inference, which is the process of deriving conclusions that are solely based on what the researcher already knows.

Applications of Data Analysis

Healthcare: The main challenge for hospitals with cost pressures tightens is to treat as many patients as they can efficiently, keeping in mind the improvement of the quality of care. Instrument and machine data is being used increasingly to track as well as optimize patient flow, treatment, and equipment used in the hospitals. It is estimated that there will be a 1% efficiency gain that could yield more than $63 billion in the global healthcare savings.

Travel: Data analytics is able to optimize the buying experience through the mobile/ weblog and the social media data analysis. Travel sights can gain insights into the customer's desires and preferences. Products can be up-sold by correlating the current sales to the subsequent browsing increase browse-to-buy conversions via customized packages and offers. Personalized travel recommendations can also be delivered by data analytics based on social media data.

Gaming: Data Analytics helps in collecting data to optimize and spend within as well as across games. Game companies gain insight into the dislikes, the relationships, and the likes of the users.

Energy Management: Most firms are using data analytics for energy management, including smart-grid management, energy optimization, energy distribution, and building automation in utility companies. The application here is centered on the controlling and monitoring of network devices, dispatch crews, and manage service outages. Utilities are given the ability to integrate millions of data points in the network performance and lets the engineers use the analytics to monitor the network.

Conclusions

This is the early stages of AI world in which machine learning is morphing from a lab curiosity to a rich, pervasive technology value-add.

ML is at the centre of a new enterprise to build computational models of intelligence. The main assumption is that intelligence (human or otherwise) can be trained by using voluminous data available on the Internet to solve the above mentioned problems where ML can be rigorously used with the help of a digital computer. Aspects of intelligent behaviour, such as

solving problems, making inferences, learning, and understanding language, have already been done using ML, and within very limited domains. ML can outperform human experts. Now the great challenge of AI and ML is to find ways of representing the commonsense knowledge and experience that enable people to carry out everyday activities such as holding a wide-ranging conversation, or finding their way along a busy street. Conventional digital computers may be capable of running such programs, or there is a need to develop new machines that can support the complexity of human thought.

Machine Learning Architects have defined, evaluated and recommended machine learning architectures and frameworks that support ML and AI initiatives.The need is to develop a ML prototype utilizing ML frameworks. There is an availability of pre-trained models and machine learning services — also called machine learning APIs which can be utilized for the designated problems. There is a need to provide a machine learning framework to construct and implement models for general purpose tasks useful for common people for successful delivery of AI-based systems.

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An Overview of "Cloud Computing"

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Abstract:

In the last few years there has been a rapid exponential increase in computer processing power, communication and data storage. But still many complex and computation intensive problems, which cannot be solved by supercomputers. In the field of computing, a lot of changes have been observed due to the increased use and popularity of the Internet and the availability of high-speed networks.

Resource sharing in a pure plug and play model that dramatically simplifies infrastructure planning is the promise of "Cloud computing".

The paper aims to provide a means of understanding the model and exploring options available for complementing your technology and infrastructure needs. Also explore some of the basics of cloud computing with the aim of introducing aspects such as:

1. Realities and risks of the model
2. Components in the model
3. Characteristics and Usage of the model

Keywords: Cloud computing, SLA, SaaS, Paas, Iaas, Daas, Cloud Service Provider, Cloud computing metaphor

Introduction:-

Cloud Computing

Cloud computing is an on demand service model for IT provision. Cloud Computing is a technology which depends on sharing of computing resources.

In Cloud Computing, the word "Cloud" means "The Internet", so Cloud Computing means a type of computing in which services are delivered through the Internet.

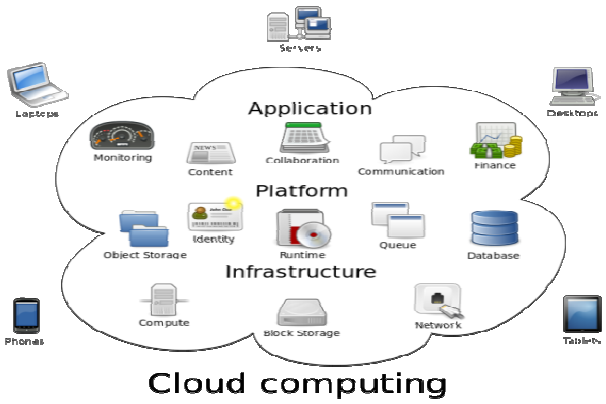


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AMRAVATI

In the past, people would run application or programs from software downloaded on a physical computer or server in their building. Cloud computing allows access tom the same kinds of applications through the internet on a virtual server.

Cloud computing is a complete new technology. It is the development of parallel computing, distributed omputinggrid computing, and is the combination and evolution of Virtualization, Utility computing, software as a service,(SaaS), Platform as a Service (PaaS), Infrastructure as a Service (IaaS), Desktop as a Service(DaaS) or as a utility. cloud computing provides shared

resources, software and information through Internet as a PAYGO (Pay-as-you-go) basis. We just by using the need internet.



Cloud computing metaphor: the group of networked elements providing services need not be individually addressed or managed by users; instead, the entire provider-managed suite of hardware and software can be thought of as an amorphous cloud.

"Cloud is a parallel and distributed computing system consisting of a collection of inter-connected and virtualized computers based on service-level agreements (SLA) which established through cooperation between the service provider and consumers."

Cloud computing is a computing example, where a large pool of systems are connected in private or public networks which provide dynamically scalable infrastructure for application, data and file storage.

Cloud computing is a practical approach for to experience direct cost benefits and it has the potential to transform a data center from a capital-intensive set up.

The idea is based on a very fundamental principal of „reusability of IT capabilities'. The difference is that to bring compared to traditional concepts of "grid computing", "distributed computing", "utility computing", or "autonomic computing".

. "Cloud is a parallel and distributed computing system consisting of a collection of inter-connected and virtualized computers that are dynamically provisioned and presented as one or more unified computing resources based on service-level agreements (SLA) established through negotiation between the service provider and consumers."



Fig. 1: Cloud computing concept

Fig. 1 shows that how users can connect to the cloud services which is provided by cloud service provider by using any device over the internet. It includes scalable resources in storage, network, and compute & also contain virtualized infrastructure and provide that services to the users.

Forrester defines cloud computing as:

"A pool of abstracted, highly scalable, and managed compute infrastructure capable of hosting end-customer applications and billed by consumption."



It cuts the operational and capital costs and permits the IT departments to focus on strategic projects instead of keeping the datacenter running. It provides the services on Infrastructure level, Platform level, and Software level, many features such as speed, scalability of resources, parallel processing, to choose another technology at any time to further work like 24/7 availability of services, device and location independent and security etc. Cloud computing has five essential features such as rapid elasticity, measured services, on-demand self-service, resource pooling, and board network access. as shown in Fig. 2.



Fig. 2: Five features of cloud computing

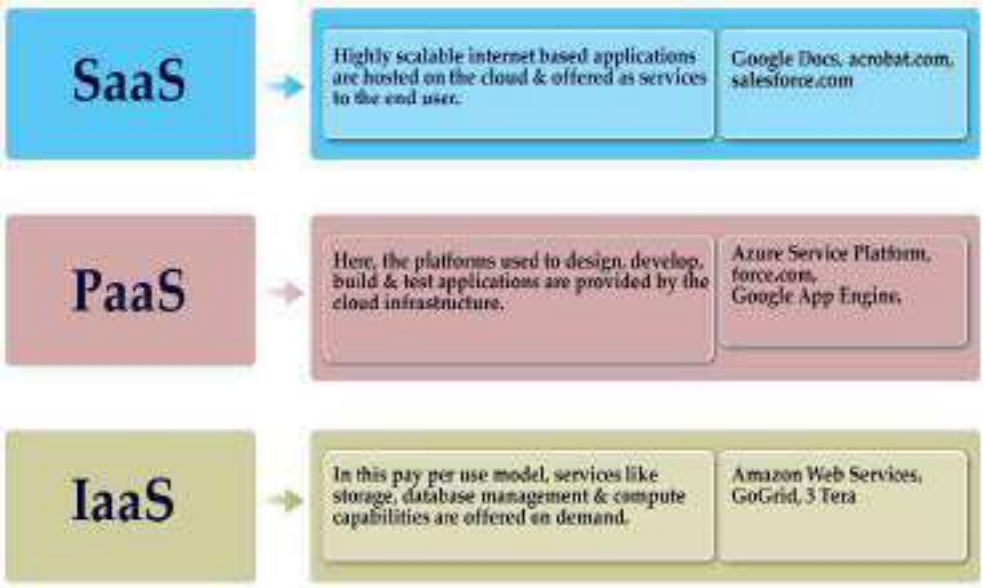
Cloud Computing Models:

Cloud service Providers following 3 types of Models:-

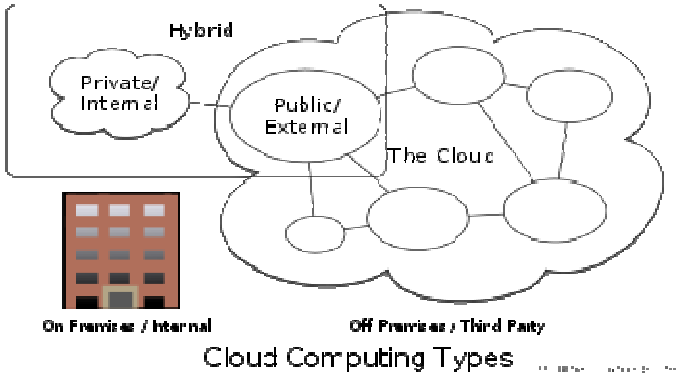
1. Software as a Service (SaaS): In this model, a complete application is offered to the customer, as a service on demand. A single instance of the service runs on the cloud & multiple end users are serviced. Today SaaS is offered by companies such as Google, Salesforce, Microsoft, Zoho, etc.

2. Platform as a Service (Paas): a layer of software, or development environment is encapsulate & offered as a service, upon which other higher levels of service can be built. In this model The customer has the freedom to build his own applications, which run on the provider‟s infrastructure. PaaS providers offer a predefined combination of OS and application servers, such as LAMP platform (Linux, Apache, MySql and PHP), classified J2EE, Ruby etc. Google‟s App Engine, Force.com, etc

3. Infrastructure as a Service (Iaas): IaaS provides basic storage and computing capabilities as standardized services over the network. Servers, storage systems, networking equipment, data centre space etc. The customer would typically deploy his own software on the infrastructure. Some common examples are Amazon, GoGrid, 3 Tera, etc.



Public, Private, Hybrid & Community Cloud:-



Cloud Computing Types

Fig. 3: cloud computing Types

Public Cloud

Public clouds are owned and operated by third parties; they deliver better economies of scale to customers, as the infrastructure costs are spread among a mix of users, giving each individual client an attractive low-cost, "Pay-as-you-go" model. One of the advantages of a Public cloud is that they may be larger than an enterprises cloud, thus providing the ability to scale seamlessly, on demand.

For example the Internet and Public
Switched Telephone Network (PSTN) etc

Private Cloud

Private clouds are built exclusively for a single enterprise. They aim of Private Cloud is to address concerns on data security

There are two variations to a private cloud:-

- On-premise Private Cloud: also known as internal clouds are hosted within one own data center.
- Externally hosted Private Cloud: This type of private cloud is hosted externally with a cloud provider.

Hybrid Cloud

Hybrid Clouds combine both public and private cloud models.. The Hybrid cloud environment is capable of providing on-demand, externally provisioned scale.

Community cloud

Community cloud implies an infrastructure shared between organizations, usually with the shared data and data management concerns. For example, a community cloud can belong to a government of a single country. Community clouds can be located both on and off the premises.

Cloud Computing Characteristic:-

1: Dynamic computing infrastructure
2: IT service-centric approach
3: Self-service based usage model
4: Minimally or self-managed platform
5: Consumption-based billing
6. Reduced Cost
7. Increased Storage
8. Flexibility
9. Data Protection
10 Data Recovery and Availability
11. Management Capabilities
12. Disaster Recovery
13. Automatic Software updates
14. Free Capital- expenditure
15. Work from anywhere
16. Document control
17. Security

Advantages of Cloud Computing

Shared Resources:

it shares resources to provide the services to multiple users.

Pay-As-You-Go:

Users only need to pay those resources which are used by them. They can demand for more resources if they required

Better Hardware Management:

It is easy for cloud service provider (CSP) to manage the hardware easily because all computers run the same hardware.

Area of Cloud Computing:

1. Banking
2. Insurance
3. Weather Forecasting
4. Space Exploration
5. Software as a service
6. Platform as a Service
7. Infrastructure- as -a-Service

Scope:-

Cloud computing is a tremendous innovation in the digital landscape that has changed the way IT solution are delivered and how end-users put them tom use. The cloud computing aspect is growing and will continue to do so.

Conclusion:-

Cloud computing is a new technology of computer network, providing the web services at lower cost comparing to normal technique. It contribute to improve the service in other related technologies like,Grid Computing, Cluster Computing, Utility Computing / Automatic Computing Distributed Computing with cloud computing, to the interface between service suppliers and multiple groups of service consumers. Cloud services will demand expertise in distributed services, procurement, risk assessment and service negotiation — these are the areas that many enterprises are only modestly equipped to handle, has changed the way IT solution are delivered and how end-users put them tom use. The cloud computing aspect is growing and will continue to do so.

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Universal Knowledge Discovery From Big Data

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Abstract-

Big data is a set of techniques and technologies that require new forms of integration to uncover large hidden values from large datasets that are diverse, complex, and of a massive scale. The one aspect that differs now (if compared with the past) would be the sheer scale and accessibility of Data, which is the direct result of the super efficient speeds in which data can now be computed. Big Data is therefore an all-encompassing term for any collection of large data sets that were once difficult to process. organizations are capturing data at deeper levels of detail and keeping more history than ever before. As a result, managing these increasing volumes of data is emerging as a key challenge for companies. The challenges include analysis, capture, curation, search, sharing, storage, transfer, visualization, and privacy violations.

Introduction:

Knowledge Discovery from Data (KDD) [1] refers to a set of activities designed to extract new knowledge from complex datasets. The KDD process is often interdisciplinary and spans computer science, statistics, visualization, and domain. Due to Increase in the amount of data in the field of genomics, meteorology, biology, environmental research and many others, it has become difficult to find, analyze patterns, associations within such large data . Interesting association is to be found in the large data sets to draw the pattern and for knowledge purpose. Big Data are the large amount of data being processed by the Data Mining environment. In other words, it is the collection of data sets large and complex that it becomes difficult to process using on hand database management tools or traditional data processing applications, so data mining tools were used. Big Data are about turning unstructured, invaluable, imperfect, complex data into usable information. [2]

The benefit of analyzing the pattern and association in the data is to set the trend in the market, to understand customers, analyze demands, predict future possibilities in Big Data typically differ from data warehouse in architecture; it follows a distributed approach whereas a data warehouse follows a centralized one. One of the architecture laid describes about adding new 6 rules were in the original 12 rules defined in the OLAP system defined the methods of data mining required for the analysis of data and defined SDA (standard data analysis) that helped analysis of data that is in aggregated form and these were much well timed in comparison with the decision taken in traditional methods. [3].Specifically, knowledge discovery processes are comprised of:

- Collection of data, storing the data, organizing the data in proper format.
- To understand the application of modern data analysis tools and methods.
- To understand the problem of structure and meaning of data.





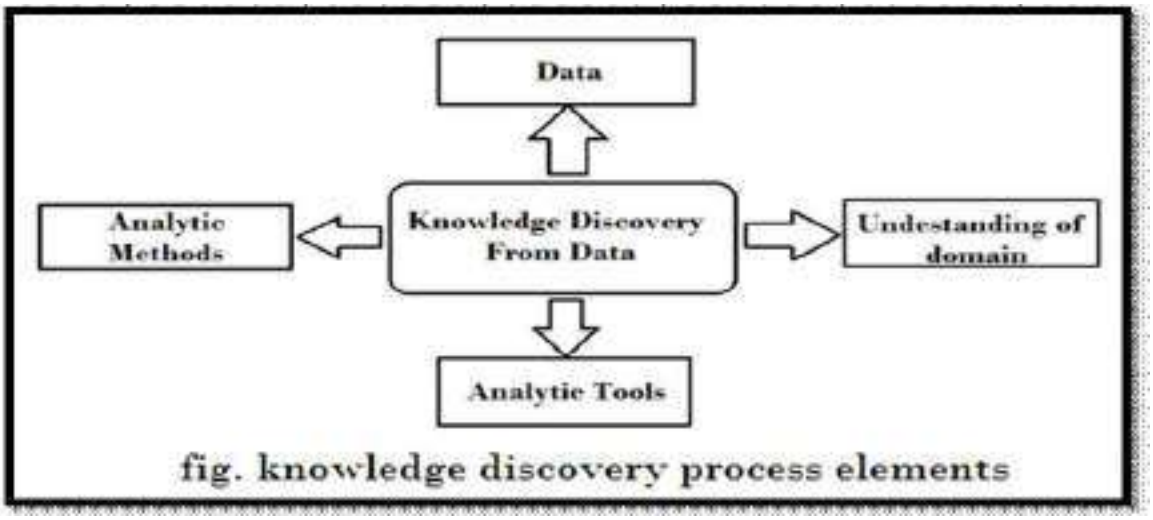


fig. knowledge discovery process elements

We believe that the application of some core principles can yield economical, comprehensive, flexible, and secure solutions for the federal government's big data needs . It helped organization to increase innovation, retain customers, and increase in operational efficiency[4] .According to Gartner definition big data is measured in 3 V's: variety, volume, velocity and value. [4][5]

Volume:

Big data uses massive datasets, including for example meta-data from internet searches, credit and debit card purchases, social media postings, mobile phone location data, or data from sensors in cars and other devices. The volume of data being produced in the world continues to increase rapidly. The Boston Consulting Group estimates total growth of 2.5 exabytes, which equals 2.5 billion gigabytes, per day[6].

Variety:

Big data often involves bringing together data from different sources. Currently it appears that big data analytics mainly uses structured data[7], e. g in tables with defined fields, but it can also include unstructured data. For example, it is possible to obtain a feed of all the data coming from a social media source such as Twitter. This is often used for 'sentiment analysis', i. e to analyse what people are saying about products
or organisations.

Velocity:

In some contexts, it is important to analyse data as quickly as possible, even in real time. Big data analytics can be used to analyse data 'in motion', as it is produced or recorded, as well as data 'at rest' in data stores. A potential application of 'in motion' analysis is in credit card payments. For example, Visa[8] is looking at using big data analytics to develop a new ways of authorising credit card payments.

Assumption I

Design principles are largely concerned with maximizing the controllable factors and thereby enabling researchers to explore, analyze, and interact with data in as easy manner as possible.

Assumption Ii:

It support variety of analytical tools: Knowledge discovery from big data science employs methods from distributed programming, data mining, statistical analysis, machine learning, visualization. These methods often employ vastly different tools and techniques. For example, programmers may use Java to write distributed computation while statisticians may feel more comfortable using R, SAS, etc.

Statistical Analysis:

1. It is concerned with summarising large datasets.
2. Most statistical tools (i.e., R, SAS) prefer to compute data over numerical data organized in tabular format.
3. It require organization step specially for unstructured data.
4. Currently in our system various statistical tools are available like SQL,R and Python.

Data Mining:

1. Data mining (the analysis step of the "Knowledge Discovery in Databases" process, or KDD) [10] an interdisciplinary subfield of computer science.
2. Each and every day the human beings are using the vast data and these data are in the different fields .It may be in the form of documents, may be graphical formats ,may be the video may be records (varying array) .
3. As the data are available in the different formats so that the proper action to be taken. Not only to analyze these data but also take a good decision and maintain the data .As and when the customer will required the data should be retrieved from the database and make the better decision .This technique is actually we called as a data mining or Knowledge Hub or simply KDD(Knowledge Discovery Process).
4. It is the computational process of discovering patterns in large data sets involving methods at the intersection of artificial intelligence, machine learning, statistics, and database systems.[11]

Data visualization and visual analysis:

1. Data visualization or data visualisation is viewed by many disciplines as a modern equivalent of visual communication.
2. A primary goal of data visualization is to communicate information clearly and efficiently to users via the information graphics selected, such as tables and charts.
3. Effective visualization helps users in analyzing and reasoning about data and evidence. It makes complex data more accessible, understandable and usable.
4. Users may have particular analytical tasks, such as making comparisons or understanding causality, and the design principle of the graphic (i.e., showing comparisons or showing causality) follows the task. Tables are generally used where users will look-up a specific measure of a variable, while charts of various types are used to show patterns or relationships in the data for one or more variables.

Assumption Ii:

Comprehensive KDD architecture provide a variety of data analysis method , it must also supply a mean of storing and processing of data. Single storage mechanism is for small data volumes like local file.system. But it is more problematic for large-scale data analysis. B, we

argu that different types of analysis and the intermediate data. structures required by these (e.g. graphs for social network analysis) call for specialized data management systems . Others have also recognized that the time of the single style database that fits all needs is gone [12].

Data Preparation and Batch Analytics :

Data preparation is the first step in the analytics pipeline. At this stage, the data may contain errors, missing values, and is often in an unusable format (i.e., a compressed binary format). In our experience, Hadoop is an ideal tool for this stage. Hadoop is a collection of open source software based on Google's BigTable [13] and Google File System [14]. It includes Map Reduce [15] component (for distributed computation) and a scalable storage component that can often replace costly SAN devices. Hadoop sub-project such as Hive and HBase offer additional data management solution for storing structured and semi-structured data sets. In oursystems we rely on HDFS as a data landing platform and use Hive as our batch-oriented data warehouse.

Processing Structured Data :

Often the product of the data preparation stage is a set of highly structured, relational data. Although Hadoop can process such data (via Hive), we have found distributed analytic databases [16] to be useful for storing and analyzing such data.

Processing Semi-structured Data

Not all data can be easily modeled using relational techniques. For example hierarchical documents, graphs, and geospatial data. Such data is extremely useful for social network analysis, natural language processing, and semantic web analysis. We provide HBase [17] and Cassandra [18] for hierarchical, key-value data organization. For graph analysis, we employ both open-source (e.g., Cray's uRiKa platform). Finally, for geospatial data we employ open-source tools (e.g., PostGIS, GeoTools) and proprietary tools (e.g., ESRI software).

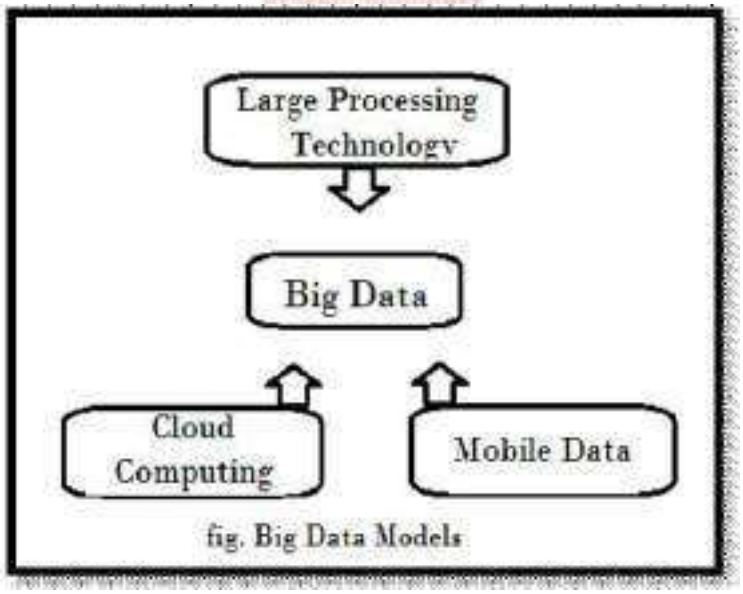


fig. Big Data Models

The semi-structured and unstructured data may not fit well in traditional data warehouses on relational databases Furthermore, data warehouses may not be able to handle the processing demands posed by sets of big data that need to be updated frequently or even continually -- for example, real-time data on the performance of mobile applications or of oil and gas pipelines. As a result, many organizations looking to collect, process and analyze big data have turned to a

newer class of technologies that includes Hadoop and related tools such as MapReduce and NoSQL databases. Those technologies form the core of an open source software framework that supports the processing of large and diverse data sets across clustered systems.

Hadoop

Hadoop is a free, Java-based programming framework that supports the processing of large data sets in a distributed computing environment. It is part of the Apache project sponsored by the Apache Software Foundation.Hadoop makes it possible to run applications on systems with thousands of nodes involving thousands of terabytes. Its distributed file system facilitates rapid data transfer rates among nodes and allows the system to continue operating uninterrupted in case of a node failure. This approach lowers the risk of catastrophic system failure, even if a significant number of nodes become inoperative.

MapReduce

MapReduce is a software framework that allows developers to write programs that process massive amounts of unstructured data in parallel across a distributed cluster of processor or stand-alone computers. It was developed at Google for indexing Web pages and replaced their original indexing algorithims and heuristics in 2004.The framework is divided into two parts:

1. Map, a function that parcels out work to different nodes in the distributed cluster.
2. Reduce , another function that collates the work and resolves the results into a single value.
3. The MapReduce framework is fault tolarent because each node in the cluster is expected to report back periodically with completed work and status updates. If a node remains silent for longer than the expected interval, a master node makes note and re-assigns the work to other nodes.

Application :

Understanding and Targeting Customers

This is one of the biggest and most publicized areas of big data use today. Here, big data is used to better understand customers and their behaviours and preferences. Companies are keen to expand their traditional data sets with social media data, browser logs as well as text analytics and sensor data to get a more complete picture of their customers. The big objective, in many cases, is to create predictive models.

Understanding and Optimizing Business Processes

Big data is also increasingly used to optimize business process. Retailers are able to optimize their stock based on predictions generated from social media data, web search trends and weather forecasts. One particular business process that is seeing a lot of big data analytics is supply chain or delivery route optimization. Here, geographic positioning and radio frequency identification sensors are used to track goods or delivery vehicles and optimize routes by integrating live traffic data.

Improving Science and Research

Science and research is currently being transformed by the new possibilities big data brings. Take, for example, CERN, the Swiss nuclear physics lab with its Large Hadron Collider, the world's largest and most powerful particle accelerator. Experiments to unlock the secrets of our universe – how it started and works - generate huge amounts of data. The CERN data center

has 65,000 processors to analyze its 30 petabytes of data. However, it uses the computing powers of thousands of computers distributed across 150 data centers worldwide to analyze the data. Such computing powers can be leveraged to transform so many other areas of science and research.

Optimizing Machine and Device Performance

Big data analytics help machines and devices become smarter and more autonomous. For example, big data tools are used to operate Google's self driving car. The Toyota Prius is fitted with cameras, GPS as well as powerful computers and sensors to safely drive on the road without the intervention of human beings. Big data tools are also used to optimize energy grids using data from smart meters. We can even use big data tools to optimize the performance of computers and data warehouses.

Future Work

Although our infrastructure is used for real-world applications, we treat these systems as a research platform and expect it to continuously evolve as the state-of-the-art advances. We have developed our knowledge discovery principles during the course of implementing these applications and standing up our own systems.

Conclusions

The big data movement has energized the software architecture world, and it has introduced complex, interesting questions for the community. As organizations continue to collect more data at this scale, formalizing the process of big data analysis will become paramount. In this paper, we introduced principle that we believe can guide organizations into developing a sound, useful, and flexible data analysis pipeline.We have instantiated these principles in our own infrastructure and havefound the principle to be useful guides.

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The Role of Cloud Computing in Education

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Abstract:

Cloud computing as an exciting development in a educational Institute and online marketing perspective. Students and administrative personnel have the opportunity to quickly and economically access various application platforms and resources through the web pages on-demand. Application of storage technology can significantly reduce the amount of cloud storage servers, thereby reducing system development costs; reduce the system caused by the server a single point of failure.

Cloud storage services meet this demand by providing transparent and reliable storage solutions In this paper shows that the cloud computing plays an important role in the fields of Educational and online Marketing and it is helpful to provide the data to the Students and online customer respectively. The results show the beneficial of the cloud computing in Educational and online marketing for customers.

Keywords: virtualization, security, cloud computing, web based storage, distributed data base.

Introduction

The nature of the Internet was constantly changing from a place used to read web pages to an environment that allows end-users to run software applications. The need for education is increasing constantly and the development and the improvement of the e-learning solutions is necessary. Also, the E- learning systems need to keep the pace with the technology, so the new direction is to use cloud computing. Cloud computing is becoming an attractive technology because of its dynamic scalability and effective usage of the resources; it can be utilized under circumstances where the availability of resources is limited.

The need for education is increasing constantly and the development and the improvement of the e-learning solutions is necessary. cloudbased applications reduce infrastructure and IT costs, increase accessibility, enable collaboration, and allow organizations more flexibility in customizing their products both for their brand and for their audience.The benefits of cloud computing are being recognized in almost all kinds of institutions across the board, with 90 percent of organizations currently using some kind of cloud-based application. First, let us understand what exactly cloud computing is and what services it provides.

Cloud Computing Challenges:

The reason for the success of Cloud computing lies in its easy-to-use computing model and the benefits it brings to the users. Cloud computing has emerged as an important solution offering enterprises a potentially cost effective model to ease their computing needs and accomplish business objectives. Some features of cloud computing are:

1. Optimized Server Utilization

As most enterprises typically underutilize their server computing res
will manage the server utilization to the optimum level.





2. On-Demand

Cloud computing provides users with customized environments that are tailed to individual requirement. This feature is more user friendly than Grid computing where the application has usually to be adapted to the target architecture.

3. Dynamic Scalability

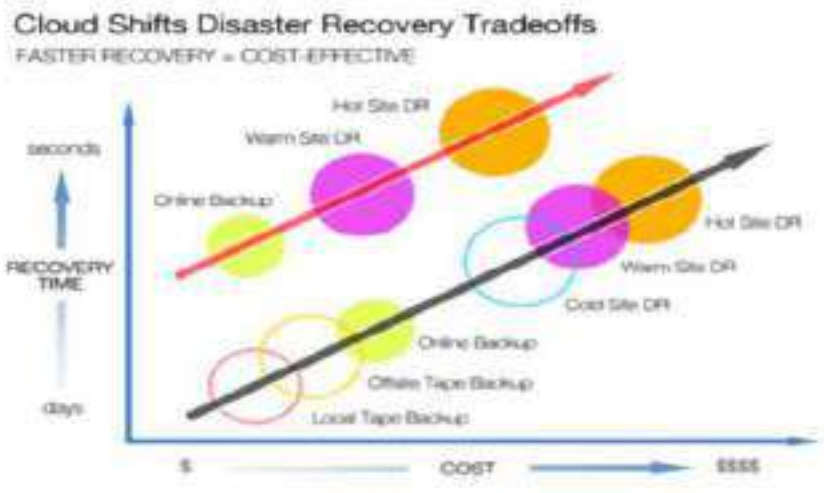
Many enterprises include a reasonably large buffer from their average computing requirement, just to ensure that capacity is in place to satisfy peak demand. Cloud computing provides an extra processing buffer as needed at a low cost and without the capital investment or contingency fees to users.

4. Disaster Recovery

It is a concern of enterprises about the resiliency of cloud computing, since data may be commingled and scattered around multiple servers and geographical areas. It may be possible that the data for a specific point of time cannot be identified. Unlike traditional hosting, the enterprise knows exactly where the location is of their data, to be rapidly retrieved in the event of disaster recovery. In the cloud computing model, the primary CSP may outsource capabilities to third parties, who may also outsource the recovery process. This will become more complex when the primary CSP does not ultimately hold the data. The Cloud technology is currently still in the development phase. As the sensitive applications and data are moved into the cloud data centers, run on virtual computing resources in the form of virtual machine. One of the most significant advantages to cloud computing is how it changes disaster recovery, making it more cost-effective and lowering the bar for enterprises to deploy comprehensive DR plans for their entire IT infrastructure.

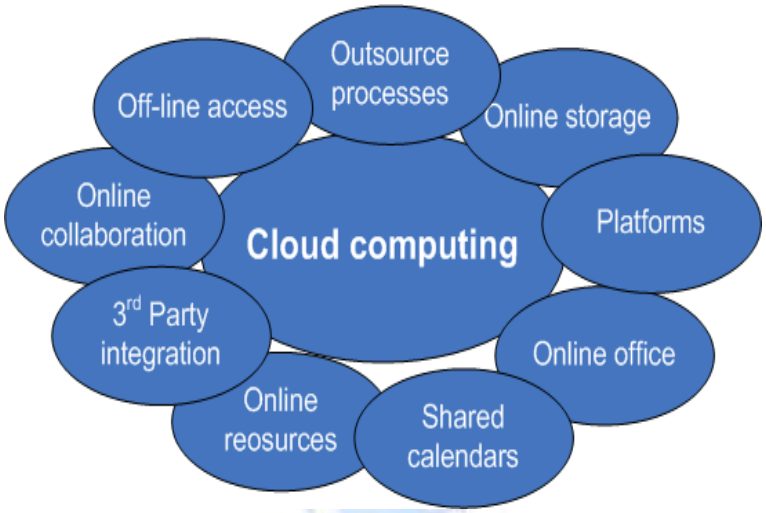
Cloud Computing delivers faster recovery times and multi-site availability at a fraction of the cost of conventional disaster recovery. With cloud computing, warm site disaster recovery becomes a very cost-effective option where backups of critical servers can be spun up in minutes on a shared or private cloud host platform. Applications and servers that are deemed less critical in a disaster can be tuned down with less resources, while assuring that the most critical applications get the resources they need to keep the business running through the disaster.

And many more application of cloud computing work but the above applications and the challenges in it.



Educational Usage Of Cloud Computing.

There was a time when, to use files (word processing files, spreadsheets, etc.) on different computers. Cloud computing is a new business model wrapped around new technologies like virtualization, SaaS and broadband internet. The safety, stability, and ease-of-use of cloud computing in education is resulting in widespread adoption in educational institutions of all sizes and types. loud computing entails using a network of remote servers hosted on the internet as opposed to a local server. This helps cut IT costs as well as simplifies content management processes for schools and educational systems. The results of a survey that have been completed in 2009 by Gartner analysts (Figure 1) about the IT trends (especially cloud computing) show that it is being used more in the areas of finance and business when compared to other sectors.



1. Back Up

An important function of the Cloud is that it automatically saves content, making it impossible to lose or delete any valuable material. This means that even if a computer crashes, all documents and content will remain safe, saved, and accessible in the cloud.

2. Storage

The Cloud allows its users to store almost all types of content and data including music, documents, eBooks, applications, photos, and much more. We share the information of Attendance and Assignment in our Institute of students in Google doc and share all the information of students on doc via using an ERP Software and utilize the cloud resources.

3. Accessibility

Any data stored in the Cloud can easily be accessed from almost any device including mobile devices such as phones or tablets. In our institute an URL provide to the students for accessing the data inside the campus or outside the campus.

4. Collaboration

The Cloud allows multiple users to work on and edit documents at the same time, it enables effortless sharing and transmission of ideas. It also provides the security to edit only those people who gain the right from admin. With this feature, group projects and or collaborative lesson plans can be optimized for both teachers and students.

5. Resource and Time Conscious

With the availability of content online, it is no longer necessary for teachers to spend time and resources printing or copying lengthy documents or lesson plans. Now, students are able to access homework assignments, lesson notes, and other materials online like ERP Systems of education institute and parents also see the details of the students. Cloud can be used in underdeveloped or emerging countries creating a way of being able to teach children who would not ordinarily have access to education. Students and teachers can share their work without having to use paper. Using paper is costly both to the environment and in monetary terms and is therefore no longer a viable way to educate.

Adavantages cloud computing in E-Commerce

For describing the different aspects of an online commerce systems, digitally enabled commercial transactions between and among organizations and individuals. Cloud computing is now evolving like never before, with companies of all shapes and sizes adapting to this new technology. The Figure 4 shows a high-level view on an E-commerce system's architecture. If used properly and to the extent necessary, working with data in the cloud can vastly benefit all types of businesses. Industry experts believe that this trend will only continue to grow and develop even further in the coming few years. While cloud computing is undoubtedly beneficial for mid-size to large companies, it is not without its downsides, especially for smaller businesses.

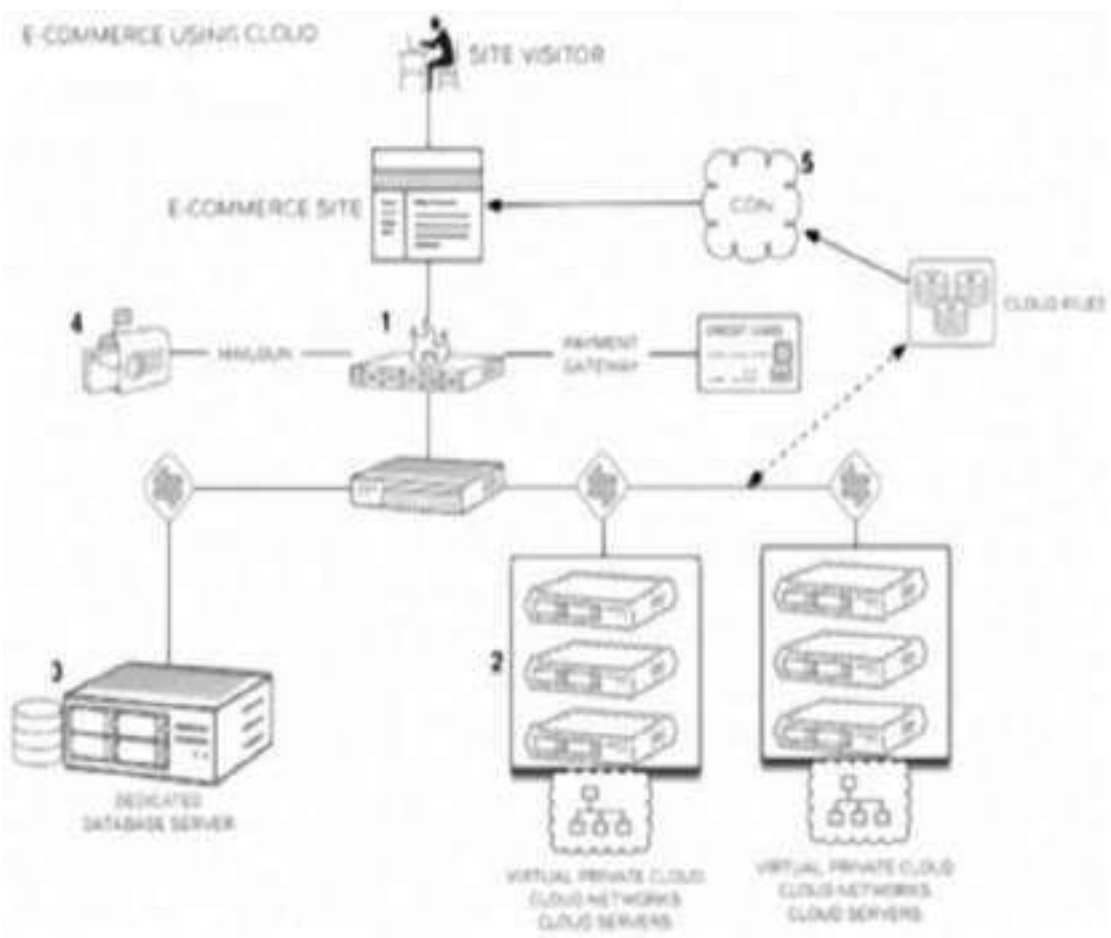


Fig:-E-commerce System

1. Unlimited Accessibility

Developing a business means being constantly connected With Cloud, you can manage your online shop from anywhere and at any time. A browser and an Internet connection are all it takes to process orders, interact with customers, schedule deliveries or generate invoices.

2. Security and Stability

Security is one of the most important advantages of the Cloud technology. In the Cloud system, the data of each client is completely partitioned, so that none of the areas interferes with the others. The connection to the servers is secured according to the highest standards, making sure that you are the only one with access to your data. It's like having your own server, without paying considerable amounts of money.

3. Full Scalability

Your business grows, so will your technical requirements. Unlike open source ecommerce solutions, which would normally require new investments for extending the technical infrastructure, a Cloud ecommerce system will always be ready to efficiently sustain your new volume of clients, orders, traffic and continuously growing product catalog.

4. Minimal Costs or No Costs

Cloud solution for E-Commerce, you don't need to worry about the initial investments. You don't need to buy your own server or pay for a separate hosting service. Depending on your business needs, you can always increase or limit the amount of resources you use and also optimize your costs thanks to the scalability of the system.

Cloud computing is probably the most cost efficient method to use, maintain and upgrade. Traditional desktop software costs companies a lot in terms of finance. Adding up the licensing fees for multiple users can prove to be very expensive for the establishment concerned.

5. Quick Deployment

Lastly and most importantly, cloud computing gives you the advantage of quick deployment. Once you opt for this method of functioning, your entire system can be fully functional in a matter of a few minutes. Of course, the amount of time taken here will depend on the exact kind of technology that you need for your business.

Various Types Of Services Provided By Cloud

A. SaaS (Anytime Anywhere apps)

It stands for Software as a Service. It describes any cloud service where consumers are able to access software applications over the internet. The applications are hosted in ―the cloud and can be used for a wide range of tasks for both individuals and organizations. Google, Twitter, Facebook and Flickr are all examples of SaaS, with users able to access the services via any internet enabled device. SaaS is beneficial to organizations in many ways like no additional hardware costs, no initial setup costs, usage is scalable, updates are automated, accessible from any location etc. This cloud service allows educational institutions to subscribe to online software hosted by a cloud provider. If proprietary software is used, educational institutions need to pay for the usage of the software. SaaS removes the need for organizations to install and run applications on their own computers or in their own data centers. This eliminates the expense of hardware acquisition, provisioning and maintenance, as well as software licensing, installation and support

B. PaaS (the operating environment in which applications run)

It stands for Platform as a Service. It is a category of cloud computing that provides a platform and environment to allow developers to build applications and services over the internet. PaaS services are hosted in the cloud and accessed by users simply via their web browser (ex: Google App Engines etc.).Platform as a Service allows users to create software applications using tools supplied by the provider. Services are constantly updated, with existing features upgraded and additional features added. It supplies an operating environment for developing applications. Some of the benefits of PaaS are: they don't have to invest in physical infrastructure, flexibility, adaptability, teams in various locations can work together, security etc. IT courses that require hands-on practice on a client-server structure, such as database systems or application development courses, PaaS is the one to use. PaaS does not typically replace a business' entire infrastructure. Instead, a business relies on PaaS providers for key services, such as Java development or application hosting. C. IaaS (the on-demand data centres) It Stands for Infrastructure as a Service. It provides access to computing resource in a virtualized environment, ―the Cloud, across a public connection, usually the internet. In the case of IaaS the computing resource provided is specifically that of virtualized hardware, in other words, computing infrastructure. The definition includes such offerings as virtual server space, network connections, bandwidth, IP addresses and load balancers. Some benefits of IaaS are: scalability, no investment in hardware, utility style costing, location independence, physical security of data centre locations etc. Microsoft Windows Azure and Amazon Web Service (AWS) provide IaaS. This service can mainly be used to satisfy the infrastructure needs of the students, faculties or researcher globally or locally with some specific hardware configuration for a specific task. IaaS platforms offer highly scalable resources that can be adjusted on-demand. This makes IaaS well-suited for workloads that are temporary, experimental or change unexpectedly

Implementation Of Cloud Technology In Education System

Cloud computing technology can provide solutions for the above mentioned problems in education system. Cloud computing enables users to control and access data via the Internet.The main users of a typical higher education cloud include students, Faculty, administrative staff, Examination Branch and Admission Branch as shown in Figure 1. All the main users of the institution are connected to the cloud .Separate login is provided for all the users for their respective work. Teachers can upload their class Tutorials, assignments, and tests on the cloud server which students will be able to access all the teaching material provided by the teachers via Internet using computers and other electronic devices both at home and college and 24X7. The education system will make it possible for teachers to identify problem areas in which students tend to make mistakes, by analyzing students' study records. In doing so, it will also allow teachers to improve teaching materials and methods. This will not only make it possible for students to use online teaching materials during class but they will also be able to access these materials at home, using them to prepare for and review lessons. Utilization of cloud computing systems will reduce the cost of operation because servers and learning materials are shared with other colleges

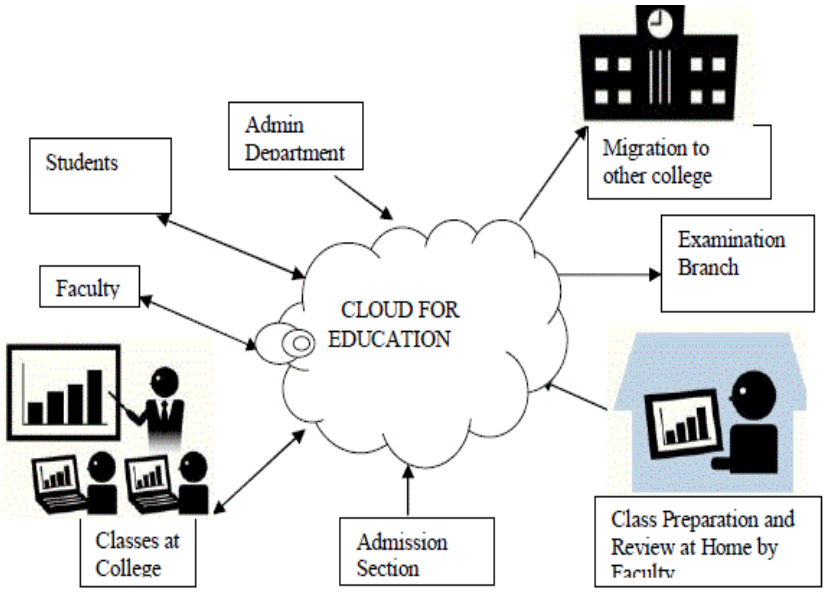


Figure 1: Services attached to Education Cloud

Figure 2: Users of an Education Cloud Computing System

In the traditional deployment model, all Information Technology resources are housed and managed in-house. Many aspects of these services and tools may be migrated to the cloud and consumed directly over the Internet either as fully functional applications (SaaS), development platforms (PaaS) or raw computing resources (IaaS).Figure 2 shows how the different categories of university users may consume cloud services.

Benefits Of Cloud Computing For Institutions And Students

1. Personalized Learning: Cloud computing affords opportunities for greater student choice in learning. Using an Internet-connected device, students can access a wide array of resources and software tools that suit their learning styles and interests.
2. Reduced Costs: Cloud-based services can help institutes reduce costs and accelerate the use of new technologies to meet evolving educational needs. Students can use office applications for free without having to purchase, install and keep these applications up to date on their computers. It also provides the facility of Pay per use for some applications.
3. Accessibility: Availability of the services is the most important and desired by the user using the education cloud.24 X7 is the availability that is needed by this system without failure. From anywhere one can login and access the information.
4. No Extra Infrastructure: Colleges and governments are now free to focus on their goals that is making more research facilities available to the students and making the environment global in spite wasting time on worrying about the buildings, labs, teachers etc.
5. Go Green: Education cloud will surely reduce the carbon footprint. 6. User Friendly: This new facility is user friendly and no need to worry about the complexity. It is easy to understand and easy to operate

Conclusion

Although still quite a vague term for some, cloud computing is definitely one of the major innovations that entered worldwide classrooms in recent years. With the ability to cut IT costs and at the same time create a modern collaborative

The cloud allows us to access our work anywhere, anytime and share it with anyone. It frees us from needing a particular machine to access a file or an application like a word processor or spreadsheet program. In the present paper a cloud education system is introduced and how it is beneficial for students, faculty and the educational institutes for providing quality education

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Multiple quantitative structure-activity relationships (QSARs) analysis for orally active trypanocidal N-myristoyltransferase inhibitors

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Human African trypanosomiasis

ABSTRACT

In the present work, OECD guidelines have been followed for developing QSAR (Quantitative Structure-Activity Relationship) models for anti-HAT (Human African trypanosomiasis) activity of two hundred and seventy pyrazole sulphonamides. The newly developed easily interpretable multiple QSAR models have been successful in identification of many privileged as well as under-privileged molecular descriptors, which could be highly useful for future use of these models by expert and non-experts of QSAR. The multiple QSAR models satisfy threshold values for many statistical parameters such as $R^2 = 0.80–0.83$, $Q^2 = 0.79–0.81$, $CCC_{ext} = 0.82–0.84$, etc. thereby assuring good external predictive ability of the models. The multiple QSAR and pharmacophoric models successfully identified that *N*,4-disubstituted-benzenesulfonamide moiety, frequency of occurrence of H-bond acceptor from Oxygen atom within nine bonds and some other pharmacophoric features that govern the anti-HAT activity of pyrazole sulphonamides. The results could be very useful to synthetic/medicinal chemists for future modifications of pyrazole sulphonamides as drug candidates.

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1. Introduction

Human African trypanosomiasis (HAT) or sleeping sickness is a vector-borne disease transmitted by the bite of an infected tsetse fly. The disease is life-threatening, if not treated properly. This disease is caused by two subspecies of the protozoan parasite *Trypanosoma brucei* (*T. b. gambiense* and *T. b. rhodesiense*) [1–6]. Although drugs like Pentamidine, Nifurtimox, Fexinidazole, etc. (see Fig. 1) are available for the treatment of this disease, unfortunately none of them is found to be satisfactory due to toxicity, treatment failures owing to resistance, and the requirement for parenteral administration, which is unsuitable in a rural African setting [2–5,7–11]. Therefore to curb this neglected disease, there is a high need to develop new drugs which target different enzyme or have different mode of action than existing drugs [12–15].

Recently, the enzyme N-myristoyltransferase (NMT) (EC 2.3.1.97), a genetically and chemically validated drug targets in kinetoplastids, has appeared as a promising drug target for the treatment of HAT, due to its essentialness for the parasite [16–18]. In mouse model experiments, it has been found that by blocking NMT in *T. brucei* leads to knockdown of RNAi. This leads to little or no possibility of *T. brucei* survival. Further, it has been pointed out that inhibition of NMT would be expected to have pleiotropic effects through its potential to affect multiple pathways. To add further, NMT has also been identified as a promising target for the treatment of other parasitic diseases including malaria, leishmaniosis, and Chagas disease. Therefore, development of a potential inhibitor of NMT is an attractive area for developing an anti-parasitic drug [16–19].

*Abbreviations: Tb*NMT, *Trypanosoma brucei* N-myristoyltransferase; HAT, Human African Trypanosomiasis; GA, Genetic algorithm; MLR, Multiple linear Regression; QSAR, Quantitative structure-activity analysis; WHO, World health organisation; ADMET, Absorption, Distribution, Metabolism, Excretion and Toxicity; OLS, Ordinary Least Square; QSARINS, QSAR Insubria; OECD, Organisation for Economic Co-operation and Development; OFS, Objective Feature Selection; SFS, Subjective Feature Selection.

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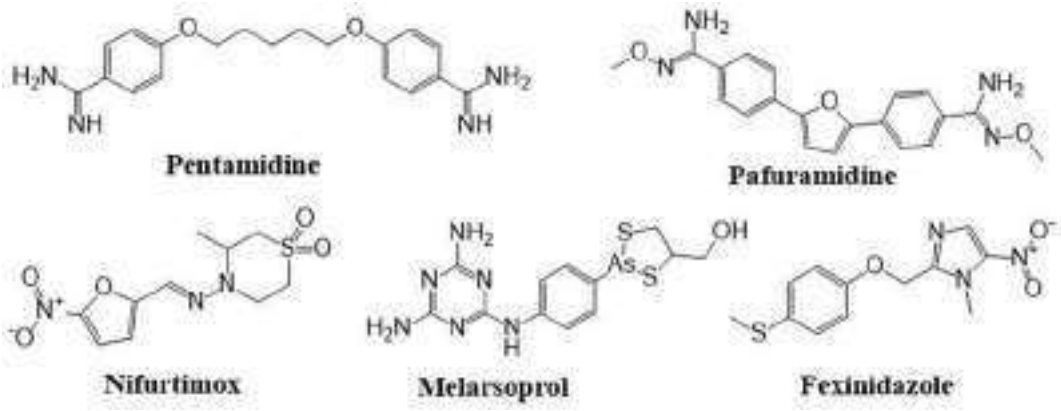


Fig. 1. Some marketed drugs for HAT.

To develop a potent NMT inhibitor, Brand et al. performed high-throughput screening (HTS) against the enzyme NMT using a library of 62,000 compounds, and identified a series of pyrazole sulphonamides as promising inhibitors for developing anti-parasitic therapeutics against *T. brucei* [16,17,19]. In continuation, they synthesized a good number of pyrazole sulphonamides and screened for *in vitro* activity against TbNMT (*T. brucei* NMT), HsNMT (Human NMT) and blood-brain barrier crossing ability, etc. The analysis revealed that many newly synthesized compounds possess activity in μM to nM range with moderate to high blood-brain barrier crossing ability, selectivity for TbNMT, metabolic instability and poor tolerance [16,17,19]. Therefore, effective modifications are necessary to achieve the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) associated goals with retained or improved anti-HAT activity. In such a situation, computer aided drug design (CADD) is an attractive tool for further lead optimization.

In recent time, computer aided techniques have emerged as economical viable alternatives to conventional 'trial and error' methodology of drug design/discovery to understand pharmacophoric requirements for simplification of lead and drug optimization. CADD is a fast and significantly result oriented popular modern technique. It encompasses unification of different scientific fields with main prominence on understanding the interactions of biologically significant molecules, to explore the key steps for disease treatment and to identify the important structural patterns governing with activity/toxicity of a molecule. When popularly used CADD methods viz. QSAR, molecular docking, pharmacophore modeling, molecular dynamics simulations, etc. [20–23] are utilized concurrently then the analysis provides effective information required for lead (and drug) optimization. These methods deliver thorough understanding of pharmacophoric patterns associated with specific activity/toxicity of a drug candidate [24–28].

Even though, Singh et al. [29] developed a 3D-QSAR (CoMFA) model, but the model was developed using small dataset of forty-one molecules only and has poor statistical performance with $r^2 = 0.571$ for the prediction set. A QSAR model is highly useful when it has good external predictive ability and interpretation in terms of structural features [30]. Hence, in the present work, first attempt has been made to develop 2D-QSAR (ligand based drug design technique) using a larger dataset of two hundred and seventy pyrazole sulphonamides using easily understandable molecular descriptors to identify the structural features that have good correlation with the HAT healing activity of pyrazole sulphonamides. Therefore, a better understanding of structural features governing anti-HAT activity of pyrazole sulphonamides would be of high importance to any drug discovery effort.

2. Experimental methodology

2.1. Experimental dataset

In the present work, anti-HAT activity values, reported by Brand et al. [16,17,19], of a diverse dataset of two hundred and seventy pyrazole sulphonamide derivatives covering different cyclic rings and a variety of substituents were subjected to QSAR analysis (See Fig. 2 and Table ST0 in supplementary material). Due to good variation in the type of substituents, the present dataset includes different types of isomers like positional, functional, etc. Consequently, the dataset covers a good chemical space.

The reported IC_{50} (μM) activity values for anti-HAT were converted to pIC_{50} ($pIC_{50} = -\log_{10}IC_{50}$) before QSAR analysis [31]. The IC_{50}, pIC_{50} along with SMILES notations of the molecules have been

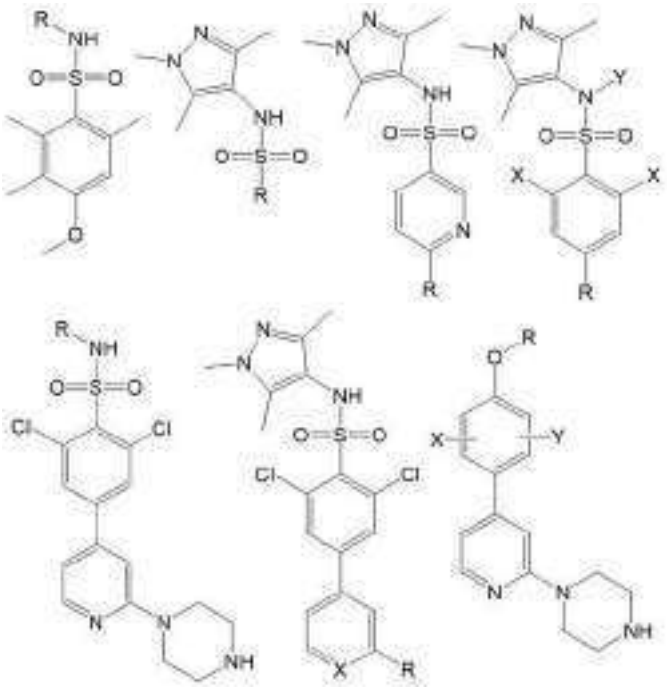


Fig. 2. Variations in pyrazole sulphonamide derivatives used in the present QSAR analysis.

tabulated in table ST0 in supplementary material.

2.2. Modeling and molecular descriptors calculation

In the present work, OECD guidelines and standard protocol suggested and applied by different researchers have been followed for successful QSAR analysis [32–37]. The standard protocol involves (1) Structure drawing: ChemSketch 12 freeware (www.acdlabs.com) was used for structure drawing, (2) Structure Optimization: It was performed using MMFF94 force field available in Avogadro software (v. 1.2) using following settings: ForceField: MMFF94, Algorithm: Steepest Descent, number of steps used for optimization: 1000. (3) Descriptor calculation: The energy minimized 3D-structures were subjected to calculation of myriad number of molecular descriptors (>29,000) using PaDEL 2.21 [38] and *PyDescriptor* [39,40] as a molecular descriptor calculator. (4) Removal of redundant variables: The molecular descriptor pool comprises 1D-to 3D-, electro-topological, finger-prints and other molecular descriptors. As all the calculated descriptors do not encompass important information, hence, objective feature selection (OFS) was accomplished using QSARINS-Chem 2.2.2 [41,42] to exclude all the redundant molecular descriptors. For this, constant, near constant (>98%) and highly correlated ($|R| > 90\%$) descriptors were rejected. OFS resulted in substantial reduction of descriptor pool to a cluster of 1384 molecular descriptors, still covering broad structural and chemical space viz. constitutional (0D-), mono-dimensional (1D-), bi-dimensional (2D-) and three-dimensional (3D-).

2.3. Model development

The QSAR analysis can be used for two types of purposes [43]: (1) Qualitative QSAR: To identify the structural/pharmacophoric features, which are responsible for the activity/toxicity profile of a con-generic series of molecules and (2) Quantitative QSAR: To estimate the activity/toxicity of a molecule before its synthesis and/or biological screening. In the present work, emphasis is on deriving Qualitative as well as Quantitative QSAR models. For this, the strategy reported in our earlier work was employed [44], in which, multiple MLR (Multilinear regression) models were built using undivided dataset, 50% training set and validating them on remaining set (50% prediction set) using random splitting. In next step, the training and the prediction sets were exchanged to develop new multiple models and validating on prediction set (which was initially the training set). This confirms that all significant structural features, which influence the anti-HAT activity of these molecules, are captured during QSAR analysis. In addition, multiple QSAR models were derived using randomly divided (training-85% and prediction-15% set prior to descriptor selection) dataset to verify the capturing of all the relevant structural and activity information (see Fig. 3). The GA (Genetic Algorithm) module of QSARINS-Chem 2.2.2 (Q^2_{loo} as the fitness function) [33,34] was used for selection of optimum number and set of molecular descriptors for each model. For every procedure used for model building, variable selection (descriptor selection) was performed separately every time, that is when using undivided dataset, divided dataset (training: 50, prediction: 50) and divided dataset (training: 85, prediction: 15). The analysis revealed that up to six descriptors there was increase in the value of Q^2_{loo}, but afterwards, it had sharp drop. Hence, the heuristic search was restricted to six descriptors using the defaults settings to avoid over-fitting and have simplicity in understanding the developed QSAR models.

2.4. Model validation

QSAR analysis is unreliable if not validated properly. Appropriate QSAR model validation confirms the external predictive ability of a developed model. Therefore, the statistical qualities and strength of QSAR models were evaluated on the basis of: (a) internal validation: through cross-validation (CV) by leave-one-out (LOO) and leave-many-out (LMO) procedure, (b) external validation: using the prediction set (c) data randomization: by Y-randomization and (d) observing if the following criteria are satisfied: $R^2_{tr} \geq 0.6$, $Q^2_{loo} \geq 0.5$, $Q^2_{LMO} \geq 0.6$, $R^2 > Q^2$, $R^2_{ex} \geq 0.6$, $RMSE_{tr} < RMSE_{cv}$, $\Delta K \geq 0.05$, $CCC \geq 0.80$, $Q^2\text{-}F^n \geq 0.60$, $r^2_m \geq 0.5$, $(1\text{-}r^2/r^2_o) < 0.1$, $0.9 \leq k \leq 1.1$ or $(1\text{-}r^2/r'^2_o) < 0.1$, $0.9 \leq k' \leq 1.1$, $|r^2_o - r'^2_o| < 0.3$ with *RMSE* and *MAE* as low as possible [2,3,11,45–47]. A QSAR model that fulfills the threshold values of above parameters has statistical robustness and good external predictive ability. Consequently, the models that do not fulfil above stated measures were excluded.

3. Results and discussion

QSAR models: Generally, for QSAR model development stepwise regression, GA, etc. algorithms are employed for subjective feature selection (SFS). This results in a good number of MLR



Fig. 3. Strategy adopted in the present work for QSAR analysis.

models having almost equivalent statistical performance, but often involving dissimilar descriptors. Usually, in such a situation, a QSAR modeler selects only one MLR model on the basis of its statistical robustness. This 'first among equals' approach has some serious drawbacks such as [2,3,11,45–47] (1) if the selected QSAR model consist of complex/esoteric descriptors then identification of smooth correlation of descriptors with appropriate structural features is relatively complicated, (2) a single QSAR model may be affected by (i) the method of splitting, composition of training and prediction sets, method implemented for descriptor selection, and (ii) some more influencing molecules in the training/prediction dataset. An easy but highly feasible solution, to overcome above-mentioned shortcomings of 'first among equals' approach, is to create multiple QSAR models based on multiple splitting. Another advantage of this solution lies in its ability to identify under-privileged yet important pharmacophoric/structural features associated with the anti-HAT activity of pyrazole sulphonamides. Consequently, in the present study, multiple QSAR models have been built. Interestingly, univariate statistical analysis for undivided dataset pointed out that anti-HAT activity has good and positive correlation ($R = 0.769$) with the descriptor C_AbSA, which signifies the absolute surface area of carbon atoms. The developed multi-linear GA-MLR QSAR models are as following:

Model-1 (Training: 50%, Prediction: 50%):

$\mathbf{pIC_{50}} = 3.33\ (\pm0.84) + 0.85\ (\pm0.36)$ * **fOacc9B** $+ 0.12\ (\pm0.01)$ * **plus_N_9B** $+ 0.39\ (\pm0.15)$ * **ringC_hy2** $- 0.15\ (\pm0.05)$ * **com_ringC_5A** $- 1.07\ (\pm0.29)$ * **AD2D327** $+ 0.12\ (\pm0.05)$ * **APC2D7_N_X**.

Model-2 (Training: 50%, Prediction: 50%):

$\mathbf{pIC_{50}} = 5.77\ (\pm0.48) - 0.15\ (\pm0.06)$ * **fOringC3A** $- 0.82\ (\pm0.28)$* **fON6B** $+ 0.96\ (\pm0.31)$* **fSacc8B** $- 0.09\ (\pm0.03)$ * **ringC_O_9B** $+ 0.26\ (\pm0.04)$* **SssCH2** $+ 4.68\ (\pm1.36)$* **GGI8**.

Model-3 (Training: 85%, Prediction: 15%):

$\mathbf{pIC_{50}} = 5.45\ (\pm0.23) + 1.74\ (\pm0.32)$ * **fOacc9B** $+ 0.83\ (\pm0.29)$ * **KRFP3542** $+ 0.51\ (\pm0.18)$ * **AD2D636** $+ 0.23\ (\pm0.04)$ * **SssCH2** $- 0.22\ (\pm0.09)$ * **com_ringN_6A** $- 0.21\ (\pm0.10)$ * **fNringC6B**.

Model-4 (Training: 85%, Prediction: 15%):

$\mathbf{pIC_{50}} = 3.49\ (\pm0.49) + 1.55\ (\pm0.32)$ * **fOacc9B** $+ 0.10\ (\pm0.01)$ * **plus_N_9B** $+ 1.06\ (\pm0.29)$ * **KRFP3542** $+ 0.87\ (\pm0.19)$ * **AD2D636** $- 0.13\ (\pm0.05)$ * **com_Cplus_7A**$- 0.19\ (\pm0.09)$ * **SubFPC1**.

Model-5 (Training: 100%):

$\mathbf{pIC_{50}} = 3.47\ (\pm0.47) + 1.35\ (\pm0.30)$ * **fOacc9B** $+ 0.08\ (\pm0.01)$ * **plus_N_9B** $+ 1.02\ (\pm0.26)$ * **KRFP3542** $+ 0.94\ (\pm0.18)$ * **AD2D636** $- 0.13\ (\pm0.04)$ * **com_Cplus_7A** $- 0.45\ (\pm0.20)$ * **ringN_don_2Ac**.

The statistical parameters along with their details for all the derived models have been tabulated in Table 1. Further details of the statistical parameters are available in supplementary material.

Table 1
Statistical parameters for newly derived models 1–5 in the present work.

S.No.	Statistical Parameter	Model-1	Model-2	Model-3	Model-4	Model-5
	N_{tr}	135	135	230	230	270
	N_{ex}	135	135	40	40	–
Fitting Criteria						
	R^2_{tr}	0.83	0.83	0.81	0.81	0.80
	$R^2_{adj.}$	0.83	0.82	0.81	0.80	0.80
	LOF	0.40	0.43	0.44	0.44	0.46
	Kxx	0.25	0.23	0.27	0.27	0.31
	ΔK	0.10	0.11	0.10	0.09	0.08
	$RMSE_{tr}$	0.59	0.60	0.63	0.63	0.65
	MAE_{tr}	0.48	0.48	0.50	0.50	0.52
	RSS_{tr}	47.42	48.00	91.20	91.30	112.86
	CCC_{tr}	0.91	0.91	0.90	0.89	0.89
	s	0.61	0.61	0.64	0.64	0.66
	F	106.90	104.45	160.37	158.16	176.89
Internal Validation Criteria						
	R^2_{cv} (Q^2loo)	0.82	0.81	0.80	0.80	0.79
	$RMSE_{cv}$	0.62	0.63	0.65	0.65	0.66
	MAE_{cv}	0.50	0.50	0.52	0.51	0.53
	$PRESS_{cv}$	52.58	53.59	97.80	97.48	119.54
	CCC_{cv}	0.90	0.90	0.89	0.89	0.88
	Q^2_{LMO}	0.81	0.81	0.79	0.80	–
	R^2_{Yscr}	0.04	0.04	0.03	0.03	–
	Q^2_{Yscr}	−0.06	−0.06	−0.04	−0.04	–
External Validation Criteria						
	θ^*	−6.61	−9.22	−8.38	−10.27	–
	$RMSE_{ex}$	0.85	0.79	0.81	0.78	–
	MAE_{ex}	0.63	0.65	0.69	0.57	–
	$PRESS_{ext}$	97.46	83.33	25.94	24.19	–
	R^2_{ex}	0.68	0.71	0.70	0.74	–
	Q^2-F^1	0.66	0.71	0.69	0.73	–
	Q^2-F^2	0.66	0.71	0.69	0.73	–
	Q^2-F^3	0.66	0.71	0.69	0.71	–
	CCC_{ex}	0.82	0.83	0.83	0.84	–
	r^2m *aver.*	0.56	0.59	0.58	0.57	–
	r^2m *delta*	0.07	0.22	0.14	0.24	–
	R^2-*ExPy*	0.68	0.71	0.70	0.74	–
	R'^2_o	0.63	0.61	0.63	0.58	–
	k'	1.00	1.00	0.97	1.00	–
	1-(R^2/R'^2_o)	0.07	0.15	0.10	0.21	–
	r'^2m	0.53	0.48	0.51	0.45	–
	R^2_o	0.66	0.71	0.69	0.73	–
	k	0.98	1.00	1.01	0.98	–
	1-(R^2-*ExPy*/R^2_o)	0.02	0.00	0.01	0.01	–
	r^2m	0.59	0.70	0.65	0.69	–

The experimental and predicted pIC_{50} by various models along with the status of the molecule are available in the supplementary material.

From Table 1, it is clear that all the developed QSAR models have acceptable statistical performance and satisfy threshold values for many parameters. Consequently, models 1–4 possess good external predictive ability, which is reflected from high value of Q^2-F^n, R^2_{ex}, CCC_{ex}, etc. as well as robust with respect to internal validation ($R^2_{cv} > 0.80$, $CCC_{cv} > 0.87$, etc.). Therefore, the models could be useful for prediction of anti-HAT activity for yet-to-be synthesized pyrazole sulphonamide derivatives. The close value of $R^2_{adj.}$ with R^2_{tr}, for all the models, indicates that the models have been built using appropriate number of molecular descriptors. The statistical significance of all the developed models is reflected from the high value of Fischer ratio (F) [2,3,11,45–47].

The descriptor **fOacc9B**, which stands for frequency of occurrence of H-bond acceptor atom from oxygen atom within nine bonds, has a positive coefficient in model 1, 3, 4 and 5. Hence, any increase in occurrence of H-bond acceptor atom from oxygen atom at nine bonds will be favourable for activity augmentation. Some interesting examples that prove the role of this descriptor are following compared pairs of molecules: **37** ($IC_{50} = 0.29$ μM) with **41** ($IC_{50} = 0.002$ μM) though**37** and **41** are positional isomers, **48** ($IC_{50} = 0.007$ μM) with **41** ($IC_{50} = 0.002$ μM).

The molecular descriptor **plus_N_9B**, which corresponds to the presence of positively charged atoms at a distance of nine bonds from N atoms, has positive coefficient in model 1, 4, and 5. Therefore, such a combination of N and positively charged atoms is beneficial for increasing activity against NMT.

In model 3, 4, and 5, the 2D-molecular descriptor **KRFP3542** (represents *N*,4-disubstituted-benzenesulfonamide moiety) has positive coefficient. Therefore, the presence of *N*,4-disubstituted-benzenesulfonamide moiety is in favour of anti-HAT activity of pyrazole sulphonamides.

In the model 2, the descriptor **fSacc8B** (frequency of occurrence of Sulphur and H-Bond acceptor within eight bonds) has positive coefficient. Hence, in future modifications such a combination of Sulphur and H-bond acceptor must be considered for better anti-HAT activity.

The descriptors **fOacc9B** and **fSacc8B** and **KRFP3542** synchronously highlight the importance of *N*,4-disubstituted-benzenesulfonamide moiety and the presence of Oxygen (as H-bond acceptor) atom. This is confirmed by the difference in the activity of **5** ($IC_{50} = 14$ μM) and **7** ($IC_{50} = 42$ μM).

The negative coefficient of the descriptor **com_Cplus_7A** (number of positively charged Carbon atoms present within 7 Å from center of mass (com)), in the model 4 and 5 indicates that number of positively charged Carbon atoms present within 7 Å from center of mass must be as low as possible. Alike hint is highlighted by the negative coefficient of the descriptor **com_ringC_5A**, which represents number of ring Carbon atoms present within 5 Å from center of mass (com), in model 2. Therefore, the presence of ring Carbon atoms within 5 Å from center of mass has negative effect on anti-HAT of pyrazole sulphonamides. This is established by the difference in activity of following pairs of molecules: **211** ($IC_{50} = 1.1$ μM) with **222** ($IC_{50} = 12$ μM) and **18** ($IC_{50} = 2.8$ μM) with **181** ($IC_{50} = 42$ μM).

In addition, similar insinuation is provided by the negative coefficient of the descriptor **fOringC3A** (frequency of occurrence of ring carbon atoms within 3 Å from Oxygen atom), in model 2. Hence, the frequency of occurrence of ring carbon atoms within 3 Å from Oxygen atom must be kept low for better activity. An example to vindicate this observation is significant difference in activity of **18** ($IC_{50} = 2.8$ μM) with **181** ($IC_{50} = 42$ μM).

Another descriptor which specifies the role of ring Carbon atoms in deciding the activity is **fNringC6B** (frequency of occurrence of ring Carbon atoms within six bonds from Nitrogen atoms) has negative coefficient in model 3. Thereby, such ring Carbon atoms must be avoided to have better activity.

APC2D7_N_X, which represents the presence of N-X (halogen) at a topological distance of 7, has positive coefficient in model 1. Consequently, increasing such pattern of Nitrogen and Halogen atoms will enhance the activity. For example, compare **52** ($IC_{50} = 0.003$ μM) with **53** ($IC_{50} = 0.12$ μM). This observation additionally points out the importance of pyrazole moiety attached to sulphonamide group. Another descriptor which point outs similar pharmacophoric pattern, with positive coefficient (model 3–5), is **AD2D636**. It corresponds to the presence of C and halogen atoms X at a topological distance of nine from each other. To increase the anti-HAT activity, the value of this descriptor must be as high as possible.

In Fig. 4, one of the most active molecule has been used as a reference only for a better visualization and understanding of various molecular descriptors viz. **fOacc9B**, **KRFP3542**, **fSacc8B**, **com_Cplus_7A**, **com_ringC_5A** and **APC2D7_N_X**.

The descriptor **ringC_hy2** (number of ring Carbon atoms possessing partial charge in the range 0 to −0.099) has positive coefficient in the model 1. Henceforth, the number of such Carbon atoms in the molecule must be increased to have better activity profile.

AD2D327, which stands for the presence of N–S at a topological distance of 5, has negative coefficient in model 1. Therefore, increase in number of N–S at a topological distance of 5 will diminish the anti-HAT activity. Another descriptor which provides additional information about the presence of Nitrogen atoms is **com_ringN_6A**, which signifies number of ring Nitrogen atoms present within 6 Å from center of mass, has negative coefficient in model 3. Therefore, any Nitrogen atom which is at a topological distance of 5 and simultaneously present in a ring must be avoided.

The negative coefficient of **fON6B**, which represents frequency of occurrence of Nitrogen and Oxygen within six bonds, in model 2, indicates that higher occurrence of Nitrogen and Oxygen within six bonds could lead to reduced activity for pyrazole-sulphonamides. Same is true for **ringC_O_9B** (number of ring Carbon atoms at a distance from nine bonds from oxygen atoms).

In model 2, for 2D-descriptors **SssCH2** (sum of atom-type E-State $-CH_2-$) and **GGI8** (a topological charge descriptor which stands for topological charge index of order 8) have positive coefficients. Therefore, for an improved activity their values must be augmented as high as possible.

The negative coefficient of **SubFPC1** (number of primary Carbon atoms) in model 4 indicates that lowering the number of such Carbon atoms will be favourable for anti-HAT activity. The descriptor **ringN_don_2Ac**, which denotes the sum of partial charges on donor atoms present within 2 Å from ring Nitrogen atoms.

Although we have compared the anti-HAT activities of pairs of molecules of the dataset in terms of descriptors like **fOacc9B**, **fSacc8B**, **KRFP3542**, **APC2D7_N_X**, etc., we make it clear that the collective or converse effect of confounding factors/descriptors have further influence on the activity profile of the compounds.

As mentioned earlier, metabolism and Blood Brain Barrier (BBB) related optimizations are essential for drug development. Therefore, in the present work, pharmacokinetic and bioavailability associated parameters were estimated for thirty most active compounds of the present dataset using SwissADME server (http://www.swissadme.ch/index.php) [48]. The results for ten compounds have been presented in Table 2. For the rest of the molecules the results are available in supplementary material.

From Table 2, it appears that the compounds are potential

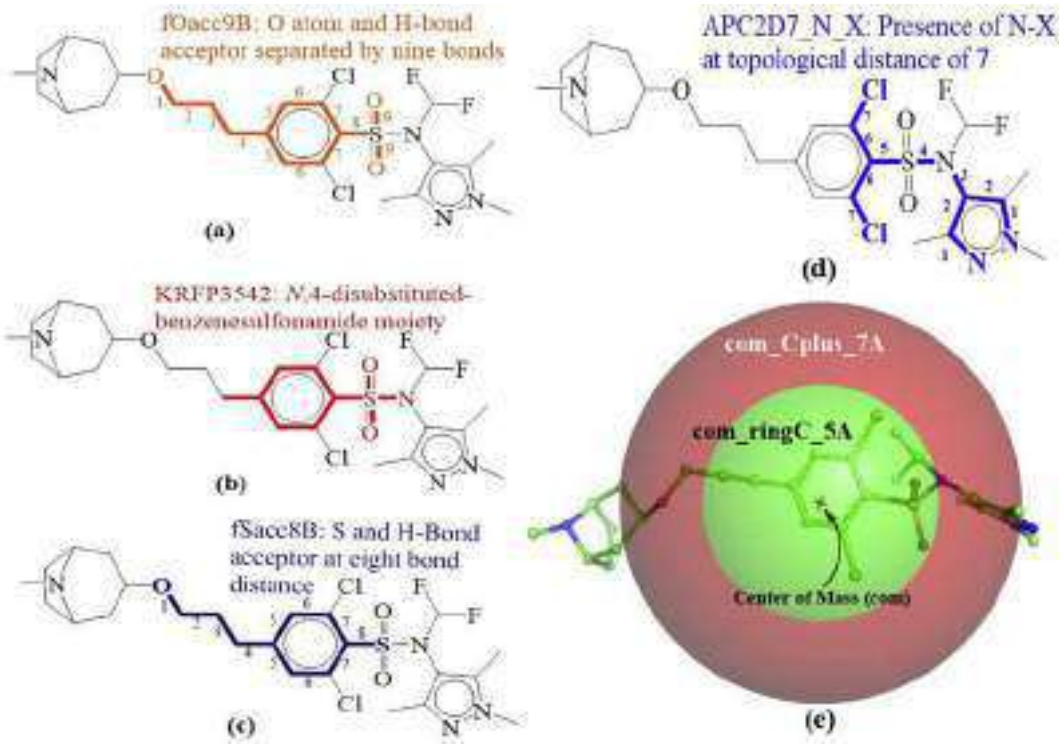


Fig. 4. Pictorial representation of various molecular descriptors viz. (a) **fOacc9B**, (b) **KRFP3542**, (c) **fSacc8B**, (d) **APC2D7_N_X** and (e) **com_Cplus_7A** and **com_ringC_5A**, using (most active) as a reference only.

Table 2
Pharmakokinetic and bioavailability estimations for selected active compounds.[a].

S.N.	GI absorption	BBB permeant	Inhibitor					LogP	Lipinski #violations	Bioavailability Score
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4			
41	High	No	No	Yes	Yes	Yes	Yes	4.63	0	0.55
46	High	No	No	Yes	Yes	Yes	Yes	4.87	1	0.55
52	High	No	No	Yes	Yes	Yes	Yes	3.11	0	0.55
54	High	No	No	Yes	Yes	Yes	Yes	4.56	0	0.55
56	High	No	No	Yes	Yes	Yes	Yes	2.94	0	0.55
58	High	No	No	Yes	Yes	Yes	Yes	3.81	0	0.55
64	High	No	No	Yes	Yes	Yes	Yes	4.29	1	0.55
72	High	No	No	Yes	Yes	Yes	Yes	4.04	0	0.55
74	High	No	No	No	Yes	Yes	Yes	3.13	1	0.55
75	Low	No	No	Yes	Yes	Yes	Yes	4.48	1	0.55

[a] Estimated using SwissADME server (http://www.swissadme.ch/index.php).

CYP3A4 and CYP2D6 inhibitors, but poor BBB permeant, for which a plausible reason pointed out by Brand et al. [16,17,19] is high logP (lipophilicity) and PSA (Polar Surface Area) of the molecules. A good strategy to diminish lipophilicity and increase activity is to decrease number of aromatic carbon atoms that vicinal to center of mass (COM) of molecule (negative coefficient of **com_ringC_5A** in model 2) or reduce number of primary Carbon atoms as suggested by the negative coefficient of **SubFPC1** (number of primary Carbon atoms) in model 4. Thus, the results of the present QSAR work for anti-HAT activity are in consensus with pharmacokinetic and bioavailability estimations.

Conclusion: In the present work, new easily interpretative multiple QSAR models have been successful developed to identify various privileged as well as under-privileged molecular descriptors, which could be highly useful for future use of these models by expert and non-experts of QSAR. The multiple QSAR models have good external predictive ability, which is vindicated by their ability to satisfy threshold values for many statistical parameters such as $R^2_{tr} = 0.80–0.83$, $Q^2_{LOO} = 0.79–0.81$, $CCC_{ext} = 0.82–0.84$, etc. The multiple QSAR and pharmacophoric models successfully identified many pharmacophoric features that govern the anti-HAT activity of pyrazole sulphonamides.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.molstruc.2018.07.080.

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QSAR study of anti-Human African Trypanosomiasis activity for 2-phenylimidazopyridines derivatives using DFT and Lipinski's descriptors

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Abstract

The quantitative structure-activity relationship (QSAR) of sixty 2-phenylimidazopyridines derivatives with anti-Human African Trypanosomiasis (anti-HAT) activity has been studied by using the density functional theory (DFT) and statistical methods. Becke's three-parameter hybrid method and the Lee-Yang-Parr B3LYP functional employing 6−31G(d) basis set are used to calculate quantum chemical descriptors using Gaussian 03W software, and the five Lipinski's parameters were calculated using ChemOffice software.

In order to obtain robust and reliable QSAR model, the original dataset was randomly divided into training and prediction sets comprising 48 and 12 respectively. An optimal model for the training set with significant

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statistical quality was established. The same model was further applied to predict pEC_{50} values of the 12 compounds in the test set, further showing that this QSAR model has high predictive ability. It is very interesting to find that the anti-HAT of these compounds appear to be mainly governed by four factors, i.e., the number of H-bond donors, the lowest unoccupied molecular orbital energy, the molecular weight and the octanol/water partition coefficient. Here the possible action mechanism of these compounds was analysed and discussed, in particular, important structural requirements for great anti-HAT activity will be by increasing molecular size and substitute the 2-phenylimidazopyridines derivatives with polar, ionic, stronger accepting electron ability group and heteroatoms attached to one or more hydrogen atoms. Based on this proposed QSAR model, some new compounds with higher anti-HAT activities have been theoretically designed. Such results can offer useful theoretical references for future experimental works.

Keyword: Pharmaceutical chemistry

1. Introduction

Human African Trypanosomiasis (HAT) or African sleeping sickness is one of the infectious diseases grouped under the term Neglected Tropical Diseases, which inflict a devastating effect on the health and economy of nearly 150 countries [1, 2, 3]. In Africa, the number of cases has dropped drastically; however, approximately 3,000 new infections of both East and West African Trypanosomiasis have been reported by the World Health Organization in 2015 [4]. HAT-affected 60 zones covering an area of about 8 million square kilometers between 14° north latitude and 20° south latitude [5]. Most cases of HAT are caused by the protozoans *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which are transmitted to humans through the bite of tsetse flies in rural areas of sub-Saharan Africa.

The disease has two stages: the initial stage is characterized by the spread of the parasite in the blood and the lymphatic system; and in the second stage, the parasite crosses the *blood−brain barrier* (BBB) in which the parasites spread into the central nervous system [6, 7, 8]. Symptoms of this later stage include sleep disturbance, cognitive dysfunction, coma, and death.

Current treatment for the treatment of HAT includes *suramin, pentamidine*, *melarsoprol*, *eflornithine*, or a combination of *nifurtimox* and *eflornithine* (Chemical structures of existing anti-HAT medicines are shown in Fig. 1) [6, 9, 10, 11]. These existing medicines are insufficient, antiquated, toxic, prone to resistance, and require parenteral administration [12, 13, 14, 15, 16, 17]. A new drug, effective for late stage disease that is nontoxic and orally administered, is urgently needed.

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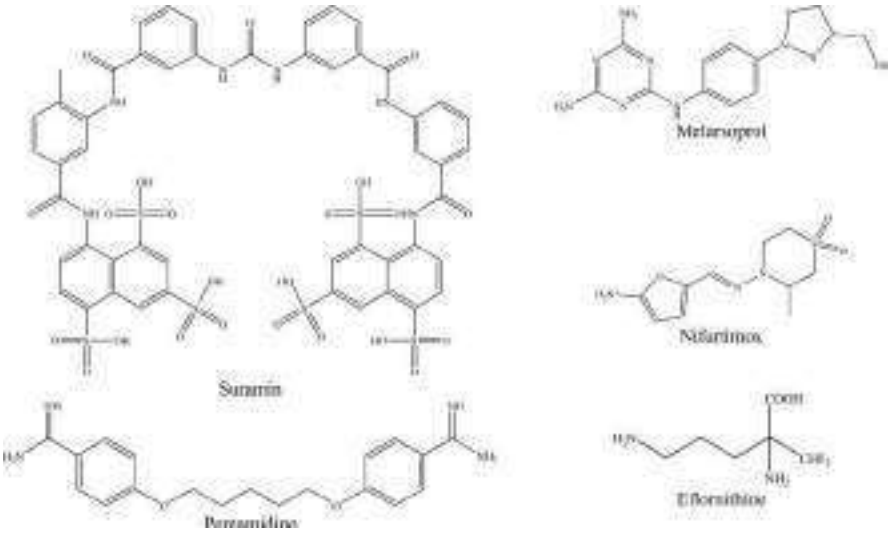


Fig. 1. Chemical structures of existing anti-HAT medicines.

In order to open a new way in anti-HAT drug research, a series of sixty 2-phenylimidazopyridine derivatives were synthesized and studied for their anti-HAT activities by *Tatipaka* et al. [18] to design a better analogue, with rich metabolic stability in liver microsomes, of substituted oxazolopyridine identified as an attractive lead due to good whole-cell activity on *Trypanosoma brucei rhodesiense*, no cytotoxicity on mammalian cell lines, acceptable exposure in the central nervous system, and satisfactory aqueous solubility.

The main focus of the present study is to develop a QSAR model able to correlate the structural features of the 2-phenylimidazopyridine derivatives with their anti-HAT activities.

In general, the QSAR models are based on the assumption that the activity of a certain chemical compound related to its structure through a certain mathematical algorithm. This relationship can be used in the prediction, interpretation, and assessment of new compounds with desired activities, reducing and rationalizing time, efforts, and cost of synthesis as well as new product development. The basic assumption to drive a QSAR model is presented in the form of a mathematical function associating the chemical properties to the effect (activity). Therefore, the effect is like the function *"f"* of the chemical properties *"x": y = (x)*. To find this algorithm, a number of chemical compounds with known values of the studied effect (y) are considered. For each chemical compound, myriad numbers of parameters (called as chemical descriptors) are calculated. Then, QSAR models are built that provides a quite accurate value, similar to the real experimental value. The final step is to check if the obtained QSAR models are able to predict the activity values for other chemicals not used to build up the model (external validation). Indeed, it is very important to generate a model which worked not only for the chemical

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substances used within the training set but also for other similar chemicals. Consequently, the challenge is to define the correct statistical properties of the model [19, 20].

The significance and novelty of findings presented in this work are reflected from the fact that we have used quantum chemistry descriptors which describes electron proprieties of congeneric structures used in this study, and we have used the five Lipinski's descriptors to describes compounds could be potential orally administered drugs. The use of density functional theory (DFT) is justified for the reason that some comparative QSAR studies have shown that the descriptors calculated using the DFT method can improve the accuracy of the results and lead to more reliable QSARs [19].

A flow chart for the development of the QSAR model along with the various validation methods used in this work is demonstrated in Fig. 2.

2. Materials and method

2.1. Selection of dataset and generation of molecular descriptors

2.1.1. Data set

In this stage, the data set of the anti-HAT activities of sixty 2-phenylimidazopyridines derivatives were collected from the literature [18, 35]. The molecular structures of the studied molecules with their activity are presented in Fig. 3 and Table 1. All experimental activity values EC_{50} (of compound required to inhibit growth by 50%) were converted to the negative logarithm of EC_{50} ($pEC_{50} = -\log_{10}(EC_{50})$).

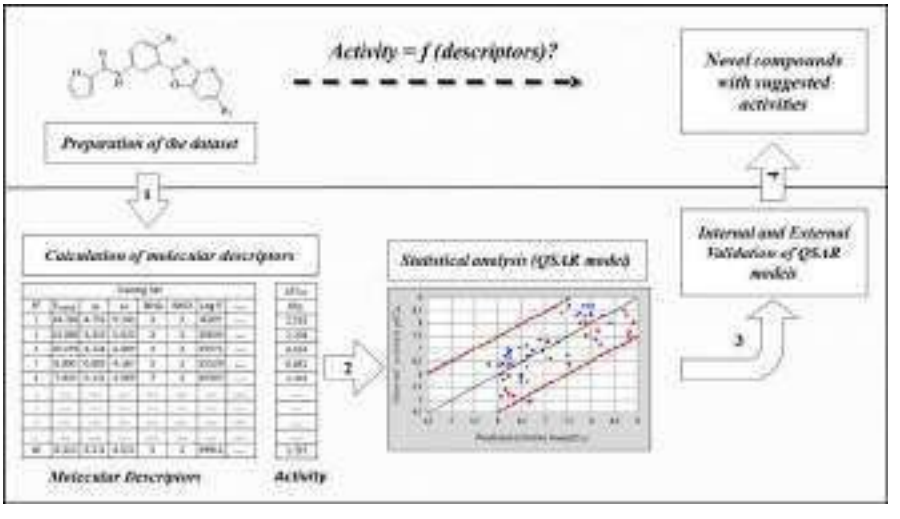


Fig. 2. Flow chart of the methodology used in this work.

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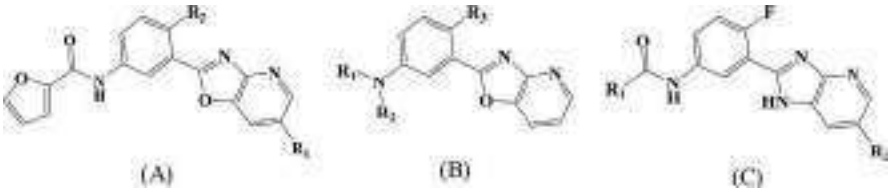


Fig. 3. Chemical structures of the studied compounds skeletons.

2.1.2. Molecular descriptors

Electronic and Lipinski's parameters were calculated using *Gaussian 03W* and *ChemOffice* programs, respectively [21, 22], to predict the correlation between these descriptors of the studied molecules with their anti-HAT activities and to develop linear model. Table 2 shows the used descriptors in this study.

2.2. Data set

In this stage, linear QSAR model was developed and evaluated to predict the studied activities of compounds. The descendent multiple linear regression (MLR) analysis available in *XLSTAT* software [23], based on the elimination of aberrant descriptors (one by one) until a valid model (including the critical probability: *p-value* <0.05 for descriptors and for the model), was employed to find a linear model of the activity of interest, which takes the form below:

$$Y = a_0 + \sum_{i=1}^{n} a_i x_i$$

Where:

Y: the studied activity, which is, the dependent variable; a_0: the intercept of the equation; xi: the molecular descriptors; a_i: the coefficients of those descriptors.

This method is one of the most popular methods of QSAR due to its simplicity in operation, reproducibility and ability to allow easy interpretation of the features used. The important advantage of the linear regression analysis is its transparent nature, therefore, the algorithm is accessible and predictions can be made easily [20].

In order to propose models and to evaluate quantitatively the physicochemical effects of the substituents on the studied activities, we submitted the data matrix constituted obviously from the used variables (descriptors) corresponding to the dataset molecules to a MLR. We use the coefficients R^2, MSE and *p-value* to select the best regression performance [24]. Where:

1. The R-squared (R^2) also called the coefficient of determination, which is the proportion of variance (%) in the dependent variable that can be explained by the independent variable. Since R^2 value is adopted in various research disciplines, there is no standard guideline to determine the level of predictive acceptance.

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Table 1. Chemical structures and anti-HAT activities of studied compounds.

	N°	R_1	R_2	R_3	pEC_{50}
(A)	1	H	Cl		6.658
	2	H	F		6.921
	3	H	CH_3		6.367
	4	H	CN		6.398
	5	Br	F		6.638
	6	CN	F		6.420
	7	Phenyl	F		7.398
	8 (*)	4-fluorophenyl	F		7.301
	9	3-chlorophenyl	F		7.301
	10	4-MeO-phenyl	F		6.770
	11 (*)	4-phenylphenyl	F		6.377
(B)	12	5-methylfuran-2-carbonyl	H	F	6.699
	13	3-methylfuran-2-carbonyl	H	F	7.000
	14	3-furanoyl	H	F	6.824
	15	benzoyl	H	Cl	5.149
	16	oxazole-5-carbonyl	H	F	5.721
	17	2-thiophenyl	H	Cl	5.824
	18 (*)	3-pyridinecarbonyl	H	F	5.155
	19	pyrazine-2-carbonyl	H	F	6.046
	20 (*)	N-methylpyrrole-2-carbonyl	H	F	5.959
	21 (*)	methylsulfonyl	H	Cl	5.215
	22	2-furancarbothioyl	H	F	6.387
	23	2-furanoyl	2-acetyl	F	6.301
	24	2-furanoyl	2-furanoyl	F	6.921
	25	benzyl	Benzyl	F	5.959
	26	methylcarbamoyl	H	F	5.420
	27	isopropylcarbamoyl	H	Cl	6.000
	28	phenylcarbamoyl	H	Cl	4.921
	29	dimethylcarbamoyl	H	Cl	6.398
	30	1-pyrrolidinoyl	H	Cl	7.046
	31	1-piperidinoyl	H	Cl	5.721
(C)	32	2-furanyl	H		6.699
	33 (*)	2-furanyl	Cl		7.155
	34	2-furanyl	F		6.699
	35	2-furanyl	5-Cl		5.000
	36	2-furanyl	7-Cl		6.921

(*continued on next page*)

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Table 1. (*Continued*)

N°	R_1	R_2	R_3	pEC_{50}
37	N-pyrrolidinyl	Cl		7.301
38	N-pyrrolidinyl	phenyl		8.699
39	N-pyrrolidinyl	3-methoxyohenyl		8.000
40 (*)	N-pyrrolidinyl	2-methoxyphenyl		8.301
41	N-pyrrolidinyl	3-chlorophenyl		8.699
42	N-pyrrolidinyl	2-chlorophenyl		8.301
43	N-pyrrolidinyl	3-acetylphenyl		8.523
44	N-pyrrolidinyl	3-methylphenyl		8.699
45 (*)	N-pyrrolidinyl	3-trifluoromethyoxyphenyl		7.523
46 (*)	N-pyrrolidinyl	3-methyl-4-fluorophenyl		7.699
47 (*)	N-pyrrolidinyl	3-NH_2-phenyl		8.000
48	N-pyrrolidinyl	3-furanyl		8.398
49	N-pyrrolidinyl	3-thiophenyl		8.699
50	N-pyrrolidinyl	2-thiophenyl		8.398
51	N-pyrrolidinyl	3-pyridyl		8.301
52 (*)	N-pyrrolidinyl	5-(2-chloropyridyl)		8.000
53	N-pyrrolidinyl	4-(2-chloropyridyl)		8.398
54	N-pyrrolidinyl	5-(3-methylpyridyl)		8.000
55	N-pyrrolidinyl	5-(2-methoxypyridyl)		8.301
56	N-pyrrolidinyl	5-(3-pyrrolidino)		7.699
57	N-pyrrolidinyl	5-(3-chloropyrimidinyl)		8.301
58 (*)	N-pyrrolidinyl	5-pyrimidinyl		7.523
59	N-pyrrolidinyl	5-(2-methoxypyrimidinyl)		7.222
60	N-pyrrolidinyl	5-(2-chloropyrimidinyl)		7.398

(*): Test set compounds. $pEC_{50} = -\log_{10}(EC_{50})$.

Henseler et al. [25] and Hair et al [26, 27] proposed a rule of thumb for acceptable R^2 with 0.75, 0.50, and 0.25 are described as substantial, moderate and weak respectively.

Hence, Zikmund et al. and Moore et al. proposed other rule of thumb for interpreting the strength of a relationship based on its R-squared value (use the absolute value of the R-squared value to make all values positive) [28, 29]:

- If R-squared value $R^2 < 0.3$ this value is generally considered a none or very weak effect size,
- If R-squared value $0.3 < R^2 < 0.5$ this value is generally considered a weak or low effect size,
- If R-squared value $0.5 < R^2 < 0.7$ this value is generally considered a Moderate effect size,

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Table 2. Values of parameters calculated for the studied compounds.

N°	E	μ	E_{HOMO}	E_{LUMO}	MW	NHA	NHD	NRB	log P
1	-40922.340	7.904	-6.113	-1.901	340.049	6	2	3	3.843
2	-31116.982	7.495	-6.062	-1.826	324.079	7	2	3	3.243
3	-29486.806	6.018	-5.939	-1.713	320.104	6	2	3	3.989
4	-30936.391	11.034	-6.432	-2.241	331.083	6	2	3	3.518
5	-101076.674	6.975	-6.153	-2.043	401.990	7	2	3	4.182
6	-33626.856	7.421	-6.348	-2.466	349.074	8	2	4	2.921
7	-37404.050	7.610	-5.949	-1.884	400.110	7	2	4	5.131
8	-40104.179	6.960	-5.983	-1.936	418.101	8	2	4	5.373
9	-49909.639	8.257	-6.067	-2.012	434.071	7	2	4	5.854
10	-40520.225	7.508	-5.686	-1.802	430.121	8	2	5	5.236
11	-43691.129	7.708	-5.839	-1.910	476.142	7	2	5	7.019
12	-32186.636	5.317	-6.146	-1.987	339.102	6	2	3	3.796
13	-32186.624	5.231	-6.245	-2.003	337.086	6	1	7	2.724
14	-31116.792	6.390	-6.030	-1.870	324.079	7	2	3	3.243
15	-40982.768	7.474	-6.166	-1.924	350.070	5	2	3	4.667
16	-31553.426	5.145	-6.267	-1.966	327.090	8	3	3	2.793
17	-49770.221	7.034	-5.890	-2.125	366.047	4	2	2	4.727
18	-31613.730	5.406	-6.222	-1.915	335.095	7	2	3	3.314
19	-32050.206	6.769	-6.173	-2.301	336.090	8	2	3	2.881
20	-31646.188	6.852	-5.952	-1.909	336.102	6	1	4	2.903
21	-47607.896	5.054	-6.359	-2.028	323.013	5	1	3	1.935
22	-39904.311	7.314	-5.869	-2.111	340.056	6	2	3	3.303
23	-35270.067	8.211	-6.247	-1.968	365.081	7	0	5	2.329
24	-40426.686	5.467	-6.361	-1.970	418.084	9	1	5	4.774
25	-36519.016	6.360	-5.499	-1.613	410.167	6	1	5	6.650
26	-27466.414	8.042	-5.960	-1.761	286.087	5	2	4	1.896
27	-39411.369	8.621	-5.993	-1.822	330.088	4	2	5	3.053
28	-42489.155	1.786	-5.891	-1.916	365.081	5	3	4	4.707
29	-38341.359	8.507	-5.957	-1.812	316.073	4	1	4	2.091
30	-40448.111	9.131	-5.884	-1.777	343.097	5	2	3	3.828
31	-41517.874	8.542	-5.927	-1.804	357.112	5	2	3	4.387
32	-30576.266	3.031	-6.117	-1.602	323.095	7	3	3	3.625
33	-43081.767	4.761	-6.292	-1.885	357.056	7	3	3	4.483
34	-33276.260	4.502	-6.216	-1.786	341.086	8	3	3	4.002
35	-43081.927	4.900	-6.281	-1.815	357.056	7	3	3	4.483
36	-43081.878	1.860	-6.339	-1.780	357.056	7	3	3	4.483
37	-42608.017	4.941	-6.020	-1.827	360.103	6	3	3	3.179
38	-36389.529	4.940	-5.774	-1.680	402.174	6	3	4	4.209

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Table 2. (*Continued*)

N°	E	μ	E_{HOMO}	E_{LUMO}	MW	NHA	NHD	NRB	log P
39	-39505.695	4.609	-5.694	-1.673	432.184	7	3	5	4.236
40	-39505.605	4.478	-5.577	-1.544	432.184	7	3	5	3.676
41	-48895.128	5.536	-5.913	-1.803	436.135	6	3	4	4.951
42	-48895.018	5.269	-5.881	-1.704	436.135	6	3	4	4.701
43	-40543.039	6.462	-5.862	-1.776	444.184	7	3	5	3.749
44	-37459.374	4.947	-5.736	-1.655	416.189	6	3	4	4.708
45	-47606.991	5.648	-5.912	-1.805	486.156	10	3	6	5.345
46	-40159.542	4.670	-5.759	-1.699	434.180	7	3	4	4.880
47	-37895.697	6.101	-5.482	-1.614	417.184	7	4	4	3.162
48	-36328.934	4.630	-5.691	-1.680	392.153	7	3	4	3.385
49	-45117.304	5.511	-5.726	-1.688	408.130	6	3	4	5.213
50	-45117.314	5.785	-5.634	-1.763	408.130	6	3	4	5.423
51	-36825.916	3.244	-5.931	-1.806	403.169	7	3	4	4.245
52	-49331.575	4.023	-6.029	-1.933	437.130	7	3	4	5.010
53	-49331.591	4.764	-6.111	-2.046	437.130	7	3	4	5.010
54	-37895.779	2.889	-5.899	-1.776	417.184	7	3	4	4.833
55	-39942.234	2.459	-5.734	-1.714	433.179	8	3	5	5.154
56	-42577.963	2.351	-5.259	-1.654	472.227	8	3	5	5.112
57	-49331.478	4.961	-6.042	-1.940	437.130	7	3	4	5.010
58	-37262.327	5.486	-6.061	-1.960	404.164	8	3	4	3.338
59	-40378.895	3.634	-5.918	-1.830	434.175	9	3	5	4.373
60	-49767.937	6.555	-6.138	-2.084	438.125	8	3	4	4.065

- If R-squared value $R^2 > 0.7$ this value is generally considered strong effect size.

2. The mean square error (MSE): measure the average squared difference between the predicted and experimental activities values.

$$MSE = \frac{1}{N}\sum_{1}^{N}\left(y_i^{pred} - y_i^{obs}\right)$$

N: The number of data points

y_i^{pred}: The predicted (calculated by the model) value for data point i.

y_i^{obs}: The actual (observed) value for data point i.

The MSE is always strictly positive, and a good model will be with MSE values closer to zero, i.e. the good model will be with minimize the sum of the squared difference between the true and estimated values [30].

3. *P-value*: the significance level, which gives an indication of the probability that a QSAR is a significant occurrence.

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In order to assess the significance of the models and its accurate prediction ability for new compounds:

4. The variance inflation factor VIF [31] to detect the absence of the multicollinearity between descriptors was used; models with descriptors correlated with each other are not significant. The VIF was defined as $1/(1-R^2)$, where R is the coefficient of correlation between one descriptor and all other descriptors in model. A VIF value greater than 5.0 indicates that the model is unstable; a value between 1.0 and 4.0 indicates that the model is acceptable [32].
5. In addition, an internal validation procedure (leave-one-out cross validation) was employed, in which one compound is removed and the rebuilt model with the remaining molecules is used to predict the response of the eliminated compound. This one is then returned and a second is removed, and the cycle is repeated, and so on until all compounds have been removed one by one, and an overall correlation coefficient R_{cv} is computed [33]. A model is considered acceptable when the value of R^2_{cv} exceeds 0.6 [27, 32].
6. After the model is built, an external prediction is necessary. This one remains the only way to determine both the generalizability of QSAR model for new chemicals and the true predictive power of the models. In this external validation, the obtained model was used to predict the activities of a test set comprising compounds that are similar to though not used in the training set. This is usually performed by splitting a data set into a training set a test set, typically in a 1:5 ratio [34].
7. A model is valid only within its training domain and new molecules must be considered as belonging to the domain before the model is applied (OECD Principle 3 [35]). Without applicability domain (AD), each model can predict the activity of any compound, even with a completely different structure from those included in the study. Therefore, the AD is a tool to find out compounds that are outside of the built QSAR model and it detects outliers present in the training set compounds. There are several methods for defining the applicability domain (AD) of QSAR models [36], but the most common one is determining the leverage values hi ($hi = x_i^t (X^t X)^{-1} x_i$ ($i = 1,2,\ldots n$)) for each compound, where: x_i: the descriptor row-vector of query compound, X: the n*(k-1) matrix of k model descriptor values for *n* training set compounds and the superscript *t* refers to the transpose of matrix/vector [37]. In this study, we use the *Williams* plot; in this plot, the applicability domain is established inside a squared area within standard deviation $\pm$ x (in this study $x = 2.5$; "three sigma rule" [38]) and a leverage threshold h* ($h^* = 2.5*(k+1)/n$) [39]. Where: n is the number of training set compounds, k is the number of model descriptors. The leverage (h) greater than the warning leverage (h*) suggested that the compound was very influential on the model [40].
8. Further, the y-randomization approach was performed to ensure the robustness of a predictive model. Often, it is used along with the cross-validation. It consists of

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repeating the calculation procedure with randomized activities and subsequent probability assessment of the resultant statistics. The dependent variable vector is randomly shuffled and a new predictive model is developed using the original independent variable matrix. The new predictive models (after several repetitions) are expected to have low R^2 and R^2_{cv} values. If the opposite happens, then an acceptable model cannot be obtained for the specific modelling method and data [41]. Another parameter, cRp^2 is also calculated which should be more than 0.5 for passing this test: $cRp^2 = R^* \sqrt{(R^2 - (Average\ Rr)^2)}$. Where: Average Rr = average 'R' of random models [42].

3. Results and discussions

3.1. Molecular descriptors

From the results of the density functional theory DFT (B3LYP/6-31G (d)) calculations, following quantum chemistry descriptors were obtained for building the model: total energy E, dipole moment μ, highest occupied molecular orbital energy E_{HOMO} and lowest unoccupied molecular orbital energy E_{LUMO}.

The five Lipinski's parameters calculated are: molecular weight MW, number of H-bond acceptors NHA, number of H-bond donors NHD, number of rotatable bonds NRB and octanol/water partition coefficient log P (Table 2).

3.2. Multiple linear regression (MLR)

The QSAR analysis was performed using calculated molecular descriptors and the experimental values of the anti-HAT activities for the forty-eight 2-phenylimidazopyridines derivatives (effect). The established MLR model is represented by the following equation along with the values of the statistical parameters:

$$pEC_{50} = 3.036 + 1.196\ \mathbf{E_{LUMO}} + 0.019\ \mathbf{MW} + 0.301\ \mathbf{NHD} - 0.398\ \mathbf{logP} \quad (1)$$

$R^2 = 0.598$; $R = 0.773$; MSE = 0.508; p-value $< 10^{-4}$

The values of calculated activities from Eq. (1) have been presented in Table 3 and the correlations of calculated and observed activities values are illustrated in Fig. 4.

The *p-value* is lower than 0.0001, it means that we would be taking a lower than 0.01% risk in assuming that the null hypothesis (no effect of the explanatory variables) is wrong D equation has statistically significance. Therefore, we can conclude with confidence that the selected variables do bring a significant amount of information.

The value of R^2 and the MSE indicate that the proposed model is predictive and reliable.

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Table 3. Observed and predicted activities using the MLR models for the training set.

N°	pEC_{50}	MLR	Residues	N	pEC_{50}	MLR	Residues
1	6.658	6.250	0.408	30	7.046	6.463	0.584
2	6.921	6.278	0.643	31	5.721	6.472	-0.751
3	6.367	6.041	0.326	32	6.699	6.676	0.024
4	6.398	5.804	0.595	34	6.699	6.645	0.054
5	6.638	7.115	-0.477	35	5.000	6.720	-1.720
6	6.420	6.112	0.308	36	6.921	6.762	0.159
7	7.398	6.891	0.507	37	7.301	7.283	0.019
9	7.301	7.091	0.210	38	8.699	7.842	0.857
10	6.770	7.514	-0.744	39	8.000	8.406	-0.406
12	6.699	6.148	0.551	41	8.699	8.040	0.660
13	7.000	6.217	0.783	42	8.301	8.258	0.043
14	6.824	6.225	0.599	43	8.523	8.703	-0.180
15	5.149	6.084	-0.935	44	8.699	7.938	0.761
16	5.721	6.647	-0.926	48	8.398	7.981	0.417
17	5.824	6.121	-0.297	49	8.699	7.545	1.154
19	6.046	6.081	-0.035	50	8.398	7.371	1.027
22	6.387	6.214	0.173	51	8.301	7.695	0.606
23	6.301	6.643	-0.342	53	8.398	7.744	0.654
24	6.921	6.968	-0.047	54	8.000	7.762	0.238
25	5.959	6.499	-0.540	55	8.301	8.010	0.291
26	5.420	6.174	-0.754	56	7.699	8.835	-1.136
27	6.000	6.472	-0.472	57	8.301	7.872	0.429
28	4.921	6.661	-1.740	59	7.222	8.201	-0.979
29	6.398	6.301	0.097	60	7.398	8.094	-0.696

The VIF values of all four descriptors in MLR model are smaller than 4.0 (VIF = 1.173, 2.170, 1.270 and 2.094 for E_{LUMO}, MW, NHD and log P, respectively) indicating that there is no collinearity among the selected descriptors and the resulting model has good stability.

The obtained model was validated internally by the *leave-one-out* cross validation technique, the cross-validation coefficient R^2cv for the model was determined based on the predictive ability of the model. The value of R^2cv is higher than 0.5 (R^2cv = 0.509), it indicates the better predictively of the model.

True predictive power of this model is to test their ability to predict perfectly the pEC_{50} of compounds from an external test set (compounds that were not used for the developed model), the pEC_{50} of the remained set of 12 compounds are deduced from the quantitative model proposed with the compounds used in training set by

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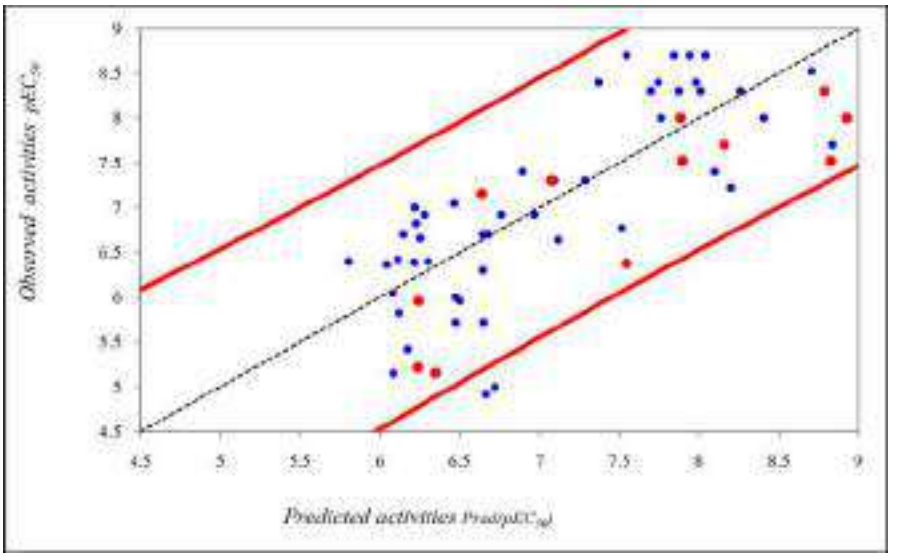


Fig. 4. Correlations of observed and predicted activities (training set in blue and test set in red) values calculated using MLR models.

MLR. This model will be able to predict the activities of test set molecules in agreement with the experimentally determined value. The observed and calculated pEC_{50} values are given in Table 4. The predictive capacity of the models that was judged, the higher value of R^2test (R^2test = 0.700) indicate the improved predictively of the model.

In the Eq. (1), the number of H-bond donors NHD, the lowest unoccupied molecular orbital energy E_{LUMO} and the molecular weight MW influence positively the

Table 4. Chemical descriptors, observed and MLR predicted activities for the test set.

Test Set					pEC_{50}	
N°	E_{HOMO}	MW	NHD	logP	Obs.	MLR
8	-1.936	418.101	2	5.373	7.301	7.072
11	-1.910	476.142	2	7.019	6.377	7.543
18	-1.915	335.095	2	3.314	5.155	6.351
20	-1.909	336.102	1	2.903	5.959	6.239
21	-2.028	323.013	1	1.935	5.215	6.235
33	-1.885	357.056	3	4.483	7.155	6.636
40	-1.544	432.184	3	3.676	8.301	8.783
45	-1.805	486.156	3	5.345	7.523	8.824
46	-1.699	434.180	3	4.880	7.699	8.156
47	-1.614	417.184	4	3.162	8.000	8.922
52	-1.933	437.130	3	5.010	8.000	7.880
58	-1.960	404.164	3	3.338	7.523	7.892

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activities and the octanol/water partition coefficient log P influence negatively the activities.

By definition:

- Molecular weight MW is the sum of the masses of all the atoms in the molecular formula of the molecule. This descriptor has been used as a descriptor in systems such as transport studies where diffusion is the mode of operation. It is an important variable in QSAR studies pertaining to cross resistance of various drugs in multidrug resistant cell lines [43, 44]. For orally delivered drugs, the molecular weight must be less than or equal to 500 Daltons [45].
- Partition coefficient octanol-water (Log P) is the ratio of concentrations of a substance in a mixture of two solvents, octanol and water. Both solvents are immiscible and therefore form two phases [46].

$$\mathrm{LogP} = \log \frac{[\mathrm{Octanol}]}{[\mathrm{Water}]}$$

The LogP is the most useful parameter for the characterization of hydrophobicity (and polarity) of compounds [47]. It is an important variable in QSAR studies because the distribution of chemicals between fatty and aqueous phases of a biological system could totally account for the variation in activities [48]. For orally delivered drugs, the partition coefficient octanol-water must be less than 5 [45].

- The number of H-bond Donors NHD is a crucial descriptor in the description of diverse processes occurring in condensed media such as dissolving, partitioning, solubilisation, etc. Drug action and bioavailability critically depends on aqueous solubility, blood-tissue distribution, and specifically on hydrogen binding to receptor active sites and transport proteins [49]. For orally delivered drugs, the hydrogen bond donors must be less than 5 [45].
- The lowest unoccupied molecular orbital energy, E_{LUMO}: HOMO and LUMO refer to highest occupied molecular orbital and lowest unoccupied molecular orbital. According to the frontier orbital theory, the nucleophilic attack occurs by electron flow from the HOMO of the nucleophile into the LUMO of the electrophile. In stable molecules, occupied electrons always reside into orbitals with negative energies and unoccupied orbitals have positive energies. The energies of HOMO and LUMO are related to the reactivity of the molecule: molecules with electrons at accessible (near-zero) HOMO levels tend to be good nucleophiles because it does not cost much to donate these electrons toward making a new bond. Similarly, molecules with lower LUMO energies tend to be good electrophiles because it does not cost much to place an electron into such an orbital [50, 51].

Comparing the importance of each descriptor on pEC_{50} of 2-phenylimidazopyridines, one must know the standardized coefficient or the *t-test* values of them in the model

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equation. The bigger the absolute value of the *t-test* value is, the greater the influence of the descriptor is. The *t-test* values for our model descriptors are 1.928, 5.714, 1.883 and -2.639 for E_{LUMO}, MW, NHD, and logP, respectively. This means that the *t-test* value of logP is larger than that of other three descriptors, which indicate that in this model, the influence of MW on activity is stronger than that of the others.

Consequently, if we want to increase the value of the activity, we will:

- Decrease the logP (with negative sign in the model) value, for which we must substitute the 2-phenylimidazopyridines derivatives for hydrophilic ("water-loving") substituents. This means that a substitution with a polar and ionic group (such as: -OH, -COOH, $-NH_2$) may lead to high activity values.
- Increase the E_{LUMO} value, for which we suggests the substitution of the 2-phenylimidazopyridines derivatives with a stronger accepting electron ability group, positively charged or neutral species having vacant orbitals that are attracted to an electron rich centre (such as ROX, BH, $-NO_2$).
- Increase the NHD (with positive sign in the model) value, for which substituting the 2-phenylimidazopyridines derivatives by heteroatom attached to one or more hydrogen atoms.
- Increase the MW value, for which increasing the molecular size.

In the conclusion, these results illustrates that to increase the anti-HAT, we will increase the molecular size and substitute the 2-phenylimidazopyridines derivatives with polar, ionic, stronger accepting electron ability group and heteroatoms attached to one or more hydrogen atoms.

This study is in agreement with the conclusions of a previous QSAR studies [52] which revealed the importance the presence of five membered rings, especially the pyrrolidine ring, is beneficial for the HAT activity of the present series of molecules; and the interesting pattern of H-bond donor/acceptor nitrogen atoms in attaining various tautomeric forms, thereby, providing additional flexibility to the molecules to acquire bioactive tautomeric form(s) while interacting with the target receptor.

Further, before performing the external validation of a model, it is very important to check for the presence of systematic error that violates the basic assumptions of the least squares regression model. If high systematic error (bias) is present in the model, then such model should be discarded and performing any external validation test is of no use on such biased model. Xternal Validation Plus is a tool that checks the presence of systematic errors in the model and further computes all the required external validation parameters, while judging the performance of actual prediction quality of a QSAR model based on recently proposed MAE-based criteria [53];

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Table 5. Output file summarize the information including all the external validation parameters that are required to judge the performance of prediction quality of the MLR model.

User Input File Info.	File Name	Sample_TestSet.xlsx
Model biasness test	nPE/nNE	0.3333
	nNE/nPE	3.0000
	|MPE/MNE|	0.3620
	|MNE/MPE|	2.7623
	AAE - |AE|	0.1447
	R'2 (Residuals; serial correlation)	0.0421
	R'2 (Residuals and Yobs values)	0.1383
	R^2Test (100% data)	0.6997
	R_0^2Test (100% data)	0.6978
	$R_0^{2'}$Test (100% data)	0.6123
Classical Metrics	Q2F1 (100% data)	0.4622
(for 100% data)	Q2F2 (100% data)	0.4291
	Scaled Avg.Rm'2 (100% data)	0.5094
	Scaled DeltaRm'2 (100% data)	0.2532
	CCC(100% data)	0.7351
	R'2Test (95% data)	0.7330
	R0'2Test (95% data)	0.7321
Classical Metric	R0"2Test (95% data)	0.4763
(after removing	Q2F1 (95% data)	0.5674
5% data with	Q2F2 (95% data)	0.5506
high residuals)	ScaledAvgRm2 (95% data)	0.5028
	ScaledDeltaRm2 (95% data)	0.2536
	CCC(95% data)	0.7703
Error-based metrics (for 100% data)	RMSEP (100% data)	0.7834
	SD (100% data)	0.4210
	SE (100% data)	0.1215
	MAE (100% data)	0.6718
	RMSEP (95% data)	0.7181
Error-based metric	SD (95% data)	0.3896
(after removing 5% data	SE (95% data)	0.1175
with high residuals)	MAE (95% data)	0.6145
	MAE+3*SD (95% data)	1.7834
	NCompTest	12.0000
Number of test set compounds.	Train range	7.8195

(*continued on next page*)

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Table 5. (*Continued*)

User Input File Info.	File Name	Sample_TestSet.xlsx
Range and Mean (train and test)	TrainYMean	6.7604
	Test range	3.1460
	TestYMean	7.0173
Distribution of observed response values of Test set around Test mean (in %)	%Y (±0.5)TestMean	16.6667
	%Y (±1.0)TestMean	66.6667
	%Y (±1.5)TestMean	83.3333
	%Y (±2.0)TestMean	100.0000
Distribution of observed response values of Test set around Train mean (in %)	%Y (±0.5)TrainMean	16.6667
	%Y (±1.0)TrainMean	58.3333
	%Y (±1.5)TrainMean	75.0000
	%Y (±2.0)TrainMean	100.0000
Distribution of prediction errors (in %)	%NComp>(0.1*TR)	41.6667
	%NComp>(0.15*TR)	16.6667
	%NComp>(0.2*TR)	0.0000
	%NComp>(0.25*TR)	0.0000
Threshold values utilized to judge the model predictions	(0.1*TrainingSetRange)	0.7820
	(0.15*TrainingSetRange)	1.1729
	(0.2*TrainingSetRange)	1.5639
	(0.25*TrainingSetRange)	1.9549
RESULT (MAE-based criteria applied on 95% data)	Prediction Quality	MODERATE

Xternal Validation Plus indicates the absence of systematic errors in the model and a moderate performance of prediction quality of a QSAR model based on proposed MAE-based criteria (Table 5).

In the next step, all calculations were repeated with randomized activities of the training set compounds as well to evaluate model robustness (y-randomization test). In the present case, 100 random trials were run for the MLR model. None of the random trials could match the original model (Table 6). The standalone QSAR-tools ("Programs") available online at http://dtclab.webs.com/software-tools and http://teqip.jdvu.ac.in/QSAR_Tools/ ("Websites") was employed in the y-randomization.

The average value of R, R^2 and R^2_{CV} are 0.282, 0.087 and -0.155 respectively, the cRp^2 value equal a 0.557 (more than 0.5), and all the new QSAR models having significantly low R^2 and R^2_{CV} values for the 100 trials, which confirm that the developed QSAR models are robust.

The applicability domain (AD) of the MLR models was evaluated by leverage analysis expressed as *Williams* plot (Fig. 5), in which the standardized residuals and the

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Table 6. Y-randomization test results for MLR models.

Random	R	R^2	R^2_{CV}	Random	R	R^2	R^2_{CV}	Random	R	R^2	R^2_{CV}	Random	R	R^2	R^2_{CV}
1	0,119	0,014	-0,319	26	0,141	0,020	-0,246	51	0,212	0,045	-0,230	76	0,219	0,048	-0,185
2	0,382	0,146	-0,049	27	0,398	0,158	-0,122	52	0,278	0,077	-0,113	77	0,202	0,041	-0,222
3	0,419	0,176	0,013	28	0,242	0,059	-0,270	53	0,349	0,122	-0,073	78	0,249	0,062	-0,248
4	0,212	0,045	-0,159	29	0,388	0,150	-0,072	54	0,251	0,063	-0,235	79	0,341	0,116	-0,112
5	0,196	0,039	-0,177	30	0,133	0,018	-0,224	55	0,354	0,125	-0,136	80	0,154	0,024	-0,192
6	0,368	0,135	-0,148	31	0,273	0,074	-0,165	56	0,282	0,079	-0,096	81	0,314	0,099	-0,178
7	0,459	0,210	-0,040	32	0,317	0,100	-0,130	57	0,239	0,057	-0,251	82	0,166	0,028	-0,184
8	0,390	0,152	-0,022	33	0,232	0,054	-0,169	58	0,270	0,073	-0,144	83	0,302	0,091	-0,121
9	0,319	0,102	-0,139	34	0,282	0,079	-0,175	59	0,300	0,090	-0,151	84	0,347	0,120	-0,224
10	0,323	0,104	-0,177	35	0,169	0,029	-0,194	60	0,296	0,088	-0,201	85	0,377	0,142	-0,066
11	0,176	0,031	-0,235	36	0,166	0,028	-0,195	61	0,283	0,080	-0,107	86	0,256	0,066	-0,168
12	0,293	0,086	-0,145	37	0,174	0,030	-0,253	62	0,336	0,113	-0,086	87	0,318	0,101	-0,225
13	0,488	0,238	0,104	38	0,403	0,162	-0,072	63	0,404	0,164	-0,007	88	0,398	0,158	-0,057
14	0,377	0,142	-0,052	39	0,243	0,059	-0,145	64	0,442	0,195	0,003	89	0,253	0,064	-0,139
15	0,317	0,101	-0,119	40	0,458	0,210	-0,025	65	0,317	0,101	-0,109	90	0,458	0,210	0,004
16	0,395	0,156	-0,086	41	0,261	0,068	-0,197	66	0,348	0,121	-0,160	91	0,396	0,157	-0,068
17	0,245	0,060	-0,268	42	0,166	0,028	-0,230	67	0,164	0,027	-0,228	92	0,430	0,185	-0,070
18	0,264	0,070	-0,150	43	0,231	0,053	-0,193	68	0,263	0,069	-0,299	93	0,256	0,065	-0,150
19	0,246	0,060	-0,154	44	0,201	0,041	-0,235	69	0,210	0,044	-0,202	94	0,279	0,078	-0,224
20	0,305	0,093	-0,138	45	0,271	0,073	-0,122	70	0,285	0,081	-0,104	95	0,194	0,038	-0,191
21	0,154	0,024	-0,179	46	0,225	0,051	-0,238	71	0,190	0,036	-0,287	96	0,260	0,068	-0,122
22	0,269	0,073	-0,257	47	0,336	0,113	-0,075	72	0,349	0,122	-0,080	97	0,204	0,042	-0,268
23	0,151	0,023	-0,225	48	0,373	0,139	-0,071	73	0,285	0,081	-0,142	98	0,324	0,105	-0,182
24	0,286	0,082	-0,149	49	0,261	0,068	-0,171	74	0,210	0,044	-0,192	99	0,279	0,078	-0,261
25	0,142	0,020	-0,313	50	0,364	0,132	-0,088	75	0,219	0,048	-0,152	100	0,120	0,014	-0,217
Average				R		R^2		R^2_{CV}				cR_p^2			
				0,282		0,087		-0,155				0,557			

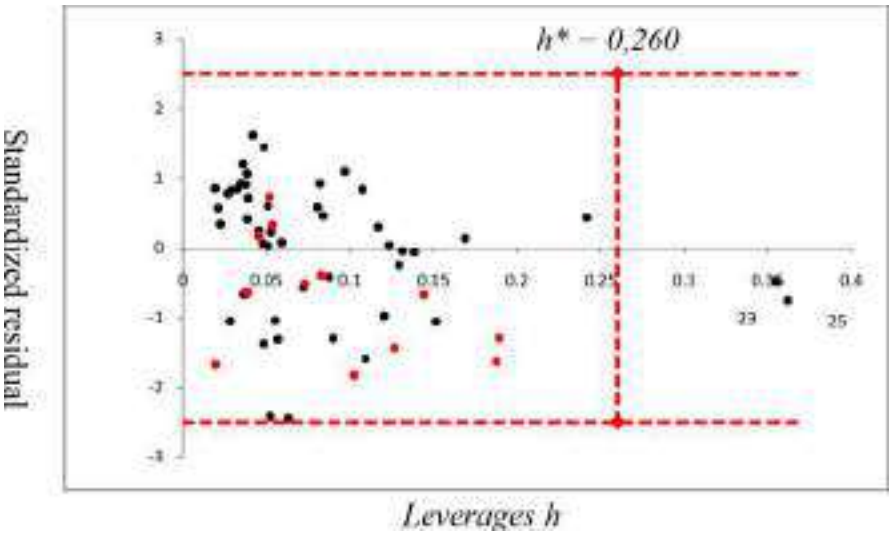


Fig. 5. Williams plot of standardized residual versus leverage for the MLR model (With: h* = 0.260 and residual limits = ±2.5); Train samples in black colour and test samples in red colour).

leverage threshold values (h* = 0.260) were plotted. Any new value of predicted pEC_{50} data must be considered reliable only for those compounds that fall within this AD on which the model was constructed.

From the Fig. 5, it is obvious that all the compounds have a standard deviation into the ±x interval (x = 2.5) and there is two responses outliers both in training set and no response outside in test set. These outliers (compounds 23 and 25) have a higher leverage which is greater than h* value of 0.260. These erroneous predictions could probably be attributed to the structural of these outsides (Fig. 6); maybe the selected

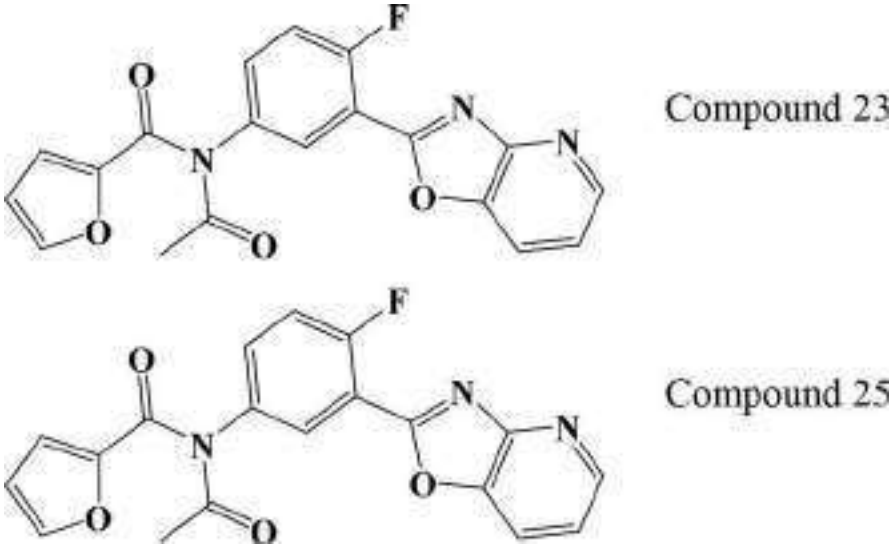


Fig. 6. Chemical structures of the outsides compounds.

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descriptors do not pay much attention to these substructures or their mechanism of action may be different. The predictions of these two compounds are extrapolations of the model, but fortunately they are all ''good leverage'' chemicals.

The results obtained by MLR are very sufficient to conclude the performance of the models. Consequently, we can design new compounds with improved values of activity than the studied compounds using this model.

Taking into account the above results, we added suitable substitutions and then we moved to calculate their activities using the proposed models Eq. (1). Therefore, the suggested model will reduce the time and cost of synthesis as well as the determination of the anti-HAT activity for the 2-phenylimidazopyridines derivatives.

According to the above discussions, the MLR model could be applied to other 2-phenylimidazopyridines derivatives accordingly to Table 1 and could add further knowledge in the improvement of new way in anti-HAT drug research. If we develop a new compound with better values than the existing ones, it may give rise to the development of more active compounds than those currently in use.

In this way, we carried out structural modification starting from compounds having the highest pEC_{50} values as template (38, 41, 44, and 49). The structures of the designed compounds and their parameter values calculated by the same methods, as well as the pEC_{50} values theoretically predicted by the MLR model are listed in Table 7.

Table 7. Values of descriptors, calculated anti-HAT activity pEC_{50} and leverages (h) for the new designed compounds (derivatives of the skeleton (C) of the Fig. 1).

	Designed compounds	E_{LUMO}	MW	NHD	logP	pEC_{50}	leverage
X_1	R_1=COOH; R_2=COOH	-2.129	421.095	5	2.773	8.837	0.436
X_2	R_1=NO_2; R_2= NO_2	-2.658	427.117	7	0.745	9.125	1.596
X_3	R_1=NH_2; R_2= p-PhNH_2	-1.680	363.138	5	1.796	8.669	0.588
X_4	R_1=N-pyrrolidinyl; R_2= m-PhNO_2	-1.780	446.163	4	4.048	8.919	0.170
X_5	R_1=N-pyrrolidinyl; R_2= p-PhNO_2	-1.934	446.163	4	4.048	8.735	0.145
X_6	R_1=N-pyrrolidinyl; R_2= p-PhOH	-1.627	418.168	4	3.733	8.698	0.191
X_7	R_1=N-pyrrolidinyl; R_2= m,p-Ph$(OH)_2$	-1.650	434.163	3	3.327	8.834	0.208
X_8	R_1= N-pyrrolidinyl; R_2=3-thio-2,4-dihydroxyphenyl	-1.493	440.120	5	3.926	9.498	0.395
X_9	R_1= N-pyrrolidinyl; R_2=3-methyl-4-hydroxyphenyl	-1.600	432.184	4	4.182	8.817	0.176
X_{10}	R_1= N-pyrrolidinyl; R_2=3-methyl-6-hydroxyphenyl	-1.543	432.184	4	3.932	8.984	0.214
X_{11}	R_1= N-pyrrolidinyl; R_2=3-methyl-5-hydroxyphenyl	-1.637	432.184	4	4.232	8.753	0.164

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4. Conclusion

The results of the QSAR analysis suggest that derivatives of 2-phenylimidazopyridines with the following structural feature may exhibit great anti-HAT activity by increasing molecular size and substitute the 2-phenylimidazopyridines derivatives with polar, ionic, stronger accepting electron ability group and heteroatoms attached to one or more hydrogen atoms.

According to developed model, the most important findings of this research are that we have designed and suggest some new compounds with possible great activities. Consequently, the proposed models can be used in anti-HAT drug research for the 2-phenylimidazopyridines derivatives. These results encourage the collaboration between theoretical researchers and pharmacologists, academic or industrial, because the last ones many times are groping new drugs.

Declarations

Author contribution statement

Samir Chtita: Analyzed and interpreted the data; Wrote the paper.

Mounir Ghamali, Abdellah Ousaa, Assia Belhassan, Abdelali Idrissi Taourati: Analyzed and interpreted the data.

Adnane Aouidate: Conceived and designed the experiments.

Vijay Hariram Masand: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Mohammed Bouachrine: Contributed reagents, materials, analysis tools or data.

Tahar Lakhlif: Conceived and designed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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Quinoxalinones Based Aldose Reductase Inhibitors: 2D and 3D-QSAR Analysis

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This work is dedicated to Dr. Paola Gramatica, Italy for her outstanding contributions toward enrichment of QSAR and Cheminformatics.

Abstract: In the present work, 2D- and 3D-quantitative structure-activity relationship (QSAR) analysis has been employed for a diverse set of eighty-nine quinoxalinones to identify the pharmacophoric features with significant correlation with the aldose reductase inhibitory activity. Using genetic algorithm (GA) as a variable selection method, multivariate linear regression (MLR) models were derived using a pool of molecular descriptors. All the six-descriptor based GA-MLR QSAR models are statistically robust with coefficient of determination (R^2) > 0.80 and cross-validated $R^2 > 0.77$. The derived GA-MLR models were thoroughly validated using internal and external and Y-scrambling techniques. The CoMFA like model, which is based on a combination of steric and electrostatic effects and graphically inferred using contour plots, is highly robust with $R^2 > 0.93$ and cross-validated $R^2 > 0.73$. The established QSAR and CoMFA like models are proficient in identify key pharmacophoric features that govern the aldose reductase inhibitory activity of quinoxalinones.

Keywords: Aldose Reductase Activity · Quinoxalinones · QSAR · CoMFA like model

1 Introduction

Diabetes Mellitus (DM), caused by insulin deficiency or insulin resistance, is a chronic long-term metabolic disorder characterized by high glucose level in blood (Hyperglycemia).[1] DM has global presence with ill-effects on public health. A close link has been revealed between glucose metabolism via the overactive polyol pathway (also known as the sorbitol-aldose reductase pathway) and long-term various diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts, and stroke by damaging blood vessels and peripheral nerves.[1–2]

In the polyol pathway, the enzyme aldose reductase (ALR2, EC 1.1.1.21) is responsible for the catalytic reduction of glucose to sorbitol in the presence of NADPH as a cofactor in the first and rate-controlling step of this metabolic pathway (Figure 1).[1a] Sorbitol is oxidized into fructose by sorbitol dehydrogenase along with reduction of NAD+ to NADH. Under normal conditions (normoglycemia), glucose is mostly phosphorylated to glucose-6-phosphate by hexokinase and then enters the glycolytic pathway, however, due to a relatively low affinity of ALR2 for glucose only a minor amount of glucose (~3% of glucose utilization) is metabolized through the polyol pathway.[1–2] However, the polyol metabolic pathway is activated during hyperglycemia leading to higher flux of glucose (~30% of glucose utilization) through the polyol pathway, thereby, causing higher accumulation of sorbitol, mainly in tissues demonstrating insulin-independent uptake of glucose, such as lens, kidney, retina, and peripheral nerves. Unfortunately, with the increase in concentration of sorbitol, the activity of sorbitol dehydrogenase does not augment proportionately.[1–2]

The enzyme aldose reductase (ALR2), which is a member of the aldo-keto reductase superfamily, has received wide attention from medicinal chemists, as the development and progression of chronic diabetic complications are related to the activation and/or overexpression of ALR2.[1–2] Therefore, inhibition of ALR2 offers an attractive strategy and alternant approach to avert and deferment the progress and increase

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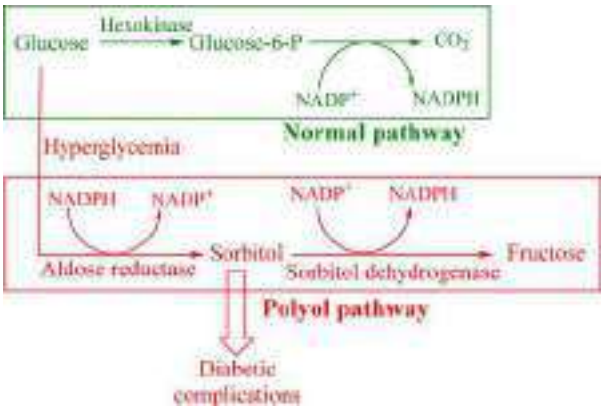


Figure 1. The normal and polyol pathways of glucose metabolism.

significant rational method for recognizing new potent lead/drug candidates and a good alternative to animal testing. CADD is a method of choice in drug designing process due to faster, economical, and result oriented high success. QSAR, molecular docking, pharmacophore modeling, etc. are some of the popular CADD methodologies that are routinely employed for identifying structural features having connection with the activity profile.[3]

Recently, research group of Wang *etal*[1b,2] reported the synthesis and aldose reductase inhibitory activity of diverse quinoxalinones. The quinoxalinones were found to be efficient inhibitors of aldose reductase with activity ranging from μM to nM. In addition, molecular docking and SAR (structure-activity relationship) were performed to under-

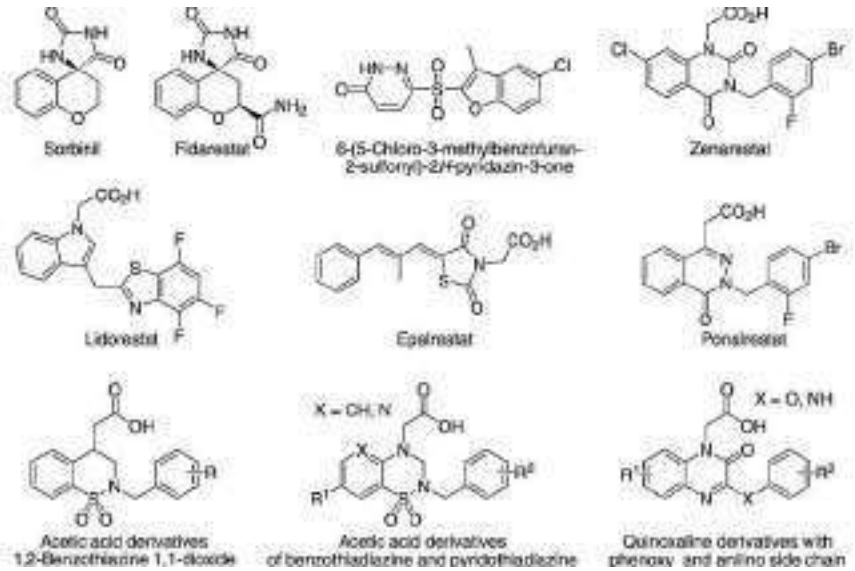


Figure 2. Previously reported aldose reductase inhibitors (ARIs).

of different diabetic complications. At present only one drug 'epalrestat' is marketed for the treatment of neuropathy in Japan, India and China. In past few decades, structurally diverse Aldose reductase inhibitors (ARIs) have been reported (Figure 2).[1b,2] Unfortunately, many of the clinically tested ARIs have been found to be inappropriate as drug candidates because of adverse pharmacokinetics, toxic effects or low efficacy, only few of them have reached advanced clinical stages.[1–2] Therefore, the search for development of highly efficient, safer and potent ARIs still persists.

Modern medicinal chemists go for various strategies to improve the pharmacological and ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profiles and devise a feasible synthetic route for an available lead candidate (i.e. lead optimization). In modern drug designing process, computer-aided drug design (CADD) is a

stand the different structural features that are important to augment the activity profile of quinoxalinones as aldose reductase inhibitors. But, a thorough justification for various SAR results is still required for pharmacophoric feature identification. Surprisingly, till this date, for aldose reductase inhibitory activity of quinoxalinones only one attempt has been made to develop predictive and robust CoMFA like model (ligand based drug design) using a small dataset of thirty-five quinoxalinones only.[4] According to one school of thought,[3b,c,e,f,5] QSAR and CoMFA like modeling are preferable techniques for lead optimization as these techniques not only provide in-depth idea about pharmacophoric features, but, are efficient to predict the activity of a yet to be synthesized drug candidate. Therefore, the main emphasis of the present work was to derive thriving QSAR and CoMFA like models to predict the activity and to

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determine the structural features governing the aldose reductase inhibitory activity profile of novel quinoxalinones.

2 Experimental Methodology

Data set: The dataset selected for the present work comprises eighty-nine structurally diverse quinoxalinones with different type of substituents like –F, –Cl, –OH, etc. at various positions.[1b,2] The compounds were assayed against ALR2 and the reported IC_{50} varies from few micro-molar (μM) to single digit nano-molar (nM). The activity expressed as IC_{50} (95% CL) values represent the concentration required to decrease enzymatic activity by 50%. The IC_{50} values were converted to pIC_{50} ($-\log_{10}IC_{50}$) for QSAR and CoMFA like analyses. The experimental activity values IC_{50}, pIC_{50} and structural substituents have been listed in Table 1.

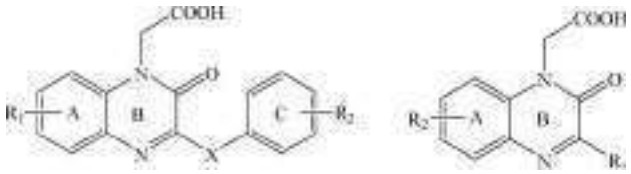


Figure 3. General structure of quinoxalinones used in the present work along with notation for aromatic rings.

3 QSAR Model Building and Validation

The structures were drawn using ChemSketch 12 freeware followed by optimization using TINKER using MMFF94 force field. *PyDescriptor*[6] and PaDEL,[7] were used to calculate a good number of 1D-to 3D-, quantum mechanical and fingerprint descriptors. This resulted in more than 28000 descriptors.[3c–e] Then, objective feature selection was performed to eliminate redundant variables, as a rule highly correlated ($R > 0.90$), constant and nearly constant variables were eliminated.[3c–e] The resultant reduced pool of descriptors consisted of 1122 descriptors only. Subjective feature selection involving genetic algorithm (GA) as a feature selection tool was employed for heuristic search of descriptors for QSAR model building. The search was limited to a set of six descriptors to avoid over-fitting and to develop easy and informative GA-MLR QSAR models. QSARINS 2.2.2 was employed to select optimum number and set of five descriptors with default settings, except for Lack of Fit (*LOF*) which was set to a value of 0.5.[5k,m,n,8] The selected fitness function used to maximize in GA was Q^2, this avoids naive Q^2 also. All the models having poor internal and external predictivity were excluded. The selected descriptors were used to build the statistically acceptable QSAR models followed by exhaustive statistical validation according to the OECD principles for QSAR model validation.[3b–f,5k,n,8c,9]

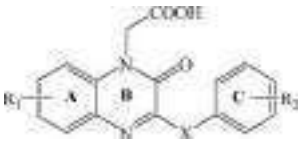
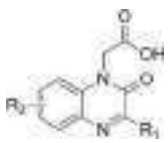
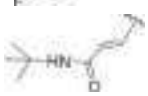
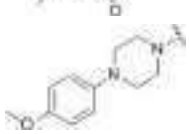
The developed QSAR models were subjected to extensive internal and external validation along with Y-randomization using QSARINS 2.2.2 to avoid over-fitting and spurious models. The different parameters for internal validation include: determination coefficient R^2, leave-one-out (LOO) cross-validation Q^2, leave-many-out (LMO) cross validation Q^2_{LMO}, coefficient of determination for Y-scrambling R^2_{Yscr}, and root mean squared error (*RMSE*). The LMO were repeated 500 times with 30% of the objects left out randomly from the training set each time; The mean value of Q^2_{LMO} has been reported. The external validation parameters are $RMSE_{ex}$, MAE_{ex}, R^2_{ex}, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, and CCC_{ex}.[3c–f,5k,n,8c,9d,e]

Applicability domain of models:[3c,e,5k,n,8c] Model validation was carried out also by checking the model applicability domain (AD), which was verified by the Williams plots. AD is a theoretical region defined by the physicochemical, structural or biological space on which the model has been developed using the training set, it's applicable to make predictions for new compounds. Thus, AD is related to interpolation rather than extrapolation. A widely accepted method for AD determination is based on leverage calculation from the diagonal values of the hat matrix using modeling molecular descriptors. It is evaluated by leverage (or hat) analysis using the formula: $h_i = x_i (X^T X)^{-1} x_i^T$ where (i = 1, …, m), x_i is the descriptor row-vector of the query compound *i*, *m* is the number of query compounds and *X* is the *np* matrix of the training set (*p* is the number of descriptors in the model and *n* is the number of compounds in the training set). The limit of the model domain is quantitatively defined by the leverage cut-off h^* and is set as $3(p+1)/n$. A leverage bigger than h^* for the training set means that the compound is very dominant in determining the model. For the prediction set (*X* outlier), it means that the prediction is the substantial extrapolation of the model and could be unreliable. Also, a compound with a standardized residual greater than 3σ (3x standard deviation units) is recognized as a Y outlier.

CoMFA like analyses: The standard procedure as mentioned in Open3DQSAR was followed to build a database of eighty-nine quinoxalinones. For successful CoMFA like analysis, appropriate alignment of 3D- structures of the molecules is very significant. To improve the success of CoMFA like analysis, Gasteiger-Marsili partial charges were assigned to all the molecules prior to descriptor calculation and alignment. For aligning the complete set of molecules, the lowest energy conformer of most active compound **61** ($IC_{50} = 0.00644$ nM) was used as a template structure in Open3DAlign. The molecules in their respective lowest conformations were superimposed on the template using the atom-based alignment option in Open3DAlign. It was followed by partial least square (PLS) analysis and 3D-contour generation with optimum number of components set to 9. Default settings and procedure as implemented in Open3DQSAR and Open3DGrid were used throughout the work.

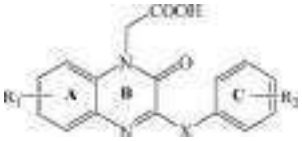
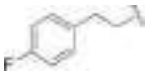
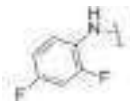
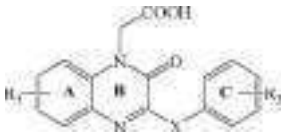
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Table 1. Substituents, experimental IC_{50} and pIC_{50} for aldose reductase activity of quinoxalinones.

S.N.	R_1	R_2	X	IC_{50}** ALR2	pIC_{50} (M)
					
1.	H	H	–	5.981	5.223
2.	H	4-F	–	3.380	5.471
3.	7-F	4-F	–	0.874	6.058
4.	7-Cl	4-F	–	1.516	5.819
5.	4-fluorophenyl	4-F	–	2.131	5.671
6.	H	4-OH	–	2.592	5.586
7.	H	2,4-$(OH)_2$	–	0.397	6.401
8.	6-F	2,4-$(OH)_2$	–	0.063	7.201
9.	6-Cl	2,4-$(OH)_2$	–	0.095	7.022
10.	6-Br	2,4-$(OH)_2$	–	0.139	6.857
11.	7-F	2,4-$(OH)_2$	–	0.032	7.495
12.	7-Cl	2,4-$(OH)_2$	–	0.069	7.161
13.	7-Br	2,4-$(OH)_2$	–	0.091	7.041
14.	4-fluorobenzyl	2,4-$(OH)_2$	–	3.34	5.476
15.	H	3-indole	–	0.639	6.194
16.	7-Br	3-indole	–	0.368	6.434
17.	7-Cl	2-benzothiophene	–	0.238	6.623
18.	H	H	O	0.468	6.33
19.	H	H	S	0.421	6.376
20.	H	4-Br	S	0.296	6.529
21.	7-F	4-Br	S	0.191	6.719
22.	7-Cl	4-Br	S	0.326	6.487
23.	7-Br	4-Br	S	0.467	6.331
24.	6-Br	4-Br	S	0.319	6.496
25.	H	4-Cl	S	0.273	6.564
26.	7-F	4-Cl	S	0.056	7.252
27.	7-Cl	4-Cl	S	0.158	6.801
28.	7-Br	4-Cl	S	0.395	6.403
29.	H	H	CH_2	1.112	5.954
30.	H	H	CH=CH	0.820	6.086
31.	H	H	CH_2–CH_2	0.143	6.845
32.	H	4-OH	CH=CH	0.182	6.74
33.	7-F	4-OH	CH=CH	0.153	6.815
34.	H	4-OCH_3	CH=CH	4.181	5.379
35.	H	3-OCH_3, 4-OH	CH=CH	0.419	6.378
36.	H	4-OH	CH_2–CH_2	0.798	6.098
37.	7-F	4-OH	CH_2–CH_2	0.652	6.186
					
38.		H	–	1.43	5.845
39.		H	–	1.86	5.73
40.		H	–	7.53	5.123

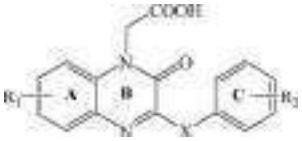
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Table 1. continued

S.N.	R_1	R_2	X	IC_{50}** ALR2	pIC_{50} (M)
					
41.		H	–	1.14	5.943
42.		6-Cl	–	0.66	6.18
43.		7-Cl	–	3.88	5.411
44.		$6\text{-}NO_2$	–	0.362	6.441
45.		$6\text{-}NO_2$	–	0.283	6.548
					
46.	H	$4\text{-}CF_3$	CH_2	0.70167	6.154
47.	H	2,4,5-3F	CH_2	0.44903	6.348
48.	H	4-F	CH_2	0.92487	6.034
49.	H	4-Cl	CH_2	0.1227	6.911
50.	H	4-Br	CH_2	0.05595	7.252
51.	H	2-F,4-Br	CH_2	0.03484	7.458
52.	7-Cl	4-F	CH_2	0.272	6.565
53.	7-Cl	4-Cl	CH_2	0.07495	7.125
54.	7-Cl	4-Br	CH_2	0.02328	7.633
55.	7-Cl	2-F,4-Br	CH_2	0.01025	7.989
56.	6-Cl	4-Br	CH_2	0.10553	6.977
57.	6-Cl	2-F,4-Br	CH_2	0.05856	7.232
58.	7-F	4-F	CH_2	0.3685	6.434
59.	7-F	4-Cl	CH_2	0.03029	7.519
60.	7-F	4-Br	CH_2	0.03359	7.474
61.	7-F	2-F,4-Br	CH_2	0.00644	8.191
62.	6-F	4-Br	CH_2	0.3016	6.521
63.	7-Y[c]	4-F	CH_2	1.7954	5.746
64.	H	2-F,4-Br	O	0.22042	6.657
65.	7-Cl	2-F,4-Br	O	0.15275	6.816
66.	7-F	2-F,4-Br	O	0.12848	6.891
67.	H	4-F	NH	0.4935	6.307
68.	H	4-Br	NH	0.15031	6.823
69.	H	2-F,4-Br	NH	0.12405	6.906
70.	H	2,4-2F	NH	1.20379	5.919
71.	H	3,4,5-3F	NH	0.98685	6.006
72.	H	4-F	O	0.03274	7.485
73.	H	4-Br	O	0.02728	7.564
74.	7-F	4-F	O	0.01906	7.72
75.	7-F	4-Br	O	0.0114	7.943
76.	7-Cl	4-F	O	0.04229	7.374

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Table 1. continued

S.N.	R_1	R_2	X	IC_{50}** ALR2	pIC_{50} (M)
					
77.	7-Cl	4-Br	O	0.03299	7.482
78.	7-Br	4-F	O	0.06298	7.201
79.	7-Br	4-Br	O	0.04348	7.362
80.	7-Br	2-F,4-Br	O	0.0471	7.327
81.	6-F	4-F	O	0.06987	7.156
82.	6-F	4-Br	O	0.04925	7.308
83.	6-F	2-F,4-Br	O	0.07479	7.126
84.	6-Cl	4-F	O	0.05039	7.298
85.	6-Cl	4-Br	O	0.02434	7.614
86.	6-Cl	2-F,4-Br	O	0.04633	7.334
87.	6-Br	4-F	O	0.04313	7.365
88.	6-Br	4-Br	O	0.01633	7.787
89.	6-Br	2-F,4-Br	O	0.03822	7.418

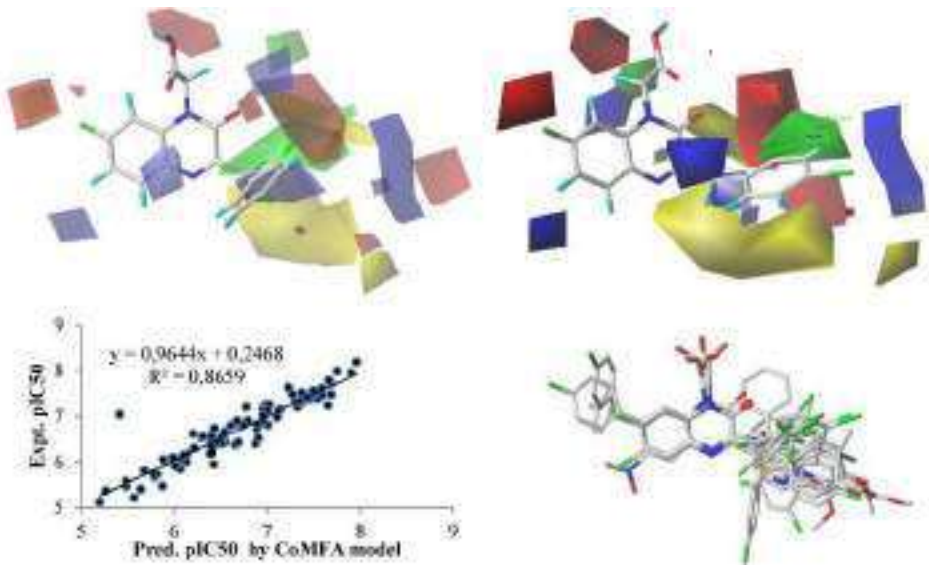


Figure 4. CoMFA like contour maps at different angles for quinoxalinones with compound **61** (most active) as a representative along with graph correlation between experimental and predicted pIC_{50} (CoMFA like model) and alignment of dataset molecules (Red: More negative charge, blue: more positive charge, Green: More bulk and yellow: Less bulky groups favourable).

4 Results and Discussion

CoMFA like analysis: CoMFA like model based on either steric or electrostatic molecular field alone had poor statistical performance with $R^2_{CV}=0.469$ and $R^2_{CV}=0.456$, respectively. However, the present CoMFA like model, comprising a combination of steric, lipophilic and electronic molecular fields, is statistically acceptable with $N_{train}=89$, leave-one-out (LOO) correlation coefficient $R^2_{CV}=0.731$, F value ($n_1=9$, $n_2=78$)$=121.961$, and $R^2=0.934$. A higher value of R^2_{CV} (>0.60) along with R^2 confirms statistical robustness of the CoMFA like model.[3d,e,9e] Further, standard error of estimate was found to be 0.190 with an optimized component of 9. This implies that the model is not only trustworthy in capturing the essence of structural features that govern the aldose reductase activity but it is very good at predicting the activity of quinoxalinones also.[3d,e,9e] The pIC_{50}values predicted by CoMFA like model have been listed in Table 2.

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Table 2. Different statistical parameters for goodness of fit, internal validation and external predictive ability for model 1–5.

S. No.	Statistical Parameter	Model-1	Model-2	Model-3	Model-4	Model-5
1.	N_{tr}	89	89	72	72	72
2.	N_{ex}	00	00	17	17	17
3.	*Number of Descriptors*	06	06	06	06	06
Fitting Criteria						
4.	R^2_{tr}	0.82	0.82	0.83	0.84	0.82
5.	$R^2_{adj.}$	0.81	0.80	0.82	0.83	0.81
6.	*LOF*	0.11	0.12	0.11	0.10	0.12
7.	*Kxx*	0.21	0.16	0.25	0.17	0.21
8.	ΔK	0.09	0.11	0.06	0.12	0.09
9.	$RMSE_{tr}$	0.29	0.30	0.27	0.26	0.29
10.	MAE_{tr}	0.22	0.24	0.21	0.21	0.22
11.	RSS_{tr}	7.58	7.87	5.38	5.03	6.22
12.	CCC_{tr}	0.90	0.90	0.91	0.92	0.90
13.	*s*	0.30	0.31	0.29	0.28	0.31
14.	*F*	63.62	60.79	54.54	58.52	49.92
Internal Validation Criteria						
15.	R^2_{cv} (Q^2loo)	0.79	0.79	0.80	0.81	0.79
16.	$RMSE_{cv}$	0.32	0.32	0.30	0.29	0.32
17.	MAE_{cv}	0.24	0.26	0.23	0.23	0.25
18.	$PRESS_{cv}$	9.05	9.10	6.36	6.23	7.48
19.	CCC_{cv}	0.88	0.88	0.89	0.90	0.88
20.	Q^2_{LMO}	0.78	0.78	0.78	0.80	0.78
21.	R^2_{Yscr}	0.07	0.07	0.08	0.09	0.08
22.	Q^2_{Yscr}	−0.10	−0.10	−0.13	−0.13	−0.13
External Validation Criteria						
23.	θ^*	–	–	−8.39°	−6.81°	−7.02°
24.	$RMSE_{ex}$	–	–	0.41	0.38	0.37
25.	MAE_{ex}	–	–	0.30	0.32	0.26
26.	$PRESS_{ext}$	–	–	2.89	2.45	2.34
27.	R^2_{ex}	–	–	0.75	0.77	0.76
28.	Q^2_{F1}	–	–	0.73	0.77	0.71
29.	Q^2_{F2}	–	–	0.70	0.76	0.71
30.	Q^2_{F3}	–	–	0.62	0.68	0.72
31.	CCC_{ex}	–	–	0.83	0.87	0.84
32.	R^2-*ExPy*	0.79	0.79	0.80	0.77	0.76
33.	R'^2_o	0.74	0.74	0.77	0.71	0.69
34.	*k'*	0.99	0.99	0.99	0.99	1.02
35.	$1-(R^2/R'^2_o)$	0.06	0.06	0.04	0.07	0.09
36.	r'^2m	0.62	0.62	0.65	0.59	0.56
37.	R^2_o	0.79	0.79	0.80	0.77	0.76
38.	*k*	0.99	0.99	0.99	1.00	0.98
39.	$1-(R^2\text{-}ExPy/R^2_o)$	0.00	0.00	0.00	0.00	0.00
40.	r^2m	0.77	0.77	0.79	0.74	0.76

The presence of red contour near position number 7 of ring A indicates that the presence of a more negative charge i.e. electron withdrawing group (EWG) at this position is highly favourable for activity augmentation. This observation is supported by comparing the activity values of following quinoxalinones, as representative examples: **3** (IC_{50} = 0.874 μM) with **4** (IC_{50} = 1.516 μM), **11** (IC_{50} = 0.032 μM) with **12** (IC_{50} = 0.069 μM) and **13** ((IC_{50} = 0.091 μM), **21** (IC_{50} = 0.191 μM) with **22** (IC_{50} = 0.326 μM) and **23** (IC_{50} = 0.467 μM), **26** (IC_{50} = 0.056 μM) with **27** (IC_{50} = 0.158 μM) and **28** (IC_{50} = 0.395 μM). Interestingly, this red contour surrounds a yellow contour, which indicates that the EWG must be less bulky in nature. This could be another plausible reason behind the high activity profile of quinoxalinones with –F compared to molecules with –Br as a substituent at this position, as well as for outlier behavior of molecule **13** in CoMFA like model. Similarly, the red contour present in the vicinity of $-CH_2-COOH$ group indicates that

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an EWG is favourable at this position, therefore, for better activity this group must be retained. This observation is further supported by the molecular docking analysis performed by Wang *etal*.[1b,2]

A blue contour close to position number 6 of ring A indicates that less electronegative groups are favourable at this position. This observation is reinforced by equating the activity values of following quinoxalinones: **50** (IC_{50} = 0.05595 μM) with **56** (IC_{50} = 0.10553 μM) and **62** (IC_{50} = 0.30160 μM), **72** (IC_{50} = 0.03274 μM) with **87** (IC_{50} = 0.04313 μM), **84** (IC_{50} = 0.05039 μM) and **81** (IC_{50} = 0.06987 μM). A big yellow contour (almost 'U' shaped with higher presence towards quinoxaline ring) spanning the meta and para positions of ring C indicate that the presence of less bulkiness in this region is in support of activity escalation. A big green contour (present opposite to yellow contour and other side of ring C away from quinoxaline ring) and a red contour are present vicinal to the ortho position of ring C representing that the presence of more bulky groups with electron withdrawing ability (i.e. highly electronegative atom) on this side could be activity promoter. This observation is accepted when the activity values of following quinoxalinones are compared: **7** (IC_{50} = 0.397 μM) with **6** (IC_{50} = 2.592 μM), **51** (IC_{50} = 0.03484 μM) with **50** (IC_{50} = 0.05595 μM), **55** (IC_{50} = 0.01025 μM) with **54** (IC_{50} = 0.02328 μM), **57** (IC_{50} = 0.05856 μM) with **56** (IC_{50} = 0.10523 μM), **61** (IC_{50} = 0.00644 μM) with **60** (IC_{50} = 0.03359 μM), a few examples to mention.

A conceivable reason for the presence of yellow and green contours close to each other and spanning the opposite sides of the similar region of ring C could be the huge variations or absence of the linker between ring B and C, which causes good variations in angle and distance for ring C during alignment of all the molecules in the dataset.

A blue contour, which represents the presence of more positive charge is favourable in this region, is present between ring B and C. A comparison of compounds **1** (IC_{50} = 5.981 μM), **18** (IC_{50} = 0.468 μM), **19** (IC_{50} = 0.421 μM), **29** (IC_{50} = 1.112 μM), **30** (IC_{50} = 0.820 μM) and **31** (IC_{50} = 0.143 μM) indicates that $-CH_2-CH_2-$ is a better linker for increasing the activity. Another reason for this could be the additional high flexibility provided by this linker.

5 QSAR Analysis

The principal objective of the present work is to employ conventional QSAR to acquire extensive information about the structural moieties that govern the activity. Recently, our group successfully proved that single splitting based QSAR models are neither best suitable to judge external predictive ability nor getting maximal information.[3c,e] Therefore, multiple models were built using 80% training set and validating them on remaining set (20% prediction set) using random splitting. Furthermore, QSAR model was built using whole dataset (no splitting) to confirm the identification of all the significant structural-activity information.

The GA-MLR analysis resulted in statistically acceptable QSAR models 1–5, which satisfy recommended threshold values for many statistically parameters that are essential to judge the goodness of fit and external predictive ability. The QSAR models are also able to shed light on the structural features that govern the aldose reductase activity. The developed QSAR models are as follow:

Model-1 (Full set model): pIC_{50} = 5.97 (±0.32) + 0.93 (±0.33)****all_F_5Ac*** + 1.26 (±0.37)****MATS8m*** + 20.67 (±5.23) ****R2v+*** − 1.99 (±0.56)****O_lipo_2Bc*** − 0.05 (±0.02)****Cplus_AbSA*** − 0.19 (±0.06)****RDF115p***

Model-2 (Full set model): pIC_{50} = 7.30 (±0.24) + 1.03 (±0.34)****all_F_5Ac*** + 1.28 (±0.36)****N_all_3Bc*** + 1.18 (±0.38) ****MATS8 m*** + 0.59 (±0.16)****F08[N−Br]*** − 1.64 (±0.59)****O_lipo_2Bc*** − 0.23 (±0.06)****RDF115p***

Model-3 (Divided set model): pIC_{50} = 2.01 (±1.00) + 0.84 (±0.22)****acc_F_5Ac*** + 27.87 (±4.92)****R2v+*** + 0.90 (±0.34) ****B10[C−O]*** + 10.48 (±4.10)****HATS1e*** − 0.64 (±0.28) ****fBrS10A*** − 2.39 (±0.63)****acc_F_5Bc***

Model-4 (Divided set model): pIC_{50} = 11.66 (±0.77) + 0.72 (±0.34)****all_F_5Ac*** − 0.40 (±0.16)****fCN7B*** − 0.75 (±0.21) ****fFO8B*** − 1.02 (±0.24)****GATS8e*** − 3.71 (±0.88)****SPH*** − 1.40 (±0.29)****Mor19e***

Model-5 (Divided set model): pIC_{50} = 6.44 (±0.42) + 1.21 (±0.38)****B10[C−O]*** + 1.08 (±0.32)****lipo_N_5Ac*** + 2.52 (±0.62)****all_N_7Ac*** − 0.41 (±0.18)****B08[O−F]*** − 2.00 (±0.63)****C_F_3Ac*** − 0.26 (±0.07)****RDF115p***

The 3D-descriptor ***all_F_5Ac***, which stands for sum of partial charges on all atoms which are within 5 Å from Fluorine atom, has positive coefficient in model 1, 2, and 4. Therefore, its value must be as high as possible. This descriptor provides information about the role of local environment in the vicinity of F atom in deciding the activity. As the number of positively charged atoms like H-atoms in the vicinity of F atom increases, its value increases. Another similar descriptor with positive coefficient in model 3 is ***acc_F_5Ac***, which corresponds to sum of partial charges on H-bond acceptor present within 5 Å from F atom. These descriptors have been depicted using the molecule **11** as a representative in the Figure 5.

The descriptor ***N_all_3Bc*** stands for sum of partial charges on all atoms which are at a distance of three bonds from Nitrogen atoms. This descriptor has positive coefficient in model 2, thereby increasing it value will increase the bioactivity. This descriptor highlights the role of local environment with three bond distance around N atoms in determining the activity. This descriptor has been depicted using the most active molecule **11** as a representative in the Figure 5. Similarly, the positive coefficient of ***lipo_N_5Ac*** in model 3 highlights the importance of local environment around N atoms. The descriptor ***lipo_N_5Ac*** corresponds to sum of partial charges on all lipophilic atoms which are present within 5 Å from N atoms. Same is true for ***all_N_***

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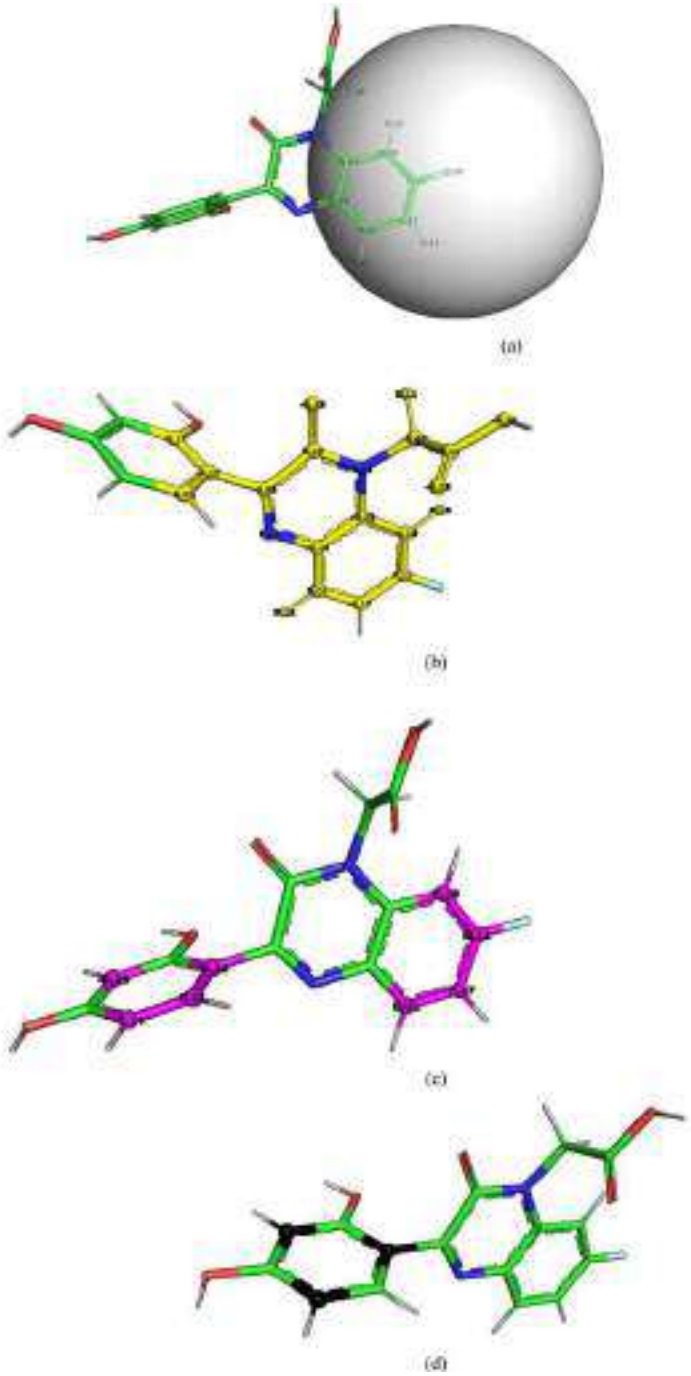


Figure 5. 3D-representation of (a) ***all_F_5Ac*** and ***acc_F_5Ac*** (the gray sphere has radius of 5 Å with F as the center) and (b) ***N_all_3Bc*** (atoms within three bonds from N atoms have been shown with yellow colour) (c) ***lipo_N_5Ac*** (lipophilic atoms within 5 Å from N atoms have been shown with magenta colour) (d) ***O_lipo_2Bc*** (lipophilic atoms which are within two bonds from O atoms have been shown as black) using the molecule **11** (as a representative only).

7Ac (sum of partial charges on all atoms within 7 Å from N atoms).

The 2D frequency fingerprints descriptor ***F08[N–Br]*** has positive coefficient in model 2. This topological descriptor stands for frequency of N and Br at a topological distance of 08. It has positive coefficient in model 2, hence, in future its value must be increased to improve the activity. A comparison of activity of **19** (IC_{50} = 0.421 μM) with **20** (IC_{50} = 0.296 μM), **48** (IC_{50} = 924.87 nM) and **49** (IC_{50} = 122.70 nM) with **50** (IC_{50} = 55.95 nM), **52** (IC_{50} = 272.00 nM) and **53**

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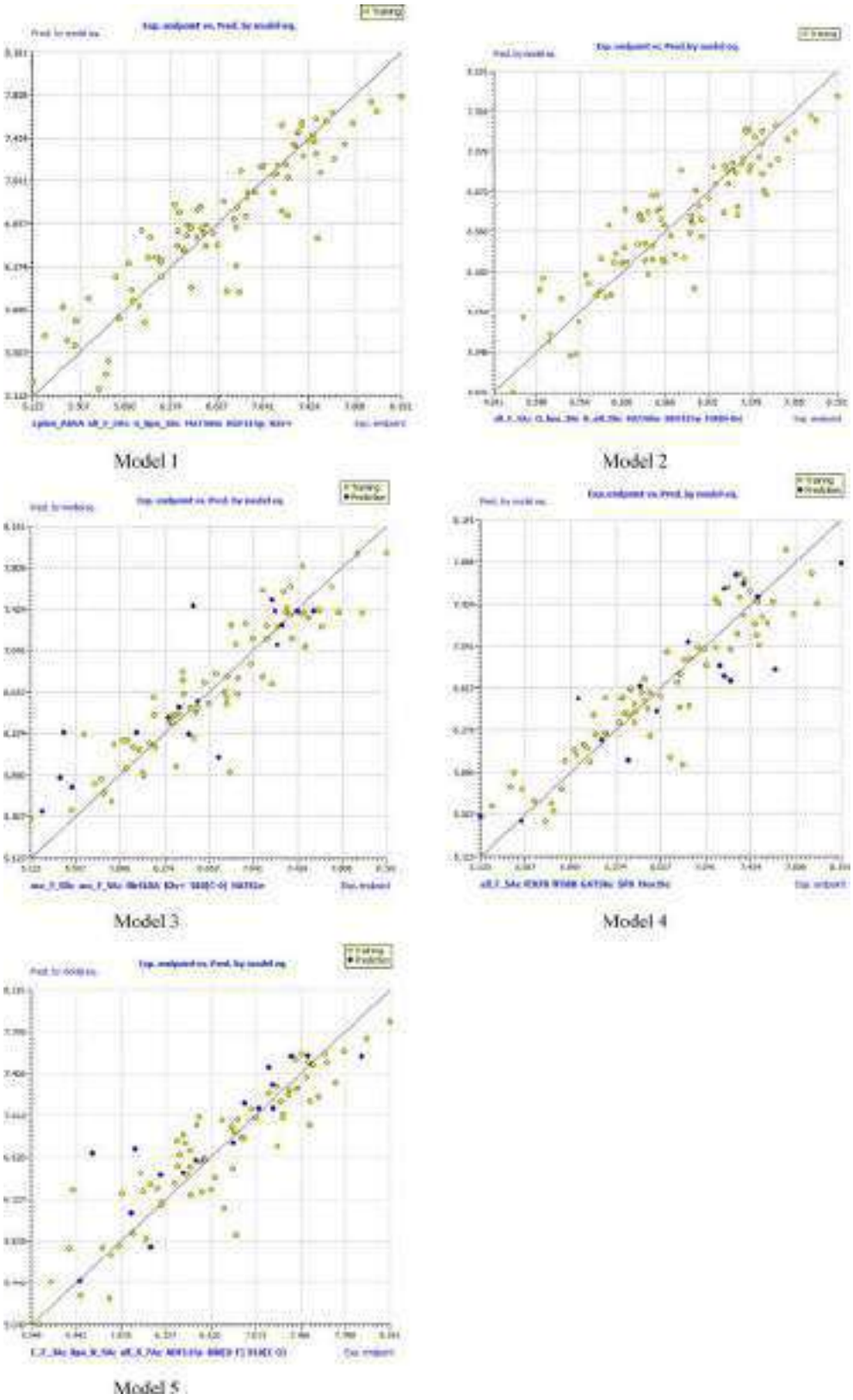


Figure 6. Correlation graph between predicted and experimental pIC_{50} values by QSAR models 1 to 5.

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Table 3. Status of the molecule and predicted pIC_{50} values by QSAR and CoMFA like models.

Mol id	Pred. pIC_{50} (CoMFA like model)	Status	Pred. by model 1	Pred. by model 2	Status	Pred. by model 3	Status	Pred. by model 4	Status	Pred. by model 5
1	5.572	Training	5.6607	5.7039	Prediction	5.5551	Training	5.5913	Training	5.4509
2	5.49	Training	5.5711	5.4625	Training	5.5691	Prediction	5.4483	Prediction	5.4694
3	5.888	Training	5.7820	5.9281	Training	6.1262	Training	5.9884	Training	5.8561
4	5.679	Training	6.1909	6.1381	Training	5.6527	Training	5.7382	Training	5.7930
5	5.788	Training	5.1844	5.3122	Training	5.8155	Training	5.4405	Training	5.7728
6	5.484	Training	5.9947	5.8911	Training	6.2693	Training	5.6317	Prediction	6.6589
7	6.875	Training	6.5511	6.7699	Prediction	6.5173	Training	6.6482	Training	6.7559
8	6.773	Training	6.7737	7.1975	Training	6.7320	Prediction	6.7688	Training	6.7283
9	6.96	Training	7.1699	7.2294	Training	6.9216	Training	7.0145	Training	6.9898
10	6.966	Training	7.1314	6.9896	Training	7.2804	Training	6.9246	Training	6.9743
11	7.461	Training	6.5355	6.9874	Training	7.0849	Training	7.0518	Training	7.1438
12	7.159	Training	7.1853	7.0553	Training	7.1584	Prediction	6.8708	Prediction	7.0882
13	6.961	Training	7.1853	7.0553	Training	7.1584	Training	6.8708	Prediction	7.0882
14	5.411	Training	5.7924	5.5363	Prediction	5.7807	Training	5.7419	Training	5.3300
15	5.881	Training	6.1892	6.2641	Training	6.1576	Training	6.2439	Training	6.2050
16	6.403	Training	6.6143	6.4250	Training	6.7709	Training	6.3516	Training	6.5321
17	6.55	Training	6.5710	6.5281	Training	6.7474	Prediction	6.4523	Training	6.3185
18	6.209	Training	6.4655	6.7399	Training	6.3774	Training	6.5651	Training	6.7797
19	6.409	Training	6.4242	6.4543	Training	6.4435	Training	6.4243	Prediction	6.4804
20	6.301	Training	6.6200	6.6987	Training	6.2392	Training	6.5444	Training	6.5848
21	6.892	Training	6.8542	7.1923	Training	6.8277	Training	6.9921	Training	6.9658
22	6.517	Training	6.5373	6.7733	Prediction	6.2706	Prediction	6.6810	Prediction	6.5969
23	6.415	Training	6.5915	6.7177	Training	6.4448	Training	6.5818	Training	6.5405
24	6.393	Training	6.7903	6.9468	Training	6.5110	Training	6.6273	Training	6.9242
25	6.399	Training	6.4654	6.2645	Training	6.5097	Training	6.6172	Training	6.6067
26	6.989	Training	6.7313	6.7428	Prediction	7.0982	Training	7.0124	Training	6.9877
27	6.615	Training	6.7049	6.5544	Training	6.6700	Training	6.7132	Training	6.9128
28	6.514	Training	6.6529	6.1446	Training	6.4553	Training	6.6577	Training	6.4550
29	6.424	Training	5.9709	6.2941	Training	6.2169	Prediction	6.5691	Prediction	6.6963
30	6.077	Training	6.3502	6.2563	Training	5.9203	Training	6.4155	Training	6.3694
31	6.69	Training	6.0451	5.9895	Training	5.9204	Training	5.9590	Training	5.8944
32	6.428	Training	6.0564	6.3016	Prediction	6.0531	Training	6.0297	Training	6.1447
33	7.008	Training	6.2806	6.7346	Training	6.6102	Training	6.4848	Training	6.5237
34	5.27	Training	5.9232	5.9797	Prediction	5.8750	Training	5.7587	Training	5.7680
35	6.658	Training	6.4301	6.2801	Training	5.9762	Prediction	6.0002	Training	6.8368
36	5.989	Training	6.5406	6.3502	Training	5.8926	Training	6.2334	Prediction	5.7823
37	6.387	Training	6.3187	6.7875	Training	6.4497	Training	6.5758	Training	6.1662
38	6.063	Training	5.8121	6.0447	Training	6.1786	Training	5.9911	Training	6.2853
39	5.824	Training	5.3178	5.3295	Training	5.8574	Training	5.6110	Training	5.3034
40	5.205	Training	5.2484	4.9415	Training	5.4876	Prediction	5.4885	Training	5.0493
41	6.008	Training	6.0665	5.9625	Training	5.9519	Training	6.0519	Training	5.9082
42	6.146	Training	6.3373	6.4119	Training	6.6107	Training	6.2528	Prediction	6.4596
43	5.641	Training	5.6202	6.0982	Prediction	6.2865	Training	5.8904	Training	6.3177
44	6.467	Training	6.0907	6.2882	Training	6.6498	Training	6.4419	Training	6.2690
45	6.507	Training	6.5770	6.2855	Training	6.4708	Training	6.4708	Training	6.2993
46	6.099	Training	6.3595	6.2427	Training	6.1892	Prediction	6.1881	Training	6.3312
47	6.4	Training	6.7598	6.6931	Training	6.3827	Training	6.4343	Training	6.6423
48	6.102	Training	6.5970	6.6312	Prediction	6.2833	Training	6.1220	Training	6.3073
49	6.792	Training	6.9459	6.5217	Training	6.7884	Training	6.9267	Prediction	7.1327
50	7.02	Training	7.0675	6.8188	Training	7.2587	Prediction	6.7282	Training	7.0301
51	7.587	Training	7.4543	7.3229	Training	7.3840	Training	7.2450	Training	7.3771
52	6.313	Training	6.6436	6.6374	Prediction	6.5725	Training	6.2228	Training	6.6036
53	7.002	Training	6.9436	6.7640	Training	6.7989	Training	7.0308	Prediction	7.4650
54	7.233	Training	7.2423	7.3010	Training	7.2692	Prediction	6.8384	Training	7.5154
55	7.75	Training	7.6694	7.6979	Training	7.3944	Training	7.4320	Training	7.7321
56	7.103	Training	6.9407	6.9052	Training	7.2902	Training	7.0322	Training	7.0798
57	7.654	Training	7.1941	7.1706	Prediction	7.4154	Training	7.5850	Training	7.1464
58	6.689	Training	6.6498	6.9345	Training	6.8509	Training	6.5155	Training	6.6873
59	7.372	Training	7.1163	6.9498	Training	7.3456	Training	7.3145	Training	7.4872

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Table 3. continued

Mol id	Pred. pIC_{50} (CoMFA like model)	Status	Pred. by model 1	Pred. by model 2	Status	Pred. by model 3	Status	Pred. by model 4	Status	Pred. by model 5
60	7.597	Training	7.3951	7.4578	Training	7.8263	Training	7.1475	Prediction	7.5797
61	7.962	Training	7.7967	7.9371	Training	7.9516	Prediction	7.7946	Training	7.8985
62	6.911	Training	6.8114	6.8058	Prediction	7.4629	Training	6.7435	Training	7.0015
63	5.779	Training	5.4339	5.6595	Training	5.7248	Training	5.5374	Training	5.6979
64	6.548	Training	6.4709	6.3384	Training	6.5554	Training	6.5866	Training	6.4340
65	6.745	Training	6.6237	6.6898	Training	6.5554	Training	6.7897	Prediction	6.7607
66	6.959	Training	6.7252	6.8254	Training	7.1020	Prediction	7.0825	Training	6.8191
67	6.221	Training	6.8254	6.4408	Prediction	6.4261	Training	6.3506	Training	6.3854
68	6.9	Training	6.8050	6.6603	Training	6.8023	Training	6.7858	Training	6.8650
69	6.678	Training	6.8860	6.6998	Training	6.6478	Training	6.5001	Training	6.8055
70	6.012	Training	6.3027	5.9284	Training	6.2158	Training	6.1015	Prediction	6.0988
71	6.14	Training	5.9272	5.9071	Training	6.1549	Training	6.1521	Training	6.4803
72	7.275	Training	7.2841	7.1560	Training	7.0776	Prediction	7.4918	Training	6.9279
73	7.492	Training	7.5741	7.2485	Prediction	7.4159	Training	7.2551	Training	7.1878
74	7.684	Training	7.3746	7.5072	Training	7.6348	Training	7.9275	Training	7.3249
75	7.9	Training	7.7501	7.7438	Training	7.9451	Training	7.7084	Prediction	7.5734
76	7.471	Training	7.2626	7.2412	Training	7.1613	Training	7.6520	Training	7.2687
77	7.688	Training	7.5972	7.5911	Training	7.3985	Training	7.4451	Training	7.5124
78	7.327	Training	7.5418	7.2690	Prediction	7.5132	Prediction	7.5655	Training	7.2903
79	7.544	Training	7.5703	7.6001	Training	7.3775	Training	7.3268	Training	7.5352
80	7.307	Training	7.4757	7.6001	Training	7.4014	Training	7.4877	Training	7.5733
81	7.142	Training	7.1067	7.1833	Training	7.2713	Training	7.4344	Prediction	7.3035
82	7.359	Training	7.3541	7.3154	Training	7.5921	Training	7.1613	Training	7.2491
83	7.123	Training	7.0946	7.2416	Training	7.6055	Training	7.4770	Training	7.2229
84	7.368	Training	7.3719	7.2714	Prediction	7.2763	Prediction	7.6933	Training	7.2040
85	7.587	Training	7.6577	7.6465	Training	7.4194	Training	7.4452	Training	7.5931
86	7.349	Training	7.4787	7.5841	Training	7.4433	Training	7.7013	Prediction	7.5733
87	7.448	Training	7.5326	7.1794	Training	7.6351	Prediction	7.6187	Training	7.2658
88	7.666	Training	7.5525	7.5817	Training	7.3985	Training	7.3411	Training	7.6202
89	7.428	Training	7.4023	7.5343	Prediction	7.4118	Training	7.5491	Training	7.5974

(IC_{50} = 74.95 nM) with **54** (IC_{50} = 23.28 nM) supports this observation.

The ***MATS8 m*** is a 2D- autocorrelations descriptor which represents Moran autocorrelation-lag 8/weighted by atomic masses. It has positive coefficient in model 1 and 2. Another descriptor with positive coefficient in model 1 is ***R2v+***, a GETAWAY descriptor that stands for R maximal autocorrelation of lag 2/weighted by atomic van der Waals volumes. Therefore, for better activity profile, the values of ***MATS8m*** and ***R2v+*** must be as high as possible. Same is true for ***HATS1e*** (see model 3), a GETAWAY descriptor, which corresponds to leverage-weighted autocorrelation of lag 1/ weighted by atomic Sanderson electronegativities. In model 3 and 5, the descriptor ***B10[C–O]*** (presence/absence of C–O at a topological distance of 10). This 2D- binary fingerprints descriptor has positive coefficient in both the models. Henceforth, such a combination of C and O is in favour of activity profile.

The descriptor which has negative correlation, indicated by its negative coefficient in model 1 and 2, is ***O_lipo_2Bc.*** ***O_lipo_2Bc*** stands for sum of partial charges on lipophilic atoms which are within two bonds from O atoms. Therefore, in future optimizations, the value of this descriptors must be decreased by introducing electron donating groups as substituents on ring C.

Cplus_AbSA (absolute surface area of positively charged carbon atoms) has negative coefficient in model 1, which indicates that lower its value, better the activity. This could be achieved by reducing the number of positively charged Carbon atoms, which in turn, is achievable if number of electron withdrawing groups attached to Carbon are diminished. Another descriptor with negative association with activity is ***fBrS10A*** (frequency of occurrence of Br and S with a separation of 10 Å). This descriptor has negative coefficient in model 3, which specifies that such a combination of Br and S atoms must be avoided for better activity. A comparison of activity of **24** (IC_{50} = 0.319 μM) with **88** (IC_{50} = 0.01633 μM), **23** (IC_{50} = 0.467 μM) with **79** (IC_{50} = 0.04348 μM), **22** (IC_{50} = 0.326 μM) with **54** (IC_{50} = 0.02328 μM) and **77** (IC_{50} = 0.03299 μM), **21** (IC_{50} = 0.191 μM) with **60** (IC_{50} = 0.03359 μM) and **75** (IC_{50} = 0.0114 μM), and **20** (IC_{50} = 0.296 μM) with **50** (IC_{50} = 0.05595 μM), **68** (IC_{50} = 0.15031 μM) and **73** (IC_{50} = 0.02728 μM) is in favour of this opinion.

Interestingly, ***acc_F_5Bc*** (sum of partial charges on F atoms present within five bonds from H-bond acceptor

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atom) has negative coefficient in model 3. Therefore, for better activity profile, its value must be as low as possible. This observation is supported by comparing the activity of following pairs of molecules: **2** (IC_{50} = 3.380 μM) with **3** (IC_{50} = 0.874 μM), **7** (IC_{50} = 0.397 μM) with **8** (IC_{50} = 0.063 μM), **7** (IC_{50} = 0.397 μM) with **11** (IC_{50} = 0.032 μM), **20** (IC_{50} = 0.296 μM) with **21** (IC_{50} = 0.191 μM), **25** (IC_{50} = 0.273 μM) with **26** (IC_{50} = 0.056 μM), and **32** (IC_{50} = 0.182 μM) with **33** (IC_{50} = 0.153 μM). Another negatively associated descriptors, having negative coefficients in model 4, with activity are ***fCN7B*** (frequency of occurrence of C and N atoms with a separation of seven bonds) and ***fFO8B*** (frequency of occurrence of F and O atoms with a separation of eight bonds). Therefore, such a combination of C with N and F with O atoms must be sidestepped to have better activity. This indicate that, in general, the presence of F atom at the position number 4 of ring A is unfavouable for activity. Same is true for the 2D- binary fingerprints descriptor ***B08[O–F]*** (presence/absence of O–F at topological distance of 08), having negative coefficient in model 5, has negative relationship with the activity.

C_F_3Ac, which represents sum of partial charges on C atoms present within 3 Å from F atoms, has negative impact on activity as evident from its negative coefficient in model 5. Therefore, its value must be minimized in future optimization to have superior activity. The difference in activity of following pairs of compounds **64** (IC_{50} = 0.22042 μM) with **73** (IC_{50} = 0.02728 μM), **65** (IC_{50} = 0.15275 μM) with **77** (IC_{50} = 0.03299 μM), and **66** (IC_{50} = 0.12848 μM) with **75** (IC_{50} = 0.0114 μM) is in favour of this observation.

In models 1,2, and 5, the Radial Distribution Function descriptor ***RDF115p*** (Radial Distribution Function – 11.5/ weighted by atomic polarizabilities) has negative coefficient. Similarly, ***GATS8e***, a 2D autocorrelations descriptor which represents Geary autocorrelation-lag 8/weighted by atomic Sanderson electronegativities, has negative influence (negative coefficient in model 4) on activity profile of quinoxalinones as aldose reductase inhibitors. Likewise, the 3D-MoRSE descriptors ***Mor19e*** (3D-MoRSE – signal 19/ weighted by atomic Sanderson electronegativities) and ***SPH*** (spherosity geometrical descriptors) have negative coefficient in model 4. Therefore, the values of ***RDF115p***, ***GATS8e***, ***SPH*** and ***Mor19e*** must be minimal to have better aldose reductase inhibitory activity.

Though we have equated the activities of quinoxalinones as aldose reductase inhibitors in terms of a good number of molecular descriptors like ***all_F_5Ac***, ***acc_F_5Ac***, ***N_all_3Bc***, ***lipo_N_5Ac***, ***O_lipo_2Bc***, etc., we make it clear that the combined or converse effect of confounding factors/descriptors do have added effect on the activity profile of the compounds.

The different statistical parameters for goodness of fit, internal validation and external predictive ability for model 1–5 have been tabulated in the Table 2.

The different statistical parameters for model 1–5, depicted in the Table 2, point out that all the developed models satisfy various statistical parameters like R^2_{tr}, Q^2_{Fn}, R^2_{ex} and CCC_{ex}, etc., which are necessary to establish the internal and external predictive ability of a model.[3c,e,5k,m,n,8,10] The models 1 and 2 are based on undivided dataset (no splitting) whereas models 3–5 have been developed using a divided dataset (80% training and 20% prediction set using random splitting method). The success of the strategy of developing multiple QSAR models is evident from the fact that models 1–5 comprise different descriptors, thereby, capturing most relevant structure-activity information.[3c,e] For all the models, the close value of R^2_{ad} with R^2 indicates that adequate number of descriptors have been used for model building.[3c,e]

The predicted pIC_{50} values by developed QSAR models have been shown in Figure 6 and tabulated in Table 3.

6 Conclusions

In conclusion, multiple QSAR models and thriving CoMFA like model have been reported possessing statistically acceptable internal and external predictive ability. Both analyses provide concurrent and complementary results and are well supported by the molecular docking analysis performed by Wang *etal*. Both analyses indicate that steric repulsion and electrostatic characters have significant correlation with the aldose reductase activity. The developed QSAR and CoMFA like model offer helpful insinuations for optimization of aldose reductase activity of quinoxalinones with improved activity profile. The models could be used to design new ligands with better activity, prior to their actual synthesis.

7 Abbreviations

CoMFA	Comparative Molecular Field Analysis
GA	Genetic Algorithm
MLR	Multiple Linear Regression
QSAR	Quantitative Structure-Activity Relationship
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicity
CADD	Computer Aided Drug Designing
EWG	Electron withdrawing group
OLS	Ordinary Least Square
QSARINS	QSAR Insubria

Conflict of Interest

None declared.

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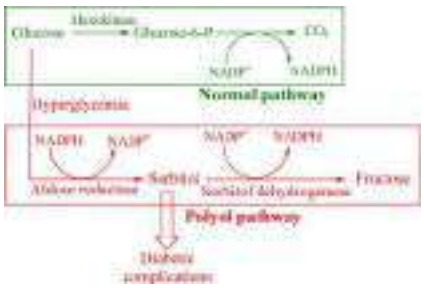
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FULL PAPER



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1 – 15

Quinoxalinones Based Aldose Reductase Inhibitors: 2D and 3D-QSAR Analysis

Research Paper

Antiinflammatory Activity of Triazine Thiazolidinone Derivatives: Molecular Docking and Pharmacophore Modelling

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Some 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one derivatives were prepared by cyclo-condensation reaction between 2-amino-4,6-dichloro-1,3,5-triazine, substituted aromatic aldehyde and ethyl-2-mercaptoacetate, with an yield in the range 76-86 %. Prepared compounds showed antiinflammatory activity. The halogenated electron-withdrawing groups on the phenyl ring of 4-thiazolinone generated antiinflammatory activity. Among the synthesized compounds, 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(2,5-difluorophenyl)thiazolidin-4-one showed better antiinflammatory activity with 72 and 79 % inhibition for TNF-α and IL-6, respectively. Also, molecular docking and pharmacophore modelling performed for this active antiinflammatory compound highlighted that hydrophobicity as an important feature for activity optimization.

Key words: Triazine thiazolidinone, antiinflammatory activity, molecular docking, pharmacophore modeling

Medicinal chemistry has an important role in medicine and health care. The leading objective of medicinal chemistry is to design and synthesize therapeutically potential molecules, study their pharmacokinetic and pharmacodynamic properties, and thoroughly test them as human therapeutic agents. It has been established that infections due to multidrug-resistance (MDR) microbes is a serious concern worldwide and an important issue, also. According to AR threat report in 2013, in the USA annually, at least two million infections and 23 000 deaths occurred[1] and in the latest report, according to WHO's new Global Antimicrobial Surveillance System, there is an extensive existence of antibiotic resistance among 500 000 people with suspected bacterial infections across 22 countries[2].

The solution for this is actively look for new drugs with newer mechanisms of action. In this context, fundamentally the focus should be on understanding the principles and ecological factors, which can affect MDR in bacteria[3,4]. Rapid growth of MDR strains of pathogens result in a severe resistance development towards presently available antimicrobial drugs in the market.

In spite of several efforts during the last few decades to develop new antimicrobials, the efforts were not completely successful to control the rapid upsurge of resistance genes evolving among both Gram-positive and Gram-negative pathogens[5]. In this regard, there is an urgent need to develop new and improved antimicrobial drugs. Antimicrobial research is important not only for development of effective treatments but also for the increased business potential of the pharma industry[4,6]. Recently thiazole, a five-membered ring heterocycle with three carbons, one sulphur atom and one nitrogen atom; and its derivatives thiazolidinones having carbonyl group at 2, 4 or 5-position have been a focus of therapeutic interest[7,8]. It has been revealed by Palekar *et al.*[9], Hamama *et al.*[10], Kumar *et al.*[11], Kaminskyy *et al.*[12], Samadhiya *et al.*[13] and others[14] that in different synthetic drugs pharmacological activities are associated with the thiazolidinone ring

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system as a core structure. Substituents at 2, 3 and 5-position are useful for varying the properties but greatest difference in structure and properties has been exerted by groups attached to carbon atom in 2-position[15]. As the thiazolidinone possesses almost all different types of pharmacological activities, it has been considered as supernatural moiety or magic moiety i.e. a wonder nucleus[16-19]. On the other hand, triazine derivatives are another important class of heterocycles having wide range of biological activities including antimicrobial, anticancer, antimalarial, antiviral, antitubercular and antiHIV[20].

Furthermore, several systems of heterocyclic compounds having triazine linked-thiazolidinones have been synthesized and their pharmacological activities were examined[21-23]. The thiazolidinones bearing triazine analogues have been found to be potential bioactive molecules[24-27]. Therefore, it was thought worthwhile to develop a scheme which combines biolabile nuclei, 1,3,5-triazine and thiazolidinones together in a molecular framework so that their additive effect can increase already existing antimicrobial potential. In line with this, our earlier work on aryl substituted 3-(4,6-dichloro-1,3,5-triazin-2-yl)thiazolidin-4-ones contributed for evaluation of the antibacterial and antimicrobial activity[28].

In the present work, aryl substituted 3-(4,6-dichloro-1,3,5-triazin-2-yl)thiazolidin-4-ones (fig. 1) were synthesized from aromatic aldehyde, 4,6-dichloro-1,3,5-triazin-2-amine and ethyl 2-mercaptoacetate using dry ethanol. The structure of these compounds was confirmed on the basis of ^{1}H nuclear magnetic resonance (NMR), and mass spectra. Antiinflammatory activity of all the synthesized compounds was screened. In the structure activity relationship (SAR) study, the biological activity of these molecules was compared with that of a reference compound. Furthermore, in recent years, different computational techniques have gained popularity to get insight into the mechanism of action of small molecules and streamline the future optimizations to achieve required objectives. Therefore, molecular docking, which is a structure-based drug design technique study was performed to determine the pharmacophore model (ligand-based drug design) to understand the key structural features, which could help in further optimization of triazine-thiazolidinone derivatives to obtain better drug candidates.

MATERIAL AND METHODS

For the synthesis of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one derivatives, 2-amino-4,6-dichloro-1,3,5-triazine, substituted aromatic aldehyde and ethyl-2-mercaptoacetate were obtained from commercial sources. The solvent dry ethanol was purified by distillation before use. IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr pellet method at the Department of Chemistry, Dayanand College, Solapur. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 model using direct injection probe technique and the ^{1}H NMR was determined in $CDCl_3$ solution on a Bruker Ascend-TM 400MHz-NMR spectrometer at S.A.I.F. Division, Indian Institute of Technology, Bombay.

Synthesis of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenyl thiazolidin-4-one (4a):

The synthesis of the target compounds was accomplished via one-pot multicomponent reaction. A mixture of 2-amino 4,6-dichloro-1,3,5-triazine (1, 1 mmol, 0.164 g), benzaldehyde (3, 1 mmol, 0.106 g) and ethyl-2-mercaptoacetate (2, 1 mmol, 0.120 g) was refluxed for 2 h in dry ethanol (20 ml) as reported in our previous article[23]. The progress of reaction was monitored by TLC (toluene:acetone, 4:6). The excess alcohol was evaporated in the vacuum. The resulting crude product was added to crush ice. The solid obtained was washed with water, dried and recrystallized from ethanol to afford final respective compounds (4a). Similarly remaining compounds (4b-l) were prepared. The synthetic strategy for novel compounds triazine based thiazolidinones is outlined in fig. 2. The structure of all synthesized compounds was confirmed on the basis of ^{1}H NMR, mass spectra and elemental analysis. The products were further ascertained by physical and analytical analyses.

Spectral data:

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one (4a), pale yellow solid; yield-

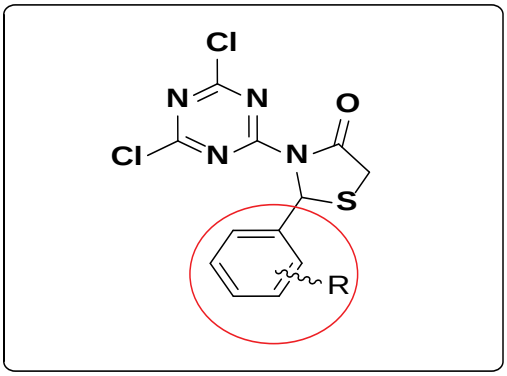


Fig. 1: Design scaffold

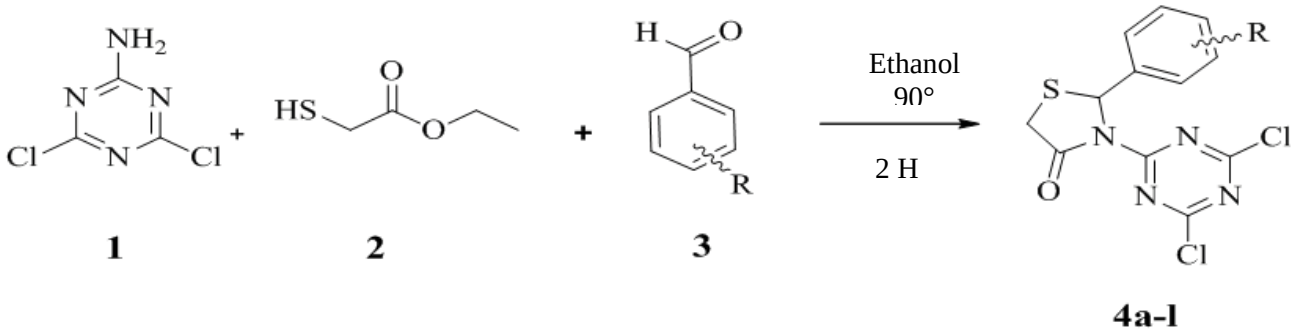


Fig. 2: Synthesis of aryl substituted 3-(4,6-dichloro-1,3,5-triazin-2-yl)thiazolidin-4-one derivatives
R=4a-l; 4a=phenyl, 4b=4-methoxy, 4c=2-fluoro, 4d=2-fluoro-4-bromo, 4e=2-bromo, 4f=2-fluoro-5-chloro, 4g=3-methyl, 4h=4-nitro, 4i=2-hydroxy, 4j=3-methoxy, 4k=2,5-difluoro, 4l=3-CN

80 %, melting point (mp)- 138-140°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41-6.85 (m, 5H), 5.33 (s, 1H), 3.40 (d, *J*=7.1 Hz, 2H). IR (KBr): ν (cm^{-1}) 2842 (C-H str. in aromatic ring), 1723 (C=O of thiazolidinone), 1660 (-C=C- str. in aromatic ring), 814 (C-N- str. in s-triazine). MS (70 eV) *m/z*: 325.96 [M^+ 100 %], 327.96 [M+2, 66.66 %], 329.96 [M+4, 11.11 %]. Anal. calcd. for $C_{12}H_8Cl_2N_4OS$: C, 44.05; H, 2.46; N, 17.12: S, 9.80; found: C, 43.98; H, 2.35; N, 17.00: S, 9.60 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(4-methoxyphenyl)thiazolidin-4-one (4b), pale yellow solid; yield- 82 %, mp- 140-142°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (m, 2H), 6.89 (m, 2H), 5.34 (d, 1H), 3.82 (s, 3H), 3.43 (d, *J*=7.2 Hz, 2H). IR (KBr): ν (cm^{-1}) 2838 (C-H str. in aromatic ring), 1720 (C=O of thiazolidinone), 1655 (-C=C- str. in aromatic ring), 813 (C-N- str. in s-triazine). MS (70 eV) *m/z*: 355.98 [M^+, 100 %], 357.98 [M+2, 66.66 %], 358.98 [M+3, 11.66 %], anal. calcd. for $C_{13}H_{10}Cl_2N_4O_2S$: C, 43.71; H, 2.82; N, 15.68: S, 8.98; found: C, 43.30; H, 2.45; N, 15.48: S, 8.40 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(2-fluorophenyl) thiazolidin-4-one (4c): pale yellow solid, yield- 78 %, mp- 145-147°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (td, *J*=7.5, 1.9 Hz, 1H), 7.32 (td, *J*=6.6, 5.8, 3.7 Hz, 1H), 7.18 (td, *J*=7.6, 1.2 Hz, 1H), 7.06 (ddd, *J*=9.5, 8.3 .1.2 Hz, 1H, Ar-H), 5.94 (d, *J*=7.4 Hz, 1H), 4.25 - 4.10 (m, 2H). IR (KBr): ν (cm^{-1}) 2836 (C-H str. in aromatic ring), 1715 (C=O of thiazolidinone), 1629 (-C=C- str. in aromatic ring), 809 (C-N- str. in s-triazine). MS (70 eV) *m/z*: 343.90 [M^+, 100%], 345.90 [M+2, 66.66 %], 347.11 [M+4, 11.11 %], anal. calcd for $C_{12}H_7FCl_2N_4OS$: C, 41.75; H, 2.04; N, 16.23: S, 9.29; found: C, 41.55; H, 2.00; N, 16.10: S, 9.10 %.

2-(4-bromo-2-fluorophenyl)-3-(4,6-dichloro-1,3,5-triazin-2-yl)thiazolidin-4-one (4d): pale yellow solid, yield- 76 %, mp- 145-147°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48-7.42(m, 1H), 7.33 (dd, *J*=8.4, 2.0 Hz, 1H), 7.25 (dd, *J*=9.4, 1.9 Hz, 1H), 5.86 (s, 1H), 4.20 - 4.13 (m, 2H). IR (KBr): ν (cm^{-1}) 2830 (C-H str. in aromatic ring), 1719 (C=O of thiazolidinone), 1650 (-C=C- str. in aromatic ring), 810 (C-N- str. in s-triazine) cm^{-1}. MS (70 eV) *m/z*: 424.8 [M^+, 60 %], 424.8 [M+2, 100 %], 424.8 [M+4, 46 %], 424.8 [M+6, 6 %], anal. calcd for $C_{12}H_6FBrCl_2N_4OS$: C, 33.99; H, 1.43; N, 13.21: S, 7.56; found: C, 33.41; H, 1.35; N, 13.10: S, 7.20 %.

2-(4-bromophenyl)-3-(4,6-dichloro-1,3,5-triazin-2-yl) thiazolidin-4-one (4e), pale yellow solid, yield- 80 %, mp- 160-162°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53-7.47(m, 2H), 7.41-7.34 (m, 2H), 5.34 (s, 1H), 4.17 (q, *J*=7.2 Hz, 2H). IR (KBr): ν (cm^{-1}) 2830 (C-H str. in aromatic ring), 1721(C=O of thiazolidinone), 1656 (-C=C- str. in aromatic ring), 811 (C-N- str. in s-triazine). MS (70 eV) *m/z*: 403.86 [M^+, 60 %], 405.86 [M+2, 100 %], 407.86 [M+4, 46 %], 409.86 [M+6, 6 %], anal. calcd. for $C_{12}H_7BrCl_2N_4OS$: C, 35.49 ; H, 1.74 ; N, 13.80; S, 7.90, found: C, 35.30; H, 1.45; N, 13.48; S, 7.20 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(4-chloro-2-fluorophenyl) thiazolidin-4-one (4f), pale yellow solid, yield- 81%; mp: 155-157°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.69 (dd, *J*=6.4, 2.6 Hz, 1H), 7.41 (ddd, *J*=8.7, 4.6, 2.6 Hz, 1H), 6.95 (dd, *J*=9.6, 8.7 Hz, 1H), 5.86 (s, 1H), 4.17 (m, 2H). IR (KBr): ν (cm^{-1}) 2820 (C-H str. in aromatic ring), 1720 (C=O of thiazolidinone), 1651 (-C=C- str. in aromatic ring), 812(C-N- str. in s-triazine). MS (70 eV) *m/z*: 377.93[M^+, 100 %], 379.93 [M+2, 100 %], 381.93 [M+4, 33 %], 383.93 [M+6, 4 %], anal. calcd. for $C_{12}H_6FCl_3N_4OS$: C, 37.97 ; H, 1.59 ; N, 14.76: S, 8.45; found: C, 37.41; H, 1.35; N, 14.30: S, 8.20 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-m-tolylthiazolidin-4-one (4g), pale yellow solid, yield- 86 %, mp- 140-142°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37-7.33(m, 2H), 7.32-7.27 (m, 2H), 5.88 (s, 1H), 2.21 (s, 3H), 4.22-4.27 (d, *J*=7.2 Hz, 2H). IR (KBr): ν (cm^{-1}) 2842 (C-H str. in aromatic ring), 1718 (C=O of thiazolidinone), 1660 (-C=C- str. in aromatic ring), 814(C-N- str. in s-triazine). MS (70 eV) *m/z*: 340.6 [M^+, 100 %], 342.6 [M+2, 66.66 %], 344.6 [M+4, 11.11 %], anal. calcd. for $C_{13}H_{10}Cl_2N_4OS$: C, 45.76; H, 2.95; N, 16.42: S, 9.40; found: C, 45.56; H, 2.65; N, 16.10: S, 9.30 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(4-nitrophenyl) thiazolidin-4-one (4h), pale yellow solid, yield- 78 %, mp- 170-172°. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66 (m, 2H), 6.85(m, 2H), 5.84 (s, 1H), 4.19-4.12 (m, 2H). IR (KBr): ν (cm^{-1}) 2836 (C-H str. in aromatic ring), 1721 (C=O of thiazolidinone), 1641 (-C=C- str. in aromatic ring), 807(C-N- str. in s-triazine). MS (70 eV) *m/z*: 370.8 [M^+, 100 %], 372.8 [M+2, 66.66 %], 374.8 [M+4, 11.11 %], anal. calcd. for $C_{12}H_7Cl_2N_5O_3S$: C, 38.72 ; H, 1.90 ; N, 18.82: S, 8.62; found: C, 38.41; H, 1.65; N, 18.40: S, 8.40 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one (4i), pale yellow solid, yield- 82 %, mp- 160-162°; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, *J*=11 Hz, 1.8 Hz, 1H), 7.32 (d, *J*=6.5, 5.7, 3.6 Hz, 1H), 7.18 (d, *J*=7.5, 1.3 Hz, 1H), 7.06 (dd, *J*=9.4, 8.2 .1.2 Hz, 1H, Ar-H), 5.92 (d, *J*=7.5 Hz, 1H), 4.21 - 4.12 (m, 2H), IR (KBr): ν (cm^{-1}) 2838 (C-H str. in aromatic ring), 1722 (C=O of thiazolidinone), 1630 (-C=C- str. in aromatic ring), 806 (C-N- str. in s-triazine), MS (70 eV) *m/z*: 341.7 [M^+, 100 %], 343.7 [M+2, 66.66 %], 345.7 [M+4, 11.11 %], anal. calcd for $C_{12}H_8Cl_2N_4O_2S$: C, 42.00; H, 2.35; N, 16.33: S, 9.34; found: C, 41.90; H, 2.10; N, 16.10: S, 9.20 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(3-methoxyphenyl)thiazolidin-4-one (4j), pale yellow solid, yield- 80 %, mp- 141-143°, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15 (s, 1H, Ar-H), 7.93 (m, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.46 (m, 1H, Ar-H), 5.37 (d, *J*=7.1 Hz, 1H), 3.75(s, 3H), 3.38 (d, 2H); IR (KBr): ν (cm^{-1}) 2834 (C-H str. in aromatic ring), 1717 (C=O of thiazolidinone), 1625 (-C=C- str. in aromatic ring), 806 (C-N- str. in s-triazine), MS (70 eV) *m/z*: 355.7 [M^+, 100%], 357.7 [M+2, 66.66 %], 359.7 [M+4, 11.11 %], anal. calcd for $C_{13}H_{10}Cl_2N_4O_2S$: C, 43.71; H, 2.82; N, 15.68: S, 8.98; found: C, 43.50; H, 2.75; N, 15.42: S, 8.60 %.

3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-(2,5-difluorophenyl)thiazolidin-4-one (4k), pale yellow solid, yield- 75 %, mp- 178-180°. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (dd, *J*=6.3, 2.5 Hz, 1H), 7.39 (dd, *J*=8.6, 4.5,2.5 Hz, 1H), 6.85 (dd, *J*=9.5, 8.6 Hz, 1H), 5.80 (s, 1H), 4.15 (m, 2H), IR (KBr): ν (cm^{-1}) 2825 (C-H str. in aromatic ring), 1725 (C=O of thiazolidinone), 1650 (-C=C- str. in aromatic ring), 813(C-N- str. in s-triazine) cm^{-1}, MS (70 eV) *m/z*: 361.1 [M^+, 100%], 363.1 [M+2, 66.66 %], 365.1 [M+4, 11.11 %], anal. calcd for $C_{12}H_6Cl_2F_2N_4OS$: C, 39.69; H, 1.67 ; N, 15.43: S, 8.83; found: C, 39.50; H, 1.44; N, 15.33; S, 8.32 %.

3-(3-(4,6-dichloro-1,3,5-triazin-2-yl)-4-oxothiazolidin-2-yl)benzonitrile (4l), pale yellow solid, yield- 78 %, mp- 145-147°, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 7.34-7.21 (m, 1H, Ar-H), 7.04-7.02 (m, 1H, Ar-H), 5.78 (s, 1H), 3.40-3.36(m, 2H), IR (KBr): ν (cm^{-1}) 2835 (C-H str. in aromatic ring), 1724 (C=O of thiazolidinone), 1640 (-C=C- str. in aromatic ring), 806(C-N- str. in s-triazine), MS (70 eV) *m/z*: 350.8 [M^+, 100%], 352.8 [M+2, 66.66 %], 354.8 [M+4, 11.11 %], anal. calcd for $C_{13}H_7Cl_2N_5OS$: C, 44.33; H, 2.00 ; N, 19.88; S, 9.10; found: C, 44.10; H, 1.90; N, 19.56: S, 8.89 %.

Antiinflammatory assay:

Proinflammatory cytokine production by lipopolysaccharide (LPS) in THP-1 cells was measured according to the method described by Hwang *et al.*[29]. During the assay, THP-1 cells were cultured in RPMI 1640 culture medium (Gibco BRL, Pasley, UK), containing 100 U/ml penicillin and 100 mg/ml streptomycin containing 10 % foetal bovine serum (JRH). Cells were differentiated with phorbol myristate acetate (PMA, Sigma). Following cell plating, the test compounds 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one (4a-l) in 0.5 % dimethyl sulfoxide were added to each well separately and the plate was incubated for 30 min at 37°. Finally, LPS (*Escherichia coli* 0127:B8, Sigma Chemical Co., St. Louis, MO) was added, at a final concentration of 1 µg/ml in each well. Plates were further incubated at 37° for 24 h in 5 % CO_2. After incubation, supernatants were harvested and assayed for tumor necrosis factor (TNF)-α and IL-6 by ELISA as described by

the manufacturer (BD Biosciences). The percent inhibitions were measured at 10 µM concentration. The dexamethasone was used as standard drugs. The results are tabulated in Table 1.

Molecular docking:

Literature and RCSB Protein Data Bank (www.rcsb.org) survey revealed that no TNF-α trimer has been cocrystallized with small molecules; however a TNF-α dimer structure binding with a small molecule SPD304 is available. Therefore, for molecular docking, the 3D-structure of human TNF-α with antagonist SPD-304 (PDB code: 2AZ5, resolution: 2.1 Å) was downloaded and subjected to minimization using UCSF Chimera (http://www.cgl.ucsf.edu/chimera/). Molecular docking was performed using NRG Suite[30,31], a python and C++ based PyMOL plugin, which detects surface cavities in proteins and use them as target binding-sites for docking simulations with the aid of FlexAID[30,31]. In the present work, following default settings were used to get optimum performance of NRGsuite: binding sites input method, spherical shape; spacing of three dimensional grid: 0.375Å; side chain flexibility- no; ligand flexibility- yes; ligand pose as reference- yes; constraints- no; HET groups-included water molecules; vander Walls permeability-0.1; solvent types- no type; number of chromosomes-1000; number of generations- 1000; fitness model-share; reproduction model- population boom; number of TOP complexes- 10.

Pharmacophore modelling:

For pharmacophore modelling, PyMOL 2.1[32] along with its plugin LIQUID and LigFit were used with default settings. The molecules (three most active) were aligned to get consensus pharmacophore model.

TABLE 1: ANTIINFLAMMATORY ACTIVITY OF 3-(4,6-DICHLORO-1,3,5-TRIAZIN-2-YL)-2-PHENYLTHIAZOLIDIN-4-ONE DERIVATIVES

Compounds (4a-l)	Substituent R	% Inhibition at 10 µM	
		TNF-α	IL-6
4a	H	12	20
4b	4-OMe	32	29
4c	2-F	**70**	**76**
4d	2-F, 4-Br	54	57
4e	4-Br	22	23
4f	2-F, 5-Cl	**60**	**67**
4g	3-Me	10	18
4h	4-NO_2	15	20
4i	2-OH	22	29
4j	3-OMe	45	54
4k	2-F, 5-F	**72**	**79**
4l	5-CN	30	29
Reference drug	Dexamethasone (1 µM)	75	81

RESULTS AND DISCUSSION

The synthesis of different 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenyl thiazolidin-4-ones (4a-l) were successfully achieved by the reaction between aromatic aldehyde, 4,6-dichloro-1,3,5-triazin-2-amine and ethyl 2-mercaptoacetate in dry ethanol and yield of the product obtained was from 76 to 86 %. The antiinflammatory activity of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2 phenylthiazolidin-4-ones were recorded on the basis of reference standard drug dexamethasone and tabulated in Table 1. Some of the compounds showed highest (4c, 4f and 4k) antiinflammatory activity. To understand the structural feature, which steer the activity profile, all the molecules were docked in the active site of TNF-α. For the sake of convenience and representation, herein, we present the docking pose for most active molecule 4k. Fig. 3 shows the molecular docking poses for molecule 4k, as a representative, within the active site of the enzyme TNF-α and fig. 4 shows the consensus pharmacophore model for most active molecules after alignment.

In this multicomponent reaction (fig. 2), synthesis of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenyl thiazolidin-4-ones was obtained in good to better yield. This cyclo-condensation multicomponent reaction starts with reaction of 4,6-dichloro-1,3,5-triazin-2-amine and aldehyde, which on further reaction with ethyl 2-mercaptoacetate gives the cyclic intermediates and finally results into product. The mechanism of this cyclo-condensation multicomponent reaction is shown is fig. 5.

From antiinflammatory activity data of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-ones (Table 1), it was observed that the compounds 4c, 4f, and 4k were found to be comparatively active as TNF-α and IL-6 inhibitor (up to 60-72 % TNF-α and 67-79 % IL-6 inhibitory activity), while compounds 4k (72 % and 79 %) exhibiting highest inhibition against TNF-α and IL-6, respectively at 10 µM. It is to be noted that the compound found to be equieffective to 1 µM dexamethasone. The compounds 4d and 4j exhibited moderate activity (45-57 % inhibition) while other compounds exhibited low (4b, 4e, 4i, 4l) to very low (4a, 4g, 4h) activity at same level of concentration. The substitution of functional group such as $–OCH_3$, -OH, -Cl and –F showed significant activity. The

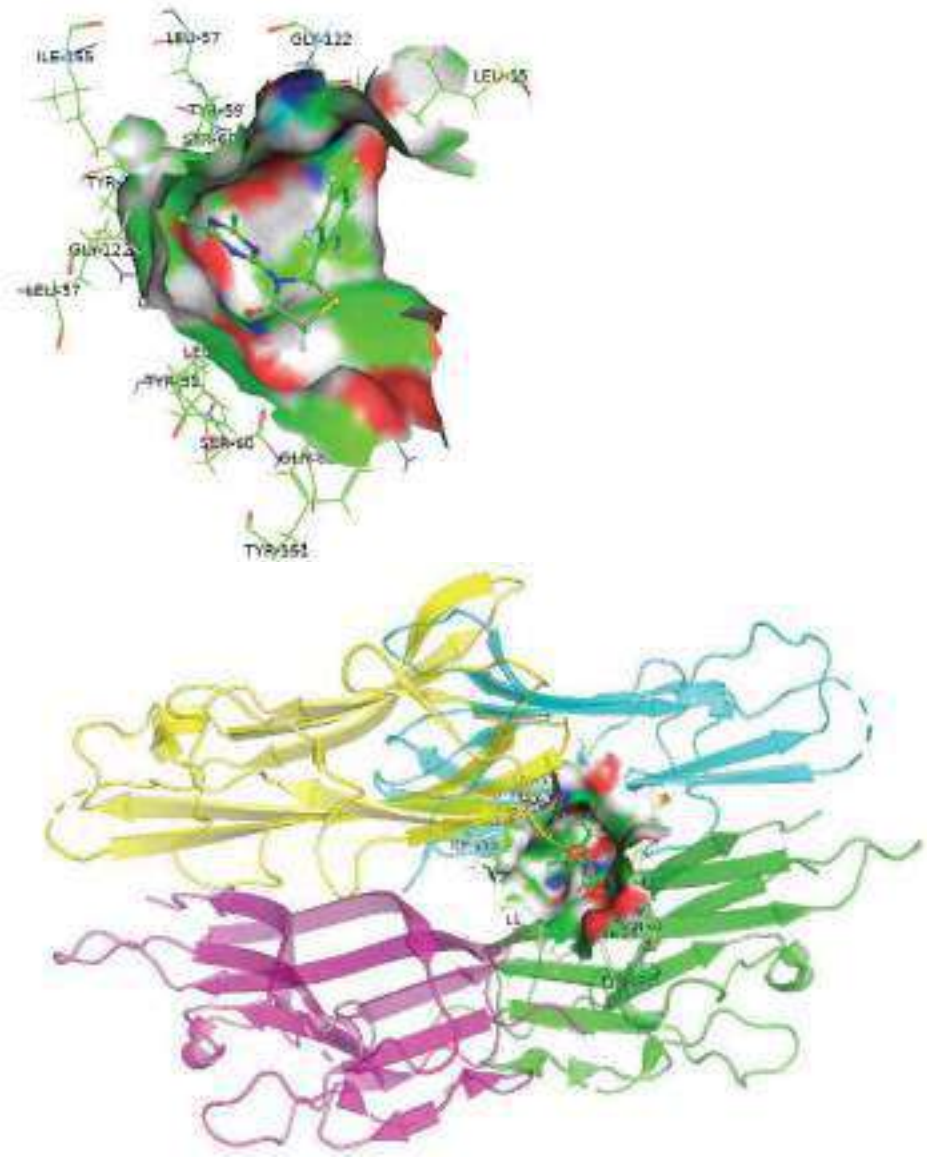


Fig. 3: Docking poses for molecule 4k
Molecular docking poses for the representative molecule 4k within the active site of the enzyme TNF-α

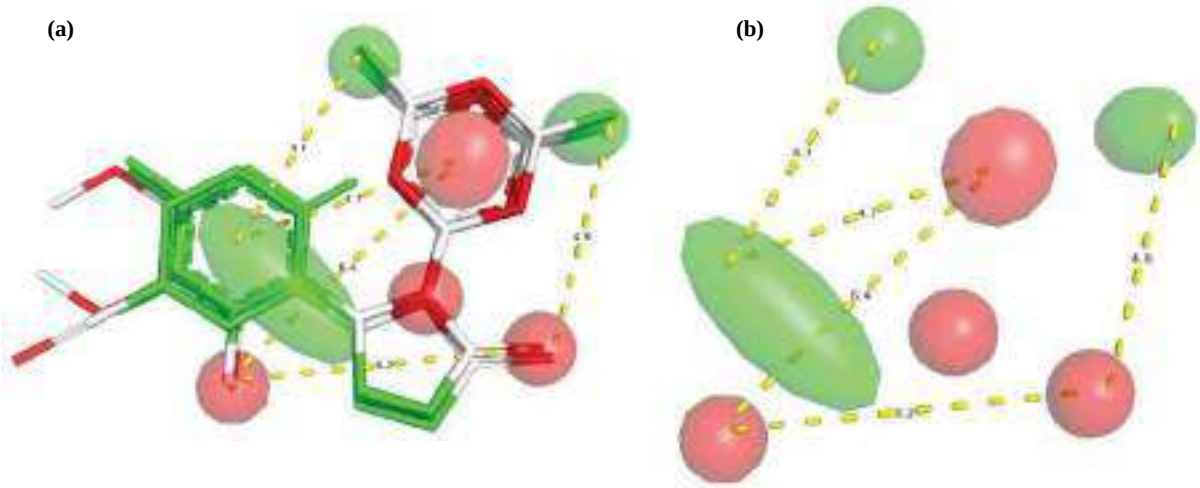


Fig. 4: Consensus pharmacophore model for most active molecules after alignment
(a) Pharmacophore model with molecules as visible, (b) pharmacophore model with molecules made invisible (green contour: hydrophobic, red contour: H-bond acceptor)

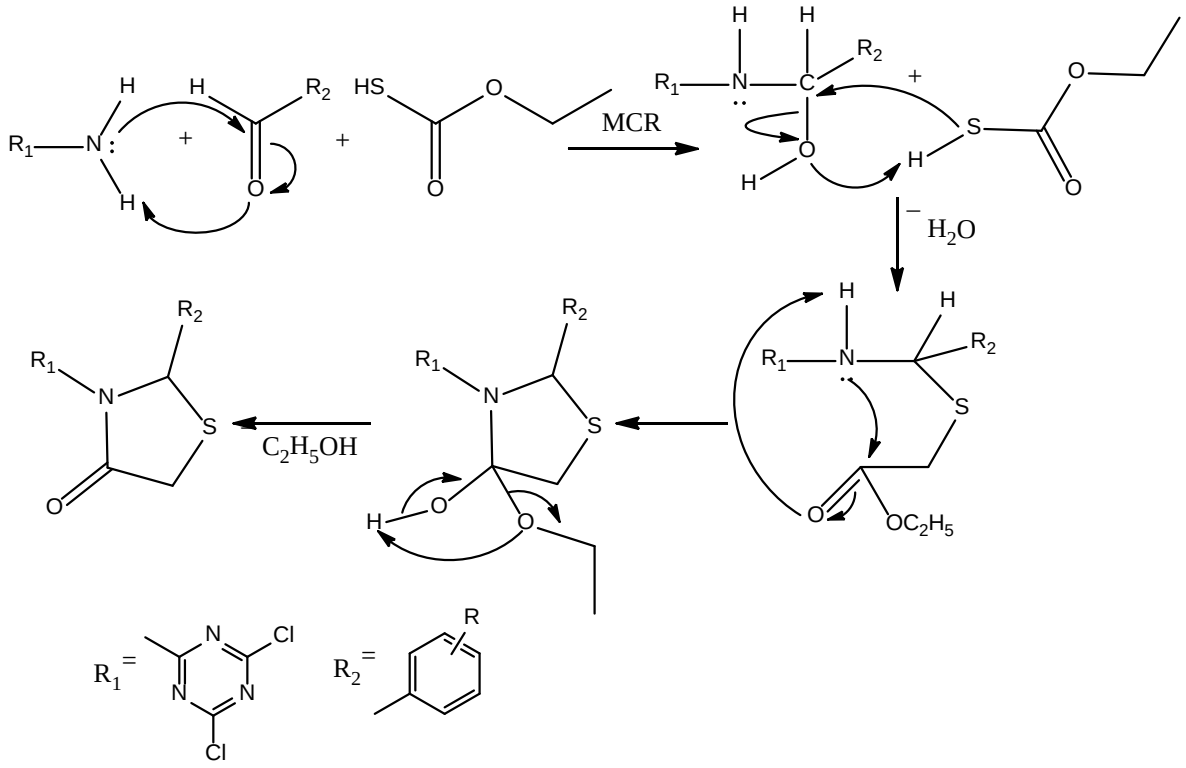


Fig. 5: Mechanism of the multicomponent reaction
Multicomponent reaction involved in the synthesis of aryl substituted 3-(4,6-dichloro-1,3,5-triazin-2-yl) thiazolidin-4-ones

antiinflammatory activity data shows that presence of fluorine group at C-2 and C-5 of phenyl ring plays an important role in the activity. The presence of 'F' group at C-5 enhances the antiinflammatory activity (4k). Because of the presence of chlorine instead of fluorine at C-5 compound (4f) little bit reduces the activity. Further, it was observed that the presence of fluorine at position-2, bromine at position-4 and methoxy group at position-3 on phenyl ring showed moderate activity. Interestingly, the presence of other functional groups on different position on phenyl such as 4-OMe, 4-Br, 3-Me, 2-OH, 4-NO_2 and 5-CN exhibits low to very low activity.

It was revealed from these SAR studies that the presence of a halide (electron donating deactivating group) -F and -Cl at C-5 position tolerates the procytokine activity. It was found that fluorine imparts the special characteristics that enhance therapeutic efficiency and improved pharmacological properties in active molecules. Thus, the compound 4k and 4c were found to be potential antiinflammatory agents amongst the series of compounds studied.

The molecular docking analysis for most active molecule 4k revealed that the molecules have hydrophobic and polar interactions with the receptor residues (fig. 3). From the docking pose, it appeared that the molecule 4k adopted a claw-like shape and presented at the interface of two chains of the enzyme. Its aromatic ring was found to be responsible for hydrophobic interactions with nearby residues viz. Leu55, Leu120, and Tyr59. The importance of hydrophobic part of molecules has also been highlighted by the consensus pharmacophoric analysis (fig. 4).

The two chlorine atoms on the triazine ring also favors hydrophobic interaction with the residues *viz.* SER60, Tyr151, Gly122, and Leu120. Therefore, presence of two chlorine atoms is a good feature for retentions in the future optimizations. The five membered thiazolidinone rings has contributed as a bridge and added additional flexibility to adopt the appropriate conformation inside the active site of the receptor. This ring is closer to chain B of the receptor and responsible for polar interactions with the following residues of chain B *viz.* Ser60 and Gln61. It appeared that docking and pharmacophore analyses provide similar results and highlight hydrophobic as important feature for activity optimization.

In the present work, all molecules (4a-4l) were subjected to molecular docking in the active site of human TNF-α. Table 2 contains the docking scores for the molecules. For the sake of validation of molecular docking, the original ligand (SPD304) was also docked

TABLE 2: DOCKING SCORES FOR MOLECULES 4A-4L AND ORIGINAL LIGAND (SPD304)

ID	SMILES	Docking score
4a	Clc1nc(Cl)nc(N2C(=O)CSC2c2ccccc2)n1	-5.9930043
4b	Clc1nc(Cl)nc(N2C(=O)CSC2c2ccc(OC)cc2)n1	-6.1437421
4c	Clc1nc(Cl)nc(N2C(=O)CSC2c2c(F)cccc2)n1	-5.9163222
4d	Brc1cc(F)c(C2N(c3nc(Cl)nc(Cl)n3)C(=O)CS2)cc1	-6.1437573
4e	Brc1ccc(C2N(c3nc(Cl)nc(Cl)n3)C(=O)CS2)cc1	-5.9886723
4f	Clc1nc(Cl)nc(N2C(=O)CSC2c2c(Cl)cccc2F)n1	-6.1999474
4g	Clc1nc(Cl)nc(N2C(=O)CSC2c2cc(C)ccc2)n1	-6.0782661
4h	Clc1nc(Cl)nc(N2C(=O)CSC2c2ccc([N+](=O)[O-])cc2)n1	-6.4120026
4i	Clc1nc(Cl)nc(N2C(=O)CSC2c2c(O)cccc2)n1	-5.9833794
4j	Clc1nc(Cl)nc(N2C(=O)CSC2c2cc(OC)ccc2)n1	-6.1720862
4k	Clc1nc(Cl)nc(N2C(=O)CSC2c2c(F)cccc2F)n1	-5.9358053
4l	Clc1nc(Cl)nc(N2C(=O)CSC2c2cc(C#N)ccc2)n1	-6.3134403
SPD304	FC(F)(F)c1cc(-n2c3c(c(C[N+](CC[N+](CC4=C(O)c5c(OC4)cc(C)c(C)c5)C)C)c2)cccc3)ccc1	-7.6338243

in the active site of the receptor and its docking score is also tabulated in Table 2. From the Table 2, it is clear that the original ligand (SPD304) has better binding with the receptor than the molecules 4a-4l. Therefore, future modifications are required to increase selectivity and activity profile of triazine thiazolidinone derivatives, synthesized in the present work, for human TNF-α.

In summary, a series of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one derivatives (4a-l) were synthesized in good to better yield by condensation cyclisation reaction between substituted aromatic aldehyde, 4,6-dichloro-1,3,5-triazin-2-amine and ethyl 2-mercaptoacetate using dry ethanol. The SAR study, suggested that the halogenated electron-withdrawing groups imparted greater antiinflammatory activity from the title hybrid skeleton. Furthermore, molecular docking and pharmacophore analyses provided similar results and highlighted hydrophobic moieties as prominent features for activity optimization.

Conflict of interest:

Authors have no conflict of interest.

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TO STUDY INTERMOLECULAR INTERACTION OF SUBSTITUTED THIOCARBAMIDOPHENOL AND Cu(II) AND Cd(II) ION IN 70% MIXED SOLVENT MEDIA

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Abstract

Pharmacodynamics and pharmacokinetics of drug received importance in the study of drug potency. Physicochemical parameter of newly synthesized molecules reasonably influence to different steps of pharmacodynamics. Intermolecular interactions and stability constant related to activity synthesized molecules. Present work concerning to the interaction newly synthesized 4-Phenylthiocarbamidophenol (L_1) and 4-(p-Chloro)phenylthiocarbamido phenol (L_2) and Cu(II) and Cd(II) metal ions in 70% ethanol-water mixture. Jobs method of continuous variation is used through this investigation. The stiochiometry of complex formation found to be 1:1. This investigation helps to understand drug effect and drug activity of newly synthesized drugs.

Keywords :- 4-Phenylthiocarbamidophenol (L_1) and 4-(p-Chloro) phenylthiocarbamido phenol (L_2), Stability constant, Jobs Method of Continuous variation.

INTRODUCTION

Drugs Potency closely related to molecular structure and their ionic interactions. Interaction of newly synthesized molecules with deferent metal ions has received some major importance to understand their intra and inter molecular interactions. Solution equilibrium of molecule possible to understood from complex formation ability of ligands and activity of complexes. Physical properties of lignads are relatively corresponding to complexation and its knowledge bear to know composition as well as conformation of complex formation. Drug activity, drug effect, transmission of drug and absorption of drug all these four factors are depending on stability constant of molecule. Absorption directly proportional to concentration and it is alter by different physical parameters of molecules. Spectrophotometric technique more efficiently examines absorption. Thus this technique has a great significance in measurments of stability constant and confirmation of complex formation in solution. Wagh [1] and Deshamukh [2] determined log K value of chalcones pyridine carboxylic acids and hydroxyl ethyl benzene. Galhan et al [3] studied (E)-2-(mercaptophe -nylaminoethylene)-3-oxo-N-p-tolylbutamide with some metal ion by spectrophotometrically. Boldescu et al [4] Spectrophotometrically studied sangurine-bcyclodextrin complex formation. Spectrophotometrically determination of phenylprine hydrochloride and salbutamol sulphate drugs in pharmaceutical preparation using diazotized metacloprine hydrochloride was carried out by Al-Abachi and Abed [5]. Alsamarrai et al [6] investigated ephedrine-hydrochloride by spectrophotometrically. Saleha et al [7] investigated sulphsalazine antibiotics drugs. Investigation of ion complex formation of anti-hypertensive drug mehtyldopal was studied [8]. Meshram [9] studied complexation by interaction of Dy (III) with lincomycine and lyrodoxin in 70%





ethanol-water medium. Spectrophotometric study of diflunisal febuxostate metaxalone, fexofenadine methyl ester and linezolide pharmaceutical dosages using tetracynoethelene was carried out by Shrinivas et al[10] .

Wadekar and Tayade [11] studied conditional stability constants and confirmation of complex formation of Cu (II), Cd (II) and Cr (III) complex with substituted thio- carbamidonaphthols Spectrophotometrically. Valtierra –Alvardo et al [12] investigated complex formation equilibrium of Cu(II). Solvent effect on dissociation of ammonium and pyridinium ion was studied by Ohataki [13]. Investigation of effect of dielectric constant on Cu(II) –Complexes of phthalic acid in various percentage of dioxane-water mixture was carried by Palaskar [14]. To study the interaction of *4-Phenylthiocarbamidophenol* (L_1) and *4-(p-Chloro)phenylthiocarbamido phenol (L_2) and Cu* (II) and Cd(II) metal ions spectrophotometrically. This investigations helps to understand metal-ligand stability constant and confirmation of complexes formation of these interaction at 0.1 M ionic strength. Job method of continuous variation used to through current work. It is specially associated to study of effect of solvents, effect of ligands and group as well as effect of metal ions during formation of complexes.

MATERIALS and METHOD :

Experimental

4-Phenylthiocarbamidophenol (L_1) and *4-(p-Chloro)phenylthiocarbamido phenol (L_2)*, has been synthesized in laboratory by standard method. The nitrate salts of Nickel was used & their solutions were prepared in double distilled water. The solutions of potassium nitrate was prepared (1M) & used for maintaining ionic strength constants. Absorption are measured by UV Spectrophotometer model 106, (Systronic make) with an accuracy = ± 0.005 was used.

RESULTS and DISCUSSION

Spectrophotometric Measurement

Job's Method

Jobs method of continuous variation method is reliable to examine formation of complex [15]. Jobs method consist of equimolar solutions of metal and ligand varying proportion in such manner that total concentration of metal plus ligand is constant in resulting mixtures[16]. The compositions of metal ions solution (1 x10 $^{-2}$ M) & ligand (1x 10^{-2}M) were prepared in ten series. Ionic strength was maintained constant (0.1M) by adding an appropriate amount 0f 1M KNO3 solution in 10 ml volume (λmax) was determined using one of the compositions at which there is maximum absorption. The absorption for all the compositions were recorded at a constant wave length (λmax). The data of absorption & % composition of metal ion and ligand solutions at constant pH can be used to construct the curves. It was observed that 1:1 complex formation occurs in the pH range of 3 to 6. Each solution is diluted up to 15 ml and recorded absorption at same (λ max). Conditional stability constants of metal ligand complexes were calculated for all the systems using following expression.

$$K = \frac{X}{(a1-x)(b1-x)} = \frac{X}{(a2-x)(b2-x)}$$

K = Conditional stability constants of complex. X = Concentration of complex.
a1 & a2 = Concentration of metal ions; b1 & b2 = Concentration of ligand.
Conditional stability constants of metal ligand complexes showed in Table-1

Table – 1: Determination of Conditional Stability of Metal Ligand Complexes

System	Conditional stability constant K	Log K
L_1+Cu(II)	1.4930 X 10^{-3}	0.1741 X 10^{-3}
L_2+Cu(II)	2.4740 X 10^{-3}	0.3934 X 10^{-3}
L_1+Cd(II)	1.8060 X 10^{-3}	0.2568 X 10^{-3}
L_2+Cd(II)	1.4590 X 10^{-3}	0.1641 X 10^{-3}

CONCLUSION

Table No. 1 reveals that resultant values obtain for L_1 and L_2 are fairly good. There is no appreciably change in log K values. This indicated the simultaneously complex formations.

L_2+Cu(II) interaction has more Log K value than L_1+Cu(II) interaction. It indicate that L_2 able to form more stable complex with Cu(II) than L_1 and L_1+Cd(II) interaction has more Log K value than L_2+Cd(II) interaction. It indicate that L_1 able to form more stable complex with Cd(II) than L_2 .

Variation in Log K values observed due to direct interfere of dielectric constant, solvent-solvent interaction, solute-solvent interaction and solute-solute-solvent interaction. This investigation helps to study of drug activity and drug effect of newly synthesized drugs.

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SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SOME NEWLY SYNTHESIZED PROPANE-1,3-DIONE (β-DIKETONES) DERIVATIVES

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A B S T R A C T

A simple,efficient and new series of propane-1,3-diones i.e.β-diketone derivatives (4a-d) were prepared via Baker-Venkataraman rearrangement from substituted 2-benzoyloxy acetophenones (3a-d) with potassium hydroxide in pyridine medium and obtained in good yields.The structures of the titled compounds were confirmed by spectral data studies of IR and 1H NMR.The antibacterial and antifungal activity of these newly synthesized compounds (4a-d) were screened by paper disc method and appeared to be significant.

Keywords: 2-Benzoyloxy acetophenones ,Propane-1,3-diones, IR and 1H NMR , Antifungal activity, Antibacterial activity

1.Introduction

Development of simple synthetic steps to widely used organic compounds using readily available of reagents are one of the most important objectives of organic synthesis. In Baker-Venkataraman rearrangement thesynthesis from o-aryloxy acetophenone to β-diketones was utilized. The β-diketones was shows various pharmacological activities like, prophylactic antitumor1, antioxidant2, antisunscreen agents3and biological activity4.The β-diketones have been widely used for the synthesis of heterocyclic compounds such as flavones5,pyrazoles6,2-mercapto pyrimidine7etc.Now recently β-diketones are well known to have keto-enol tautomerism and reported that they have important pharmacophores for the HIV-integrase (1N) inhibitiors8.Substituted propane 1,3-diones are used in various drug containing the heterocyclic moieties, such as isoxazole, carbazole, imidazole and thiazole etc. The β-diketones are used as a ligand in co-ordination chemistry9-10. The synthesis of substituted propane -1,3-diones (β-diketones) are of tremendous important in organic chemistry and medicine, so by focusing on these aspects we are going to synthesized β-diketones asa precursor for different heterocyclic compounds and study their spectroscopic data and antimicrobial properties.

2. Materials and Methods

All solvents and chemicals were of research grade, highest purity and commercially available. The melting points were taken in open capillaries using paraffin Thiele's tube. All the synthesized compounds were purified by recrystallization method. The IR spectra were recorded on Shimadzu IR affinity-1FTIR spectrophotometer in KBr pallets and values were expressed in cm-1.1H NMR spectra were recorded on Bruker Avance II 4000 NMR spectrophotometer in DMSO-d_6 as a solvent and TMS as an internal standard.

3.Synthesis of substituted propane-1,3-diones (β-diketones) (4a-d)

The synthesis involves the following steps.

3.1. General procedure for the synthesis of 4-bromo phenyl acetate (1)

4-bromo phenol (0.05mol) fused with acetic anhydride(5ml) and add sodium acetate. The mixture was refluxed for about 1hr. then cooled for 15 min. and poured in ice crushed water. Acetate layer was separate out by separating funnel and wash several times by water. The product was purified by distillation process to obtained a pure 4-bromo phenyl acetate (1).

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3.2. General procedure for the synthesis of5-bromo,2-hydroxy acetophenone (2)

Place anhydrous aluminum chloride (120 g) in kjeldal flask and add 4-bromo phenyl acetate (1) (40 ml) drop wise in a flask. Heat the reaction mixture in oil bath for 60 min at 120^0C temperature. The reaction mixture was cooled and add in to acidified ice crushed water to get crude product. It was purified by dissolving product in acetic acid and decompose in ice cold water to get 5-bromo,2-hydroxy acetophenone (2).

3.3 General procedure for the synthesis of 2-substituted benzoyloxy 5-bromo acetophenone (3a-d)

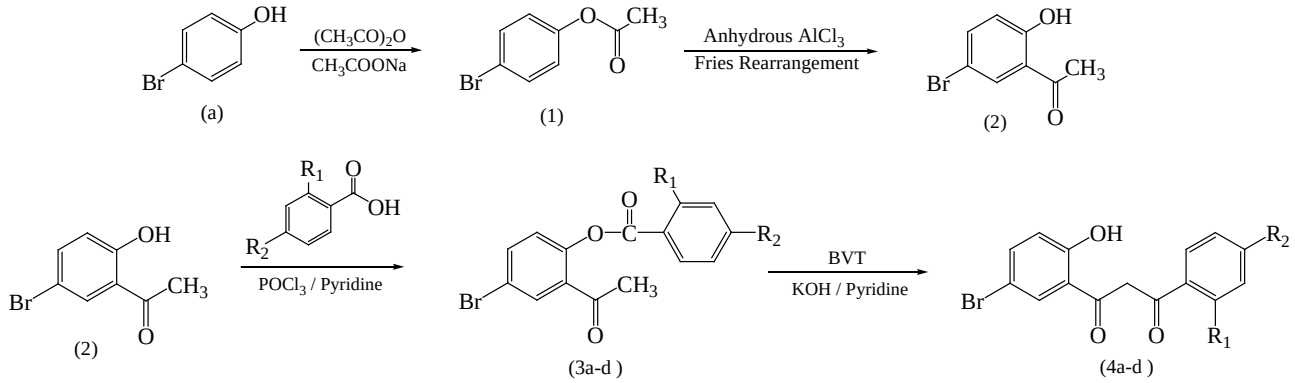
Place 5-bromo,2-hydroxy acetophenone (2) (0.05mol) and substituted benzoic acid (0.05mol) were dissolved in dry pyridine at 0^0C.Then add $POCl_3$ dropwise with constant stirring bellow 10^0C temperature. The reaction mixture was allowed to stand for overnight at room temperature. The reaction mixture was poured in ice cold acidified 10% HCl. Then the product was wash by 10%$NaHCO_3$ and several times by water. Recrystallized the product by ethanol to obtained a series of 2- substituted benzoyloxy 5-bromo acetophenone (3a-d).

3.4 General procedure for the synthesis of substituted propane-1, 3-diones(β-diketones) (4a-d)

A series of substituted propane-1,3-diones (4a-d) was synthesized by Baker–Venkataraman transformation reaction as shown in **figure 1**. Take 2-substituted benzoyloxy 5-bromo acetophenone (3a-d) (0.05mol) was dissolved in dry pyridine. The reaction mixture was heated up to 60^0C and add pulverized KOH slowly with constant stirring. After 5-6 hr. the reaction mixture was acidified by dil. HCl (1:1) in ice cold water. The crude product was filtered, washed with $NaHCO_3$(10%) and several times by water. Recrystallized the product from ethanol-acetic acid mixture to get substituted propane 1,3-diones (β-diketones) (4a-d) having good yield as shown in **table1**

.

Figure 1. Scheme for the synthesis of substituted propane-1,3-diones (β-diketones) (4a-d)



R_1 – H, Cl R_2 - CH_3, NO_2, H, Cl.

4. Spectral data of all substituted propane -1,3-diones(4a-d)

4.1: 1-(5'-bromo-2'-hydroxy phenyl)-3-(4'-methyl phenyl) propane-1,3-dione(4a)

Solid, dark yellow colour, IR (KBr): 3335 cm^{-1}(Phenolic -OH stretch),3034 cm^{-1}(Aromatic C-H stretch), 2945 cm^{-1}(Aliphatic C-H stretch),1690 cm^{-1}(C=O stretch),1505 cm^{-1}(Aromatic C=C stretch).^{1}H NMR (DMSO-d_6): δ 4.8 (S,1H of OH), δ 2.5 (S, 3H of CH_3), δ 3.44 (S, 2H of CH_2), δ 7.2-8.12(m,7H of Ar C-H).

4.2: 1-(5'-bromo-2'-hydroxy phenyl)-3-(4'nitrophenyl) propane-1,3-dione(4b)

Solid dark yellow colour, IR (KBr):3388 cm^{-1}(Phenolic -OH stretch), 2918 cm^{-1}(Aromatic C-H stretch), 2858 cm^{-1} (Aliphatic C-H stretch),1652 cm^{-1}(C=O stretch),1564 cm^{-1}(Aromatic C=C stretch),1377 cm^{-1}(C-N stretch).^{1}H NMR (DMSO-d_6): δ 6.7 (S, 1H of OH), δ 3.36 (S, 2H of CH_2), δ 6.85-8.30 (m, 7H of Ar C-H).

Table 1 – Physical data of substituted propane-1,3-dione (β-diketones) (4a-d).

Entry	Compound Code	R_1	R_2	M.F.	M.W.	M.P. (^oC)	Yield%
1	4a	H	CH_3	$C_{10}H_{13}BrO_3$	335.18	154-156	72 %
2	4b	H	NO_2	$C_{15}H_{10}B_rNO_5$	364.15	190-192	68%
3	4c	Cl	H	$C_{15}H_{10}BrClO_3$	353.6	112-114	70%
4	4d	H	Cl	$C_{15}H_{10}BrClO_3$	353.6	114-116	74%

M.F.-Molecular formula, M.W.-Molecular weight, M.P.-Melting points

4.3: 1-(5'-bromo-2'-hydroxyphenyl)-3-(2'chlorophenyl) propane-1,3-dione(4c)

Solid dark brown colour,IR (KBr): 3300 cm^{-1} (Phenolic -OH stretch), 3131 cm^{-1}(Aromatic C-H stretch), 2918 cm^{-1} (Aliphatic C-H stretch), 1703 cm^{-1} (C=O stretch),1559 cm^{-1}(Aromatic C=C stretch),766 cm^{-1}(C-Cl stretch).^{1}H NMR (DMSO-d_6): δ 3.53 (S, 1H of OH), δ 2.63 (S, 2H of CH_2), δ 6.92-8.19 (m,7H of Ar C-H).

4..4: 1-(5'-bromo-2'-hydroxyphenyl)-3-(4'chlorophenyl) propane-1,3-dione(4d)

Solid dark yellow colour,IR (KBr): 3310 cm^{-1} (Phenolic -OH stretch), 3124 cm^{-1} (Aromatic C-H stretch), 3042 cm^{-1} (Aliphatic C-H stretch), 1733 cm^{-1} (C=O stretch), 1558 cm-1(Aromatic C=C stretch), 709 cm^{-1}(C-Cl stretch). ^{1}H NMR (DMSO-d_6): δ 4.76 (S, 1H of OH), δ 3.87 (S, 2H of CH_2), δ 6.97-8.11 (m, 7H of Ar C-H).

5.Antimicrobial activity

5.1 Antibacterial Activity

The Synthesized substituted propane-1,3-diones (β-diketones) (4a-d) was screened by antibacterial activity against gram +ve *Staphylococcus aureus* and gram –ve *Salmonella typhi* bacteria by paper disc method[11].The compounds 4a-d was tasted at 50 µg/ml,100 µg/ml and 250µg/ml of concentration in DMSO solvent in which sterile filter paper disc was dipped. Dried the disc and placed the nutrient ager plates spreaded with bacteria. After 24 hr. of incubation at 37^0C the dimeter of zone of inhibition were measured in mm by metric ruler scale and compared with standard ampicillin at 25 µg/ml concentration as antibiotic drug. The results of screening are given in **table 2**.

Table 2 - Antibacterial activity of substituted propane-1, 3-dione (4a-d)

Zone of inhibition (in mm) at µg/ml concentrations							
Entry	Compound Codes	*Staphylococcus aureus* (Gram +ve)			*Salmonella typhi* (Gram –ve)		
		50	100	250	50	100	250
1	4a	--	--	--	--	--	--
2	4b	9.0	7.0	8.0	--	--	--
3	4c	9.0	6.0	7.0	--	--	--
4	4d	8.0	8.0	14.0	7.0	7.0	7.0
5	Std.	24.0	24.0	24.0	24.0	24.0	24.0
6	Control	--	--	--	--	--	--

Std.-Ampicillin, Control-DMSO Solvent," -- "denoted No zone of inhibition

5.2 Antifungal Activity

The synthesized substituted propane-1,3-diones (β-diketones) (4a-d) was also screened for antifungal activity against *candida albican* and *aspergillus niger* by using paper disc method at 50 µg/ml,100 µg/ml and 250 µg/ml concentration in DMSO solvent. The zone of inhibition was measured in mm scale. The antifungal activity of the synthesized compounds was compared with standard Fluconazole at 25 µg/ml concentration as an antibiotic drug. The result of antifungal data was found to be very poor. The β-diketones (4a-d) does not show any zone of inhibition.

Result and Discussion

A series of substituted propane-1,3-diones(β-diketones) (4a-d) was synthesized by Baker–Venkataraman transformation to get good yield. Among the all compounds 4b,4c and 4d shows comparatively better zone of inhibition than 4a against *Staphylococcus aureus*(*Gram +ve)*and 4d show good activity than 4a,4b and 4c against *S. typhi* (Gram –ve). The observed data of antifungal activity were found to be inactive. Compound 4a,4b,4c and 4d does not shows any zone of inhibition at any concentration.

Conclusion

In the present work newly synthesized substituted propane-1,3-diones (β-diketones) (4a-d) involves different steps to get good yield in a short time period. The structure of β-diketones was elucidated on the basis of ^{1}H NMR and IR spectral data. In antibacterial activity only compound 4b,4c and 4d shows zone of inhibition against *s. aureus*. The only compound 4d shows zone of inhibition against *s. typhi*. The result of antifungal activity is negative in which compound 4a-d does not show any zone of inhibition against *candida albican* and *aspergillus nigar*. We are continuing our research work in extending of β-diketones (4a-d) for further synthesis of hetero cyclic compounds

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Synthesis And Characterisation of newly Synthesized Isoxazoline

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Abstract:

A new series of bromo and nitro substituted isoxazolines (3a-d) were synthesized by reacting bromo and nitro substituted chalcones (2a-d) with hydroxyl amine hydrochloride respectively. All these compounds were characterized by means of their UV,IR,^{1}H NMR, spectroscopic data and elemental analysis.

Keywords: Chalcones,Isoxazolines

INTRODUCTION:

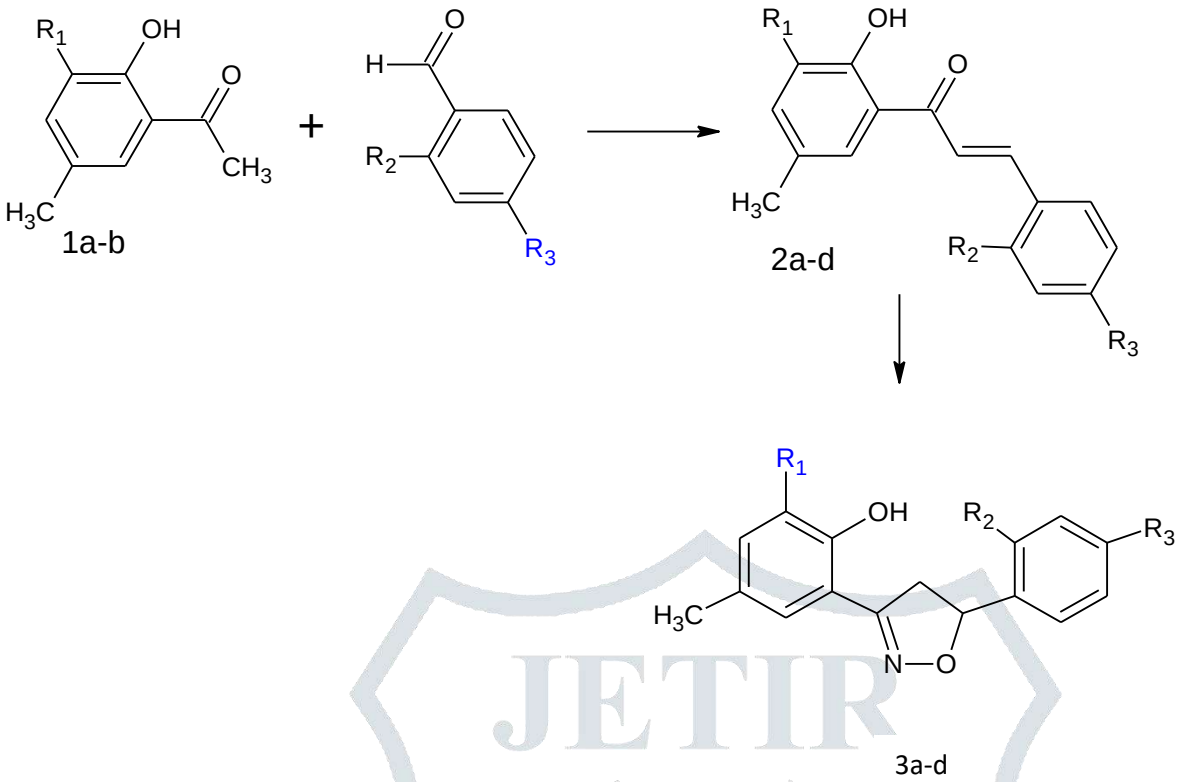
The dihydroderivatives of isoxazole (a) are known as isoxazolines. A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of atoms in the ring. Compounds incorporating heterocyclic ring systems continue to attract considerable interest due to the wide range of biological activities. Amongst them five membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Five membered heterocycles like isoxazoline have found wide applications pharmaceutical and agrochemical agents.

Experimental

General procedure for synthesis of chalcones (2a-d)

A mixture of substituted acetophenones (0.01 mole) and substituted benzaldehyde (0.01 mole) was stirred in ethanol (15 ml) and to this solution 10% potassium hydroxide added gradually with constant stirring. The reaction mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dil. HCI. The product precipitates out was filtered washed with $NaHCO_3$ solution and crystallized from ethanol Scheme 1

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General procedure for synthesis of isoxazolines (3a-d)

Bromo and nitro substituted chalcone (2a-d) (0.01 mol) and hydroxyl amine hydrochloride (0.02mol) was refluxed in ethanol (20 ml) and piperidine (0.5ml) for about 1.5 hrs. After cooling; the reaction mixture was acidified with HCl. The solid product thus separated was filtered, washed first with sodium bicarbonate solution (10%) and then with water. Finally it was crystallized from ethanol to get isoxazolines (3a-d). Physical and analytical data of compounds are given in table 1.

Physical and analytical data of compounds (2a-d,3a-d).

table 1.

Compound no.	R_1	R_2	R_3	M.F.	m.p.^{0}C	Yield %	C %	H %	N %
2a	Br	H	Cl	$C_{16}H_{12}O_2BrCl$	101	72	53.98	3.01	--
2b	NO_2	H	Cl	$C_{16}H_{12}O_4NCl$	115	68	59.95	3.01	4.01
2c	Br	Cl	Cl	$C_{16}H_{11}O_2BrCl_2$	82	72	49.01	2.03	--
2d	NO_2	Cl	Cl	$C_{16}H_{11}O_4NCl_2$	102	78	54.02	2.99	3.10
3a	Br	H	Cl	$C_{16}H_{13}BrClNO_2$.	120	60	52.01	3.07	3.00
3b	NO_2	H	Cl	$C_{16}H_{13}ClN_2O_4$.	135	76	56.9	3.02	8.00

3c	Br	Cl	Cl	$C_{16}H_{12}BrNO_2Cl_2$.	160	70	47.00	2.03	3.02
3d	NO_2	Cl	Cl	$C_{16}H_{12}Cl_2N_2O_4$.	145	80	51.90	3.02	7.01

Results and Discussion

The structure of synthesized compounds (2a-d,3a-d) were confirmed on the basis of spectral and elemental analysis .The IR spectrum of **2a-d** exhibited a band due to –OH str.(3350.88cm^{-1}), >C=O str. (1691.59 cm^{-1}),-C=C-str.(1613.84 cm^{-1}), -Cl str.(1135.52 cm^{-1}),-Br str.(1059cm^{-1}).Futher,in^{1}H NMR spectrum, the appearance of a signal at δ 2.4 (s,3H,-CH3), 7.09 to 7.83(m,6H, Ar–H), 7.85(d,1H,-COCH=CH-),8.2(d,1H,-COCH=CH-),11.17(s,1H,-OH)confirms the presence of chalcone.

Similarly ,the structure of compounds **3a-d** was confirmed on the basis of spectral and elemental analysis.The IR spectrum of **3a-d** exhibited a band due to H-bonded O–H stretching (3241.21cm^{-1}), aromatic stretching, >C–H (3087.43 cm^{-1}), Aliphatic C–H stretching 2922.35, –C=N- str.(1582.55cm^{-1}), >C–O stretching (1288.00 cm^{-1}) and -C–Br stretching (1102.97 cm^{-1}). Further, in their in^{1}H NMR spectrum, the appearance of a signal at δ 2.33 (s,3H,Ar-CH_3); δ 3.5 (d, 2H, Heterocyclic –CH_2–CH–) , δ 5.06 (s,1H,-Ar–OH), δ 6.8 (t, 1H, Heterocyclic –CH2–CH–), δ 7.09-7.54 (m,6H,Ar–H) δ 1.2 (s,1H,-CH), δ 2.5(s,1H,-NH), δ 2.3.3 (s,3H,-CH3), δ 6.9(d,1H, =C–H), δ 7.3 to 8.3(m,11H, Ar–H), and δ 12.3(s,1H,-OH) confirms the presence isoxazoline.

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Metal-Ligand Stability Constants of Ni(II) and Co(II) ,Cu(II) Metal Ions Complexes With Some Substituted Isoxazoline Ph –Metrically

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Abstract:

The stepwise stability constant values of substituted isoxazolines with Ni(II) and Co(II) ,Cu(II) metal ion have been studied at 0.1M ionic strength pH-Metrically in 70% Dioxane - Water mixture by Bjerrum method as adopted by Calvin Wilson. The values of proton-ligand stability constant (pK) and metal-ligand stability constant (log K) are calculated and from the data obtained it is observed that metal ions formed 1:1 complexes with ligands L1 and L2 using half integral & pointwise calculation method.

Keywords: Metal ions with Ni(II) and Co(II) ,Cu(II)

L1:- :- (2-hydroxy-3-bromo-5-methylphenyl)-6-(3-Indole)-2-iminophenyl-3,6-dihydro-1,3-thiazine

L_2 :- (2-hydroxy-3-nitro-5-methylphenyl)-6-(3-Indole)-2-iminophenyl-3,6-dihydro-1,3-thiazine

Solvent –70% Dioxane -Water mixture

Introduction:

Substituted isoxazoline are an important class of heterocyclic compound and have attracts many researchers because of its application in medicinal field. The stability constant for the metal complexes are widely used in various fields such as biological processes, pharmaceuticals, analytical processes etc. Metal complexes play a very vital role in nature,with the view to understand the bio-inorganic chemistry of metal ion. Shelke et al.[5] have investigated the interaction between UO_2(II) and Cu(II) with dicarboxylic acids in dioxane-water mixture.

Narwade et al.[1]have studied the equilibrium constant of Fe(III) with substituted chalcones at 0.1 M ionic strength potentiometrically.Sawalakhe and Narwade[2] have studied role of dielectric constants on substituted pyrazoline - complexes potentiometrically.Sawalakhe et al.[3] have studied stability constants of Cu(II) complexes with some substituted diketones at 0.1 M ionic strength by pH-metric technique. Gudadhe et al.[4] have studied the formation constants and stability constants of Thorium(IV) complex with some substituted pyrazolines.Gopal Narain et al.[5] studied characters of some Cobalt(II) complexes with substituted pyrazoles. Raghuwanshi et al.[6] showed confirmation of complex formation of N, O and S containing hetrocycle with Cu(II) metal ion.Tayade V.B. et al7 had studied proton-ligand and metal-ligand stability constants of 3,5-diarylpyrazolines, pyrazoles, isoxazolines and isoxazoles potentiometrically.Ramteke et al.[8]determined stability constants of 4-(2-chlorophenyl)-3-(3-furanoyl-5-(2-hydroxyphenyl) pyrazole with Cu(II), Ni(II), Co(II) and Nd(III) metal ions in 70% dioxane-water mixture.

Experimental:

The solution of ligands L1 and L2 were prepared in 70% dioxane-water mixture. The solution of NaOH, HNO3, KNO3 and metal ions CU (NO3)3,CO(NO3)3, and Ni(NO3)3 were obtained from BDH grade chemicals. The NaOH solution was standardized with oxalic acid, kept in pyrex vessel and used as a titrant for pH titrations. The 1.0 M KNO3 solutions were prepared to maintain the 0.1 M ionic strength of the solution. The metal nitrates were used to prepared the metal solution and were standardized by usual procedure.

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Measurements:

All measurements were carried out at 30±0.10C . Systronic microprocessor based pH meter with magnetic stirrer and combined glass and calomel electrode assembly used for pH measurements. The sensitivity of pH is 0.01 units . the instruments could read pH in the range 0.00 to 14.00 in the step of 0.005. The pH meter was switched ON on half an hour before starting the titration for initial warm up of the instrument. It was calibrated before each titration with an aqueous standard buffer solution of pH 7.00 and 9.20 at (30±0.10C) prepared from a 'Qualigens' buffer tablets. The hydrogen ion concentration was measured with combine glass electrode.

Procedure:-

Experimental procedure involves following three set of titrations

- Free acid titration (HNO3 , 1 x 10-2 M)
- Free acid + ligand titration (20 x 10-4M)
- Free acid + ligand + metal ion titration (4 x 10-4 M).

were carried out with standard NaOH solution (0.1M) in presence of inner atmosphere by bubbling a contant flow of nitrogen gas. Data obtained from the titration was used to plot a graph between volume of NaOH and pH values, they are called acid , ligand and metal titration curves.

Result and Discussion:

Substituted isoxazolines is considered as monobasic acid having only one replaceable H+ ion from –OH group.

HL H+ + L

It is observed from titration curve for all the system that ligand curves start deviating from free acid (HNO3) curves at about 3.5 and deviated continuously upto pH-11. The deviation shows that dissociation of –OH group in substituted isoxazoline.

Proton-ligand formation number $\mathbf{n_A}$ were calculated from acid titration curve (A) and acid ligand titration curve (A+L) by standard method. It was found that values of nA decreases with increased pH of solution due to replacement of H+ ion from –OH group. The proton-ligand formation number were calculated by Irving and Rossotti expression.

$$\bar{n}_A = \gamma - \frac{(V_2 - V_1)(N + E^0)}{(V^0 + V_1)(T_L^0)}$$

V0:- is the initial volume of solution, E0 and T0L :- are initial concentrations of mineral acid and ligand respectively. , V_1 and V_2 are the volumes of alkali of a normality N during the acid and ligand titration at a given pH, γ is the number of replaceable proton from the ligand.

Determination of $\bar{n}_A$ Values

System – Ligand (L_1) Medium – 70% Methanol-water

$E° = 1.00 \times 10^{-2}$ M $T_L° = 20.00 \times 10^{-4}$ M Temp. = 30 ± 0.1°C

N = 0.10 N $\mu = 0.1$ M $V^0 = 25$ ml

Table 1

pH	V_1	V_2	$V_2 - V_1$	$\bar{n}_A$
6.00	6.00	5.85	.05	.95
6.25	6.00	6.05	.05	.90
6.50	6.00	6.10	.10	.86
6.75	6.00	6.15	.15	.81
7.00	6.00	6.20	.20	.72
7.25	6.00	6.27	27	.63
7.50	6.00	6.36	.36	.55
7.75	6.00	6.41	.41	.4875

Determination of $\bar{n}_A$ Values System – Ligand (L_2)

Table – 2

pH	V_1	V_2	$V_2 - V_1$	$\bar{n}_A$
5.75	6.00	6.04	0.04	.96
6.00	6.00	6.08	.08	.92
6.25	6.00	6.12	.12	.88
6.50	6.00	6.16	.16	.84
6.75	6.00	6.20	.20	.80
7.00	6.00	6.25	.25	.75
7.25	6.00	6.30	.30	.70
7.50	6.00	6.34	.34	.66
7.75	6.00	6.40	.40	.60
8.00	6.00	6.46	.46	.54
8.25	6.00	6.51	.51	.49
8.50	6.00	6.55	.55	.45

Fig. 1
Plot between n_A Vs pH
System : (L_1)

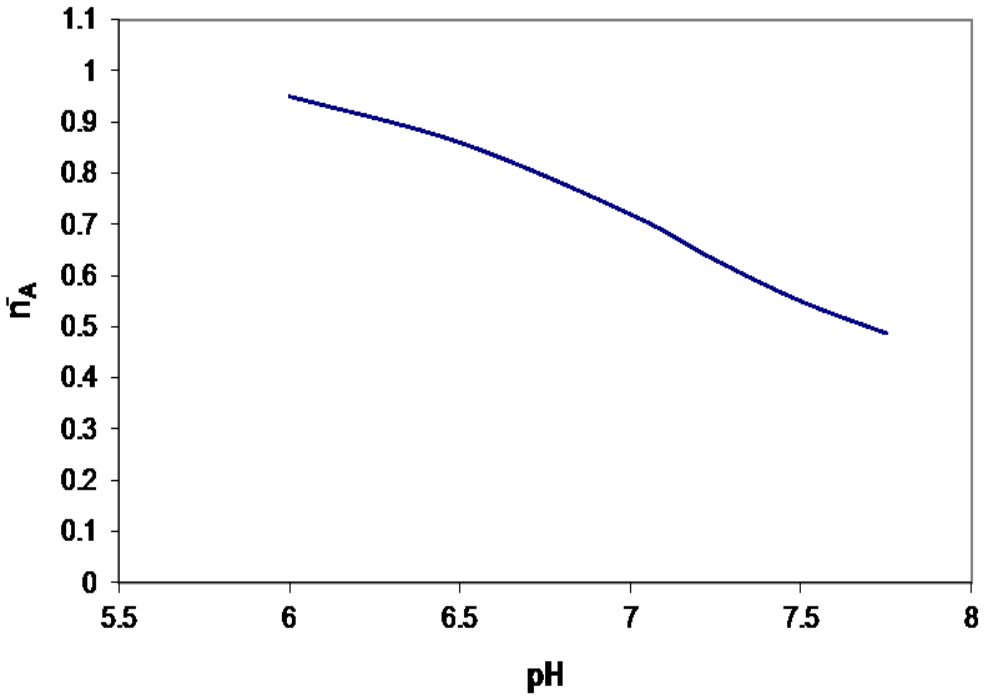


Fig. 2
Plot between π_A Vs pH
System : (L_2)

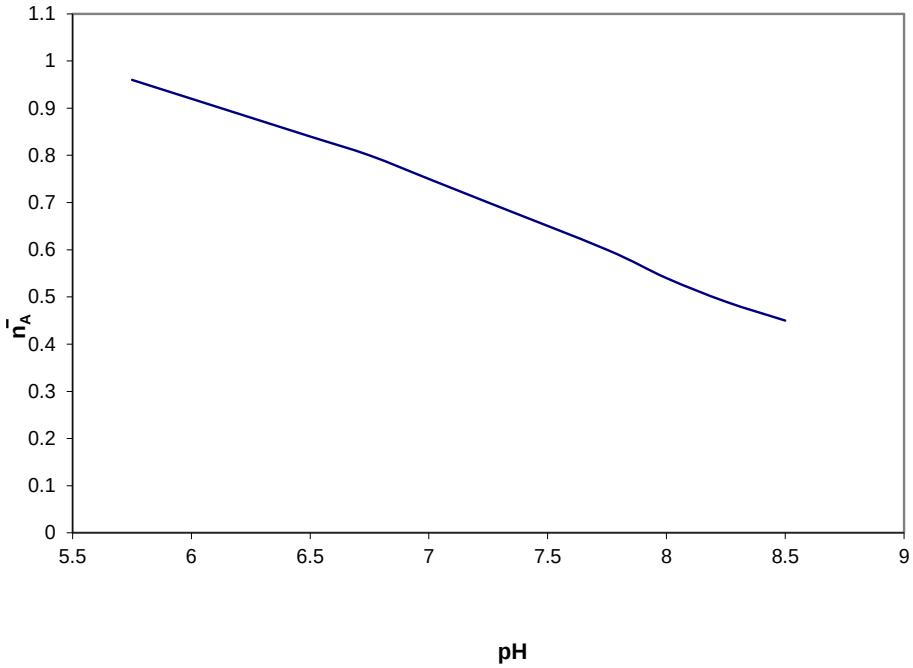


Table 3
Determination of Proton-Ligand Stability Constants (pK)

No.	Ligands	pK Value
L_1	3-(2-hydroxy-3-bromo-5-methyl phenyl)-5-(3-indyl)-isoxazoline	8.78
L_2	3-(2-hydroxy-3-nitro-5-methyl phenyl)-5-(3-indyl)-isoxazoline	8.33

Table 4
Metal-Ligand Stability Constants (log K)

System	Metal-Ligand Stability Constants (Log K)	
	log K_1	**log K_2**
L_1-Ni(II)	6.09	7.36
L_1-Cu(II)	6.13	7.24
L_1-Co(II)	5.62	6.34
L_2-Ni(II)	6.01	7.03
L_2-Cu(II)	6.76	8.51
L_2-Co(II)	7.00	9.21

Conclusion;

It was observed from above table-4 that log K2values are greater than log K1 values for all metal complexes. The difference between log K1 and K2 is greater than 1 which shows the formation of stepwise complex. If the difference is smaller than 1 then that shows the formation of simultaneous complexes. The higher values of ratio (logK1/logK2) indicate the more stable stepwise complex formation.

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Common Pharmacophore Pattern for Anthelmintic Activity of A Pesticide Tolfenpyrad (TFP)

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Abstract:

The present work is based on the technique of pharmacophoric modeling to identify important structural features and their common pattern which is associated with anthelmintic activity of a registered pesticide Tolfenpyrad (TFP) and its derivatives. A dataset of forty derivatives of TFP, covering broad chemical space, was utilized for the present work. The analysis involved a number of steps to arrive at a common pharmacophoric pattern. The results highlight the importance of aromatic rings and local environment in the molecule. The results shall avail deeper understanding of anthelmintic activity of a registered pesticide Tolfenpyrad (TFP) and its derivatives to a greater extent.

Keywords: Common Pharmacophore modeling, Drug designing, anthelmintic activity, Tolfenpyrad

Introduction:

Gastrointestinal roundworms (nematodes) are parasitic worms which cause severe decline in production especially in industries like dairy, meat, etc. Therefore, a variety of chemicals are used for controlling these pathogens. Unfortunately, recent reports have indicated that excessive and uncontrolled use of these drugs has resulted in appearance of resistance and tolerance to many anthelmintic agents. Therefore, repurposing of drug(s) or designing a new drug in time is essential to curb these parasites [1-4]. In last two decades, CADD (Computer Assisted Drug Designing) has appeared a rapid, cheaper and an alternative to traditional approaches like Free-Wilson, Topliss approach, etc. due to fast developments in computers, biochemistry, mathematics and medicinal chemistry.

Pharmacophore modeling, QSAR (Quantitative Structure-Activity relationships), Molecular docking and many branches of CADD are routinely used by medicinal chemists to derive a better drug candidate possessing suitable chemical and biological profiles. Pharmacophore modeling is more popular and used when the 3D- structure of protein (target enzyme) with which a drug and its derivatives interact is unknown. In such a situation, pharmacophore modeling is used to derive a common pattern which is linked with the desired bioactivity [6-8]. Hence, in this work, we have established a consensus pharmacophore model for anthelmintic activity of a registered pesticide Tolfenpyrad (TFP) and its derivatives

In 2019, Le et al [1] described anthelmintic activity of a registered pesticide Tolfenpyrad (TFP) and its analogues. TFP is a pyrazole-5-carboxamide class of complex I inhibitor. The recently synthesized compounds were tested for L3 motility and L4 development of H. contortus larvae and activity values (IC_{50}) varies from micromolar (µM) to nanomolar (nM) range. Though, SAR (Structure Activity Relationships) were conversed in good details by them, but no effort was accomplished to generate consensus pharmacophore model. Hence, in this work, we derived consensus model using Tolfenpyrad (TFP) and its analogues for their activity against L4 development of H. contortus larvae. The results shall a better understanding of structural features and their inter-relationships when developing a new drug for parasites.

Experimental Methodology:

Dataset:

The dataset consists of forty TFP derivatives exhibiting the anthelmintic activity, reported as IC_{50}, in µM to nM range (1.69 to 0.0007 µM). The complete dataset has good alteration with respect to substitution pattern, thereby broadening the chemical space coverage [1]. Hence worth, the carefully chosen dataset is big enough and broad to develop a consensus pharmacophore model. The dataset has been tabulated in table 1.

Table 1. Different TFP derivatives along with reported IC_{50} for L4 used in the present work

S.N.	SMILES notation	L4 (IC_{50})
1.	C18H15Cl2N3O2	0.0007 ± 0.0001
2.	C18H15ClFN3O2	0.0008 ± 0.0001
3.	C19H17Cl2N3O2	0.0008 ± 0.0001
4.	C19H18ClN3O2	0.003 ± 0.004
5.	C20H20ClFN4O2	0.003 ± 0.004
6.	C19H17ClFN3O2	0.004 ± 0.004
7.	C18H16Cl2N4O2	0.008 ± 0.009
8.	C19H18FN3O2	0.01 ± 0.007
9.	C19H19ClN4O2	0.01 ± 0.01
10.	C20H20ClFN4O2	0.019 ± 0.011
11.	C17H14Cl2N4O2	0.02 ± 0.01
12.	C21H22ClN3O2	0.03 ± 0.005
13.	C20H21ClN4O2	0.03 ± 0.01
14.	C18H16ClFN4O2	0.03 ± 0.02
15.	C20H20ClFN4O2	0.03 ±0.02
16.	C20H18Cl2FN3O2	0.035 ± 0.005
17.	C21H21ClFN3O2	0.04 ± 0.005
18.	C20H19ClFN3O2	0.04 ± 0.01
19.	C20H18Cl2FN3O2	0.04 ± 0.01
20.	C20H20ClN3O	0.04 ± 0.01
21.	C21H22ClN3O	0.04 ± 0.02
22.	C18H17ClN4O2	0.04 ± 0.03
23.	C19H19FN4O2	0.05 ± 0.03
24.	C21H23N3O2	0.057 ± 0.002
25.	C21H21ClFN3O2	0.06 ± 0.03
26.	C21H22FN3O	0.07 ± 0.06
27.	C20H20ClN3O2	0.08 ± 0.006
28.	C21H21ClFN3O2	0.08 ± 0.03
29.	C19H19N3O2	0.13 ± 0.10
30.	C21H21ClFN3O2	0.14 ± 0.05
31.	C21H21ClN6O2	0.16 ± 0.11
32.	C17H14ClFN4O2	0.17 ± 0.09
33.	C20H21ClN4O	0.19 ± 0.08
34.	C18H17FN4O2	0.19 ± 0.15
35.	C20H20FN3O	0.19 ± 0.15
36.	C19H19ClN4O	0.23 ± 0.12
37.	C21H19ClN4O3	0.34 ± 0.32

38.	C20H21ClN4O3	0.45 ± 0.04
39.	C20H21FN4O	0.97 ± 0.46
40.	C20H18N4O2	1.69 ± 0.67

Development of Pharmacophore model [6-8]**:**

The complete procedure to derive a consensus model for pharmacophoric pattern identification encompasses many steps like structure drawing, their optimization by suitable method, alignment by appropriate method and creation of model. These steps were accomplished using the standard procedure reported in literature [6-8]. A brief description of these four main steps is as following:

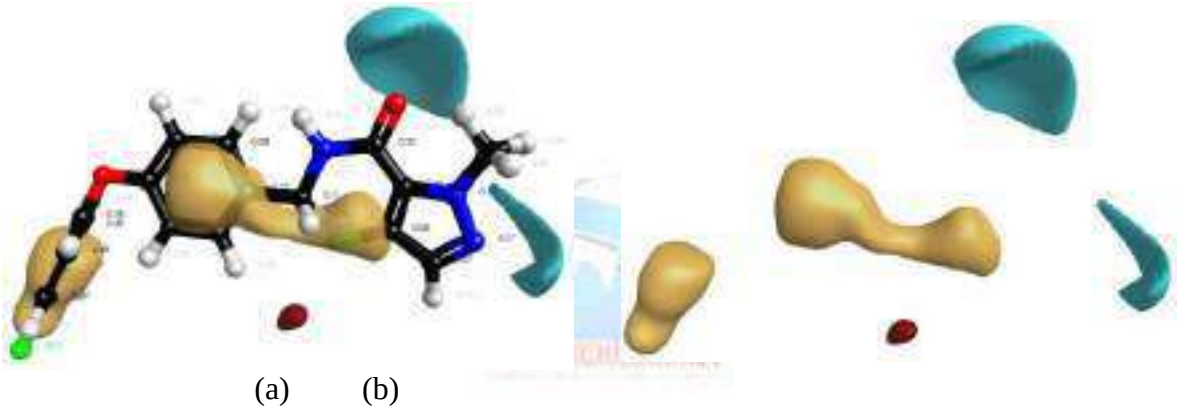
Step-1: The structures were drawn using ChemSketch 2012 freeware

Step-2: PM3 semi-empirical method was used for structure optimization using MOPAC 2012 on Linux

Step-3: Alignment of all the TFP derivatives using Open3dAlign software installed on Linux

Step-4: Using the default settings, consensus pharmacophore model was formed using PyMOl 2.2

Results and Discussion:



(a) (b)

Figure 1. 3D- representation of consensus pharmacophoric pattern using the active molecule **1** as a representative only (Yellow: Hydrophobic, Blue: Negative and Red: Positive charged regions) (a) With molecule and (b) without molecule

The consensus pharmacophore modeling recognized four regions of importance with respect to anthelmintic activity of TFP and its analogues. These four regions are: (1) Two hydrophobic regions (shown by yellow contours): one of the hydrophobic regions extends from benzene ring to a five membered heterocyclic ring whereas the other is due to remaining benzene ring, (2) Two negatively charged regions (shown by blue contour): the first negative region is due to linker -CO-NH- and the other is due to two N atoms of a five membered heterocyclic ring. Thus, the anthelmintic activity of TFP and its analogues varies with hydrophobic/lipophilic and negatively charged regions. The linker -CO-NH- and two N atoms of a five membered heterocyclic ring must be retained in future optimizations along with two benzene rings with appropriate substituents to have optimum logP.

Conclusions:

The present work successfully highlighted the importance of various structural patterns associated with anthelmintic activity of TFP and its analogues.

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Microwave Synthesis and Wound Healing Effect of Δ^2 – Pyrazoles ointment In Albino Rats

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Abstract

Microwave irradiation, as conventional way has been used for variety of applications including pyrazole synthesis. Effect of 3-(3, 5-dichloro-2-hydroxyphenyl)-1-phenyl-5-(pyridin-2-yl)-1H-pyrazol-4-yl) (furan-2-yl) methanone (FP_3) ointment was studied on the wounds of albino rats. The ointment of the Δ^2 –Pyrazoles produced significant result on tested albino rats. The ointment of Δ^2 –Pyrazoles (FP_3) wounds were found to be epithelialise faster and rate of wound contraction was higher, as compare to the control wounds.

Keywords: Δ^2 –Pyrazoles, Microwave synthesis, IR, NMR,Wound healing activity.

Introduction:

Five membered heterocyclic compounds with an additional hetero atom are termed as azoles. The azoles containing two nitrogen atoms in the 1, 2-position is designated as pyrazoles. The generic name pyrazole was given by Knorr[1] et al in 1883. Microwave irradiation, as conventional way has been used for variety of applications including pyrazole synthesis. The short reaction time and expanded reaction range offered by microwave assisted synthesis are suited for the chemist all over the globe. Laurence[2] et al studied microwave assisted pyrazole reactions.

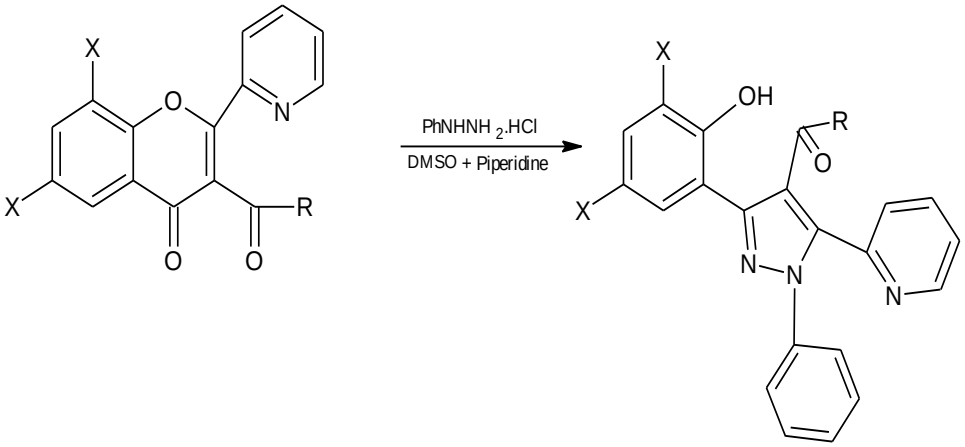
Most of the skin and their related problems heal by pyrazole and their derivatives. The synthetic five membered heterocyclic drugs as pyrazoles is the special type of drugs in pharmaceuticals. Malpani[3] carried out pharmaceutical studies regarding wound healing activity of pyrazole moiety in plant extract. Jha[4] et al reported excision and incision wound healing activity of flower head alcoholic extract of sphaeranthus indicus linn. in albino rats. Hence, the present study was deals the effect of 3-(3, 5-dichloro-2-hydroxyphenyl)-1-phenyl-5-(pyridin-2-yl)-1H-pyrazol-4-yl) (furan-2-yl) methanone (FP_3) on albino rats with special reference to wound healing activity.

Materials And Methods:

Synthesis of (3-(3,5-dichloro-2-hydroxyphenyl)-1-phenyl-5-(pyridin-2-yl)-1H-pyrazol-4-yl) (furan-2-yl) methanone (FP_3)

A mixture of 6,8-Dichloro-3-(furan-2-carbonyl)-2-(pyridin-2-yl)-4H-chromen-4-one (FP_2) (0.01mol) and phenylhydrazine hydrochloride (0.02) was irradiated in DMSO (20 ml)

containing (0.5 ml) piperidine for 3 min.15 sec in microwave. After cooling the mixture was decomposed into the ice and solid product thus obtained crystallized from 50% ethanol-methanol mixture. The black colored shining crystals of the compound (FP_3) were obtained. Yield: 61%, m.p:198 ^{0}C.



Where X = H, Cl and R= C_6H_5, C_4H_4O

MW, 800 W, time: 3 min. 15 sec, Solvent: DMSO.
Microwave: 3 min. 15 sec , Yield: 61%
Conventional: 2 hour, Yield: 60%

The conformation of structure of (3-(3,5-dichloro-2-hydroxyphenyl)-1-phenyl-5-(pyridin-2-yl)-1H-pyrazol-4-yl) (furan-2-yl) methanone (FP_3) compound on the basis of spectral result.

Spectral data for compound (FP_3)

FTIR:- (KBr, cm-1): (FP3):- 3354 (OH – stretching), 3074 (Ar-C-H stretching in CH_3), 1666 (C=O Stretching), 1447 (C=N stretch), 1033 (C-O stretch), 754 (C-Cl stretch),

H1 NMR: - (400MHz, CDCl3, δ ppm): 6.96 to 8.2655 (m, 14H, Ar-H), 11.97 (s, 1H, OH).

(c) UV: - The UV-VIS spectrum of the compound (FP_3) recorded in CHCl3 showed λmax value 410 nm corresponding to n→π*

Synthesis of (3-(3,5-dichloro-2-hydroxyphenyl)-1-phenyl-5-(pyridin-2-yl)-1H-pyrazol-4-yl) (furan-2-yl) methanone (FP_3) ointment

Trituration method (rubbing or reducing to a fine powder) used as the ointment base. 0.5 gm pyrazole (FP_3) compound was taken. 10 g of ointment base was taken (white soft paraffin was used as an ointment base). Ointment base was first melted. The Compound (FP_3) was trituted with the small quantity of ointment base until a homogeneous product was formed. Remaining quantity of ointment base was added step by step at the end of this process we get homogenous ointment. The doses of ointment were prepared once a day and applied within the 12 hours from the preparation

Animals used

The proposed study deals with the incision wound model of albino rats, weighing 250 to 280g were procured and maintained at standard housing conditions. The care of laboratory animals was taken according to the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (registration number 729/02/a/ CPCSEA). The healthy albino rats were selected for the wound healing activity. This, interdisciplinary part of proposed study

was carried out after getting permission from the Institutional Animal Ethical Committee, Pusad (CPCSEA/IAEC/CP_PL-15/01-02PD02).

Wound Model

The animals of group (I) are considered as the Control Group rat which is treated with simple ointment base. Group (II) are considered as Reference or Standard Group where rats were treated with 5 % w/w povidine iodine. Group (III) animals were treated with Low Dose of pyrazole (FP_3) ointment and group (IV) were treated with High Dose of compounds pyrazole (FP_3) 2.5 % w/w ointment tropically on wound created on dorsal side of rats. Full thickness excision wound was made on the shaved back of the rat by removing a 500sq mm piece of skin and the day on which wound was made considered as the day zero.

Group I:

Group I was the Control Group rats in which the rats were immediately after cutting and cutting areas were covered with propylene glycol as a simple ointment base once in a day for 24 days.

Group II:

Group II was the Standard Group rats. They were treated with reference standard (5% w/w) povidine iodine once a day for 24 days.

Group III:

Group III was the Low Dose group of rats which were treated with low dose of chlorosubstituted pyrazole (FP_3) ointment once a day for 20 days.

Group IV:

Group IV was the high dose group of rats were immediately after cutting, cutting areas were covered with high dose chlorosubstituted pyrazole (FP_3) ointment once a day for 24 days.The wounds were observed in all groups every day. After 8 ^{th,} 16th days and 24 th days, the rats were evaluated.

Result and discussion

The representations of experimental data related to wounds were shown in Table 1.1 and graph 1.2. The contraction rates of group I to group III of experimental wounds were found to contract much faster as compared to control wound. Finally on 24th day after cut wound creation, the control group rats showed 64.26 % of wound contraction indicating the natural healing property of skin. The standard drug povidine iodine treated rat shows 96.6% of wound contraction. The group III of low dose of pyrazole (FP_3) ointment shows 97.66% wound contraction and high dose of pyrazole (FP_3) ointment shows 97.79% indicating faster wound healing

Measurement of wound Contraction:

The test animals were observed daily and the evaluation of percentage wound closure were made on 8 th, 16th and 24 th wounding days percentage was determined using the formula:

$$\text{Percent of Wound Contraction} = \left[\quad\right]$$

Where, A_d = Wound area on corresponding days. A_o = Wound area on zero day.

Group I: Control Group of rats treated with simple ointment base






Fig. (a) 0 day **Fig. (b) 8 days** **Fig. (c) 16 days** **Fig. (d) 24 days**

Group II: Standard drug (5% w/w povidine iodine)

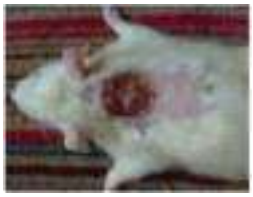





Fig. (a) 0 day **Fig. (b) 8 days** **Fig. (c) 16 days** **Fig. (d) 24 days**

Group III: Low dose of pyrazole (FP_3) ointment






Fig. (a) 0 day **Fig. (b) 8 days** **Fig. (c) 16 days** **Fig. (d) 24 days**

Group IV: High dose of pyrazole (FP_3) ointment






Fig. (a) 0 day **Fig. (b) 8 days** **Fig. (c) 16 days** **Fig. (d) 24 days**

Table 1.1 :- Percentagewise effect of treatments on wound contraction

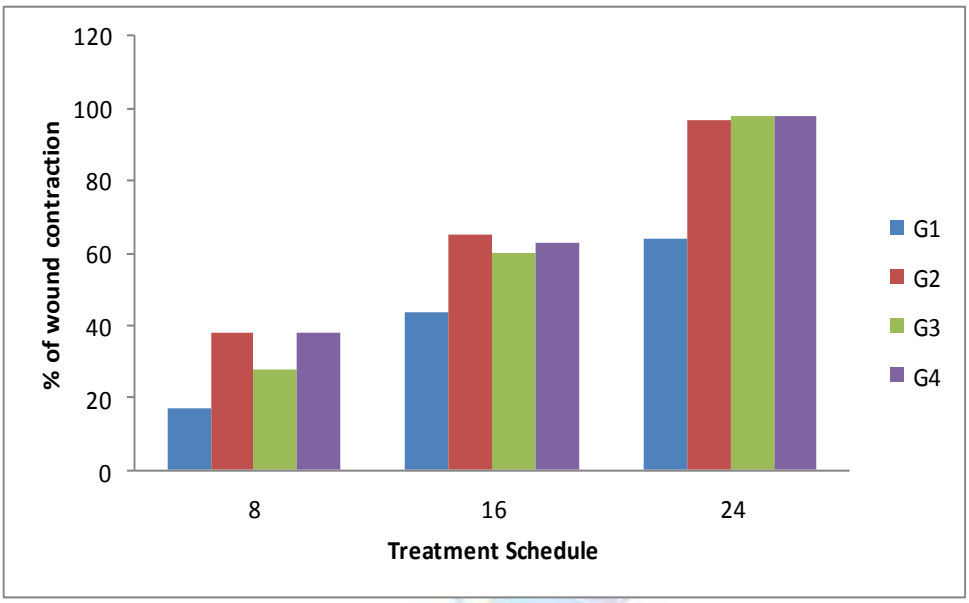
Treatments	0^{th} day	8^{th} day	16^{th} day	24^{th} day	Epithelia-lization time in days
Group I (Control)	**0%** ±2.76	**17.21 %** ±1.62	**43.85%** ±1.90	**64.26%** ±1.36	**24** ±0.42
Group II (Povidine iodine)	**0%** ±2.80	**38%** ±1.30	**65%** ±1.42	**96.6%** ±1.12	**17** ±0.64
Group III Low dose of pyrazole (FP_3) ointment	**0%** ±0.85	**28%** ±2.00	**60%** ±1.41	**97.66%** ±0.41	**21** ±0.66

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Group III **High dose of pyrazole (FP_3) ointment**	**0%** ±1.2	**38%** ±2.22	**62.78%** ±1.53	**97.79%** ±0.30	**18** ±0.66

Graph 1.2 :- Variation of wound contraction % with treatment schedule

Where, G1= Group I, G2= Group II, G3= Low dose (FP_3) Group III, G4= High dose (FP_3) Group IV.



Concusion:-

From the tabulated data was concluded that the wound healing activity of the compound (3-(3,5-dichloro-2-hydroxyphenyl)-1-phenyl-5-(pyridin-2-yl)-1H-pyrazol-4-yl) (furan-2-yl) methanone (FP_3) high dose was found closer (wound contraction 97.79% onday 24thday and epithelization time on day 18) to that of standard drug povidine iodine (96.6%) wound contraction on 24thday and epithelization period on day 17). The presence pyrazole compound might have been favoured a significant wound healing activity. It is observed that the p-value for rows among the four groups is 0.000316* and calculated thought the days is 0.002477** both the values of * and ** is less than 0.05 ($p < 0.05$). The investigation prove that reatment of pyrazole (FP_3) compound has increased healing potential of cut wounds in albino rats.

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Research Article

Synthesis and growth promoting effects of some newly synthesized bromo and nitro substituted isoxazolines on some edible mushroom.

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ABSTRACT

A mushroom (*Agaricus bisporus*) is one of the many species of fungi. About 3,000 different species of fungi can be found in Western Europe, approximately 50 of which are edible fungi, the mushroom is by far the most familiar one. A fungus is actually the visible fruit body of a mould and as such only a small part of that mould. The mould fungus, or mycelium, grows under the ground, invisible to the naked eye. This is a tight network of fine threads, which with some species can even extend across a surface area of several hectares. The present study deals with the effect of newly synthesized bromo and nitro substituted isoxazolines for their growth promoting impact on oyster mushrooms.

KEYWORDS

Oyster mushrooms, bromo and nitro substituted isoxazolines.

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1. INTRODUCTION

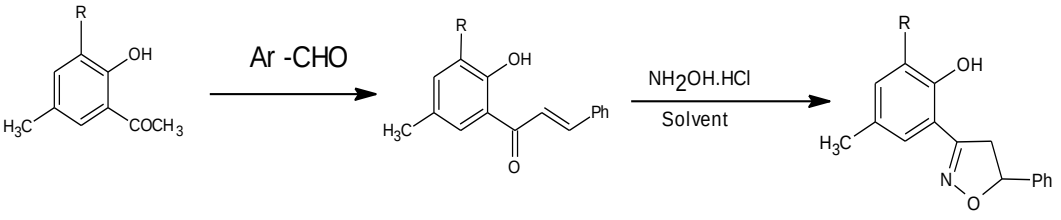
Mushroom cultivation is a profitable agribusiness world-wide. More than 2000 species of edible mushrooms exist in nature, but only approximately 22 species are intensively cultivated [1] could be employed for foods and medicines. In the fungal classification system proposed by Ainsworth and followed by J. Webster [2], almost edible mushrooms are members of the subdivision Basidio mycotina and Ascomycotina [3]. Mushrooms are a good source of protein, vitamins and minerals and are known to have a broad range of uses both as food and medicine. A high nutritional value of oyster mushrooms has been reported with protein (25-50%), fat (2-5%), sugars (17-47%), mycocellulose (7-38%) and minerals (potassium, phosphorus, calcium, sodium) of about 8-12% [4]. The cultivation of edible mushrooms has become an attractive economic alternative over past few years, mainly due to increase in its demand and market value [5,6]. Oyster mushrooms are one among the cultivable varieties. They are wide spread in temperate zones, can grow at moderate temperature and are suitable to grow in most places in India [7,8]. Oyster mushrooms are grown from hyphae (threadlike filaments) that become interwoven into mycelium and propagated on a base of steam sterilized cereal grain usually Wheat grains. This mycelium-impregnated cereal grain is called spawn and is used to inoculate mushroom substrate [8].

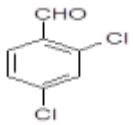
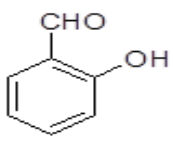
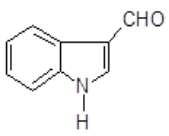
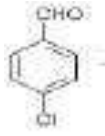
In the present study, the newly synthesized bromo and nitro substituted isoxazolines were assayed for their growth promoting impact on oyster mushrooms with predetermined periodicity.

2. MATERIALS AND METHODS

2.1. Synthesis of bromo and nitro substituted isoxazolines

A mixture of 1-(2-hydroxy-3- bromo and nitro -5-methyl phenyl-3-(4-chlorophenyl)-chalcone (Iva) (0.01 mole) and hydroxyl amine hydrochloride (0.02 mole) was refluxed in ethanol (20ml) and piperidine (0.5ml) for about 1.5 hrs. After cooling the reaction mixture was acidified with HCl (1:1).The solid product thus separated was filtered, washed first with sodium bicarbonate solution (10%) and then with water. Finally it was crystallized from ethanol to get the compound.



R=  ,  ,  , 

Spectral analysis of final compound is given below:

A) IR, 3241.21, (Vb);O-H stretching, 3087.43 (m), Aromatic C-H stretching; 2922.35 (s) Aliphatic C-H stretching; 1582.55, (s), >C=N stretching; 1288.00(s),>CO stretching; 1102.97, (s),>C-Br stretching

B) PMR : 2.3,s,3H,Ar-CH_3; 6.5,t ,1H, Heterocyclic -CH_2-CH-,6.9,d,2H, Heterocyclic -CH_2-CH-,7.1 - 8.4,m,5H,Ar-H, 12.4,s,1H,Ar-OH

2.1. Classification of Oyster Mushroom

Scientific classification

Kingdom – Fungi
Phylum – Basidiomycota
Class – Agaricomycetes
Order – Agaricales
Family – Pleurotaceae
Genus – Pleurotus
Species – ostreatus

2.2. Materials

1. Spawn (Source:- Agriculture College, Amravati)
2. Soya bean Straws.
3. Water bath
4. Hot Air Oven
5. Plastic Bags

2.3. Substrate Preparation

Oyster mushroom was grown on substrates soyabean straw. Since soyabean straw is easily available, cheap and widely used. It is used was fresh and well dried. It was chopped into 3-5 cm pieces and soaked in fresh water for 15-16 hours. Excess water was drained off. This was subjected for sterilization to minimizing contamination problem and gives higher and almost constant yields using hot water treatment maintained at 60-80°C for 1 hour. The sterilized substrate was taken out and allowed to lower down the temperature. When the sterilized substrate had cooled down to room temperature, it was ready for filling and spawning. At this stage, substrate moisture content was about 70%. Polythene bags were used for its cultivation. The spawns of experimental species P. sajor-cajuie, P. pulmonarius were procured from Shivaji agricultural agencies and cultivated in the culture house of the ICAR affiliated Krushi Vidyan Kendra, Durgapur (Badnera) Dist. Amravati. Spawning can be done in layer spawning. The experimental setup was divided into two parts i.e. 'A'-control group plants and 'B'-treated group plants. The spawns were inoculated and cultivated by the conventional methods. Substrate was filled in bag, pressed to a depth of 8-10 cm and broadcasted with a handful of treated spawn above it. Similarly, 2^{nd} and 3^{rd} layers of substrate were put and simultaneously after spawning, the bags were closed and 20-25 pin-holes were made on all sides of the packets. Similarly the untreated spawns were filled in control group beds (bags). After proper labeling, spawned bags were stacked on racks in neat and clean place, in closed position. Temperature at 25-35°C and

humidity at 70-85% was maintained by spraying water twice a day on walls and floor. It took 20-25 days when bags were fully covered. During this incubation period, appropriate temperature of the incubation room was maintained. After the complete development of mycelium, the packets were taken out of the incubation room and shifted to growing room, where the packets were hanged to bamboo frame. During the harvesting of mushroom beds were irrigated according to need. When the first primordial initiation was observed, the test compounds were sprayed on the mushroom with specific intervals. Mushroom crop was harvested before the fruiting body showed any splitting on the edges. The yields of mushroom crop from various bags with different parameters viz. length, diameter, weight and colour were recorded. The results of field experiments with test compounds are tabulated and shown in Fig. no. 1 and 2:

Table 1. Effect of titled compounds (Va-h) on oyster mushroom:-Pleurotussajor-caju spp.

Treated Bags	**Compound**	**D (cm)**	**T (cm)**	**L (cm)**	**Weight of Dry Bag (g) (After Harvesting)**	**Total**		**Colour**
						Fresh	**Dry**	
1	Va	7.7	0.5	5.8	0.925	211	20.43	White
2	Vb	8.4	0.4	5.8	0.982	195	17.59	White
3	Vc	10.9	0.6	6.9	0.975	225	21.31	Creamy
4	Vd	11.01	0.5	6.3	0.955	205	18.89	White
5	Ve	9.92	0.4	5.5	0.966	208	21.22	White
6	Vf	9.84	.0.5	6.2	0.978	209	20.45	White
7	Vg	8.64	0.6	6.4	0.976	207	20.99	Creamy
8	Vh	9.43	0.6	5.7	0.967	208	21.89	Creamy
9	1,4 Dioxane	6.0	0.4	6.1	0.895	174	19.13	White
10	Control	6.8	0.3	5.5	0.853	204	20.00	White

D=Diameter, T=Thickness, L=Length

2.4. Analysis of Mushroom Samples Treated With Test Compounds

The samples of P. sajor-caju collected during the experimental study of growth promoting impact were sun-dried and immediately proceeded for analysis of % crude fibre, % crude protein and elemental detection with special reference to N, P, K and S. The analysis of crude fibre percentage of the samples was carried out at Food Testing Laboratory, Krishi Vigyan Kendra, Durgapur (Badnera) Dist. Amravati using Pelicans FBS-06 (P) Laboratory Manuals & AOAC Method, whereas percentage of crude protein and element detection were determined at Analytical Lab, using Leaf method of analysis. The Kjeldahls method, UV spectrophotometer and Flame photometer were used for the analysis of N, P, K and S elements. The results of analysis obtained for treated mushroom samples are tabulated in table no. 2:

Table 2. Analytical results of dry oyster mushroom:-Pleurotussajor-caju spp. Treated with titled compound.

Sr. No.	Sample	% of Crude Fibre	% of Crude Protein	% N	% P	% K	% S
1	Va	8.0	15.13	2.421	0.3040	2.558	0.1262
2	Vb	8.72	16.00	2.560	0.3111	2.934	0.1367
3	Vc	10.3	20.27	3.246	0.3232	2.760	0.1320
4	Vd	9.83	18.90	3.024	0.2975	2.441	0.1314
5	Ve	10.65	17.05	2.574	0.2745	2.567	0.1378
6	Vf	9.67	18.01	2.654	3.1943	2.647	0.1475
7	Vg	7.89	16.77	3.143	0.3953	2.849	0.1541
8	Vh	8.44	17.23	3.143	0.3173	2.563	0.1498
9	1,4 Dioxane	8.06	13.25	2.122	0.272	2.344	0.1356
10	Control	5.64	15.95	2.554	0.364	2.741	0.1410

3. RESULTS AND DISCUSSION

A species of Oyster mushroom was treated with test compounds to examine the efficacy of the newly synthesized compounds (Va-h) on the morphology of treated mushroom species with inclusion of analysis of treated samples. When the treated and control species of mushroom were compared with reference to their morphological characters, it was interesting to note that the treated species exhibited significant growth in diameter and thickness of caps as well as lengthening of stripes. In addition to this, there was remarkable increase in the yields because of that healthy growth and disease free environment. The analytical results obtained for all the treated mushroom samples clearly show the increase in the value of crude fibre percentage as well as the crude protein percentage. The presence of elements like N, P, K and S were also analysed in the treated mushroom samples.. However, further investigation and a systematic approach in the light of agricultural science would certainly prove to be a potential tool for the growth promoting and creating ecofriendly environment for mushroom cultivation.

4. CONCLUSION

On the basis of chemical analysis and spectral data, it is concluded that, the synthesis of titled compounds was achieved successfully. Besides this, enhancement of the yields reveals the healthy growth due disease free environment. The newly synthesized compounds also showed noticeable enhancement in the nutritive values i.e. increase in crude fibre percentage and crude protein percentage. In this regard, the nitro substituted isoxazolines were found more effective in the enhancement of nutritive value.

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Assessment of Molecular Interactions of 4-Ethyl Thiocarbamidophenol on Acoustic Parameters Base

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ABSTRACT

Acoustic parameters assessment significantly able to disclose molecular and intermolecular interaction briefly. These parameters measured more significant by ultrasonic interferometer. Present research scheme concern to measurements of ultrasonic velocity and density for solutions of 4-ethylthiocarbamidophenol (ETP) at different molar concentrations (i.e. 0.1M, 0.075M, 0.050M and 0.025M) and 300 K, in 70% compositions of ethanol-water mixtures. These determinations sustain estimation of adiabatic compressibility (β), apparent molal compressibility (k), apparent molal volume (v), intermolecular free length (Lf), relative association (RA) and specific acoustic impedance (Z). These properties were help to know about solute-solute and solute-solvent interactions in solvent. Internal structure and molecular association can be possible to understand through current investigation.

Keywords: 4-ethylthiocarbamidophenol (ETP), Interferometric measurements, Intermolecular interactions and acoustic parameters.

INTRODUCTION

Molecular structure and their interactions in solution is always received importance in various field of sciences. Ultra sound and ultrasonic interferometer significantly used in

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estimation of molecule interactions such as inter and intra ionic or molecular interactions. Since from last few decades ultra sound and ultrasonic interferometric investigation extensively used to understand molecular interactions in liquid. This investigation has important to know the properties and significances of molecules. Ultra sound and ultrasonic wave's measurements widely applicable in many evolutions and new concepts in engineering, applied, industrial, mechanics, agricultural, medicinal, forensic sciences and space research development and updating. Ultrasonic is a branch of science, which deals with waves of high frequencies. A Thiocarbamido phenol nucleus has various significances in different industrial and life sciences. Valuable information regarding internal structure, molecular association, complex formation, internal pressure and stability[1] obtained from the study of ultrasonic parameters investigation in liquid phase[2-4], liquid mixture[5-6] and electrolyte solution[7-9]. Ultrasonic interferometric study of 4-(p-chloro)phenylthiocarbamido phenol in mixed solvent media carried out by Isankar *et al*[10]. Comparative study of intermolecular interaction by inteferometric measurements of α-bromoacetophenones and cumaran-3-ones in ethanol and dioxan solvents was studied by Aswale *et al*[11] and acoustical studies on ternary mixture of toluene in cyclohexane and nitrobenzene at 308 K was studied[12]. Ultrasonic velocity and density of binary liquid mixture of diethyl ether with three non-polar solvents such as CCl_4, CS_2 and C_6H_6 at 303.15K were investigated[13] and interferometric investigated 4-ethylthiocarbamdiophenol in 60% mixed solvent media[14].

Ultrasonic investigation received more important to understand the ion solvent and solvent-solvent and structure breaking and making properties of solutes. Organic ligands solutions used through the current investigation and this study provide an excellent information concern to intra as well as intermolecular interactions. In present investigation, mainly concentrate on the assessment of ultrasonic velocity and density for solutions of 4-ethylthiocarbamidophenol (ETP) at different molar concentrations and 300K, in 70% compositions ethanol-water mixtures and estimation of adiabatic compressibility (β), apparent molal compressibility (k), apparent molal volume (v), intermolecular free length (Lf), relative association (RA) and specific acoustic impedance (Z). In the view of above current research scheme designed as "Assessment of molecular interactions of 4-ethylthiocarbamidophenol on acoustic parameters base". This investigation regarding to know effect of concentrations on various acoustical properties and effect of acoustic parameters on molecular interactions.

MATERIAL AND METHODS

All AR grade chemicals used through current work. Freshly prepared solution used during study. The solvents were purified by standard method. 0.1M, 0.075M, 0.050M and 0.025M solutions of ETP in 70% ethanol-water mixture were prepared. Ethanol was purified by standard procedure[15]. Densities were measured with the help of bicapillary pyknometer (10.1 % kg m^{-3}). Pyknometer used is of Borosil make. Weighing was made on Citizen CY 104 one pan digital balance (± 0.0001 gm). A special thermostatic arrangement was done for density and ultrasonic velocity measurements. Elite thermostatic bath was used in which continuous stirring of water was carried out with the help of electric stirrer and temperature

variation was maintained within ± 0.1 ^{0}C. The speed of sound waves was obtained by using variable path, Single crystal interferometer (Mittal Enterprises, Model MX-3) with accuracy ± 0.03% and frequency 1 MHz was used in the present work. The densities and ultrasonic velocity of liquids in ethanol solvent were measured at 300 K for the calculation of intermolecular free length and the value of Jacobson's constant[16] (K = 631) was taken.

RESULTS AND DISCUSSION

Ultrasonic velocities and densities of ETP in 70% ethanol-water mixture investigated through present work and it is tabulated in following Table No.1.

Table-1.1: Average Ultrasonic Velocity of Water at 300K.

Sr. No.	No. of Rotation of Screw	Micrometer Reading (mm)	Difference Between Reading (mm)	Distance Travelled By Screw in One Rotation	Average Ultrasonic Velocity (m/sec)
1	5	26.4705	1.6105	0.61465	1398.708956
2	10	24.8642	5.5300	2.18285	
3	15	19.3372	3.0708	1.20041	
4	20	16.2664	4.4071	1.73277	
5	25	11.8593	4.5219	1.78301	
6	30	7.3374	4.0715	1.6004	
7	35	3.2659	2.0059	1.17213	
8	40	1.2663		10.45377	

Table-1.2: Average Ultrasonic Velocity of Pure Ethanol 300K (β_0)

Sr. No.	No. of Rotation of Screw	Micrometer Reading (mm)	Difference Between Reading (mm)	Distance Travelled By Screw in One Rotation	Average Ultrasonic Velocity (v_0) (m/sec)	Density (d_0) (Kg. m^{-3})	$\beta_0 \times 10^{-10}$ (Pa^{-1})
1	5	15.2623	4.9016	1.9321	1243.64	1030.00	5.843517555
2	10	10.3686	2.0211	0.7845			
3	15	8.3374	3.1108	1.2161			
4	20	5.2265	3.3795	1.3199			
5	25	1.8569		5.4374			

Table-1.3: Average Ultrasonic Velocity of 70% Ethanol 300K (β_0)

Sr. No.	No. of Rotation of Screw	Micrometer Reading (mm)	Difference Between Reading (mm)	Distance Travelled By Screw in One Rotation	Average Ultrasonic Velocity (v_0) (m/sec)	Density (d_0) (Kg. m^{-3})	$\beta_0 \times 10^{-10}$ (Pa^{-1})
1	5	16.8193	3.5422	1.39301	1336.98	1030.52	5.172074651
2	10	13.2705	3.9280	1.52925			
3	15	9.3775	3.1075	1.21513			
4	20	6.2752	3.8942	1.48981			
5	25	2.4757		6.65083			

Table-1.4: Acoustic Parameters at Different Concentration of [ETP] at 300 K in 70% E-W

Conc. C (Mole/lit)	Average Ultrasonic Velocity Us (m/sec)	Density d_s ($Kg.m^{-3}$)	β s$x10^{-10}$ (pa^{-1})	ϕ_V (m^3mol^{-1})	ϕ_k $x10^{-10}$	L_f (A_0)	R_A	$Z * 10^4$ ($Kgm^{-2} sec^{-1}$)
0.1	1593.587	1034.32	3.7714	0.1885	-8.9981	0.0155	0.982	161.741
0.075	1445.427	1027.52	4.6011	0.256	-1.0204	0.0168	1.007	145.301
0.050	1270.737	1025.12	5.941	0.2771	21.855	0.0186	1.048	126.999
0.025	1172.687	1021.12	6.9857	0.3158	53.761	0.0199	1.072	116.430

CONCLUSION

Table-1.4 reveals acoustic parameters of ETP at different concentration such as 0.1M, 0.075M, 0.050Mand 0.025M and 300K in 70% ethanol-water mixture. Table-1.4 reveals that Ultrasonic Velocity (Us), Density (ds) and decreases along with decreasing concentration from 0.1M to 0.025M. Acoustic parameters such as adiabatic compressibility (βs), Apparent molar volume (φv), Apparent molar compressibility (φk), Intermolecular free length (Lf), Relative association (RA) increases and Specific acoustic impedance (Z) decreases along with decreasing concentration from 0.1M to 0.025M. This acoustic parameters investigation help to understand molecular interactions occur and responsible for breaking and making of their structure in solution.

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Viscometric Measurements of (2e)-1-(4-Thiocarbamido Phenyl)-3-(3,4-Dimethoxyphenyl)Prop-2-En-1-one in 60% Ethanol-Water Mixture at Various Temperatures and Constant Concentration.

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Abstract :

Present investigation are carried out viscometric measurements of (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one at various temperatures and constant concentration to evaluate the dilution effect on solute-sovent interation.

Keywords :

Ethanol-water mixture, viscometric measurements, 2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one etc.

Introduction:

Viscosity is one of the important physical properties of liquid. By knowing viscosity, it becomes easy to find out the behavior of solution in vivo. It briefs the information regarding the interaction of solute and solvent interaction also the ability or action of drug in the human body to react. Viscosity measurements play a crucial role in biochemical, agricultural, pharmaceutical, medicinal, and industrial and drug sciences. We get valuable suggestions regarding solvent-solvent, solvent-solute and solute-solute interactions by viscometric measurements in drug sciences. Drug behavior like absorption, transmission and its effect will directly relate to its viscosity measurements and solvent interactions in the human body.

Literature survey reveals that, drugs which are excellently consumable and highly reactive against the revelatory bacterias. Hense, it's the need of todays era to find the drugs and

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also know the activity of the drug suddenly in vivo. Its is the need of chemist to find their physical properties viz, viscosity, refractive index, acoustic study and others .

Thocarbamides are the important class of drugs against various disease causing bacteria's. These are widely synthesized screened against class of pathogens. Here, in the present investigation, (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one is selected or their viscometric studies to find its probable activity in vivo.

Experimental:

Chemicals used in the present investigation are MERKS PVT. LTD. Water used for the preparation of solution was double distilled. Electronic balance used was Mechaniki Zaktady Precyzyjnej Gdansk balance (Poland make [±0.001gm]) to weigh our compounds. Viscosity was measured by Oswald's viscometer. It was kept in Elite thermostatic water bath and temperature variation was maintained at 28°C (±0.1) for each measurement. Densities were determined by bicapillary with a 1 mm internal diameter. Special care about to maintain thermal equilibrium in between viscometer and water bath, by sufficient time.

The present study deals with the viscosity investigation of (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one at 0.1M concentration in 60% ethanol-water system separately at varying temperatures. Freshly preparedly solutions were employed or every reading. The viscometric readings were taken as described in literature.

Observations And Calculations:

Molecular interactions in terms of β-coefficient of solute is figured with the help of data obtained in our work. The results obtained are stated in Table No. 1. According to Jone's-Dole equation, $(\eta r-1)/\sqrt{C} = A+\beta\sqrt{C}$ at different temperatures keeping the concentration 0.1 M. A and β-coefficient values calculated are enlisted in Table No 2.

Table No.1

Viscosity Measurements At Different Concentrations And Determination Of Relative And Specific Viscosities At Different Temperatures At 0.1m

Medium - 60% Ethanol-Water							
Conc.	Temp. (°C)	$\sqrt{C}$	Time t (sec.)	Density $\rho x10^3$ ($kg.cm^{-3}$)	η_r	$\eta_{sp}=\eta_r-1$	$(\eta_r-1)/\sqrt{C}$ (pa's)
0.1 M	25	0.316	51	1.0375	1.799745	0.799745	2.530838
	30	0.316	51	1.0315	1.789337	0.789337	2.497901
	35	0.316	48	1.0294	1.680653	0.680653	2.153965
	40	0.316	40	1.015	1.27193	0.27193	0.860537

TABLE – 2

A and β Co-Efficient Values from Graphs for 60%.

FOR (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one

"A"	β (Slope "m")
2.010811	0.05109

Result And Discussion:

The relative viscosity was determined by using following formula

η_r = Ds x ts / Dw x tw.:

While,the relative viscosities have been analyzed by Jone's-Doles equation as ,

$(\eta r-1)/\sqrt{C} = A+\beta\sqrt{C}$

The graph are plotted in between $(\eta r-1)/\sqrt{C}$ versus$\sqrt{C}$. The graph for each system gave linear straight line gave value of β-coefficient.

It was conclude from this research that, density and relative viscosity decreases with decrease in concentration. This is supported by the information that as the concentration decreases the number of solute molecule decreases as well as percentage of solvent molecules increases in the solution due to which solvation effect increases.

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Synthesis and Antimicrobial Screening of Some 6-Substituted Derivatives of 2-Phenyl-4h-Chromen-4-one

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Abstract:

The present research work deals with the synthesis of some 6-substituted-2-phenyl-4H-chromen-4ones i.e. substituted flavones by cyclization of corresponding 1-substituted-3-substituted propane-1,3-diones in glacial acetic acid with small amount of conc.H_2SO_4. The structures of synthesized compounds were established on the basis of spectral data studies o IR and ^1H NMR and were screened for their in vitro antimicrobial activity by performing disc diffusion method.

Keywords: 2-Phenyl-4H-chromen-4-ones, Flavones, Propane-1,3-diones, Antimicrobial.

Introduction:

Flavonoids are group of aromatic oxygen-bearing heterocyclic pigments widely distributed in lower and higher plants. Flavones (flavus = yellow) are the class of flavonoids family. These 'yellow' colored compounds have 2-phenylchromen-4-one backbone structure and usually found in human diet especially in fruits, vegetables, flowers, tea, red wine, and juices. They are also found in variety of medicines and natural products. Due to unique and flexible structure, these compounds could exert direct and indirect beneficial effects on health. In recent years, synthesis of flavones has attracted considerable attention of researchers worldwide due to their dominant medicinal properties such as biocidal[1-5], pharmaceutical[6-7], anti-oxidant[8-10] anti-HIV[11], anti-cancer[12], anti-inflammatory[13], anti-osteoporotics[14] and anti-diabetic[15]. A literature survey clearly indicates that, flavones are synthesized by cyclodehydration of 1-(2'-hydroxyphenyl)-3-phenylpropane-1,3-dione[16], by oxidative cyclization of 2'-hydroxy chalcones[17], by Auwers method[18] and via intermolecular Witting reaction[19]. It has been observed that substituted propane-1,3-diones are the best intermediate for the synthesis of flavones. Hence, in the present work, we describe the synthesis of some 6-substituted-2-phenyl-4H-chromen-4-ones from corresponding 1-(5'-substituted-2'-hydroxyl phenyl)-3-phenylpropane-1,3-diones in acidic condition and explored them for their in vitro antibacterial and antifungal activities.

Materials And Methods:

The chemicals used were of highest purity obtained from Merck, Loba and S.D Fine chemicals Ltd. Melting points (uncorrected) were measured by Thiele's melting point apparatus. The synthesized compounds were characterized by IR and ^1H NMR spectroscopic techniques. IR spectra were recorded in KBr using a Shimadzu IRAffinity-1 spectrophotometer and ^1H NMR spectra on a Brucker Avance II 400MHz NMR instrument in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard.

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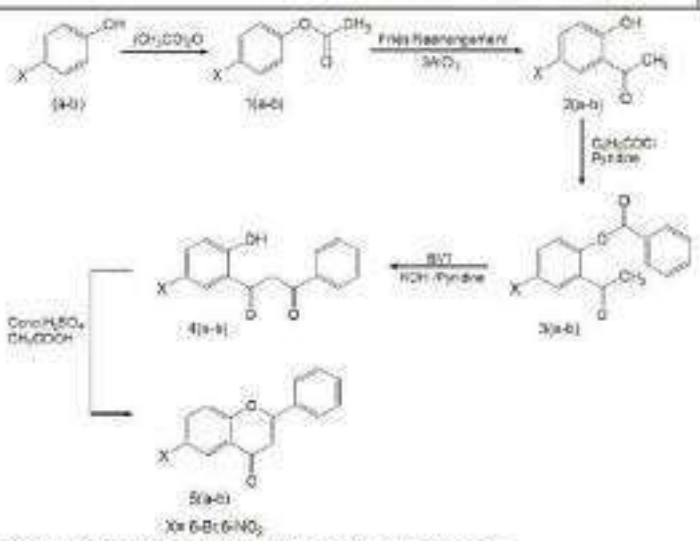


Figure 1: Reaction scheme for synthesis of substituted flavones

General procedure for synthesis of substituted flavones:

Initially, 4-substituted phenol (a-b) was refluxed with acetic anhydride in presence of dry anhydrous sodium acetate for 1.5 hr and then it was allowed to cool followed by their decomposition in water. The two layers were formed out of which separate lower acetate layer by means of separating funnel and then purified by distillation. The resultant product 1(a-b) undergone through Fries reamangement with anhydrous $AlCl_3$ and then decomposed by 10% ice-cold HCl, which was filtered and crystallized by glacial acetic acid to get substituted acetophenones 2(a-b). The prepared substituted acetophenone 2(a-b) and benzoyl chloride were dissolved in dry pyridine. The reaction mixture was shacked vigorously for about 30 min. The warmed reaction mixture was poured over crushed ice containing 1M HCl. The product thus obtained was filtered, washed with ice-cold methanol and then with water to get 2-benzoyloxy-5-substituted acetophenones 3(a-b) which was heated with pulverized KOH in pyridine at 60^{0}C for 15 minutes and acidified with 10 % glacial acetic acid resulting in the formation 1-(5'-substituted-2'-hydroxy phenyl)-3-phenylpropan-1,3-diones 4(a-b) by Baker-Venkatraman Transformation[20-21]. Finally, the obtained 1-substituted-3-substituted propane-1,3-diones 4(a-b) was refluxed in glacial acetic acid with 3-4 drops of conc. H_2SO_4 at 100^{0}C for about 1hr. After cooling, the reaction mixture was poured over crushed ice, filtered the separated product and washed with plenty of water. The obtained crude products were recrystalized by petroleum ether to get respective 6-substituted-2-phenyl-4H-chromen-4-ones 5(a-b) i.e. substituted flavones. The reaction scheme for synthesis of substituted flavones is shown in Figure 1 and their physical data are given in Table 1.

Table 1: Physical characteristic data of substituted flavones

Compound Code	Compound Name	Mol. Formula	Mol. Weight	M.P. (^{0}C)	Yield (%)
5a	6-bromo-2-phenyl-4H-chromen-4-one	$C_{15}H_9BrO_2$	301.14	192-194	74

5b	6-nitro-2-phenyl-4H-chromen-4-one	$C_{15}H_9NO_4$	267.24	170-172	82

Results And Discussion:

The 6-substituted-2-phenyl-4H-chromen-4-ones 5(a-b) were synthesized successfully in good yields (Table 1). The synthesized compounds were characterized by spectral data studies of IR and ^{1}H NMR. The IR and ^{1}H NMR spectra showed all the expected peaks which correspond to various groups present in each compound.

The Spectral data of synthesized substituted flavones are shown below:

(5a)-6-bromo-2-phenyl-4H- chromen-4-one:

IR (KBr) in cm^{-1} : 526 (C-Br stretch),1118(C-O linkage), 1620 (C=C Aromatic), 1697(C=O stretch), 3059 (C-H Alkene stretch), 3059 (C-H Aromatic).^{1}H NMR in δ ppm: 2.5 (s,1H,C=C-H), 7.26-7.5 (m,5H,Ar-H), 6.9 (d,1H,Ar-H), 8.0 (d,1H,Ar-H), 8.1(d,1H,Ar-H), 2.52 (s,Impurity).

(5b)-6-nitro-2-phenyl-4H-chromen-4-one:

IR (KBr) in cm^{-1}: 852 (p-substituted benzene), 1053(C-O linkage), 1321 (-NO_2 symmetric), 1508 (C=C Aromatic), 1616 (C=O stretch), 3085 (C-H Alkene stretch), 3085 (C-H Aromatic stretch). ^{1}H NMR in δ ppm: 2.54 (s,1H,C=C-H), 6.8-7.8 (m,3H,Ar-H),7.9-8.6 (m,5H,Ar-H), 4.9 (broadpeak,1H,O-H (H_2O),1.24 (s,1H,Impurity).

Antimicrobial screening :

The synthesized compounds 5(a-b) were purified, characterized and screened for their antimicrobial activity against Escherichia coli, Staphylococcus aureus and Candida albicans by disc diffusion method[22] using standard Tetracycline and Griseofulvin for bacteria and fungus respectively for comparison of activity. Compounds and standards were dissolved in DMSO to form a solution of 100µg/ml and used. The following Table 2 indicates the antimicrobial activity of test compounds 5(a-b) with their zones of inhibition in mm. From the results it was found that, the compounds 5a and 5b showed better zones of inhibition against Escherichia coli and Staphylococcus aureus as compared to Candida albicans.

Table 2: Anti-microbial activity of substituted flavones :

Compound Code	Zone of inhibition in mm		
	E.coli	S.aureus	C.albicans
5a	11	09	08
5b	13	12	10
Tetracycline	13	21	-
Griseofulvin	-	-	21

Conclusion:

In summary, we have synthesized some 1-substituted-3-substituted propane-1,3-diones from 4-substitured phenols and convert them to respective substituted flavones. The antimicrobial activity reveals that, the synthesized flavones 5a and 5b were found to be active and inhibits the growth of both bacteria as well as fungus but shows more activity towards bacteria E.coli and S.aureus as compared to fungus C.albicans. This increase in activity may be due to bromo and nitro substitution in flavones ring. As the concentration increases its activity may also increases.

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विद्येविना मति गेली, मतीविना नीति गेली
नीतिविना गति गेली, गतिविना वित्त गेले
वित्तविना शूद्र खचले, इतके अनर्थ एका अविद्येने केले

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Constructive Dialogue: Dramatic form of Ernest Hemingway's Short Stories

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Ernest Hemingway, the twentieth centu American writer is widely acknowledged for l experiments in English prose. In fact some of tl aspects of prose style were so revolutionary that attracted instant negative criticism. It took almo three decades for the critics to assess the value o his experiments in prose style, when he was awarde the NobelPrize in the 1950s. Apart from the ver popular "terse, compact and 'stripped to the bone' aspect of his style, Hemingway's real experiment have remained confined more or less to th knowledge of Hemingway critics and hardcor Hemingway fans and enthusiasts. Omission an concision, repetition and juxtaposition, blending o expressionism and impressionism, differen focalization techniques and constructive dialogue are some of the stylistic aspects that are central to Hemingway's prose-fiction. Most of these stylistic aspects were employed by Hemingway's predecessors like Chekhov, Strandhel, Maupassant, Crane, Kipling, Joyce and others in their own way. Hemingway's contribution was that he made these aspects unique by introducing variations, alterations and changes to suit his beliefs, themes and purpose. It is this aspect of originality that made Hemingway stand tall among the prose stylists of all times.

The paper proposes to demonstrate Hemingway's uniqueness as a prose-stylist, while keeping in mind the prime objective of making the common reader familiar with the writer's not-so-accessible strengths.

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Hemingway, in many ways, was a product his age. The typical character of his age—riddled h conflicts, wars, regime change and punctured h socio-political and economical changes—forms basis of the backdrop of the banal and dark ture of his themes. Hemingway himself was a y conscientious reader and liked to keep track whatever remarkable he read. He was a great irer of the master storytellers, across the guages, already mentioned above. From a very ng age Hemingway started picking the elements effe e storytelling. Though admirer of the sters, he followed them in a limited way: copying e but picking up something from everybody ore making it his own. Hemingway's description he aftermath of the war in the stories reminds us the ultra-naturalism of Stephen Crane. But he fers from Crane's naturalism by introducing zanne's technique of painting landscapes, layer layer. This technique of using "overlapping planes d underlying geometric shapes" enables mingway to portray the natural landscape by ping in mind the narrator's perspective. (67 illard) Similarly his use of repetitions can be ibuted to the writings of Gertrude Stein. However mingway's repetitions in his best stories are so tle that one is hardly aware of them and still cannot ain u fected by their cumulative impact. Unlike t of Stein the repetitions in Hemingway make their nt without overshadowing the prime thematic ncern. Use of dialogue in Hemingway's case is haps his most original contribution to the elopment of English fiction. Till 1920s, it was erally believed that in a short story dialogue can y have illustrative purpose. The constructive ction of dialogue was believed to have meant only dramatic works. This belief was cemented more ause the likes of Henry James already advocated concept of "illustrative function" of the dialoguein stories. Hemingway, for the first time nonstrated that dialogue can have perfectly ural constructive function even in the non-matic writings like short stories.

Short story as an art form differs from drama in many ways. The most significant point of departure though may be that drama is a performing form and that the story is not. However Hemingway's concept of art challenged this very traditional notion that put limitations on the story as an art form. Hemingway believed that every story plays out in the mind of the reader and its success depends on how well he reads between the lines and under the surface of the iceberg! It is due to this belief that Hemingway relied on the dialogue heavily in some of his best stories. In these stories the dialogue is manipulated in such a manner that it altogether removes the narrator's role as an illustrator. The stories like "Hills like White Elephants," "Light of the World," "The Killers," and othershave dialogue constructing the tale with multiple dimensions of meaning without any intrusion of narrative voice. Secondly by means of his constructive dialogue, Hemingway provided voice to those who had been till then kept silent and mute by the other writers. Hemingway while describing the characters from the troubled world, and those considered as social untouchables, successfully captured the difficulties of their world in their own dialect.

Hemingway used dialogue aiming at achieving the things which were thought by others as impossible in short fiction: characterization, emphasizing the theme and taking the story forward. The following analysis here shows that uniquely written dialogue can achieve all these objectives without any help from separatecommentary from the prose-writer.

The specialty of Hemingway's constructive dialogue is that even the crudeness of everyday common conversation has been taken to the level of an exclusive art. In his most famous story for its constructive dialogue, "Hills Like White Elephants," a few sentences of everyday conversation between a man and a woman lays bare the nature of their relationship. The man and the girl, sitting at the outside Café table on the railway station, speak in the manner any engaged couple would do:

'What should we drink?' the girl asked. She had taken off her hat and put it on the table.

'It's pretty hot,' the man said.

'Let's drink beer.' (The Collected Stories 199)

In this casual dialogue both play their role perfectly, waiting for the other to make the decision of ordering the drink first, in spite of their desire to force the individual will. The girl although asks the man to choose the drink does so only after she has taken off her hat and put that on the table. It is her hint for the man to acknowledge that the weather around them is hot. The man on the other hand even after being thus hinted, repeats her action in the words and says "it's hot." It is only after the man has acknowledged her preference; she makes the choice hinted by the man. In reality it is the man who has taken the actual decision. Here the man appears to be the one who wants everything to be controlled by him without being held responsible for anything. On the other hand the girl even though is capable of reading the man correctly, finally submits her will and keeps on playing along with the man on his terms. The dialogue having 28 words spread over one question, one factual piece of information and two statements actually provides a "nutshell-summary" of the whole story. How much more constructive can dialogue become! The story has other well illustrated achievements in dialogue like the use of "repetition and juxtaposition," "objective correlative," and "gender-based miscommunication ." Lamb, in his perceptively done analysis, shows how the use of common pronoun, "it" for ten times in a particular section of verbal exchange between the couple, has been made to refer five different subjects. The fact (which Lamb doesn't mention) that out of nine on six occasions "it" refers to the "abortion" and remaining three times to the "baby," brings out the preference given to the "termination" rather than the "growth" of their relationship. Apart from the objective correlatives of "the labeled bags," and the "landscape," there is one more, which has largely gone unnoticed, appearing as the girl's response to the man when he opens up the topic of abortion:

(1)'It's really an awfully simple operation, Jig,' the man said. 'It's not really an operation at all.'

(2)The girl looked at the ground the table legs rested on.

(3) 'I know you wouldn't mind it, Jig. It's really not anything. It's just to let the air in.'

(4)The girl did not say anything.

(5) 'I'll go with you and I'll stay with you all the time. They just let the air in and then it's all perfectly natural.'

(6) 'Then what will we do afterward?' (Italics mine; The Collected Stories200)

Here the girl looking at the ground on the background to the legs of the table firmly standing on it shows the deep shock she receives as soon as the man hints at the abortion. It is as if she herself goes under the physical procedure of abortion at that instant. The procedure is initiated by the man's words in Line 1. Asshe hears the words the "awfully simple operation" she receives very strong emotional shock so that emotionally she needs something substantial to hold on. It is for this reason that she looks at the table-legs standing on the ground. Here we could see the girl's legs shaking violently. Her emotional response has been captured powerfully only in the singular image. In fact the girl does not say "anything" till she recovers from, "an awfully simple operation." Her response in the Line 6 underlines the fact that, she has now recovered from the "the mental procedure of abortion." Now she can think about the future course— "afterward." Secondly the repetitive use of the word "anything" in Line 3 and Line 4 in place of the usual "nothing" also shows that it means "something" for the girl and the man knows that. It is his autonomous response made to come out as the result of his sudden awareness of the girl's injured state of mind. Further in the story the process of healing of the girl's injury occurs in the unique manner. The man after realizing the girl's shock, tries to justify his thoughts over and over again. The girl is so much irritated by the fake sympathy he is trying to show, that she warns him: "'I"ll Scream,' the girl said" (202)The man gets the message and stops finally his attempts of justifying his decision of abortion. The girl changes the course of conversation by involving the third person—the waitress. It clears the way for her. She smiles at the waitress brightly thanking her. This shows the girl's

acknowledgement of the existence of the world beyond her own problems. She has made peace with the painful decision thrust upon her by the man. We get the hint of her reconciliation when she responds to the man, "All right. Then come back and we'll finish the beer." (202)

The story, "Hills Like White Elephants," successfully fully presents before us the powerful drama of complex human emotions and troubled human souls. With the help of strategically placed words the writer creates all the tension without any ...ward help of extra commentary or any other stagecraft. The story with its uniquely written dialogue plays out on the stage of the minds of the readers. What better way a prose-stylist can prove the dramatic function of the dialogue in a prose story!

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Study of DC Conductivity of Polypyrrole doped with SnO_2 Nanocomposites

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ABSTRACT

The nanocomposites of PPy-SnO_2 were prepared by chemical oxidative polymerization technique using an anhydrous ferric chloride ($FeCl_3$) as an oxidizing agent and it was characterized by X-ray diffraction (XRD), field emission scanning electron microscope (FE-SEM), Fourier transform infrared (FTIR). The samples are prepared in the form of thick films by screen printing method. The effect of temperature on DC conductivity of the samples has been measured and the conductivity of sample PS3 (60 % PPy + 40 % SnO_2) was found to be maximum amongst all the prepared samples. Activation energy was found to be 0.1062 eV.

Keywords: PPy-SnO_2 nanocomposites, DC conductivity.

I. INTRODUCTION

Recently, the conducting polymers are important materials emerging with lot of applications in various fields. To improve the quality and applicability the research in the field of such polymers with some modification of existing polymers has been carried out. Some of these modifications involve preparing hybrid materials in which organic materials and inorganic oxides or salts of different metals, viz. SnO_2, ZnO, MgO etc. [1]. The most widely studied conducting polymers are polypyrrole, polyaniline, polythiophene etc. Additionally, PANI can coordinate with metal ions, giving the multi-metallic system and also preparation of nanocomposite materials with other polymers. PPy is one of the most interesting conducting polymers since it is easily deposited from aqueous and non-aqueous media, very adherent to many types of substrates, and is well-conducting and stable. Electrochemical polymerization produces thin films with a thickness of few micrometers on an electrode surface, while a chemical oxidation yields fine-grained materials [2-4]. PPy is known to be capable of storing electrical charges. The stored electrical charges can be recovered upon demand and that is why PPy can be considered as a good candidate for super-capacitor application [5-8].

The present study deals with the synthesis & characterization of PPy/SnO_2 composites and evaluation of dc conductivity for different wt. % of SnO_2 in PPy nanocomposites with an intention to know the effect of SnO_2 doping. The characterization of the composites has been done by SEM analysis techniques.

II. EXPERIMENTAL

A. Synthesis of SnO_2 nanoparticles.

All the chemicals used in this study were of GR grade purchased from Sd-fine, India (purity 99.99%). In preparation of SnO_2, 2g (0.1 M) of stannous chloride dehydrate ($SnCl_2.2H_2O$) is dissolved in 100 ml water. After complete dissolution, about 4 ml ammonia solution is added to above aqueous solution with magnetic stirring. Stirring is continued for 20 minutes. White gel precipitate is immediately formed.

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It is allowed to settle for 12 h. Then it is filtered and washed with water 2-3 times by using de-ionized water. The obtained precipitate were mixed with 0.27g carbon black powder (charcoal activated). The obtained mixer is kept in vacuum oven at 70ºC for 24 h to obtain a dried powder. Then this dry product was crushed into a fine powder by grinder. Now the obtained product of fine nanopowder of SnO_2 was calcinated at 700ºC up to 6 h in the auto-controlled muffle furnace (Gayatri Scientific, Mumbai, India.) so that the impurities from products will be completely removed.

B. Synthesis of Polypyrole (PPy)

The Py monomer, anhydrous iron (III) chloride ($FeCl_3$) and methanol were used as received for synthesis of PPy. The solution of 7 ml methanol and 1.892 g $FeCl_3$ was first prepared in round bottom flask. Then 8.4 ml Py monomer was added to ($FeCl_3$ + methanol) solution with constant stirring in absence of light. The amount of Py monomer added to the solution (1/2.33 times of $FeCl_3$) was in such a way to get maximum yield. The resulting black precipitates are filtered and washed with copious amount of distilled water until the washings are clear. PPy so obtained is dried by keeping in oven at 600ºC for 3 h. The synthesized material was characterized by using XRD, SEM.

C. Preparations of films

The thick films were prepared by using screen printing techniques. Initially, for the screen printing the thixotropic paste was formulated by mixing the sintered fine powder of pure and composite nano powder of SnO_2 and PPy in different weight percentage with a solution of ethyl cellulose (as 10% temporary binder) in a mixture of organic solvent such as butyl cellulose, butyl carbitol acetate and turpineol. The ratio of inorganic to organic part was kept as 75:25 in formulating the paste. The paste was then used to prepare thick films of pure and composite materials of SnO_2 and PPy and it was screen printed on a glass substrate. The prepared films were dried at 90-100ºC in oven for 1 h, so that all the organic materials (in the form of binders) and organic impurities can be evaporated from prepared films. For the surface conductance measurement, the electrodes of silver paint were formed on adjacent sides of the films and again, the films were subjected to heating at 70ºC for 15 minutes for drying the silver paint. The series of samples are as shown in table 1.

Table 1

S.N.	Nano composites	Sample Code
1.	Pure Polypyrrole	P
2.	80 % PPy + 20 % SnO_2	PS1
3.	70 % PPy + 30 % SnO_2	PS2
4.	60 % PPy + 40 % SnO_2	PS3
5.	50 % PPy + 50 % SnO_2	PS4
6.	40 % PPy + 60 % SnO_2	PS5
7.	30 % PPy + 70 % SnO_2	PS6
8.	20 % PPy + 80 % SnO_2	PS7
9.	Pure SnO_2	S

III. RESULTS AND DISCUSSION

A. XRD (X-ray Diffraction)

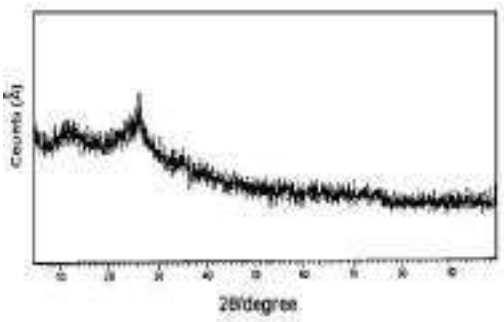


Figure. 1. XRD of pure PPy

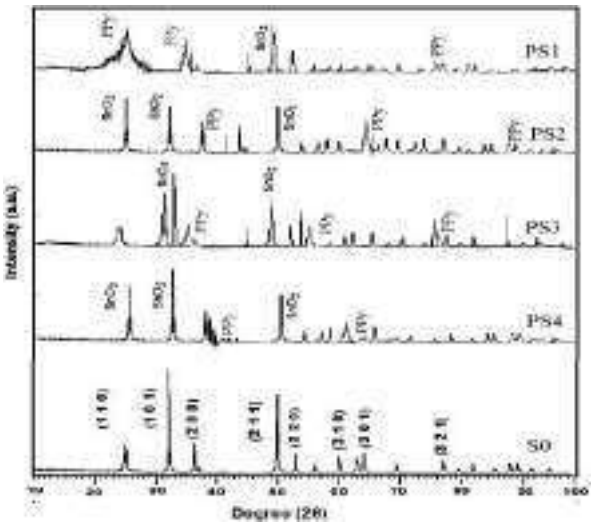


Figure.2. XRD of all composites sample

X-Ray diffraction pattern of pure polypyrrole (PPy) and their composites are as shown in figure (1 and 2). The pure PPy exhibited that, it was amorphous in nature. The broad peak occurred at 24^0 and it is characteristics of amorphous nature of polypyrrole. The broad peak occurs due to the scattering of X-rays from polymer chains at the interplaner spacing. The maximum intensity position of amorphous also depends on monomer to oxidant ratio. The X-ray diffraction patterns of composites of PPy, SnO_2 and pure SnO_2, calcinated at 200°C. Main peak, in case of pure SnO_2, is observed at 26.6° and this peak corresponds to the plane (1 1 0) of SnO_2 in tetragonal structure (JCPDS Card No.3-1114) with 100% intensity and the average crystalline size by using Scherer's formula was found to be 147.31 nm [9,10]. All the peaks are for the composites materials for molar weight percentage of various samples that are perfectly matched.

B. Scanning Electron Microscope (SEM)

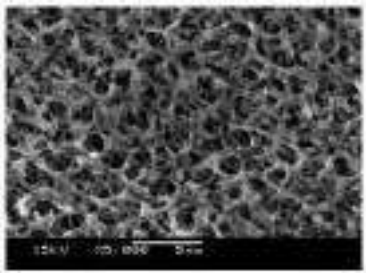


Figure. 3. SEM of Pure PPy

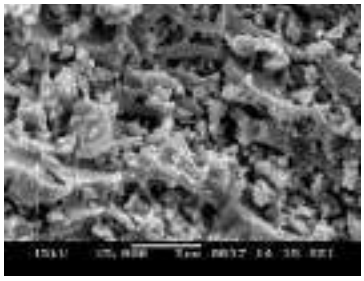


Figure. 4. SEM of PS3

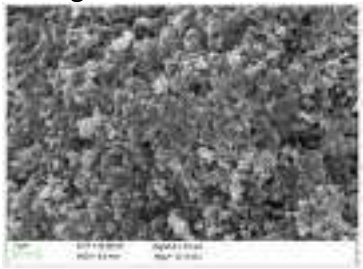


Figure. 5. SEM of Pure SnO_2

From the SEM photos, it is observed that in every inch of the region, number of pores was different and an average number of pores was taken for comparative study. From every photo, porosity was calculated for one inch region and listed in the tabular form. From above figures, it is found that number of porosity of 60PPy:40SnO_2 composition is more among the prepared and pure samples. Due to high porosity, available area for the flow of ions and charges is more and conductivity enhances. High porosity reduces the obstacle to the flow of charges and ions as collisions reduce (relaxation time increases) and charges mobility increases. This tends to high electrical conductivity.

C. DC Conductivity

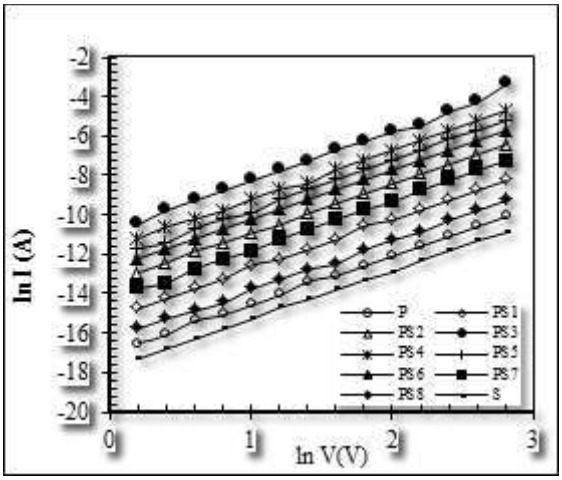


Figure. 6. DC conductivity of samples

The graph is plotted between lnI versus lnV at a constant temperature as shown in figure 6. As the doping percentage of SnO_2 in PPy increases, there is increases current with increase in voltage. It is maximum for PS3 sample (60%PPy + 40 % SnO_2) amongst the prepared samples. It is also manifested that, the nature of all the graphs is nearly straight line with constant slopes i.e. it obeys Ohm's law at temperature range 50°C to 350°C (linear ohmic material) on logarithmic scale [11].

D. Schottky Plots

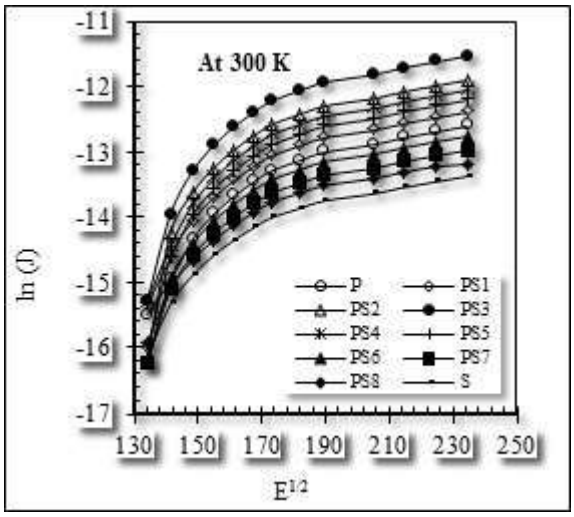


Figure. 7. Graph between Conductivity and $E^{1/2}$ at constant temperature

Then graphs are plotted between ln(J) and $E^{1/2}$ at temperatures 300 K, These graphs are known as Schottky Plots as shown in figure 7. It is observed that as electric field increases, current density increases more in the beginning and then shows saturation. Also ln(J) is maximum for PS3 sample, at constant temperature ln(J) increases. This also shows that with increase in doping of SnO_2 in PPy, ln(J) increases and becomes maximum for PS3. For sample PS3 the current density is $J = 9.8835 \times 10^{-6}$ A/m² which is minimum at temperature 300 K (room temperature).

E. Arrhenius Plot

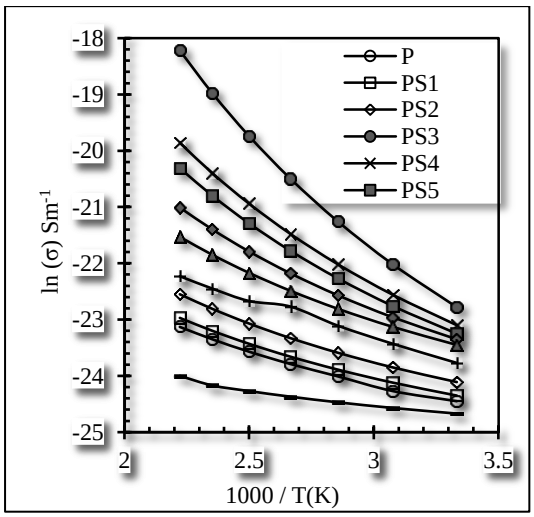


Figure. 8. Variation between ln(σ) and 1000/T(K) of all samples

The graph between ln(σ) and 1000/T(in K) is known as Arrhenius plot as shown in figure 8. It is observed that as temperature increases, ln(σ) increases. This variation is maximum for sample PS3. Due to increase of temperature, more and more charges in samples become free and contribute to the conductivity and electrical conductivity increases. As doping of SnO_2 in PPy increases, electrical conductivity increases and becomes maximum for 60%PPy + 40% SnO_2 sample (PS3 sample) and further increase in doping of SnO_2 in PPy, conductivity decreases. The value of activation energy of sample PS3 was found to be 0.1062 eV which is maximum among all the samples.

IV. CONCLUSION

The X-ray diffraction patterns of composites of PPy, SnO_2 and pure SnO_2, and it shows tetragonal structure and the average crystalline size is found to be 147.31 nm. The current–voltage (I–V) characteristics of the samples and its temperature dependence have been investigated in air at temperature 350°C. The linear nature of plots shows the semiconducting behavior and obeys Ohm's law and it is maximum for sample PS3. The value of activation energy of sample PS3 was found to be 0.1062 eV which is maximum among all the samples.

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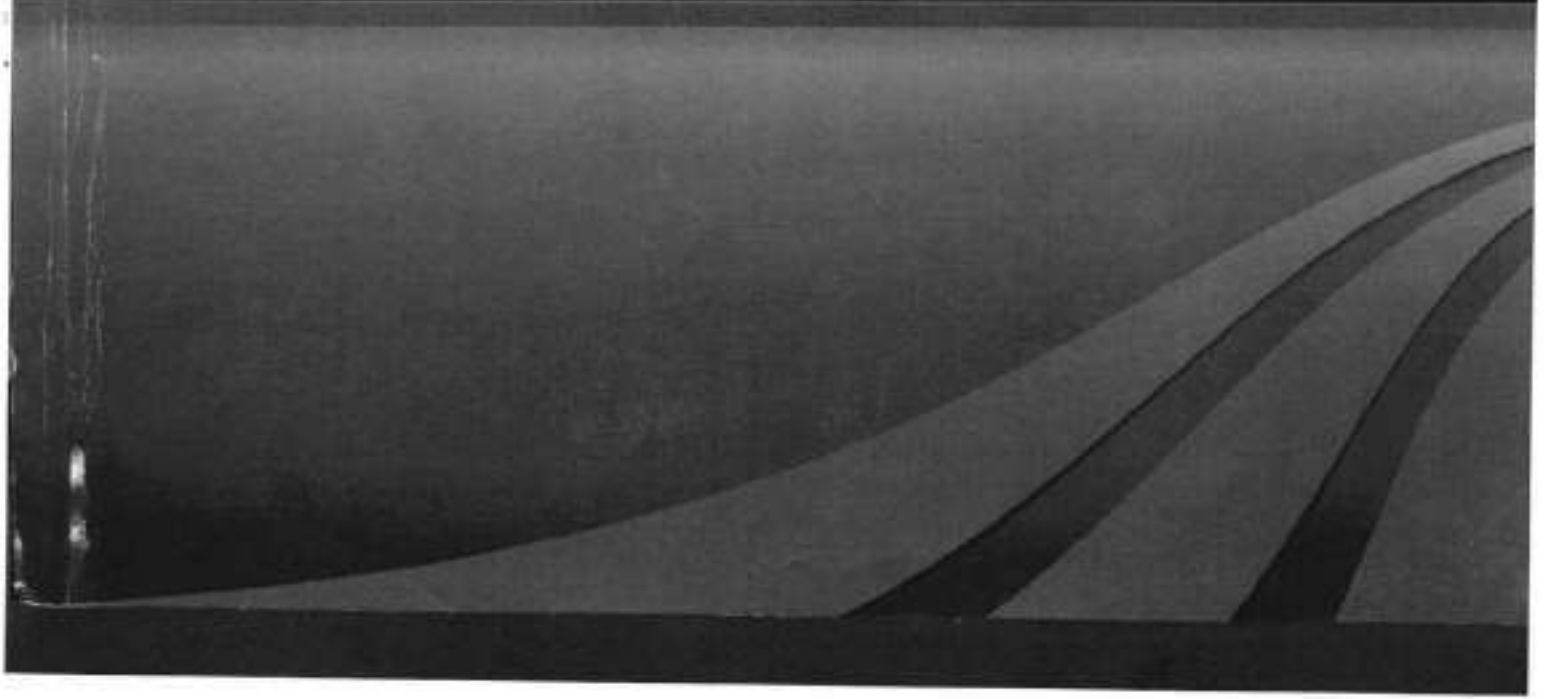
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Research Paper



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WOMEN PARTICIPATION IN LOCAL SELF GOVERNMENT ORGANIZATIONS-A SOCIOLOGICAL STUDY AND PERSPECTIVES

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ABSTRACT

After British, we got a chance to do the development of our nation. For real development of nation, there is a need to develop rural society. Government of India has framed Balwant Rai Mehta Committee to execute and implement the various schemes and plans through cumulative development program and national welfare extension plan.

This committee has suggested the three tier panchayat raj system i.e. Zilha Parishad, Panchayt Samitee and Gram Panchayat. This committee has suggested the Panchayat Raj system for complete and overall development of rural society. Therefore Balwant Rai committee is known as centralization of power. Through this committee, politicians could get developmental authority and power.

KEYWORDS: *Gram Panchayat, Panchayat samitee, Zilha Parishad*

PANCHAYAT RAJ

Panchayat Raj system is three tier system-

1. Gram panchayat -village level.
2. Panchayat samitee – Block level.
3. Zilha Parishad – District level.

The main aim of this committee is to participate local people in government.

WOMEN RESERVATION

Women Reservation is an important issue in current scenario. Today women got legislative and constitutional authority of equally and freedom. Still, women couldn't get the chance to participate in politics on the basis of fifty percent population. Through conferences, seminars awareness about women empowerment, development spread but the raising voice of women close down by male dominant society. There is a need of active and positive participation of women to get them chance in politics. Due to this effect women got chance of 33% reservation in various field.

PANCHAYAT RAJ SYSTEM AND WOMEN RESERVATION

Women got constitutional authority since independence to 1991 but expected result could not get to women. As per the 13th amendment in 1992, panchyat raj election has been declared after 5 year. On this basis of this decision, women got 30% reservation in three levels. Special posts reserve for women in local self government organizations. This decision is helpful to improve the status of women and to boost their confidence.

Kautilya had propagated the women authority. Women fought in many countries about their rights. Long struggle in England, 1998 women got authority of voting and France got in the year 1928as well as USA in 1944. 'Challenges of women change' book written by Shubhangi Gogate, Ghovtane expressed factual and logical discussion on women problems. Manjusha Gosavi also wrote on quantities and numeric analysis of women.

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'Changing status of women' written by Rajiv Kumar covered the overall situation of women from ancient time to modern time. Therefore this research is important for the women participation in Panchayat Raj system of India.

Constitution has awarded many protective and equally rights to women after independence. Awareness about authority, responsibility and use is important in Panchayat Raj. Women's changes become slow in male dominance society. This topic has been selected for research to understanding the role, efforts of women in Panchayat Raj system.



Points need to understand for women development-

1) To take the review of women status in post independence age
2) To understand the secondary place of women in politics due to the dominant attitude of men.
3) To identify the various problems of women in Indian politics.
4) To understand the women empowerment through women movements.
5) To know the causes behind the avoidance of clarence the bills and acts about 33% research of women in politics.
6) To do the study of status of women with respect to current scenario.
7) To understand the perspective of male women through the participation of women in politics.
8) To identity and understand the status of women of Wardha district in Panchayat Raj system.

OVERLOOK OF INDIAN SOCIETY REGARDING PARTICIPATION OF WOMEN IN POLITICS

1) In male dominant society, male appose and restrict to women to take part in politics, therefore the number of women in politics is less.
2) Women have more problem than men therefore women hesitate to take part into politics.
3) Sometimes women is not interested to take part in politics and she prefer the safe life in society.
4) Behind many success women, there are the men.
5) Duo to complexity of Indian society, women cannot freely movable in politics.
6) Men are the main hidden enemies in women reservation bill, therefore this bill yet to be finalized in India.

Overall information about politic has been found at some places on rules and regulations, importance of politics in panchayat raj system, Men were more aware than women about panchayat raj system. The classes should conduct for awareness among the women. After that women can run positive the panchayat raj system i.s. local self government organizations.

To provide the reservation to women in panchayat raj system is the fulfillment of political empowerment with women empowerment in India.

RECOMMENDATIONS AND SUGGESTIONS

1) There is a need of time to provide the training to women regarding panchayat raj system. Therefore government should start the classes for women.
2) Along with political sources, public administration also should teach to students for detail knowledge of local self government organizations.
3) Only reservation is not alternate solution but the gravity of knowledge is always greater to boost the confidence of women for active participation in panchayat raj system.
4) There is a need to aware the women about women power, capacity, ability, and problem solving methods.
5) Women should get the knowledge of women reservation, benefits of reservation, and rules of reservation, delay in reservation, obstacles in the progress of women's authority.
6) Strict application of legal provisions.
7) Role of women empowerment and development.
8) Awareness among the women
9). Curbing quackery, sensitization of doctors, NGOS, govt. machinery, panchayat leaders.

CONCLUSION

Strictly implementation, creation and support of legislative, judiciary will be beneficial to sort out the women related problems in India. Stop the women exploitation, rape sexually harassment, acid throwing, domestic violence, child marriages and female foeticide with proper instruments and control on these problems.

Various issues like women health, education, sports, schemes, equal sex ratio, entertainment, basic facilities, freedom, protection, sanitation arrangement should provide to women. Then definitely we can develop the healthy India. There is a need of time to frame the women empowerment program me at all levels. The great contribution expect from advocacy groups, policymakers ,social researchers, health workers, social thinkers and sociologist for the women empowerment.

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डॉ.संजय कोठारी
डॉ.दिनेश निचीत

❖ प्रकाशक ❖
संत गाडगे महाराज कला, वाणिज्य व विज्ञान महाविद्यालय, वालेगांव,जि.अमरावती
आणि आधार सामाजिक संशोधन विकास प्रशिक्षण संस्था, अमरावती

अध्यापनाचा वेळ वाया जाऊन अध्यापनावर परिणाम होणार नाही याची काळजी घ्यावी.

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संत गाडगेबाबांचे आर्थिक विचार

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प्रस्तावना

संत गाडगेबाबा एक लोकोत्तर युगपुरूष! सतत लोकसेवेत रममाण झालेले एक क्रियाशील सत्पुरूष गरीब माणसांच्या सुखासाठी ते रात्रदिवस धडपडत होते. अज्ञान, दारिद्रय, अंधश्रध्दा आणि अनारोग्याच्या अंधारात चाचपडणाऱ्या असंख्य गोरगरीब माणसांच्या हाताला हात धरून ते त्याला ज्ञान, विज्ञान आणि सुसंस्कारांच्या प्रकाशाकडे घेवून जात होते. गाडगेबाबा हा लोकजीवनाच्या विकासासाठी सतत क्रियाशील असणारा एक विचार होता. संत गाडगेबाबांनी सामाजिक कार्य करतांना आपल्या अर्थकार्यास महत्त्वाचे स्थान दिले आहे. बाबांनी किर्तनामध्ये गरिबी, लोकसंख्या, वाढणारा खर्च, बेकारी, कर्ज, अन्न, वस्त्र, निवारा, शिक्षण, आरोग्य, पाणी इत्या मुलभूत गरजा सारख्या आर्थिक समस्या लोकांसमोर मांडल्या त्यातूनच त्यांचे आर्थिक विचार स्पष्ट होतात. श्रमविषयक विचार, गरजा विषयक दृष्टीकोण, उत्पन्न–बचत विषयक विचार गाडगेबाबांच्या ध्यानीमनी रूजला होता. त्रस्थ, पिडीत, तहानलेल्या, भुकेलेल्यांना, उघड्या–नागड्या, बेघर, बेकार आणि निराधार, लोकांचे आधारस्तंभ होते. समाजात दबलेल्या, दडपलेला, दुर्बल, दुर्मुख आणि दीन माणूस बाबाच्या जीवनकार्याचा केंद्रबिंदू झाला होता. बाबांची किर्तने म्हणजे जनसामान्यांच्या आचारविचारांमध्ये आमूलाग्र क्रांती घडवून आणणारी तुतारी होती. समाज जीवनाची सांस्कृतिक, आर्थिक शैक्षणिक घडी बसविण्यासाठी सामान्यांच्या काळजाला जाऊन भिडणारी ती एक आर्त किंकाळीच होती.

गरीबांना अन्न, वस्त्र आणि निवारा हेच देवाचे

Vidya Bharati Mahavidyalaya College Amravati

PRINCIPAL VIDYA BHARATI MAHAVIDYALAYA AMRAVATI

भजन असते अशी व्यापक विचारांची मांडणी करत होते गाडगेबाबा. जीवनभर गरीबी भोगलेले आणि श्रीमंती माहिती नसलेले समाजाला ज्ञान विज्ञानाचे धडे देणारे समाजाला नवी साद घालणारे गाडगेबाबा कर्मयोगी होते.

"प्रपंच करावा नेटका ।
असू नये तो फाटका ।।"

अशा शब्दामधून बाबा माणसांच्या डोक्यावर सदुपदेशाच्या काठीचे फटकारे मारत होते. गाडगेबाबांच्या संदेशातून भुकेलेल्यांना अन्न, तहानलेल्यांना पाणी, उघड्या नागड्यांना वस्त्र, गरीबांना शिक्षण, गरीबांचे हुंडयविना लग्न, बेघरांना आसरा, निराशांना हिंमत, पशुपक्षांना अभय, रोग्यांना औषध, बेकारांना रोजगार, हाच बाबांचा दहा कलमी संदेश होता. हाच रोकडा धर्म होता. हीच मानवविकासाची गुरूकिल्ली होती, हाच समाज प्रगतीचा ध्येय ध्यास होता. गाडगेबाबांनी कीर्तनाच्या माध्यमातून अज्ञानाच्या अंधःकारात झोपलेल्या महाराष्ट्रातील समाजाला खडबडून जागे केले. कर्जमुक्ती, दारिद्रय मुक्ती, अज्ञानमुक्ती आणि व्यसनमुक्ती या विचारातुन समाजाला बाबांनी आदर्शपणे जगण्याचा मार्ग दाखविला. खेडयात यात्रा किंवा उत्सव प्रसंगी सर्वत्र घाण व दुर्गंध निर्माण होत असे त्यामुळे अनेक साथीचे रोग निर्माण होत असत. बाबा यातेतील घाण स्वत: स्वच्छ करीत असत. अशाप्रकारे स्वच्छतेला प्रचंड महत्व देतून स्वच्छतेचे फायदे लोकांना पटवून दिले. स्वच्छता असेल तर शरीर निरोगी राहील. रोगराई, बिमारी जवळ येणार नाही. शरीर निरोगी असेल तर कष्टाचे काम करणे कठीण जाणार नाही आणि आपोआपच स्वत:चा घरचा विकास होईल. बिमारीवर पैसा खर्च होणार नाही म्हणजेच आपोआपच बचत सुध्दा होईल. आर्थिक दृष्टया माणुस संपन्न बनेल असे बाबांचे विचार अर्थशास्त्राज्ञ नर्क्सच्या दारिद्रयाच्या दृष्टचक्राच्या आर्थिक विचाराशी मिळते जुळते आहे. विदर्भात आर्थिक दृष्टिकोनातुन संत गाडगे महाराजांचे कार्य ग्रामीण विकासाच्या वाटचालीस फार मोलाचे लाभले आहे.

भूकेलेल्यांना अन्न हा गाडगेबाबांचा संदेशाचा पहिला पाठ मनुष्य आणि इतर प्राणी यांच्या अन्न विषयक गरजा सारख्याच असतात. पोटाची भुक भागविणे हा अन्नाचा खास उपभोगाचा भाग होय. अन्नाशिवाय माणसाला जगता येत नाही. सुग्रास अन्नाच्या प्राप्तीसाठी माणसाची अहोरात्र धडपड चाललेली दिसते. गाडगेबाबा म्हणतात, काम करून खाण्यामुळे कामाची प्रतिष्ठा वाढते म्हणजेच गाडगेबाबांनी श्रमाला महत्व दिले. श्रमाचा भरपूर वापर करण्याच्या सल्ला समाजाला दिला. गाडगे बाबा भूकेलेल्यांना अन्न देत होते म्हणजे एक प्रकारे अन्न सुरक्षा देण्याचे काम गाडगेबाबांनी केले. गरीबाची गरीबी दूर झाली पाहिजे, त्यांना अन्न, वस्त्र व निवारा मिळाला पाहिजे. गरीबाला एखादी कला शिकवा म्हणजे त्याच्या पोटापाण्याची सोय होईल यातून हे सिध्द होते की, लोकाची गरीबी दूर करण्यासाठी लोकांना रोजगार दिला पाहिजे असे या विचारातून दिसते.

तहानलेल्यांना पाणी हा गाडगेबाबांचा संदेशाचा दूसरा पाठ पाणी म्हणजे जीवन. जीवन म्हणजे पाणी, पाण्याशिवाय मानव व मानवेत्तर प्राणी तडफडून मरतात इतके महत्व पाण्याचे गाडगेबाबांनी सांगितले. आजच्या पिढीला वाटते की, पुढचे तिसरे युध्द हे पाण्यासाठी होईल हे गाडगेबाबांनी कधीच ओळखले होते.

उघड्या नागड्यांना वस्त्र देण्यासाठी अबघाची संसार सुखी करण्याचे व्रत बाबांनी सांभाळले ते किर्तनातून सांगायचे, कर्ज काढुन यात्रा करू नका, गाईबैलाची काळजी घ्या, उघड्या नागड्याना वस्त्र द्या. गाडगेबाबांनी समाजातील शेवटच्या माणसाची काळजी घेतली, त्यांना पोटभर अन्न मिळावे आणि अंगभर वस्त्र मिळावे यासाठी आयुष्यभर प्रयत्न केले. गाडगेबाबांनी आयुष्यभर गरीबाला दारिद्रयाच्या दृष्टचक्रातून काढण्याचे प्रयत्न केले.

आसरा म्हणजे निवारा घर, ढन, वारा, पाऊस, हिंस्र पशूपासुन संरक्षण मिळविण्यासाठी माणसाने घर बांधले. भारतातील बहुसंख्य लोकांना अशाप्रकारचे घर नाही यासाठी गाडगेबाबानी धर्मशाळा काढल्या. माणसाला माणुस म्हणुन जगण्यासाठी अन्न, वस्त्र आणि निवाऱ्याची गरज आहे हे बाबांनी ओळखले. बाबांनी गोरगरीबांसाठी निवारे उभे केले. हजारो लोकांना आसरा देणारे बाबा खरे दिनबंधु होते.

'बेकाराईले रोजगार द्या' हा बाबांना महत्वाचा

संदेश होय. जो मनुष्य काम करतो तो सुखाने चार घास खातो. जो मनुष्य काम करत नाही त्याला भीक मागावी लागते. मानव जीवनाचे श्रेष्ठत्व नैपुण्याने केलेल्या कामावर अवलंबुन असते म्हणजे गाडगेबाबांनी श्रम विभाजनाचे महत्व आपल्या संदेशातून सांगीतलेले दिसते.

बाबांनी हजारो माणसांच्या जीवनात नवा विचार दिला, नवे ध्येय दिले, नवी दिशा दिली, नवी गती दिली, नवी जिद्द दिली, नवी हिंमत दिली आणि नवा आनंद दिला म्हणजे बाबा समाजाचे नवप्रवर्तक होते. बाबांनी समाज जोडण्याचे काम केले. बाबा साहसी होते, गाडगेबाबांनी समाजाला आशावाद शिकविला, प्रयत्नवाद शिकविला, नविन गोष्टी शिकण्याची उमेद निर्माण केली. बाबांची व्यक्ती वर्तणूक लोकांचे कल्याण, समाधान, सुख व हिंमत देणारे होते. मुठभर लोक सुखात राहतात तर डिगभर लोक दुःखात आहे ही विषमता त्यांनी ओळखली. आर्थिक विषमता हीच आपल्या समाजाची खरी कीड, ती कशी नष्ट करता येईल याकडे त्यांनी लक्ष दिले. बाबा कार्लमॉर्क्सच्या विचारशी तंतोतंत जुळणारे होते.

बाबांनी समाजाला आपल्या उत्पन्नाप्रमाणे कसा खर्च करायचा हे शिकविले. शिकलेला माणूस सुखी होईल आणि इतरांना सुखी करण्याचा मनापासुन प्रयत्न करील. समाजातला शोषित माणुस आपल्या शिक्षण विषयक कार्याचा केंद्रबिंदू मानला. शोषित माणसाला शोषणमुक्त करून त्याला सुखाचा मार्ग दाखवत होते बाबा!! ज्ञान हा तिसरा डोळा आहे. सर्वांसाठी शिक्षणाची नितांत गरज आहे, असे बाबा सांगत.

गाडगेबाबांनी ग्रामीण शिक्षणाचा पाया घातला म्हणजे गाडगेबाबा महात्मा गांधीजींच्या विचारशी मिळते जुळते आहे.

समाजातील दारिद्र्याने दृष्टचक्र नष्ट करून सृष्टचक्राची निर्मिती करायची असेल तर शिक्षण घ्या, शिक्षणाशिवाय तरणोपाय नाही.

गाडगेबाबांनी समाजाला शास्त्र शिकविले. प्रत्येक गोष्ट शास्त्रीय पध्दतीने करा असा मौलिक विचार समाजाला दिला.

महात्मा गांधीनी 'स्वच्छता म्हणजे परमेश्वर मानले' तर गाडगेबाबांनी तिला 'परमेश्वराची सेवा मानले.' त्यांच्या हातातील खराटा श्रमसंस्कृतीचे प्रतिक आहे. गाडगेबाबा श्रमप्रधान तंत्राला महत्व देणारे होते या सफाई यज्ञामागे त्यांचा शुध्दतेचा, आरोग्याचा तसेच पर्यावरणाचा उदात्त हेतू वा विचार जाणवतो.

निष्कर्ष :—

१. आज दारूबंदीसाठी, पशुहत्या थांबविण्यासाठी भ्रष्टाचाराचे निर्मूलन करण्यासाठी, जातीवाद, भाषावाद, अंधश्रध्दा, स्त्रीभ्रूणहत्या, शेतकऱ्यांची आत्महत्या थांबविण्यासाठी गाडगेबाबांचा विचारच वाचवू शकतो.

२. गाडगेबाबांचे आर्थिक विचार हे कोणत्याही सिध्दांतावर किंवा तत्त्वावर आधारित नसुन ते प्रत्यक्ष आचरणावर होते. आज प्रत्येक ग्रामीण व गरीब व्यक्तीने त्यांच्या विचारानुसार वर्तणूक केल्यास गरीबी, लोकसंख्यावाढ, कर्जबाजारीपणा, अंधश्रध्दा या सारख्या समस्या समाजात राहणार नाही आणि ग्रामीण समाजाची प्रगती होईल.

३. संत गाडगेबाबांच्या आर्थिक विचारामध्ये महात्मा गांधी, विनोबाजी, कार्लमार्क्स, प्रा. नर्क्से, प्रा. शूम्पीटर, यांच्या विचारांचे साम्य प्रामुख्याने दिसून येते.

संदर्भ :—

१. भोसले द. ता., लोकोत्तर गाडगेबाबा : जीवन आणि कार्य.

२. दांडेकर गो. नी., श्री गाडगेमहाराज मॅजेस्टिक प्रकाशन, मुंबई.

३. पाठक सुनंदा, श्री संत गाडगेबाबा विचारधन प्रकाशन, अकोला.

४. भगत रा. तु, संत गाडगेमहाराज स्मारक ग्रंथ चैतन्य प्रकाशन, कोल्हापूर.

५. केचे मधुकर, श्री संत गाडगेमहाराज साकेत प्रकाशन, औरंगाबाद.

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14.

EFFECTS OF GLOBALIZATION ON INDIAN RURAL SOCIETY AND FAMILY

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Mahatma Jyotiba Fule Mahavidyalaya, Amravati

Introduction-

Globalization is attaching the transportation, telecommunication, internet, interdependence of world views and activities. Globalization has its own characteristics and values, either positive or negative. Globalization is a vast and deep concept having effects and side effects on society. It has various causes. The main cause of globalization on developing countries is including three parameters like international market, trade, multinational production, and international finance. Every country in the world has accepted the policy of globalization and related concepts in current scenario

"Globalization can be defined as the ability to produce and good or service anywhere in the world using capital, technology and components from anywhere and to sell the output anywhere. Peter Jay 1996

Globalization has improved the overall economic status of people as well as the Indian nation in current situation. It is one type of motivation process for development of nation.

Industrialization and Globalization are always focus on industrial investment and economic growth process. In 18th century industrial revolution took place first time in United Kingdom. After that the its effects spread on all over the world which was the symbol of globalization.

The effects of science and technology on society shows with number of ways. It has issues like develop the economic growth, global economy, environment, working class structure, class system, changes in values and norms, more importance to money etc. Globalization has its own characteristics and values, either positive or negative. Globalization is a vast and deep concept having effects and side effects on society. It has various causes. The main cause of globalization on developing countries is including three parameters like international market, trade, multinational production, and international finance. Every country in the world has accepted the policy of globalization and related concepts in current scenario.

Globalization shows direct effect on Indian society.

1. Effects on family
2. Effect on marriage institution
3. Effects on status of women
4. Effects on cast and religion
5. Effects on ideology
6. Effects on work culture.
7. Effects on social institutions.
8. Effects on values, norm and social sections.
9. Effects on political system and Administration.
10. Effects on life style and behaviour with creation of social problems.

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11. Social effects, contact, family, marriages, and divorce-
12. Change in status of women-
13. Economic changes
14. Political changes
15. Changes in cast and religion
16. Educational changes
17. Global and secondary relationship
18. Existence of civilization
19. Different industrial social problems-

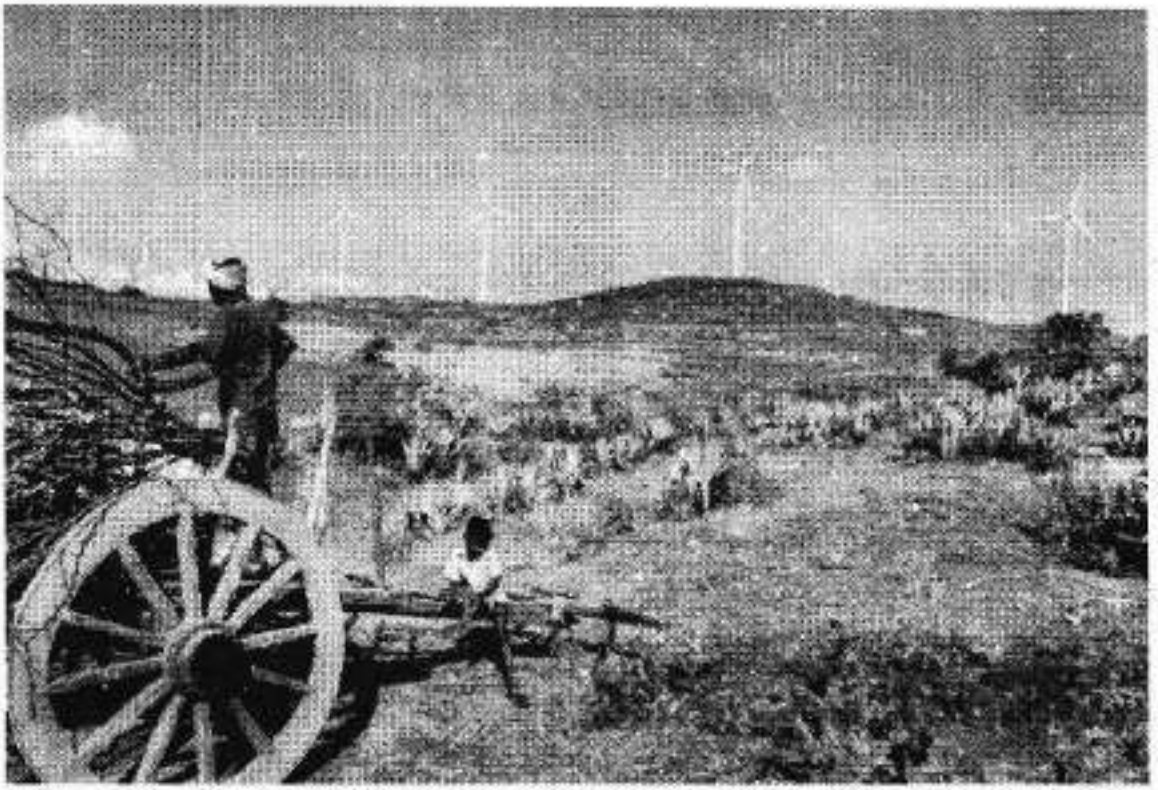
Concept of Family-

Family is a group of people where the socialization of children taking place and all the social, economical, cultural process held up. There are various types of families in society. Family is the main backbone of society. Family is the first school of man. Basic knowledge and information get to man first only by family.

The main function of family is to produce and reproduce persons, biologically and socially.

Family has special history. An ancient time the structure and scope of family were different. With relative the time it has been changing through various stages. Modern family called as a nuclear family which is a gift of modernization, urbanization and globalization. Joint family and nuclear family are the two types of family. Joint family is the characteristics of rural society and nuclear family is the quality of urban society.

Today is a global age in which all things and commodities shows the effects of global phenomenon. All the social, cultural, religious process have been changing by the effects of globalization. In today's global age, man becomes totally global and artificial.



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Family status in current scenario-

There are various effects and side effects of globalization on family. Mainly raising of the current modern social problems, avoidance of morality, difference among the relatives, anomie social structure and construction etc are the main issues in global age.

Following are the some effects of globalization on family-

1. Social effects-Its truth that by the effects of globalization, joint family is converting into nuclear family .Day by day the population of villages is going to decrees and in cities density of population becoming major problem. Along with migration cultural transmission, complexity of society, secondary relationship etc factors have been affecting in society.

2. Globlization and marginalization-Globalization has given the birth to marginalization. Centralization of wealth, class system, poverty, inequality etc are the different effects of globalization. Marginalization means slightly away from develop issues, ignorance and lack of main facilities which are utilizing by higher groups.

3. Rural Economy of India-Due to global effects and facilities, the growth of Indian rural economy has been increasing with respect to current agriculture productivity. GDP and GNP are affected by the various agriculture implementation programmes and policies.

4. Communication effects-Now a days there is an electronic communication revolution can seen in global society. As per the population the utility of cell phone and other peripheral have been in peak level. Even rural and tribal society also captured by electronic media.

5. Migrant workers-This is a latest and current problem raised in current scenario. For the searching of jobs and survival workers would like to go towards cities. Like Mumbai, Chennai, Delhi, Culcutta etc metropolitan cities are the known examples of migrant workers. They come out from their family, live single or with group in cities and earn the money. In that way most of the joint families transfer into single families.

6. Exitence of fashion and fad in family-With the process of globalization, existence of fashion and fad can seen in society. In spite of culture, civilization raised in society. Each and every stage of life effects of globalization have been noticed in society.

7. Urbanization, industrialization privatilization and modernization are the correlated concepts - Such types of all the concepts are interrelated to each other and frame, develop the particular type of network in society. All the said concepts are closely involved in globalization and affected on social, cultural and economical life of family in modern age.

8. Effects on Education system-In modern world, the effects of globalization directly shows on various contents of social parameters. Boom to the professional and commercial education with the specific development of science and technology, creation and awareness for global education, stress on the human job resources etc are the cognizance issues in globalization process. In this situation the growth and direction of family identify its path.

9. Family structure and scope-Global process affected the family structure and social construction. Small size, heterogeneous groups, money is a center of family, generation gap, secondary relationship etc effects are the gifts of globalization.

10. Divorce and Globalization- In modern, global family the number of divorce cases is increases rapidly. Main causes are global life style and environment at working places. All over India, in

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various courts the rate of divorce cases is very serious. Even we can say that symbol of degradation of family and society.

Conclusion

Today is a global world. Gloglization is process of nation prosperity and progress as per the current trend. It involves various modern process and concepts. For the development of country, there is no alternative to globalization and related issues.

But while implementation of globalization, we should not ignore our social and familiar construction in society. From all the levels, there should be always taking care and cognizance of global related issues. Identification, sort out and solve the global concerning problems as early as possible and maintain suitable frame of family and society.

Government facilitation plays a key role in this process. At the same time globalization altered available consumption choices, it has also pressured governments to change.

Globalization is close to urbanization, transportation, poverty, industrialization, educational purpose, global issues, social and cultural issues are the components of globalization.

India is a developing country. India needs various things, commodity, science and technology knowledge etc from other develop countries. Developmental countries have to pay revenue as a part of price. That money centralised to the treasury of develop countries. In that way may be we can say that globalization is a one type of side effect to developmental countries

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Study of proton-ligand and metal-ligand stability constants of Cu (II) and Mn (II) complexes with chlorosubstituted pyrazoles and isozoles in 80% DMF-water solvent using pH-meter

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Abstract : The hydrogen-ion activity in water-based solutions, its acidity or alkalinity expressed as pH scientifically is measured on the pH meter. pH meter instrument is also used to find out stability of complexes through titrations. Stability constant is equilibrium constant for the formation of a complex in solution. It is a measure of the strength of the interaction between the reagents that come together to from the complex. The proposed study deals with the proton-ligand stability constant and metal-ligand stability constant of chlorosubstituted pyrazoles and isoxazoles by Calvin Bjerrum titration on pH meter.
Key Words : pH- meter, chlorosubstituted pyrazole, chlorosubstituted isoxazole, Calvin Bjerrum titration.

Introduction:

The determination pH of a solution, we can employ number of methods like potentiometric, conductometric, cryscopic but for the purpose of titrations, we can directly use the pH meter. The pH-metric is an automatic instrument of measuring the pH of a solution. There are number of pH- meters, involving different principles, but most of the chemists use only the direct reading type pH meter. The hydrogen-ion activity in water-based solutions, its acidity or alkalinity expressed as pH scientifically is measured on the pH meter. The combined glass electrode is used in the pH meter. The glass electrode is the most widely used hydrogen ion responsive electrode and its use depends on the fact that when a glass membrane is immersed in a solution, a potential is developed which is a linear function of the solution[1].

pH meter instrument is also used to find out stability of complexes through titrations. Stability constant is equilibrium constant for the formation of a complex in solution. It is a measure of the strength of the interaction between the reagents that come together to from the complex. Ramteke[2] *et al* determined stability constants of 4-(2-chlorophenyl)-3-(3-furanoyl-5-(2-hydroxyphenyl)pyrazole with Cu(II), Ni(II), Co(II) and Nd(III) metal ions in 70% dioxane-water mixture. Pethe[3] *et al* reported the interaction of 3-(4'-bromophenyl)-4-benzoyl-5-(2-hydroxyphenyl)pyrazole and 3-(4'-chlorophenyl)-4-benzoyl-5-(2-hydroxyphenyl)pyrazole with Co(II) and Ni(II) by pH metrically.

The proposed study deals with the proton-ligand stability constant and metal-ligand stability constant of chlorosubstituted pyrazoles and isoxazoles by Calvin Bjerrum titration on pH meter.

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Materials and Methods:

Proton-ligand stability constants and metal-ligand stability constants studied on three ligands which are:

1. (3-(3,5-Dichloro-2-hydroxyphenyl)-1-phenyl-5-(1-phenylprop-1-en-2-yl)-1*H*-pyrazol-4 yl)(phenyl)methanone. (**ligand BC3**)

2. (3-(3, 5-Dichloro-2-hydroxyphenyl)-5-(1-phenylprop-1-en-2-yl) isoxazole-4-yl)(phenyl) methanone. (**ligand BC4**)

The ligands (BC3, FP3 and BC4) were completely dissolved in 80% DMF-water mixture. This is useful in pH metric titrations because all equilibrium processes that take place in water containing solvent-mixtures sensitively. The two metals selected for metal-ligand stability constants were: Cu (II) and Mn (II).

The Calvin-Bjerrum titration method was used to calculate proton-ligand stability constant and metal-ligand stability constant. The titration data were used to draw the graphs. Three kinds of titrations were performed against volume of NaOH. The ligands (BC3 and BC4) were separately titrated with metal complexes. These titrations were:

(a) Acid titration.
(b) Acid + Ligand titration.
(c) Acid + Ligand + Metal titration.

The titration procedures are:

(a) Acid titration: 5 ml HNO_3 (0.1M) + 5 ml KNO_3 (0.1M) + 35ml DMF + 5 ml water.
(b) Acid + Ligand titration: 5 ml HNO_3 (0.1M) + 5 ml KNO_3 (0.1M) + 10 ml ligand (in DMF-water 80%) + 25ml DMF + 5 ml water.
(c) Acid + Ligand + metal titration: 5 ml HNO_3 (0.1M) + 5 ml KNO_3 (0.1M) + 10 ml ligand (in DMF-water 80%) + 25ml DMF + 2 ml metal ion solution + 3 ml water.

Here 0.1 M HNO_3 acids were used for the preparation of a stock solution. The exact normality was calculated by titrating against standard sodium hydroxide solution. 0.1 M KNO_3 solution which was prepared from carbonates free double distilled water. Ionic strength of sodium hydroxide is kept constant as 0.1 M by addition of potassium nitrate solution.

The titration curves were prepared by plotting pH of solution and volume of NaOH added as shown in tables 1 to 4 and in graphs 1 to 4.The dissociation of OH^- is clearly indicated by the titration (acid + ligand) curves deviated from acid curves at pH 4.86 and continued up to pH 12.67 (Graphs 1 to 4).

Calculation of proton-ligand formation number ($\bar{n}_A$):

The proton-ligand formation numbers $\bar{n}_A$ were calculated from acid titration. The $\bar{n}_A$ values (proton-ligand formation numbers) were calculated by Irving Rossoti's expression curve (A) acid and acid + ligand titration curves (A+L).

The difference ($V_2 - V_1$) between the volumes (A+L) and (A) was measured accurately. The values of V_1 and ($V_2 - V_1$) were used in the calculations which are represented in tables 3.7 to 3.9.

$$\bar{n}_A = \gamma - \frac{(V_2 - V_1)(N + \varepsilon_0)}{(V_0 + V_1)T^0_L}$$

Where, γ = Number of replaceable hydrogen atoms per ligand molecule,
V_0 = Total initial volume of the solution
V_1 and V_2 are the volumes of alkali required during the acid and ligand titration at the given pH.
N = Normality of NaOH used for titration

ε_0 and T^0_L are the initial concentrations of free acids and the ligands

pH Metric Titration Data:

3.3.2.1 Titration data of ligand (BC3) with Cu (II):

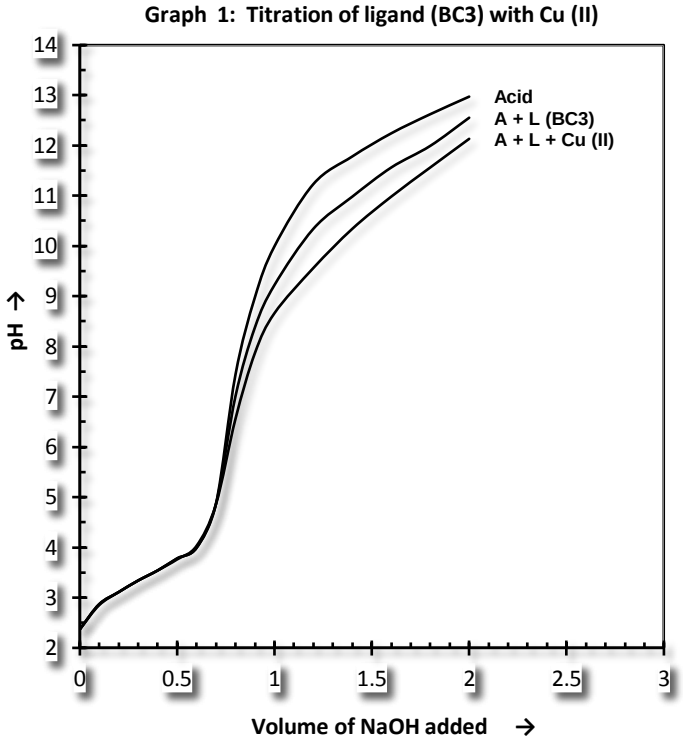
System: Ligand (BC3) with Cu (II), Medium: 80% (DMF: water), N = 0.2 N (NaOH)
Temperature = 25^0C, Ionic strength (μ) = 0.1 M KNO_3, ε_0 = 0.002 M HNO_3
T^0_m = 0.0004 M

Table 1: Titration data of ligand (BC3) with Cu (II)

Vol. of NaOH added	Acid	A+L(BC3)	A+ L+ Cu (II)
0	2.37	2.37	2.37
0.1	2.87	2.87	2.85
0.2	3.11	3.11	3.11
0.3	3.34	3.34	3.34
0.4	3.54	3.54	3.54
0.5	3.78	3.78	3.76
0.6	3.99	3.99	4.03
0.7	4.87	4.87	4.86
0.8	7.44	7.01	6.56
0.9	8.98	8.38	7.87
1.0	9.99	9.22	8.66
1.2	11.23	10.34	9.56
1.4	11.78	10.98	10.34
1.6	12.24	11.56	10.98
1.8	12.62	11.99	11.56
2.0	12.97	12.55	12.13

Table No. 2 Titration data of ligand (BC3) with Mn (II)

Vol. of NaOH added	Acid	(A+L+BC3)	A+L+Mn(II)
0	2.37	2.37	2.37
0.1	2.87	2.87	2.86
0.2	3.11	3.11	3.1
0.3	3.34	3.34	3.34
0.4	3.54	3.54	3.54
0.5	3.78	3.78	3.75
0.6	3.99	3.99	3.98
0.7	4.87	4.87	4.89
0.8	7.44	7.01	6.45
0.9	8.98	8.38	7.56
1.0	9.99	9.22	8.45
1.2	11.23	10.34	10.01
1.4	11.78	10.98	10.56
1.6	12.24	11.56	10.98
1.8	12.62	11.99	11.34
2.0	12.97	12.55	12.08



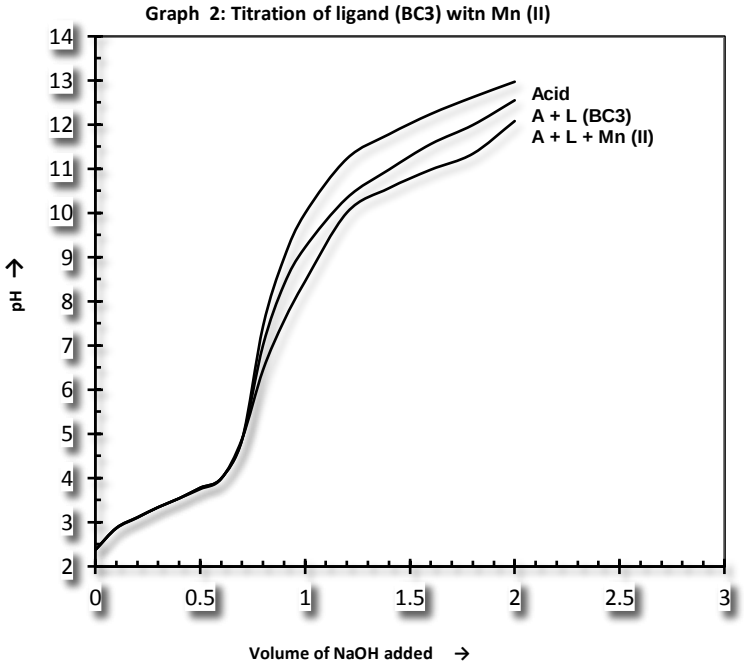


Table 3: Titration data of ligand BC4 with Cu (II)

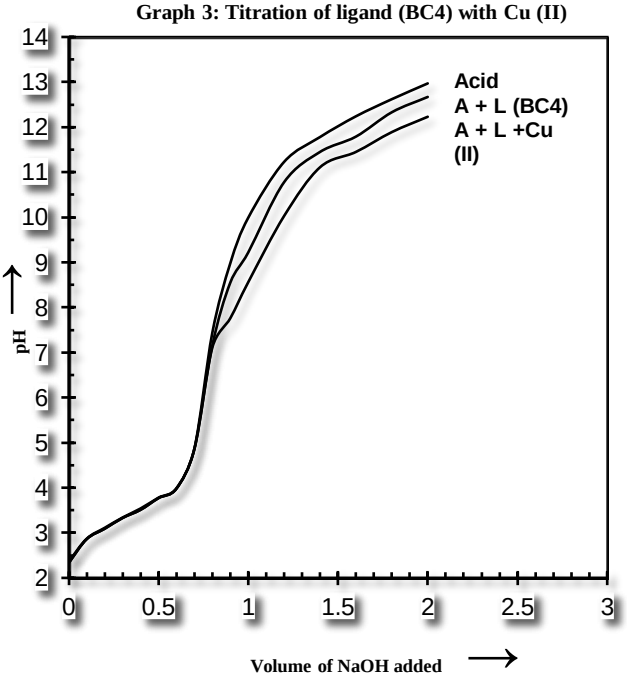
Vol. of NaOH added	Acid	A+L(BC3)	A+ L+ Cu (II)
0	2.37	2.34	2.34
0.1	2.87	2.86	2.86
0.2	3.11	3.09	3.09
0.3	3.34	3.33	3.33
0.4	3.54	3.51	3.51
0.5	3.78	3.77	3.77

0.6	3.99	3.98	3.98
0.7	4.87	4.86	4.86
0.8	7.44	7.16	7.11
0.9	8.98	8.55	7.76
1.0	9.99	9.22	8.56
1.2	11.23	10.78	10.03
1.4	11.78	11.45	11.11
1.6	12.24	11.79	11.45
1.8	12.62	12.33	11.89
2.0	12.97	12.67	12.23

Table 4: Titration data of ligand BC4 with Mn (II)

Vol. of NaOH added	Acid	A+ L (BC4)	A+ L+ Mn (II)
0	2.37	2.34	2.33
0.1	2.87	2.86	2.87
0.2	3.11	3.09	3.08
0.3	3.34	3.33	3.32
0.4	3.54	3.51	3.5
0.5	3.78	3.77	3.76
0.6	3.99	3.98	3.97
0.7	4.87	4.86	4.84
0.8	7.44	7.16	6.87
0.9	8.98	8.55	7.67
1.0	9.99	9.22	8.67
1.2	11.23	10.78	10.21
1.4	11.78	11.45	11.11
1.6	12.24	11.79	11.32
1.8	12.62	12.33	11.67
2.0	12.97	12.67	12.07

Graph 3: Titration of ligand (BC4) with Cu (II)



Graph 4: Titration of ligand (BC4) with Mn (II)

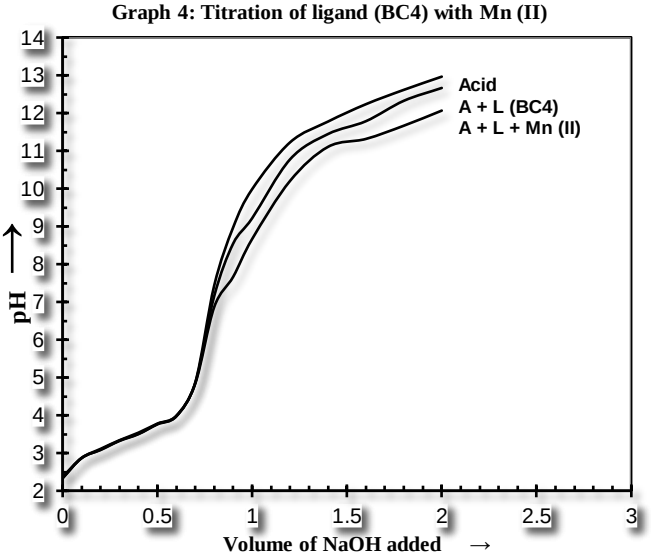


Table 1.1: Metal Complex Titration data:

Ligands	Metal ions	pH at Commencement of Hydrolysis (deviation of A + L curve from A acid curve)	pH at Commencement of Hydrolysis (deviation of A + L + M curve from A + L curve)
BC3	Cu (II)	7.01	6.56
	Mn (II)	7.01	6.45
BC4	Cu (II)	7.16	7.11
	Mn (II)	7.16	6.87

The departure of metal complex titration curve from reagent titration curve is seen at around pH 7. The pH of hydrolysis for all the metal ions under investigation was around pH = **7 to 7.6.**

The Pattern of Titration Curves:

The acids + ligand titration curves (A+L) are deviated from acid titration curves (A) for all systems at pH (4.87 for BC3), (4.86 for BC4) and continuously increased deviation up to pH (12.55 in BC3) and (12.67 in BC4). These kinds of deviations show the dissociation of -OH group of ligands. The present investigation consider the ligand (BC3 and BC4) having only one dissociable H^+ ion from -OH group.

$$HL \rightarrow H^+ + L^-$$

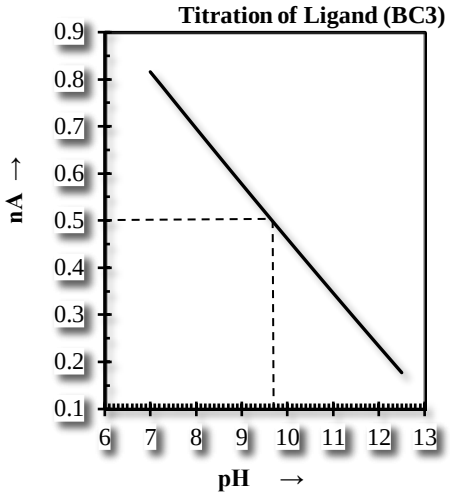
H = Acids, L = Ligand.

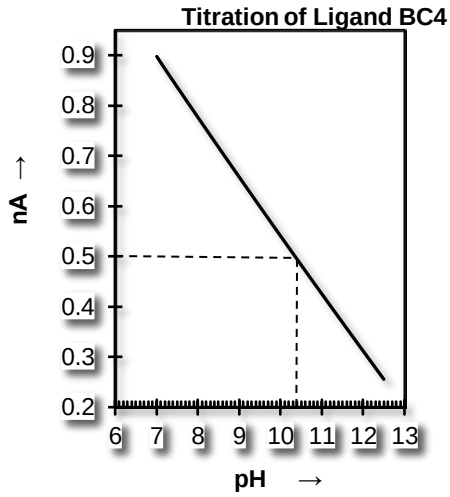
The (0.2 N) NaOH is used in the pH metric titration. The difference (V_2 and V_1) is estimated from the plot between the volume of NaOH and pH of the solution.

Calculation of proton-ligand formation number ($\bar{n}_A$):

$$\bar{n}_A = \gamma - \frac{(V_2 - V_1)(N + \varepsilon_0)}{(V_0 + V_1)T^0_L}$$

The values of $\bar{n}_A$ (average number of protons) were calculated along with the values of (V_2 - V_1) at various pH are presented in following graphs:





Graph 1. Titration of ligand (BC3) **Graph 2. Titration of ligand (BC3)**

Proton-ligand stability constant:

There are many methods for calculating pK_1 and pK_2 values. Here we have used the half integral method for determination of pK_1 values. Naik[14] *et al* and Patil[38] used half integral method and calculated pK_1 and pK_2 values. The pK values were initially calculated from formation curves $\bar{n}_A$ versus pH. The values of pH were $\bar{n}_A = 0.5$ correspond to the value of pK_1 for one dissociable group.

Table 1.1.1 Proton-ligand stability constant of BC3, and BC4 systems

Systems	proton-ligand stability constant (pK) by half integral method
BC3	9.7
BC4	10.4

Determination of metal-ligand stability constants:

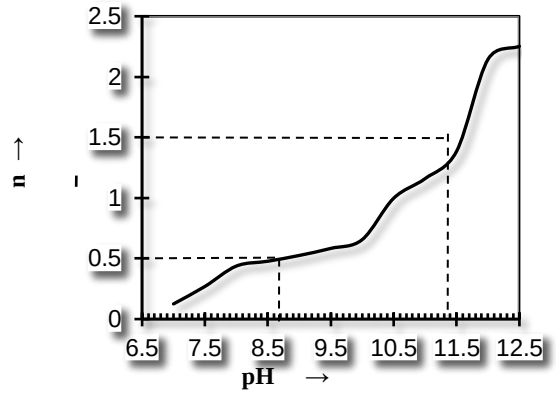
The stability constant of metal complex can be calculated by following $\bar{n}$ equation. $\bar{n}$ is defined as the average number of ligands bounds per metal atom and it can be calculated from the formula,

$$\bar{n} = \frac{(V_3 - V_2)(N + \varepsilon_0)}{(V_0 + V_2)\,\bar{n}_A\,T^0_M}$$

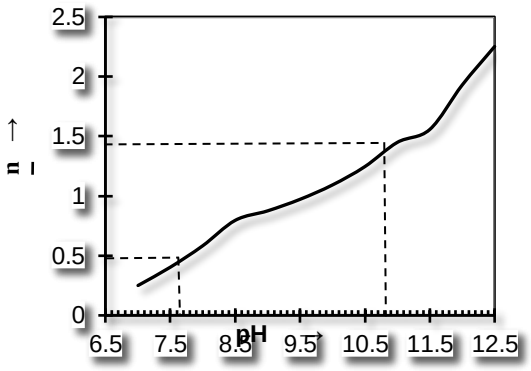
The value of $\bar{n}$ is corresponding pH value.

$$pL = \log\left[\frac{\left[H^+\right]}{K_L\left(T^0_L - T^0_M\left(\bar{n}\right)\right)}\right]$$

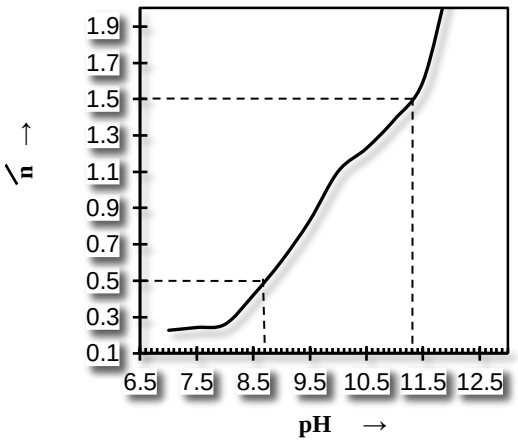
The plots of variation of $\bar{n}$ with pH that is metal-ligand formation curves are given in the graphs 3 to 6.



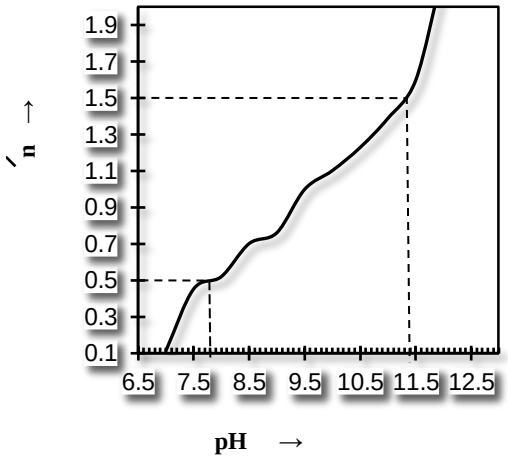
Graph 3. Ligand (BC3) with Cu (II)



Graph 4. Ligand (BC3) with Mn (II)



Graph 5. Ligand (BC4) with Cu (II)



Graph 6. Ligand (BC4) with Mn (II)

The pK values were calculated from formation curves of $\bar{n}$ versus pH. The value of pH was $\bar{n}$ = 0.5 which corresponds to the value of $\log K_1$ and the value of pH was $\bar{n}$ = 1.5 which corresponds to the value of $\log K_2$. The values of $\log K_1$ and $\log K_2$ of the complexes with metal ions were calculated by using half integral method:

Table 1.2 Metal-ligand stability constant $\log K_1$ and $\log K_2$ by half integral method

System	$\log K_1$	$\log K_2$	$\log K_1 / \log K_2$
Ligand (BC3) with Cu (II)	3.644	0.9546	2.689
Ligand (BC3) with Mn (II)	4.644	1.154	3.49
Ligand (BC4) with Cu (II)	4.443	1.953	2.49
Ligand (BC4) with Mn (II)	5.343	1.853	3.49

Result and discussion:

The proton-ligand stability constants (pK_1values) for substituted ligands were found to be 9.7 and 10.4 in BC3 and BC4 systems respectively. This is due to phenolic –OH group dissociating at 9.5 and above it in aqueous medium. The metal ligand stability constants log K1 and log K2 shows low stability at higher pH for 1:2 complexes as compare to 1:1 complex. Half cell configurations have more stability. From this tabulated data, it is observed that large difference between $\log K_1$ and $\log K_2$ values exhibits stepwise complex formation.

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SPECIAL ISSUE FOR INTERNATIONAL LEVEL CONFERENCE "ADVANCES IN SCIENCE, TECHNOLOGY & MANAGEMENT" (IC-ASTM)

IMPROVED AND SKILLFUL SYNTHESIS OF (±) FENOPROFEN, AN IMPORTANT ANTI-INFLAMMATORY AGENT

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Abstract: Several of the alpha-aryl-propionic acids are used as critical pharmaceutical agents much similar to how ibuprofen, ketoprofen, and flurbiprofen are used as non-steroidal anti-inflammatory agents. Many synthetic routes for producing arylpropionic acids have been proposed over the few years. Several of the present studies are focused on preparing pharmaceutically useful alpha-aryl-propionic acids. . The healing efficacy of this class of medicine is properly attested through the introduction and massive use of more than a dozen of compounds exemplified by ibuprofen, ketoprofen, flurbiprofen, and fenoprofen. It has been proven that appropriate alpha halo ketone can be easily transformed to ester, which on further hydrolysis yields alpha-aryl-propionic acid. A new and convenient synthesis of ether linkage utilizing Ullmann reaction has been suggested as an important step in the synthesis of Fenoprofen. In this paper, we report the total synthesis of Fenoprofen.

Keywords: Fenoprofen, Ullmann reaction, alpha halo ketone, alpha-aryl-propionic acid.

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PRINCIPAL VIDYA BHARATI MAHAVIDYALAYA AMRAVATI

INTRODUCTION

Several 2-arylpropionic acids have been described as non-steroidal anti-inflammatory agents (NSAIs), which are useful in the treatment of osteoarthritis and rheumatoid arthritis.[1] Some NSAIs also are used to treat several long term health problems. There are three general classes of drugs commonly used in the treatment of rheumatic arthritis: (a) non-steroidal anti-inflammatory agents (NSAIs) [2] such as celecoxib, diclofenac sodium, ibuprofen, etc., (b) glucocorticoids[3] such as betamethasone, prednisone etc., and (c) disease modifying anti-rheumatic drugs[4] (DMARs) such as hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, etc. The key objective of these drugs is to reduce inflammation leading to a subsequent reduction in pain intensity and improved function. In addition to anti-inflammatory effects, these agents are also known to have mild to moderate analgesic properties. Examples of some non-steroidal anti-inflammatory drugs (NSAIDs) include ibuprofen, indomethacin, nabumetone, naproxen, and others. These drugs are helpful in the treatment of mild to moderate pain, fever, and inflammation. They are effective in reducing the levels of prostaglandins, chemicals that are responsible for causing these ailments. [6] Fenoprofen, a NSAID, functions by blocking the activity of cyclooxygenases, which in turn lowers the level of prostaglandins. As a result, inflammation, swelling, pain, and fever are reduced.

Aspirin is one of the NSAIs agents which has largely been replaced by the other NSAIDs as the initial drug of choice for the management of inflammation due to its higher dosage requirement and high rate of gastrointestinal toxicity[7]. There are a large number of NSAIs available which are equally efficacious at full dosages. Fenoprofen is commercially available non-steroidal anti-inflammatory and analgesic drug used for the treatment of pain and inflammation caused due to rheumatoid arthritis and osteoarthritis. There are several synthetic routes available for the manufacture of Fenoprofen . One of the processes involves the reaction of 3-phenoxy chlorobenzene with sodium cyanoacetate followed by methylation and latter hydrolysis of cyano group.[8] Some other processes include the electrochemical synthesis of 2-aryl propionic acids by carbonyl group insertion by reaction of alpha methyl benzyl chlorides and carbon dioxide by [Co(Salen)].[9] The key step in the construction of diaryl ether unit during the synthesis of fenoprofen is by means of Ullmann reaction. This has been proved to be useful in a variety of transformation in organic synthesis.

The preparation of 3-bromoacetophenone was done using bromine and aluminium chloride.[10] Previously, the preparation of 3-bromo propiophenone was reported by reaction using 3-bromobenzonitrile and ethyl magnesium bromide. We optimized the synthesis of 3-bromopropiophenone from propiophenone, bromine, and aluminum chloride. It must be noted that the reaction using meta bromination with the commercially available propiophenone (**2)** is an important step in the synthesis of fenoprofen. Again, temperature plays a crucial role in this reaction.

The formation of C-O bond using 3,4,7,8-tetramethyl-1,10-phenanthroline (Me4Phen) or 1,10-phenanthroline as a ligand improves the Cu-catalyzed cross-coupling reactions of aryl halides with primary and secondary aliphatic, benzylic, allylic, and propargylic alcohols under mild reaction conditions.[11] Ullmann ether synthesis is an efficient method for the synthesis of diaryl ethers and is performed at 90°C using either aryl iodides or aryl bromides as the substrates under the assistance of amino acids.[12] Another general method involves developing a mild, palladium-free synthetic protocol for the cross-coupling reaction of aryl iodides and thiols using Cu catalyzed reaction and neocuproine ligand at high temperatures.[13]

Another efficient method for the synthesis of diaryl ethers under inexpensive ligand and mild conditions is the Ullmann-type coupling of aryl bromides or iodides with phenols. A number of diaryl ethers are obtained with excellent yields in acetonitrile in the presence of Cs_2CO_3 and catalytic copper(I) oxide.[14]The arylation of ethyl acetoacetate, ethyl benzoyl acetate, and dialkyl malonate under the catalysis of CuI and L-proline in DMSO proceed smoothly at lower temperatures in good yields. Both aryl iodides and aryl bromides are compatible with these reaction conditions.[15] The efficacy of copper-mediated cross-coupling reactions can be fairly increased with the initiation of mild reaction conditions and ability to employ catalytic amounts of copper. Again, the utilization of diamine-based ligands are of high importance in the synthesis of pharmaceuticals and designed materials.[16] By employing (2-pyridyl) acetone as a new supporting ligand, the copper-catalyzed coupling reactions of aryl halides with various phenolic moieties gives good yields under mild conditions. This reaction displays great functional groups compatibility and excellent reactive selectivity.[17] In this study, we have developed an effective new strategy for the synthesis of fenoprofen in good yield from propiophenone.

2. EXPERIMENTAL

2.1. General method

All manipulations were performed using standard Schlenk techniques under a dry nitrogen atmosphere. All the experiments were performed in flame-dried Schott Duran® bottles. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck; 0.25 mm thickness) and visualized under UV light followed by spraying with 5% solution of phosphomolybdic acid (PMA) in ethanol, subsequently followed by charring with a heat gun. Column chromatography was performed on 60 silica gel (Merck; 230-400 mesh). All other reagents of analytic grade were used without any further purification. ^{1}H-NMR (hydrogen-1 NMR) and ^{13}C (carbon-13 NMR) were recorded using Varian NMR 500 instrument (NMR Laboratory, Urbana, IL) at 500 MHz. The chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal and external standards for ^{1}H-NMR. Mass spectra were recorded on a Shimadzu 2010s mass spectrometer (Shimadzu Biotech, Manchester, UK). The IR spectra were recorded on a Spectrum 100 spectrometer (Waltham, MA, USA).

2.2. Procedure for the synthesis of (±) fenoprofen (1)

3-Bromopropiophenone (3):

Aluminium chloride ($AlCl_3$) (67.0 g, 502 mmol) was taken in 500 mL RBF. Propiophenone, **2** (27.0 g, 201 mmol) was added drop wise (highly exothermic) over the period of 10-15 min (temperature reaches ~ 80°C), a molten mass formed. Stir it at same temperature for 10 min. Bromine (12.46 mL, 241 mmol) was added drop wise over a period of 20 min. Continue the stirring at room temperature for 1.5 hrs. Reaction mass was poured over Concentrated HCl and ice mixture under vigorous stirring. Slowly the solid was precipitated out. Washed the solid with ice water for 3 times. Filter the solid and air dried to afford **2** (27.0 g, 63%). (mp 39°C); IR: 1691, 1567, 1458, 1417, 1211 Cm^{-1}. ^{1}H NMR (DMSO d_6): 8.08 (s, 1H); 7.97-7.94(m, 1H); 7.85-7.83(m, 1H); 7.51-7.48(m, 1H); 3.08(q, *J* = 7.2 Hz, 2H); 1.05(t, *J* = 7.2 Hz, 3H). MS$[M+H]^+$ Calculated for $C_9H_{10}BrO$:m/z 214.08, found 214.70.

General procedure for the Ullmann coupling of 3-bromopropiophenone with phenol:

A pressure tube equipped with Teflon cap was charged with magnetic stir bar, [Cu] catalyst (5-10 mol%), Base (2 eq.), 3-bromopropiophenone (1 eq.), and phenol (1.2 eq.) in a suitable solvent (mentioned in Table 2). The

tube was evacuated and purged with argon for 20 min. Under a counter flow of argon ligand (Lig 1- Lig 8) was added. The tube was refilled with argon and sealed. The reaction mixture was heated to the indicated temperature (80-120°C) for the required time. After cooling to the room temperature, reaction mixture was diluted with ethyl acetate (25 mL), and then passed through a bed of celite to remove inorganic salts and the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum.

1-(3-phenoxyphenyl) propan-1-one (4):

To a solution of Cs_2CO_3 (29.97 g, 92 mmol), 3-bromopropiophenone, **2** (10.0 g, 46 mmol), Phenol (6.62 g, 70 mmol), in dry DMF (100 mL) was added 1-(pyridin-2-yl) propan-2-one (1.24 g, 9.2 mmol). Contents were degassed for 30 min under vacuum, and then added Cu(I)Br (0.659 g, 4.6 mmol), again degassed for 10 min. under vacuum. Contents were heated at 120°C for 16 hrs. Reaction was monitored by TLC, water was added and extracted with ethyl acetate, and brine washing was given to organic layer, dried and evaporated. Crude compound was purified by column chromatography to afford **4** (7.34 g, 69.18%). IR: 1687, 1581, 1489, 1435, 1247 Cm^{-1}. ^{1}H-NMR: DMSO-d6: 7.75-7.05(m, 9H), 2.98(q, *J* = 7.2 Hz, 2H), 1.06(t, *J* = 7.2 Hz, 3H). MS[M+H]$^+$ Calculated for $C_{15}H_{15}O_2$:m/z 227.11, found 227.15.

α- Chloro-3-phenoxypropiophenone (5):

To a solution of 1-(3-phenoxyphenyl) propan-1-one, **4** (5.0 g, 22.22 mmol) in DMF (25 mL) was added Copper chloride. $2H_2O$ (7.50 g, 44.44mmol), followed by LiCl (0.932 g, 22.22mmol) and heated at 80-90°C for 15 h with constant stirring. The reaction mixture was cooled and poured over 0.5 N HCl (50 mL) and extracted with diethyl ether (30 mL X 3). The combined extract was successively washed by 0.5N HCl, aq. NaHCO3 solution, water and brine. The organic layer was dried over anhydrous sodium sulfate, filters and evaporated. The residue was purified by column chromatography on SiO_2 (100-200 mesh) using hexane as eluent to afford **5**(3.75 g, 65.10%). IR: 1691, 1580, 1488, 1436, 1258 Cm^{-1}. ^{1}H-NMR (DMSO d_6): 7.82-7.05(m, 9H), 5.73(q, *J* = 6.8 Hz, 1H), 1.58(t, *J* = 6.8 Hz, 3H). MS[M+Na]$^+$ Calculated for $C_{15}H_{13}ClO_2$m/z 260.06, found 283.85

α -Hydroxy-3-phenoxy propiophenone dimethyl acetal (6):

To a freshly prepared sodium methoxide, compound α- Chloro-3-phenoxy propiophenone, **5** (2.0 g, 7.67 mmol) in methanol (10 mL) was added drop wise under nitrogen atmosphere over 30 min. Reaction was monitored by TLC. Water was added and extracted with diethyl ether (20 mL X 3). Water washing was given to ether layer. Organic layer was dried over anhydrous sodium sulfate, filters and evaporated to afford **6** (1.6 g, 72.72%). ^{1}H-NMR: DMSO-d6: 7.45-7.35(m, 3H), 7.20-7.08(m, 2H), 7.04-6.95(m, 4H), 4.68(d, *J* = 4.4 Hz, 1H), 3.93(m, 1H), 3.18(s, 3H), 3.10(s, 3H), 0.78(d, *J* = 6.5 Hz, 3H).

Methyl α - (3-phenoxy phenyl propionate) (7):

To a solution of dimethylacetal, **6** (1.2 g, 3.9 mmol) and triethyl amine (1.05 mL, 7.5 mmol) was taken in dry DCM (12 mL) was cooled to -5^{0}C and sulfuryl chloride (0.835 g, 6.2 mmol) in dry DCM (12 mL) was added drop-wise by maintaining the reaction temperature -5°C under dry conditions under constant stirring. After complete addition of sulfuryl chloride, the reaction mixture was allowed to attain room temperature and stirred at same temperature for overnight, sat. aq. $NaHCO_3$ was added to it. The aqueous layer was extracted with DCM. The combined organic

layer was washed with water and brine, dried the organic layer, evaporated. The crude compound was purified by column chromatography over silica (100-200 mesh) using 10% Ethyl acetate in hexane to afford **7 (**0.65 g, 64.35%). IR: 1736, 1583, 1486, 1443, 1241 $cm^{-1.}$ ^{1}H-NMR (DMSO-d_6): 7.45-6.85(m, 9H), 3.78(q, *J* = 7.2 Hz, 1H), 3.58(s, 3H), 1.37(d, *J* = 7.2 Hz, 3H). MS[M]$^+$ Calculated for $C_{16}H_{16}O_3$**:**m/z 256.11, found 256.5.

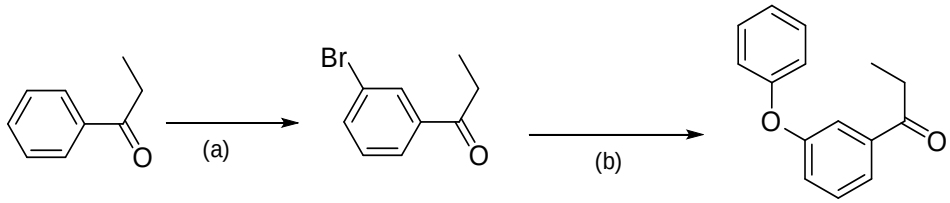
α -(3-phenoxy phenyl) propionic acid (1):

To a solution of ester, **7** (0.5 g, 0.0019 moles) in methanol (5 mL) was added 10 % aq. NaOH for alkaline hydrolysis. Contents were stirred at room temperature for 2h at room temperature. After completion of reaction acidified with 1 N HCl and extracted with ethyl acetate, dried and evaporated to afford, α-(3-phenoxy phenyl) propionic acid, **1 (**0.41 g, 86.86%). bp 169°C. **IR:** 1709, 1583, 1487, 1244 cm^{-1}**.** ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.35(s, 1H) 7.45-6.85(m, 9H), 3.67(q, *J* = 7.2 Hz, 1H), 1.30(d, *J* = 7.2 Hz, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 175.10, 156.75, 156.50, 143.48, 130.04, 129.97, 123.51, 122.49, 118.70, 117.66, 116.75, 44.54, 18.47. MS[M-H]$^-$: Calculated for $C_{15}H_{13}O_3$ m/z 241.09, found 240.90.

3. RESULT AND DISCUSSION

At first, we synthesized 3-bromopropiophenone (**3**) from propiophenone using bromine and aluminum chloride. The diaryl ether was (**4**) synthesized by Ullmann reaction using 3-bromopropiophenone and phenol. For the optimization of the Ullmann reaction, screening of various ligands (Lig 1- Lig 8) was done using different copper-catalyzed coupling reactions as shown in scheme 1**.**

I. Scheme 1:



2 **3** **4**

Reagents and conditions: (a) $AlCl_3$, Br_2, r.t., 1.5 h, 63%; (b) Phenol, **3**, 5-10 mol% [Cu], 10 mol% Lig 1-Lig 8, Base, Solvent, Ar, 80-110°C, 12-24h; 69%

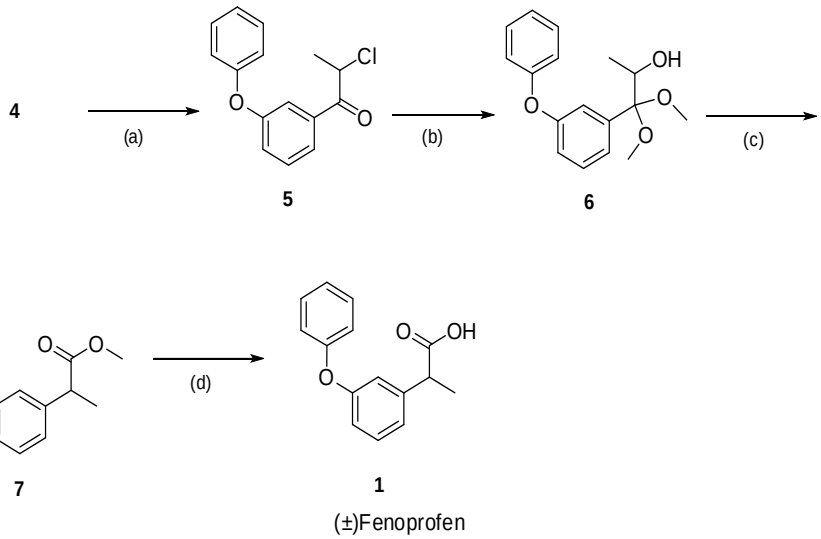
A variety of ligands such as 1,10-phenanthroline (Lig 1), 3,4,7,8-tetramethyl-1,10- phenanthroline (Lig 2), N, N-dimethylglycine.HCl (Lig 3), neocuproine (Lig 4), salicylaldoxime (Lig 5), L-proline (Lig 6), N-N-dimethylcyclohexane-1,2-diamine (Lig 7), and 1-pyridin-2-yl-propan-2-one (Lig 8) were screened in the reaction of phenol with 3-bromopropiophenone using the following catalyst system: 5-10 mol % CuI, 10 mol % ligand including the base in suitable solvent from 80°C-120°C from 12-24h (Table 1). Employing 1-(pyridin-2-yl) propan-2-one as a new supporting ligand, the copper-catalyzed coupling reactions of aryl bromide (3-bromopropiophenone) with phenol successfully proceeded in good yields. In this study, a new facile approach towards the synthesis of 1-(3-phenoxyphenyl) propan-1-one via Ullmann coupling, catalyzed by Cu(I)Br for the construction of diaryl ether fragment is described (**Entry 8 - Table 1**). Structures of ligands **Lig 1- Lig 8** were shown in **Figure 1**.

After optimizing the ligand (1-pyridin-2-ylpropan-2-one) via the Ullmann coupling condition, we were required to improve the yield of the reaction. For that purpose, screening of variety of catalysts and bases were carried out. We found that using copper bromide (CuBr), Lig 8, Cs_2CO_3 as a base in dimethyl sulfoxide solvent gives better yield (**Entry 3 - Table 2**).

After optimized Ullmann coupling condition, we used compound **4**, for the synthesis of fenoprofen. Earlier, fenoprofen could be readily prepared via cyanation reaction (NaCN, KCN, K_3FeCN_6). However, to avoid the usage of these hazardous cyanating reagents, we have proposed a better method for the synthesis of (±) fenoprofen. Our proposed method can prove to be more effective facilitating easy accessibility of raw materials as well as the use of special techniques for bulk synthesis. This is the safest route to synthesize fenoprofen. To summarize, we propose a simple and convenient method for the synthesis of Fenoprofen (**Figure 2**).

The synthesis of alpha halo ketone **(5)** from 3-phenoxy propiophenone **(4)** using copper chloride and lithium chloride in *N*,*N*-dimethyl formamide (DMF) was optimized.[18] Earlier the conversion of alpha halo ketone to aryl propionic acid was reported by photochemical transformation using propylene oxide and aqueous acetone.[19] This alpha haloketone was converted to alpha hydroxyl acetal intermediate (**6**) using sodium methoxide.[18, 20] The intermediate (**6**) converts into its chlorosulfonyl ester in situ and it rearranges to its methyl ester **(7)** in high yields.[21] The final fenoprofen (**1**) was isolated in excellent (87%) yields by basic hydrolysis of methyl ester with high purity. The sequence of reaction employed is depicted in below scheme **2**. The structure was confirmed by IR, mass, ^{1}H-NMR and ^{13}C-NMR.

Scheme 2:



Reagents and conditions: (a) $CuCl_2$, LiCl, DMF, 90°C, 15 h; 65% (b) NaOMe, MeOH; 72% (c) Et_3N, SO_2Cl_2, r.t., 16 h; 64% (d) aq. NaOH, MeOH, r.t., 2h, 87%.

4. CONCLUSION

Here, an efficient copper-catalyzed synthesis of diaryl ethers from phenol and 3-bromopropiophenone was developed after screening of different ligands (Lig 1- Lig 8). Out of legends screened, 1-(pyridin-2-yl) propan-2-one

was found to give a better yield. The CuBr-Lig 8 catalytic system showed an excellent yield at higher temperature. Our report provides an attractive addition to the existing strategies implemented for the synthesis of diaryl ethers via Ullmann coupling. We developed a concise and convenient new strategy for the synthesis of (±) fenoprofen in good yield from propiophenone with several prominent advantages of easy operation, convergence, and broad scope of applicability.

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The authors are thankful to Head of Chemistry Department and Principal of Vidya Bharati Mahavidyalaya, Amravati for providing the necessary facilities to facilitate this study.

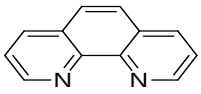
5. REFERENCES

Table 1 Standardization of Ullmann reaction using different ligands.

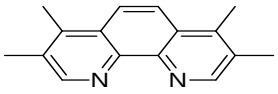
Entry	Ligand	Base	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	Lig 1	Cs_2CO_3	Toluene	80	12	26
2	Lig 2	Cs_2CO_3	Toluene	110	24	12
3	Lig 3	Cs_2CO_3	1,4-dioxne	90	24	38
4	Lig 4	^tBuONa	Toluene	110	16	--
5	Lig 5	Cs_2CO_3	DMF	110	24	13
6	Lig 6	Cs_2CO_3	DMSO	90	22	18
7	Lig 7	K_3PO_4	DMSO	80	24	16
8	Lig 8	Cs_2CO_3	DMSO	120	24	45

Table 2 Improvement of the yield of Ullmann reaction using different catalyst and bases.

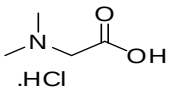
Entry	Catalyst	Base	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	CuCl	Cs_2CO_3	NMP	130	12	12
2	CuBr	K_3PO_4	Toluene	100	24	28
3	CuBr	Cs_2CO_3	DMSO	120	16	69
4	CuI	Cs_2CO_3	Dioxane	90	24	41
5	CuI	K_2CO_3	DMA	120	7	18
6	CuI	K_3PO_4	Toluene	110	18	36
7	CuI	Cs_2CO_3	Toluene	110	24	16
8	CuI	Cs_2CO_3	Dioxane	100	24	12



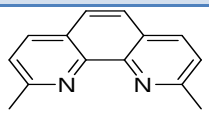
Lig 1



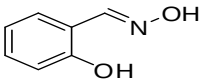
Lig 2



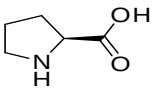
Lig 3



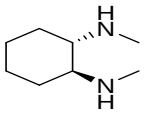
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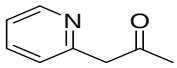
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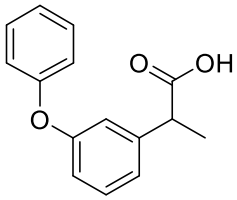
Lig 6



Lig 7



Lig 8



(±) Fenoprofen (**1**)

Figure 1 Structures of ligands **Lig 1- Lig 8**.

Figure 2 Chemical structure of (±) Fenoprofen.

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Synthesis and characterization of some newly synthesized Nitro and Bromo substituted 3, 5-diaryl isoxazolines

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ABSTRACTS
Five membered heterocycles like isoxazolines have found wide application as pharmaceutical and agrochemical agents. The present work deals with the synthesis of bromo and nitro substituted 3, 5-diarylisoxazolines from bromo and nitro substituted chalcone and hydroxylamine hydrochloride in the presence of ethanol solvent by refluxing for 2 hours.

INTRODUCTION:

The azole containing one oxygen and one nitrogen atom at 1, 2-position are designated as isoxazoles.

The dihydroderivative of isoxazole are known isoxazolines. A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of atoms in the ring. Compound incorporating heterocyclic ring systems continue to attract considerable interest due to the wide range of biological activities. Amonst them five membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Five membered heterocycles like isoxazolines have found wide application as pharmaceutical and agrochemical agents.

The synthesized 3,3-diaryl-4-aroyl isozolines from 3-aroy flavnones and 3-aroyl chomones by the action of hydroxylamine hydrochloride in ethanol[1] also the synthesis of 3-(2'-hydroxy-3'-bromo-5'-5'-ethylchalcone and hydroxylamine hydrochloride in ethanol[2] and the preparation of substituted fluro isoxazolines from flurochalcones in DMF[3].also the preparation of of some chlorosubstituted nitrogen and oygen containing heterocycles and their use in controlling horticulture crops pathogens.[4]The Clean and effeIcient synthesis of isoxazalose derivative in aquaes media Synthesis of biocyclic isoxazoles isozaxoliness via intra molecular nitrile oxidecycloaddition[5-6]. The Synthesis and characteraisation of some novel isoxazoles via chalcone intramediates and The novel isoxazolines ectoparasiticide furalaner selective inhibition of orthopad aminobutyric acid and l-glutamate gated chloride and chanels and insteticidals acaricidal activity.[7-8] Expeditious preparation of isoxazole from isoxazoline and advanced intermediate for functional materials and Synthesis of some 3,5-diary-2-isoxazolines derivatives in ionic media[9-10]

EXPERIMENTAL WORK:

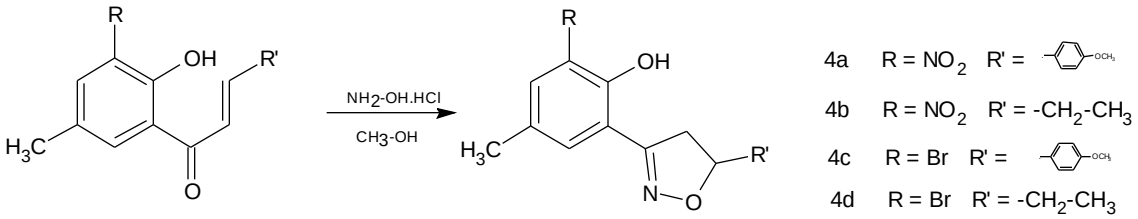
The interaction of hydroxyl amine hydrochloride and chalcones has the most convenient method for the synthesis of isoxazolines.

The synthesis of isoxazoline from 1-(2-hydroxy-3-nitro-5-chlorophenyl)-3-(4-chloro phenyl) chalcone (0.01mole) treated with ortho-chlorobenzaldehyde in presence of KOH. The melting points of these compounds were recorded on 'Tempo' melting point apparatus and are uncorrected. The carbon nitrogen hydrogen and oxygen analysis was carried out on 'Carlo Ebra 1106' analyzer. The IR spectra were recorded on 'Perkin-Elmer' Infra Red spectrophotometer. The PMR spectra recorded on DRX300 spectometer in $CDCl_3$. Purity of this compound tested by TLC.

A) preparation of 3-(2-hydroxy-3-bromo/nitro-5-chlorophenyl)-5-(4 methoxychloro-phenyl)-isoxazoline (IIa/b)

A mixture of 1-(2-hydroxy-3-bromo/nitro-5-chlorophenyl)-3-(4-chloro phenyl)- chalcone(0.01 mole) and hydroxyl amine hydrochloride (0.02 mole)was refluxed for 2.5 hr.in methanol (25ml).The reaction mixture was decomposed crystalline solid product thus separate was filtered and crystallized from ethanol.

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3 (a-d) 4 (a-d)

SPECTRAL INTERPRETATION:

Compound (4b): $C_{12}H_{14}N_2O_4$; **IR (cm^{-1}):** 3398.57 (-OH bonding), 3072.60 (Aro. stret.), 2927.94 (sp^3 C-H stret.), 1448.54 (-CH_2 bend.), 1365.60 (-CH_3 bend.), 1537.27 (NO_2 stret.), 1200 (C-O stret.), **NMR (δ ppm):** 12.86 (s, 1H, Ar-OH), 7.5-7.6 (m, 2H, Ar-H), 2.5 (d, 2H, Hetero –CH_2), 6.7 (m, 1H, Hetero –CH), 2.24 (m, 2H, -CH_2), 2.2 (t, 3H, -CH_3).

Compound (4d): $C_{12}H_{14}BrNO_2$; **IR (cm^{-1}):** 3435 (-OH bonding), 3055.24 (Aro. stret.), 2995.45 (sp^3 C-H stret.), 1319.31 (-CH_3 bend.), 578.64 (C-Br stret.), 1400.32 (-CH_2 bend.), 1319 (C-O stret.), **NMR (δ ppm):** 11.8 (s, 1H, Ar-OH), 6.8 (m, 2H, Ar-H), 2.27 (s, 3H, Ar-CH_3), 2.5 (d, 2H, Hetero –CH_2), 6.7 (m, 1H, Hetero –CH), 2.24 (m, 2H, -CH_2), 2.2 (t, 3H, -CH_3).

RESULT AND DISCUSSION

Synthesis of some Nitro and Bromo analogues of 3, 5-Diaryl Isoxazolines were achieved and their structures were confirmed on the basis of UV, IR and NMR spectral analysis.

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Synthesis and biological activities of piperazine derivatives as antimicrobial and antifungal agents

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Abstract: Apart from thiazole, benzimidazole, and tetrazole family, some of the piperazine analogs also show significant pharmacophoric activities. The synthesis of piperazine through intermediate **3** occurred via coupling of substituted benzenethiol with chloro-nitrobenzene. The nitro group of the isolated intermediate was reduced via an iron-acetic acid system. The aniline intermediate was cyclized with bis(2-chloroethyl)amine hydrochloride to obtain piperazine moiety. The synthesized substituted piperazine derivatives were screened for antibacterial and antifungal activities. The antibacterial activity was tested against *Staphylococcus aureus, Streptomyces epidermidis, Pseudomonas aeruginosa* and *Escherichia coli*, and antifungal activity was tested against *Candida albicans, Aspergillus niger, Aspergillus flavus* and *Aspergillus fumigatus*. As a result, many of the synthesized compounds showed significant antimicrobial and antifungal properties.

Keywords: Antibacterial activity; antifungal activity; piperazine derivatives. ©2017 ACG Publications. All rights reserved.

1. Introduction

Antibiotics are a class of drug that covers a wide range of pathogenic infections. Without causing any harm to the human organs or tissues, antibiotics interfere with the natural life cycle of bacteria, thus creating evolutionary pressure on them. Recently, many antibiotics-related researches have been conducted aiming at curing bacterial infections in humans. Antibiotics are now commonly used for medicinal purpose and during pre- and post-operation conditions. In critical operations involving use of oncology-based drugs, to prevent any infections, prompt antibiotic therapy is instituted.[1]

Penicillin was the first antibiotic to be discovered in 1928, followed by clinically efficient sulfonamide. After regular use of penicillin, the microbes developed resistance towards the antibiotic. Breeding of a host of penicillin-fast organisms was reported, which were transferred to other individuals leading to pneumonic conditions, because of which penicillin became ineffective.[2] Periodic supervision of these drugs has been conducted to prevent transmission of infections; however, these parameters have often been considered as a reactionary tool rather than a piece of any strategic planning and vision.[3] Hence, there is a need for a wide scope of research in finding new antibiotic molecules to overcome the bacterial infections. As the bacterium changes its nature regularly from one phase to another, studies with updated possible solutions are needed.

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To address the absence of development in the field of new anti-toxins, initially the purposes behind the hindered improvement should be comprehended. Although antibacterial and antifungal illnesses exist for long time, their clinical analysis is still difficult. Since previous two decades, various classes of antibacterial[4-10] and antifungal agents[11-17] have been found. Cotrimoxazole, Trimethoprim, sulfasalazine are few manufactured and semi-engineered antibacterial sulfa drugs. Penicillin drugs, such as Amoxicillin, Ampicillin, Penicillin G, and Cephalosporins have also been used for their bactericidal effects. Cephalosporins are known to eliminate microbes and work comparatively to penicillin. Antifungal drugs, such as Clotrimazole, Fluconazole and Amphotericin B, have been used to treat fungal infections. The most successive contagious pathogens are *Candida*, *Histoplasma*, *Stachybotrys*, *Aspergillus*, *Pneumocystis* and *Cryptococcus*, causing more than 1 million deaths globally every year. To restrict death rate, fast diagnosis and rapid execution of proper therapeutics need to be followed.[18] Due to nosocomial bloodstream infections, many deaths are reported. Majority of cases (2/3) are due to gram positive organisms and remaining due to gram negative organisms and fungi.[19]

The most common microbial infections in the hematopoietic stem cell transplant (HSCT) recipients are ~~is~~ caused by *Aspergillus*.[20] Currently, almost half of the patients suffer from invasive *aspergillosis*die, and the mortality rate for *candidemia* also remains high at approximately 50%.[21] Four classes of antifungal drugs, i.e. triazoles, polyenes, pyrimidine analogs and echinocandins, are available to treat fungal infections.[22] Increasing incidence of vancomycin-resistant *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus* have been marked as a serious menace. However, limitation to infusion-related reactions and nephrotoxicity has been exhibited by amphotericin B, an antifungal drug used to treat serious fungal illnesses.[23, 24]

Piperazines and substituted piperazines constitute an important class of pharmacophores. One of the well-known piperazine category is indinavir (trade name: Crixivan), which functions as an HIV protease inhibitor. Piperazinyl cross-linked ciprofloxacin dimers, when used against resistant bacteria strain, exhibited low antibacterial activity.[25] When piperazine derivatives were linked to benzimidazole and benzotriazole molecules, they showed antifungal activity. Similarly, piperazine derivatives, containing tetrazole nucleus, have been reported as antifungal agents.[26] The details of the scaffold synthesis included coupling reaction, which was followed by reduction of nitro group and then cyclization.[27-28] In the present study, synthesis of a series of *N*-alkyl piperazine derivatives as a new class of synthetic antimicrobial and antifungal agents is disclosed.

2. Experimental

Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plate (0.25 mm thickness) and visualized under UV light, and/or by spraying with 5% solution of phosphomolybdic acid (PMA) in ethanol, followed by charring with a heat gun. Following this, column chromatography was performed on Merck 60 silica gel (230-400 mesh). ^{1}H-NMR was recorded on Varian NMR 500 instrument at 500 MHz. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal and external standards for ^{1}H-NMR. Mass spectra were recorded on Shimadzu 2010s mass spectrometer.

2.1. Chemistry

*2.1.1. Procedure for Synthesis of **1-3***

*(2,4-Dimethylphenyl)(2-nitrophenyl)sulfane (**1**) :* To a solution of 1-chloro-2-nitrobenzene (**b**) (10.00 g, 63.47 mmol) in dry DMF (30 mL), K_2CO_3 (10.51 g, 76.16 mmol) and 2,4-dimethylbenzenethiol (9.03 mL, 66.64 mmol) were added, and the resulting reaction mixture was stirred at 25 °C for 18 h. Water (60 mL) was added and obtained mixture was stirred at 25 °C for 30 min. Yellow precipitate was then filtered off, washed with water (2 x 50 mL) and dried to afford the title compound **1** as yellow solid. Yield: 16.30 g, 99.08 %. ^{1}H NMR: ($CDCI_3$, 500 MHz) δ 8.25 (dd, *J* = 1.4, 8.2 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.32 (m, 1 H), 7.22-7.18 (m, 2H), 7.11 (m, 1H), 6.71 (dd, *J* = 1.2, 8.2 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H).

*2-((2,4-Dimethylphenyl)thio)aniline (**2**):* To a mixture of (2,4-dimethylphenyl)(2-nitrophenyl)-sulfane **(1)** (10.0 g, 38.6 mmol) and AcOH (100 mL), Fe (8.61 g, 154.4 mmol) was added, and the resulting reaction mixture was stirred at 30 °C for 16 h. The reaction mixture was then filtered through a bed of Celite, and the filtrate was concentrated. To the residue, 300 mL saturated $NaHCO_3$ and 100 mL EtOAc were added. Organic layer was separated, water layer was re-extracted with EtOAc (100 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated to afford **2** as an orange oil. Yield: 8.85 g, 99%. ^{1}H NMR: ($CDCI_3$, 500 MHz) δ 7.38 (dd, *J* = 1.5, 7.6 Hz, 1 H), 7.23 (m, 1H), 7.02 (m, 1H), 6.87 (m, 1H), 6.75-6.81 (m, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.24 (br s, 2H), 2.40 (s, 3H), 2.28 (s, 3H).

*1-(2-(2,4-Dimethylphenylthio)phenyl)piperazine (**3**):* A mixture of 2-((2,4-dimethylphenyl)thio)-aniline **(2)** (5.0 g, 21.8 mmol), bis(2-chloroethyl)amine hydrochloride (3.89 g, 21.8 mmol) and *N*, *N*-dimethylformamide (10 mL) was stirred at 110 °C for 48h. The reaction mixture was then cooled to 25 °C, the solvent was evaporated completely. Water (25 mL) and 25 mL ethyl acetate was added, and the mixture then further cooled to ~ 5°C while stirring. The formed white solid was filtered and washed with cold ethyl acetate (10 mL), and dried to afford **3** as a white powder as a HCl salt. ^{1}H NMR: ($CDCI_3$, 500 MHz) δ 7.39 (d, *J* = 7.8 Hz, 1H), 7.16 (m, 1H), 7.06-7.10 (m, 2H), 7.04 (m, 1H), 6.87 (m, 1H), 6.52 (m, 1H), 3.02-3.09 (m, 8H), 2.37 (s, 3H), 2.33 (s, 3H), 1.63 (br s, 1H, NH).

*2.1.2. Procedure for Synthesis of **4a-4p***

*2-(2-(4-(2-(2,4-Dimethylphenylthio)phenyl)piperazin-1-yl)ethoxy)ethanol (**HS-4a**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.5 g, 1.67 mmol) in DMF (5 mL) was added di-isopropyl ethyl amine (0.6 mL, 3.35 mmol) and 2-(2-chloroethoxy)ethanol (0.31 g, 2.51 mmol), which was followed by addition of potassium iodide (0.069 g, 0.41 mmol). The contents were stirred at 100 °C for 16 h. It was cooled to room temperature, water was added and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography to afford **HS-4a**, 0.23 g, 35%. IR: 3537, 3240, 3192, 3180, 3080, 3051, 3007, 2978, 2941, 2914, 2891, 2875, 2864, 2833, 2816, 2785, 2750, 2706, 2684, 25511934, 1913, 1897, 1643, 1600, 1577, 1556, 1514, 1348, 1307, 1269, 1138, 1114, 1074, 1060, 1043, 954, 923, 885, 819, 779, 761, 752, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, *J* = 9.5 Hz, 1H), 7.22 (s, 1H), 7.11-7.07 (m, 3H), 6.90-6.86 (m, 1H), 6.37 (d, *J* = 10 Hz, 1H), 4.62 (m, 1H), 3.56-3.49 (m, 4H), 3.43-3.41 (m, 2H), 2.97 (br s, 4H), 2.59-2.56 (m, 4H), 2.51 (t, *J* = 10 Hz, 2H), 2.32 (s, 3H), 2.23 (s, 3H). MS $[M+H]^+$ Calculated for $C_{22}H_{30}N_2O_2S$: *m/z* 387.21, found 387.20

*1-(4-(2-(2,4-Dimethylphenylthio)phenyl)piperazin-1-yl)-2-methylpropan-2-ol (**HS-4b**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.5 g, 1.67 mmol) in ethanol (10 mL) was added triethyl amine (0.7 mL, 5.01 mmol), which was followed by addition of 2,2-dimethyloxirane (0.31 g, 4.36 mmol) in a sealed tube. The contents were stirred at 90 °C for 6 h. The mixture was cooled to room temperature, the solvent was evaporated, water was added and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography to afford **HS-4b**, 0.4 g, 64%. IR: 3045, 2981, 2966, 1579, 1471, 1440, 1402, 1228, 1176, 1039, 960, 921, 804, 763, 754, 732 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, *J* = 9.0 Hz, 1H), 7.15-7.02(m, 4H), 6.91 (t, *J* = 9.0 Hz, 1H), 6.49 (d, *J* = 9.5 Hz, 1H), 5.20-4.80 (br s, 1H, OH), 3.84-3.78 (m, 4H), 3.36-3.09 (m, 6H), 2.35 (s, 3H), 2.28 (s, 3H), 1.48 (s, 6H). MS $[M+H]^+$ Calculated for $C_{22}H_{30}N_2OS$: *m/z* 371.22, found 371.15.

*1-(Cyclopropylmethyl)-4-(2-(2,4-dimethylphenylthio)phenyl)piperazine (**HS-4c**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.5 g, 1.67 mmol) in DMF (5 mL) was added di-isopropyl ethyl amine (0.6 mL,3.35 mmol) and (bromomethyl) cyclopropane (0.31 g, 2.51 mmol), which was followed by addition of potassium iodide (0.069 g, 0.41 mmol). The contents were stirred at 100 °C for 12 h. It was cooled to room temperature, water was added and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium

sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography to afford **HS-4c**, 0.15 g, 26%. IR: 2941, 2916, 2816, 1577, 1471, 1452, 1440, 1373, 1296, 1224, 1143, 1043, 1016, 813, 761, 750, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, *J* = 10.0 Hz, 1H), 7.14 (s, 1H), 7.10-7.01 (m, 3H), 6.85 (t, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 9.5 Hz, 1H), 3.14 (br s, 4H), 2.75 (br s, 4H), 2.36-2.32 (m, 8H), 0.98-0.88 (m, 1H), 0.55-0.53 (m, 2H), 0.15-0.14 (m, 2H). MS $[M+H]^+$ Calculated for $C_{22}H_{28}N_2S$: *m/z* 353.21, found 353.15

*1-(Cyclopentylmethyl)-4-(2-(2,4-dimethylphenylthio)phenyl)piperazine (**HS-4d**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.5 g, 1.67 mmol) in DMF (5 mL) was added di-isopropyl ethyl amine (0.6 mL,3.35 mmol) and bromomethylcyclopentane (0.41 g, 2.51 mmol), which was followed by addition of potassium iodide (0.069 g, 0.41 mmol). The contents were stirred at 100 °C for 16 h. It was cooled to room temperature, water was added and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography to afford **HS-4d**, 0.12 g, 19%. IR: 3047, 2939, 2812, 1577, 1450, 1373, 1222, 1139, 1124, 1043, 1001, 931,812, 765, 731 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, *J* = 9.5 Hz, 1H), 7.14 (s, 1H), 7.10-7.01 (m, 3H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 10 Hz, 1H), 3.10 (br s, 4H), 2.65 (br s, 4H), 2.36-2.32 (m, 8H), 2.15-2.07 (m, 1H), 1.85-1.75 (m, 2H), 1.68-1.49 (m, 4H), 1.28-1.18 (m, 2H). MS $[M+H]^+$ Calculated for $C_{24}H_{32}N_2S$**: m/z** 381.24, found 381.30

*2.1.3. General procedure for the synthesis of **4e,4f,4g,4k, 4l, 4m, 4n, 4o,4p***

To a solution of 1-(2-(2,4-Dimethylphenylthio)phenyl)piperazine (1 eq) in dry THF (10 mL) was added sodium hydride (2 eq) at 0 °C. The reaction mixture was stirred at the same temperature for 20 min, and then alkyl halide (1.5 eq) was added. The contents were stirred at room temperature for 4 h. The reaction was quenched using ice-water and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography.

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-methylpiperazine (**HS-4e**):* Yield: 0.03 g, 19%. IR: 2933, 2829, 2787, 1579, 1471, 1440, 1369, 1288, 1230, 1145, 1008, 923, 813, 763, 734 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, *J* = 9.5 Hz, 1H), 7.15 (s, 1H), 7.10-7.01 (m, 3H), 6.84 (m, 1H), 6.51 (d, *J* = 10.0 Hz, 1H), 3.12 (br s, 4H), 2.65 (br s, 4H), 2.39 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H). MS $[M+H]^+$ Calculated for $C_{19}H_{24}N_2S$: *m/z* 313.17, found 313.19

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-ethylpiperazine (**HS-4f**):* Yield: 0.2 g, 46%. IR: 2970, 2954, 2810, 2762, 1577, 1471, 1448, 1436, 1375, 1303, 1224, 1147, 1126, 1043, 1029, 952, 813, 752, 731 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, *J* = 7.0 Hz, 1H), 7.16 (s, 1H), 7.09-7.03 (m, 3H), 6.86-6.87 (m, 1H), 6.51(d, *J* = 7.5 Hz, 1H), 3.14 (br s, 4H), 2.68 (br s, 4H), 2.52 (q, *J* = 6.0 Hz, 2H), 2.37 (s, 3H), 2.33 (s, 3H), 1.16 (t, *J* = 6.0 Hz, 3H). MS $[M+H]^+$ Calculated for $C_{20}H_{26}N_2S$: *m/z* 327.19, found 327.10

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-isopropylpiperazine (**HS-4g**):* Yield: 0.16 g, 35%. IR: 2960, 2918, 2816, 1577, 1448, 1438, 1377, 1328, 1224, 1145, 1043, 979, 765, 754, 731 Cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, *J* = 10.0 Hz, 1H), 7.16 (s, 1H), 7.11-7.03 (m, 3H), 6.88-6.85(m, 1H), 6.51 (d, *J* = 9.0 Hz, 1H), 3.16 (br s, 4H), 2.82-2.73 (m, 5H), 2.37 (s, 3H), 2.33 (s, 3H), 1.13 (d, *J* = 8.5 Hz, 6H). MS $[M+H]^+$ Calculated for $C_{21}H_{28}N_2S$: *m/z* 341.21, found 341.20

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-(2-(trifluoromethyl)benzyl)piperazine (**HS-4k**):* Yield: 0.38 g, 62%. IR: 2951, 2808, 1577, 1469, 1456, 1373, 1355, 1311, 1220, 1170, 1111, 1058, 1010, 929, 817, 763, 748, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.83 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 9.5 Hz, 1H), 7.52-7.49 (m, 1H), 7.36-7.29 (m, 2H), 7.12 (s, 1H), 7.05-6.99 (m, 3H), 6.82-6.81 (m, 1H), 6.48 (d, *J* = 10.0 Hz, 1H), 3.73 (s, 2H), 3.09 (br s, 4H), 2.67 (br s, 4H), 2.33 (s, 3H), 2.28 (s, 3H). MS $[M+H]^+$ Calculated for $C_{26}H_{27}F_3N_2S$: *m/z* 457.19, found 457.36

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-(2-fluorobenzyl)piperazine (**HS-4l**):* Yield: 0.31 g, 57%. IR: 2956, 2812, 1579, 1489, 1471, 1454, 1442, 1348, 1271, 1224, 1139, 1120, 1043, 1002, 941, 931, 815, 729.cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.44-7.36 (m, 2H), 7.25-7.24 (m, 1H), 7.14-7.01 (m, 6H), 6.87-6.83 (m, 1H), 6.50 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 2H), 3.11 (br s, 4H), 2.71 (br s, 4H), 2.36 (s, 3H), 2.31 (s, 3H). MS $[M+H]^+$ Calculated for $C_{25}H_{27}FN_2S$: *m/z* 407.20, found 407.25

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-(4-nitrobenzyl)piperazine (**HS-4m**):* Yield: 0.21 g, 36%. IR: 2933, 2816, 1595, 1579, 1514, 1344, 1222, 1138, 1043, 1010, 943, 921, 850, 835, 763, 736 Cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.19 (d, *J* = 11.0 Hz, 2H), 7.56 (d, *J* = 10.5 Hz, 2H), 7.37 (d, *J* = 10.0 Hz, 1H), 7.14 (s, 1H), 7.07-7.01 (m, 3H), 6.87-6.83 (m, 1H), 6.49 (d, *J* = 9.5 Hz, 1H), 3.68 (s, 2H), 3.11 (br s, 4H), 2.67 (br s, 4H), 2.35 (s, 3H), 2.30 (s, 3H). MS $[M+H]^+$ Calculated for $C_{25}H_{27}N_3O_2S$: *m/z* 434.19, found 434.26.

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-(4-methylbenzyl)piperazine (**HS-4n**):* Yield: 0.32 g, 59%. IR: 2953, 2814, 1579, 1469, 1450, 1438, 1224, 1139, 1124, 1043, 1043, 1008, 815, 750 Cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, *J* = 9.0 Hz, 1H), 7.25-7.23 (d, *J* = 9.5 Hz, 2H), 7.14-7.13 (m, 3H), 7.05-7.00 (m, 3H), 6.84-6.81(m, 1H), 6.48 (d, *J* = 9.5 Hz, 1H), 3.55 (s, 2H), 3.09 (br s, 4H), 2.64 (br s, 4H), 2.35 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H). MS $[M+H]^+$ Calculated for $C_{26}H_{30}N_2S$: *m/z* 403.22, found 403.29.

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-(3-methylbenzyl)piperazine (**HS-4o**):* Yield: 0.38 g, 70%. IR: 2943, 2814, 1579, 1471, 1452, 1373, 1338, 1222, 1139, 1124, 1043, 1010, 929, 813, 761, 752, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, *J* = 9.5 Hz, 1H), 7.25-7.15 (m, 4H), 7.10-7.02 (m, 4H), 6.87-6.83 (m, 1H), 6.50 (d, *J* = 10.0 Hz, 1H), 3.57 (s, 2H), 3.12 (br s, 4H), 2.68 (br s, 4H), 2.37 (s, 6H), 2.32 (s, 3H). MS $[M+H]^+$ Calculated for $C_{26}H_{30}N_2S$: *m/z* 403.22, found 403.35.

*1-(4-Chlorobenzyl)-4-(2-(2,4-dimethylphenylthio)phenyl)piperazine (**HS-4p**):* Yield: 0.32 g, 56%. IR: 3066, 2926, 2821, 1575, 1469, 1220, 1138, 1043, 1008, 817, 798, 763, 729, 688 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, *J* = 10.0 Hz, 1H), 7.33-7.31 (m, 4H), 7.16-7.14 (m, 1H), 7.07 (d, *J* = 5.0 Hz, 2H), 7.05-7.02 (m, 1H), 6.89-6.84 (m, 1H), 6.51 (d, *J* = 9.5 Hz, 1H), 3.57 (s, 2H), 3.11 (br s, 4H), 2.66 (br s, 4H), 2.37 (s, 3H), 2.32 (s, 3H). MS $[M+H]^+$ Calculated for $C_{25}H_{27}ClN_2S$: *m/z* 423.17, found 423.27.

*1-(2-Chloroethyl)-4-(2-(2,4-dimethylphenylthio)phenyl)piperazine (**HS-4h**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.4 g, 1.34 mmol) in dry DMF (10 mL) was added potassium carbonate (K_2CO_3) (0.54 g, 4.02 mmol) and 1-bromo-2-chloroethane (0.22 g, 1.60 mmol). The reaction mixture was stirred at the same temperature for 16 h and the reaction was quenched using water and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography. Yield: 0.048 g, 10%. IR: 2943, 2816, 1579, 1454, 1373, 1224, 1139, 1124, 1043, 1006, 929, 813, 758, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, *J* = 9.5 Hz, 1H), 7.16 (s, 1H), 7.08-7.02 (m, 3H), 6.90-6.82 (m, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 3.66 (m, 2H), 3.13 (br s, 4H), 2.84 (m, 2H), 2.75 (br s, 4H), 2.37 (s, 3H), 2.33 (s, 3H). MS $[M+H]^+$ Calculated for $C_{20}H_{25}ClN_2S$: *m/z* 361.15, found 361.15.

*2-(4-(2-(2,4-Dimethylphenylthio)phenyl)piperazin-1-yl)ethanol (**HS-4i**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.35 g, 1.17 mmol) in dry acetone(10 mL) was added triethyl amine (0.23 mL, 1.17 mmol), which was followed by addition of 2-iodoethanol (0.09 mL, 1.17 mmol). The contents were stirred at room temperature for 6 h. The solvent was evaporated, water was added and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography to afford **HS-4I.** Yield: 0.05g, 12%. IR: 2914, 2818, 1579, 1469, 1454, 1438, 1311, 1224, 1126, 1043, 952, 813, 761, 750, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.37(d, *J* = 7.0 Hz, 1H), 7.17(s, 1H), 7.11-7.03 (m, 3H), 6.92-6.88 (m, 1H), 6.52 (d, *J* = 9.5

Hz, 1H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.33-3.31 (m, 4H), 3.06 (m, 5H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.37 (s, 3H), 2.32 (s, 3H). MS $[M+H]^+$ Calculated for $C_{20}H_{26}N_2OS$: *m/z* 343.18, found 343.20.

*1-(2-(2,4-Dimethylphenylthio)phenyl)-4-propylpiperazine (**HS-4j**):* To a solution of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (0.4 g, 1.34 mmol) in dry acetone (10 mL) was added triethyl amine (0.19 mL, 1.34 mmol) followed by addition of 1-bromopropane (0.16g, 1.34 mmol). The contents were stirred at room temperature for 6 h. The solvent was evaporated, water was added and extracted with ethyl acetate. Brine washing was performed with the organic layer, which was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by column chromatography to afford **HS-4j.** Yield: 0.26 g, 65%. IR: 2956, 2812, 1579, 1471, 1373, 1224, 1147, 1122, 1043, 1008, 931, 813, 761, 750, 729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, *J* = 9.5 Hz, 1H), 7.14 (s, 1H), 7.07-7.01 (m, 3H), 6.86-6.82 (m, 1H), 6.49 (d, *J* = 10.0 Hz, 1H), 3.11 (br s, 4H), 2.66 (br s, 4H), 2.41-2.35 (m, 5H), 2.31 (s, 3H), 1.61-1.52 (m, 2H), 0.93 (t, *J* = 9.0 Hz, 3H). MS $[M+H]^+$ Calculated for $C_{21}H_{28}N_2S$: *m/z* 341.21, found 341.25.

2.2. Biologigal Assay to Determine Antibacterial Activity

The final compounds (**4a-4p**) were tested for antibacterial and antifungal activities. The antibacterial activity was screened against Gram-positive bacteria, such as *Staphylococcus aureus and Streptomyces epidermidis*, and the Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Escherichiacoli*, in the agar disc diffusion method. The sample preparation was conducted by dissolving 1 mg of each sample in 1 ml of dimethyl sulphoxide (DMSO). For diffusion test against microbes, the agar plates were prepared by using agar solid medium. The media was poured into sterilized Petri dishes. The Petri dishes were then cooled for solidification. Then, a uniform mixture of inoculate was introduced to every Petri dish. The sterilized paper discs were loaded with samples of 1 mg/ml concentration and incubated at 37 °C. In successful reactions, clear zones of inhibition appeared around the discs. Ampicillin (19-21 mm, zone of inhibition) was used as a standard.

2.3. Biological Assay to Determine Antifungal Activity

Stock culture was prepared by transferring a loopful of fungal strain into the sterilized solid lipid micro-particles (SLM) with 25 ± 1°C incubation period for 48 h and 7 days for *Candida albicans*and *Aspergillus* species (*A. Niger, A. Fumigatus* and *A. flavus*), respectively. The stock was further sub-cultured by repeating the process mentioned above. *C. albicans* culture was harvested and diluted with the sterilized saline solution to obtain the spore count of about 1×10^7 CFU/mL. In the same manner, *Aspergillus* species cultures were harvested and the spore count was adjusted to about 1×10^7 CFU/mL with a sterilized saline solution. For inoculation of the culture, 0.1 mL of this saline solution consisting of fungal strain was used.[29-31]

2.3.1. Determination of the MIC range

A set of seven sterilized culture tubes were taken, and 1.0 mL of sterilized double strength Sabouraud liquid medium (DSSLM) was transferred aseptically to Tube I and 1.0 mL of sterilized nutrient broth was transferred aseptically to the remaining six tubes. Different concentrations of all the compounds to be tested, including the standard drug, were prepared by serial dilution method to obtain the drug concentration of 5.0 μg/mL, 2.5 μg/mL, … 0.078125 (0.08) μg/mL in Tube I to Tube VII, respectively. A control tube was also prepared by aseptically transferring 0.5 mL of sterilized DSSLM and 0.5 mL of solvent (DMSO). The culture tubes were inoculated with0.1 mL of fungal culture in a sterilized saline solution having microbial count of about 1 × 107 CFU/mL, so that the final microbial count in each culture tube would be about 1 × 106 CFU/mL. The tubes were incubated for 48 h at 25 ± 1°C. To check the turbidity, tubes were monitored under the microscope. The lower and higher concentrations gave the MIC range for the compound.[32,33]

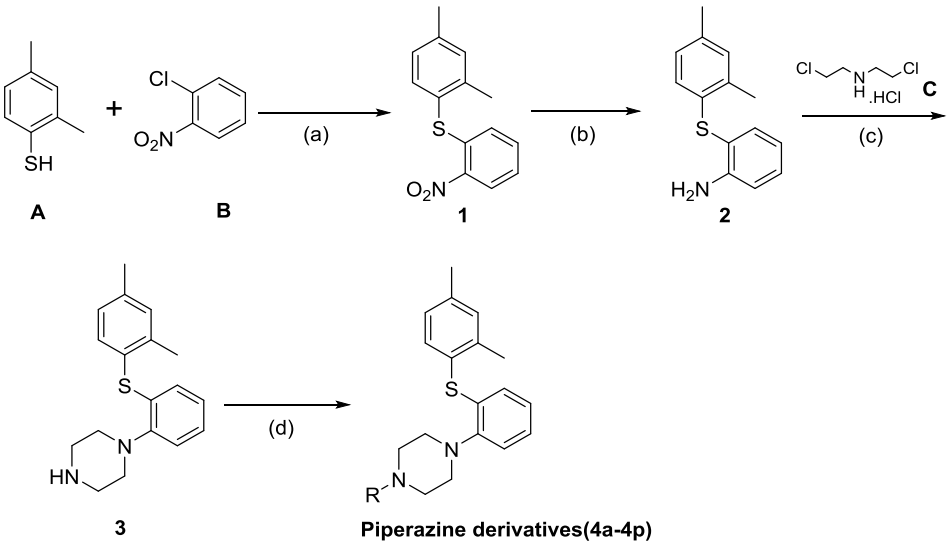
3. Results and Discussion

3.1. Chemistry

Earlier, the antimicrobial ativities of piperazine dithiocarbonate derivatives were investigated.[33] The synthesized compounds had more potency to inhibit gram-negative bacteria than gram positive ones. Among the bacterial strains, *E. faecalis* (ATCC 51922) and *P. aeruginosa* (ATCC 27853) were found to be the most susceptible ones. Few final compounds (**6a-d**) including alkyl groups in their structure displayed the same potency like that of Chloramphenicol against *E. faecalis* (ATCC 51922).

1-Chloro-2-nitrobenzene and 2,4-dimethylbenzenethiol were used as starting materials for the synthesis of piperazine derivatives. Addition[23] of 1.1 eq. of 2,4-dimethylbenzenethiol (**A**) to 1-chloro-2-nitrobenzene (**B**) in the presence of potassium carbonate (K_2CO_3) in *N*,*N*-dimethylformamide for 18 h afforded (2,4-Dimethylphenyl)(2-nitrophenyl)sulfane (**1**) in good yield (99%). The nitro group of compound (**1**) was reduced in the presence of iron in acetic acid for 16 h at room temperature to give 2-((2,4-Dimethylphenyl)thio)aniline (**2**), which was cyclized using bis(2-chloroethyl)amine hydrochloride in *N*, *N*-dimethylformamide at 110 ℃ for 48 h. Structures of the compounds were explained on the basis of spectral data and comparison with their authentic samples (**3**).

The reaction of compound (**3**) with alcohol, oxirane, cyclic alkyl halide, alkyl halides and various substituted benzyl halides yielded piperazine analogs (**4a-4p**) (Scheme 1).



Scheme 1. Synthesis of compounds **4a-4p.** a) A, B, K_2CO_3, DMF, 25°C, 18h b) Fe, AcOH, 30°C, 16h c) bis(2-chloroethyl)amine hydrochloride, DMF, 110°C, 48h d) Base, RX, solvent, 0-100°C, 4-16h.

Coupling reaction of (**3**) with different alkylating agents in the presence of base, such as sodium hydride, triethyl amine, di-isopropyl ethylamine, potassium carbonate, etc. also yielded the piperazine analogs. The products were separated on a silica gel column chromatography eluting with hexane/ethyl acetate. After the separation, structures of the compounds were determined by nuclear magnetic resonance (NMR), infrared (IR) and liquid chromatography/mass spectrometry (LCMS) studies. It was observed ~~seen~~ that the isolated products had high purity. Disappearance of a broad singlet at 1.63 ppm (piperazine NH) confirmed the coupling reaction yielding the desired products. The piperazine proton abstraction by base and nitrogen attak to the halide produced the final compounds. In piperazine, four CH_2 (8 protons) ranging from 3.02-3.09 confirmed the new product formation. Moreover, IR and LCMS data also confirmed the formation of the new compounds **4a-4p**.

3.2. Biological assay

3.2.1. In vitro Antibacterial Activity

All the isolated compounds were tested for their antibacterial activities against *Staphylococcus aureus, Streptomyces epidermidis, Pseudomonas aeruginosa* and *Escherichia coli* by agar disc diffusion method. For testing, the bacteria were obtained from agar slants. Loopful samples were grown in sterile nutrient broth medium, autoclaved at 121 °C at 15 atm for 15 min and left to grow for 48 h at 37 °C in an incubator. Ampicillin was used as reference drug for bacteria. The compound was tested at the concentration of 1 mg/mL, using DMSO as a solvent. From screening result, it was observed that most of the compounds were highly active against bacterial pathogens as well as fungus. The zone of inhibition (mm) of the final compounds against pathogenic bacterial strains is shown in Table 1.

Table 1. Antibacterial activity of newly synthesized piperazine derivatives

Compounds	***S.aureus***	***S.epidermidis***	***P.aeruginosa***	***E. Coli***
HS-4a	20	19	15	16
HS-4b	17	17	20	18
HS-4c	21	18	14	20
HS-4d	15	20	18	19
HS-4e	20	17	18	20
HS-4f	20	19	15	16
HS-4g	20	17	07	18
HS-4h	21	18	14	20
HS-4i	15	20	18	19
HS-4j	20	17	18	20
HS-4k	20	19	15	16
HS-4l	17	17	20	18
HS-4m	04	18	14	18
HS-4n	15	20	13	19
HS-4o	20	17	18	20
HS-4p	15	17	18	20
Ampicillin*	21	20	19	20

*Positive control

In general, while most of the final compounds showed better antibacterial activities, the compounds **4g** and **4m** showed moderate antibacterial activities against *P. aeruginosa and S. aureus,* respectively. 1-(2-(2,4-dimethylphenylthio)phenyl)-4-methylpiperazine (**4e)**, 1-(2-(2,4-dimethylphenylthio)phenyl)-4-propylpiperazine **(4j)**, and 1-(2-(2,4-dimethylphenylthio) phenyl)-4-(3-methylbenzyl)piperazine (**4o)** had the best antibacterial activity against pathogenic bacterial strains with a zone of inhibition in the range of 17-20 mm. The other compounds also showed good activities, except **4g** and **4m**.

3.2.2. In vitro Antifungal Activity

Antifungal activities of the newly derived piperazine derivatives were screened against pathogenic fungal strains, such as *Candida albicans, Aspergillus niger, Aspergillus flavus* and *Aspergillus fumigates* where Clotrimazol was used as the standard drug. Antifungal activities of the final compounds were conducted by using two-fold serial dilution methods. Stock solutions of the final compounds and the standard drug having the concentration 10 μg/mL were prepared in dimethyl sulfoxide (DMSO). The required dilutions were made from these stock solutions. The MIC (μg/mL) of the screened compounds by pathogenic fungi is shown in Table 2.

Table 2. Antifungal activity of newly synthesized piperazine derivatives*

Compounds	*C. albicans*	*A. niger*	*A. flavus*	*A.Fumigatus*
HS-4a	0.60	0.50	0.45	0.60
HS-4b	0.55	0.60	0.50	0.60
HS-4c	0.50	0.60	0.60	0.50
HS-4d	0.60	0.50	0.50	0.60
HS-4e	0.50	0.35	0.60	0.40
HS-4f	0.50	0.50	0.45	0.60
HS-4g	0.55	0.60	0.50	0.55
HS-4h	-	0.40	0.60	0.50
HS-4i	0.60	0.50	0.50	0.60
HS-4j	0.30	0.50	0.45	0.60
HS-4k	0.55	0.60	-	-
HS-4l	-	0.30	0.60	0.50
HS-4m	0.60	0.50	0.45	0.60
HS-4n	0.55	0.60	0.50	0.60
HS-4o	0.50	0.30	0.60	0.40
HS-4p	0.30	-	0.45	0.60
Clotrimazole$^{\phi}$	0.10	0.30	0.30	0.30

*MIC values are given as μg/mL; $^{\phi}$Positive control.

While most of the synthesized compounds showed significant antifungal activities, the compounds **4h, 4k, 4l, and 4p** showed moderate antifungal activities. The compounds **4a, 4b, 4c, 4d, 4e, 4f, 4g, 4i, 4j, 4m,** and **4n** showed better activities against *C. albicans* and *Aspergillus*. All the compounds having better activities had MIC values ranging between 0.35-0.6 μg/mL. The activities of piperazine derivatives were observed due to the alkylation of piperazine derivatives. So, Considering overall activities of the compounds **4a**, **4b**, **4e**, **4j** and **4o**, they had good antibacterial and antifungal activities.

4. Conclusion

Novel 1-(2-(2,4-Dimethylphenylthio)phenyl)-4-piperazine derivatives (**4a-4p**) were obtained through the reaction of 1-(2-(2,4-dimethylphenylthio)phenyl)piperazine (**3**) with alcohols, alkyl halides and substituted aromatic benzyl halides in presence of suitable base. The structures of the obtained compounds were characterized using conventional spectroscopic methods (NMR, IR, LCMS). The compounds (**4a-4p**) were tested for their antibacterial and antifungal activities, which showed both antibacterial as well as antifungal activities. From the screening results, it was observed that the compounds **4a, 4b, 4c, 4d, 4f, 4i, 4j** and **4o** were found to have high activity against both Gram-positive and Gram-negative bacteria and fungi, while the other compounds possessed week to modern activities. Compounds **4a, 4b, 4e, 4j** and **4o** showed maximum zone of inhibition. Thus, the compounds **4a**, **4b**, **4e**, **4j** and **4o** could be used for the antibacterial and antifungal appliations.

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PyDescriptor: A new PyMOL plugin for calculating thousands of easily understandable molecular descriptors

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ABSTRACT

The field of Quantitative Structure-Activity Relationship (QSAR) relies heavily on molecular descriptors. Among various guidelines suggested by Organisation for Economic Co-operation and Development (OECD), a very important guideline demands the mechanistic interpretation of a QSAR model. For this, a very attractive idea is to build a QSAR model using easily understandable molecular descriptors. To address this important issue, in the present work, we present an innovative chem-informatics tool, *PyDescriptor*. It can calculate a diverse pool of 11,145 molecular descriptors comprising easily understandable 1D- to 3D- descriptors encoding pharmacophoric patterns, atomic fragments and a variety of fingerprints. It is a new Python based plugin implemented within the commonly used visualization software PyMOL. *PyDescriptor* has several advantages like easy to install, open source, works on all major platforms (Windows, Linux, MacOS), easy to use through graphical user interface (GUI) and command-line, and output is saved in comma separated values (CSV) file format for further QSAR procedure. The plugin is freely available for academia.

1. Introduction

Computer Aided Drug Designing (CADD) has advanced with innovations in its thriving branches viz. Quantitative Structure-Activity Relationship (QSAR), molecular docking, pharmacophore modelling. The field of QSAR is among the oldest branches of CADD with its emphasis on prediction of activity/property (quantitative QSAR) and determination of pharmacophoric features or mechanistic interpretation (qualitative QSAR) [1–4].

Structure drawing and optimization, molecular descriptor calculations, model building and model validation are four basic steps of a typical QSAR analysis [5–8]. Molecular descriptors, which are used to represent the structural features in terms of numbers, encode valuable information about structure or patterns in the molecular structures [9–16].

Molecular descriptors have occupied unique place in chemistry, pharmaceutical sciences, quality control, etc. to provide valuable representation of molecular features in numerical and computational form for further evaluations [9–18]. With the progress of QSAR field, the types of descriptors have changed from simple and easily interpretative like number of carbon atoms, number of nitrogen atoms, log*P*, etc. to very complex descriptors like WHIM, BCUT, 3D-MoRSE, RDF, GETAWAY, and others [17,18]. These molecular descriptors are mostly classified as 1D-, 2D- and 3D- descriptors. The 1D- molecular descriptors represent bulk properties of compounds, such as the number of particular atoms, molecular weight, etc., and can be computed using molecular formula. 2D-molecular descriptors characterize structural information that can be calculated from 2D- structure of a molecule, such as the number of rings, the number of hydrogen bond acceptors, etc. 3D- molecular descriptors stand for structural information that has to be obtained from 3D- structure of a molecule, such as solvent accessible surface area with negative partial charge in the structure [17,18].

Manual calculation of descriptors like 3D-MoRSE, WHIM, BCUT, and similar complex (or esoteric [5]) descriptors was a very time consuming and laborious process [1,9–12,15,16]. To overcome this difficulty, computer programs were developed for computing descriptors either as independent software or as a part of QSAR software. The rapid developments in the field of computers and algorithms have made exact and

Abbreviations: OECD, Organisation for Economic Co-operation and Development; WHO, World health organisation; ADMET, Absorption, Distribution, Metabolism, Excretion and Toxicity; OLS, Ordinary Least Square; QSARINS-Chem, QSAR Insubria-Chemistry; GA, Genetic algorithm; MLR, Multiple linear Regression; OFS, Objective Feature Selection; SFS, Subjective Feature Selection; MMFF94, Molecular Mechanics Force Field 94; MAE, mean Absolute Error; CCC, Concordance Correlation Coefficient.

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precise calculations of theoretical molecular descriptors possible in shorter time and cost-effective [1,9–12,15,16]. At present, there are many free and commercial softwares like Dragon (Talete) [17,18], PaDEL [19], MOE [20], Schrodinger [21], ChemDes [22], etc. which can calculate a variety of molecular descriptors viz. 1D- to 3D-, constitutional, topological, fingerprints. Some of these have been developed exclusively for the calculation of molecular descriptors only such as PaDEL-Descriptor [19], ChemDes [22], etc. while others are QSAR softwares which have descriptor calculation as one of their features (e.g., CODESSA Pro [23], Accelrys Discovery Studio [24], Sybyl-x [25], MOE [20]). Also, there are some open source libraries, such as JOELib [26,27], Chemistry Development Kit [28], and Chemical Descriptors Library [29], to name a few, which have molecular descriptor calculation functionality. It is reasonable that a good descriptor calculation software should have following features [19]:

1. Free or low-priced so that it is easy to purchase it.
2. Open source so that researchers could introduce their specific molecular descriptor calculations.
3. Has an easy to use graphical user interface (GUI).
4. Independent of operating system.
5. Possibly processes different molecular file formats like mol2, mol, sdf, etc.
6. Ability to compute numerous types of molecular descriptors.

A careful analysis of various currently available molecular descriptor calculating softwares reveals that many softwares lack one or more above mentioned features, besides, having its own advantages and limitations. An important area of research in the field of molecular descriptors is introduction of new descriptors or improvements in existing descriptors with easy correlation in terms of structural and pharmacophoric patterns [1,10–16,22,28,29]. Therefore, the field of molecular descriptors is dynamic and open for future developments like introduction of new softwares with ease of use and better user control functionalities, new descriptors with enhanced abilities to capture structural features [1,10–16,22,28,29].

Among various guidelines suggested by Organisation for Economic Co-operation and Development (OECD), a very important guideline demands the mechanistic interpretation of a QSAR model. For this, a very attractive idea is to build a QSAR model using easily understandable molecular descriptors. Unfortunately, the physical correlation of esoteric descriptors like WHIM, GETAWAY, RDF, etc. with one or more structural features/patterns is very complicated and an active area of qualitative and quantitative QSAR [5]. Therefore, there is need for introduction of easily understandable molecular descriptors. In the present work, we present a new PyMOL plugin, *PyDescriptor*, which has capacity to calculate 11,145 easily understandable molecular descriptors. It is a new chem-informatics tool which transforms a variety of structural features and local environment of a molecule to understandable 1D- to 3D- descriptors, which include encoding pharmacophoric patterns, atom-centred descriptors and a variety of fingerprints. These descriptors are either available in costly commercial softwares or in operating system dependent free softwares, thereby restricting their wide use. *PyDescriptor* possesses many advantageous features and plethora molecular descriptors, which justify its usefulness and wide acceptance in the field of QSAR and allied areas.

2. Experimental details

2.1. Plugin design and availability

PyDescriptor has been written in the object-orientated programming language Python 2.7.10 (64 bit) as a plugin for the three-dimensional molecular viewer PyMOL 1.8.2 and higher versions (Schrödinger, LLC. http://www.pymol.org/). Therefore, the advantages and limitations of Python 2.7.10 and PyMOL are associated with this plugin also. PyMOL is a widely-used software proficient in rendering and ray-tracing high resolution molecular representations in publication quality [30]. Due to availability of an open-source version of PyMOL, it is an attractive choice for academic and educational use [30]. Apart from visualizations of molecular structures, PyMOL has emerged as a calculation software due to availability of different open source plugins for a variety of purposes for example APBS for electrostatic map calculation, CAVER for calculation and visualization of tunnels, MIPTOOL for LogP calculation, DYNAMICS for molecular dynamic simulations with Gromacs, a few to mention [30]. In addition, LIQUID is an open source plugin for PyMOL, which is capable of generating pharmacophore model for a molecule. The output of LIQUID is available in the form of spheres and ellipsoids in the 3D- viewer of PyMOL [31]. Though, *PyDescriptor* uses the framework of PyMOL, it has been fully coded by our group. Practical information, such as a user guide/manual and application notes, along with the plugin '*PyDescriptor*', are available free of charge from authors.

2.2. System requirements and installation

In order to use *PyDescriptor*, a working installation of PyMOL version ≥1.8.2 on a standard Linux or Windows or MacOS installations with Python 2.7.10 is essential. *PyDescriptor* can be used without any dependencies i.e. there is no need to install any other module or software. At present, the plugin has been built to use MOL2 file format containing single molecule only. MOL2 format has the benefit of storing all the essential information for atom type, position, partial charges, and connectivity. In addition, it is also a well-known standardized format that many programs can read. It is one of the few public formats capable of supporting both a chemically-accurate description of small organic molecules as well as protein or nucleic acid also. Other formats for representing molecular structure have to be converted to an MOL2 file format for use in *PyDescriptor*. For this purpose, users can use open-source programs (e.g. Open babel, Avogadro) to convert other file formats into MOL2 format. While using MOL2 file format, all atom-typing and atomic partial charges assignments need to be performed correctly with all hydrogen atoms added. After successful completion of the descriptor calculations, the molecular descriptor values are automatically saved in CSV file format.

2.3. Parsing and calculations

PyDescriptor performs the main task of reading the MOL2 files and calculating the molecular descriptor value for all the MOL2 files located in the folder (for windows users, C:\PyDescriptor). As shown in Fig. 1, when the user clicks 'Compute descriptors', the plugin executes the calculation of molecular descriptors. The values for all the molecular descriptors are entered and automatically saved iteratively into the CSV columns along with the name of MOL2 file in the first column.

The following set of codes is used to read MOL2 files:

```
import os, glob, csv, pymol
os.chdir('C:\PyDescriptor')
from pymol import cmd, stored, util
path = os.path.dirname(pymol.__script__)
cmd.delete('all')
mol_files = glob.glob(os.path.join(path, '*.mol2'))
```

***PyDescriptor* Protocol:**

- Read all the MOL2 files from a particular folder (for windows users, C:\PyDescriptor)
- Calculate the molecular descriptors for all the molecules in the given folder
- Read the name of the files and enter in the CSV file together with their corresponding descriptor values

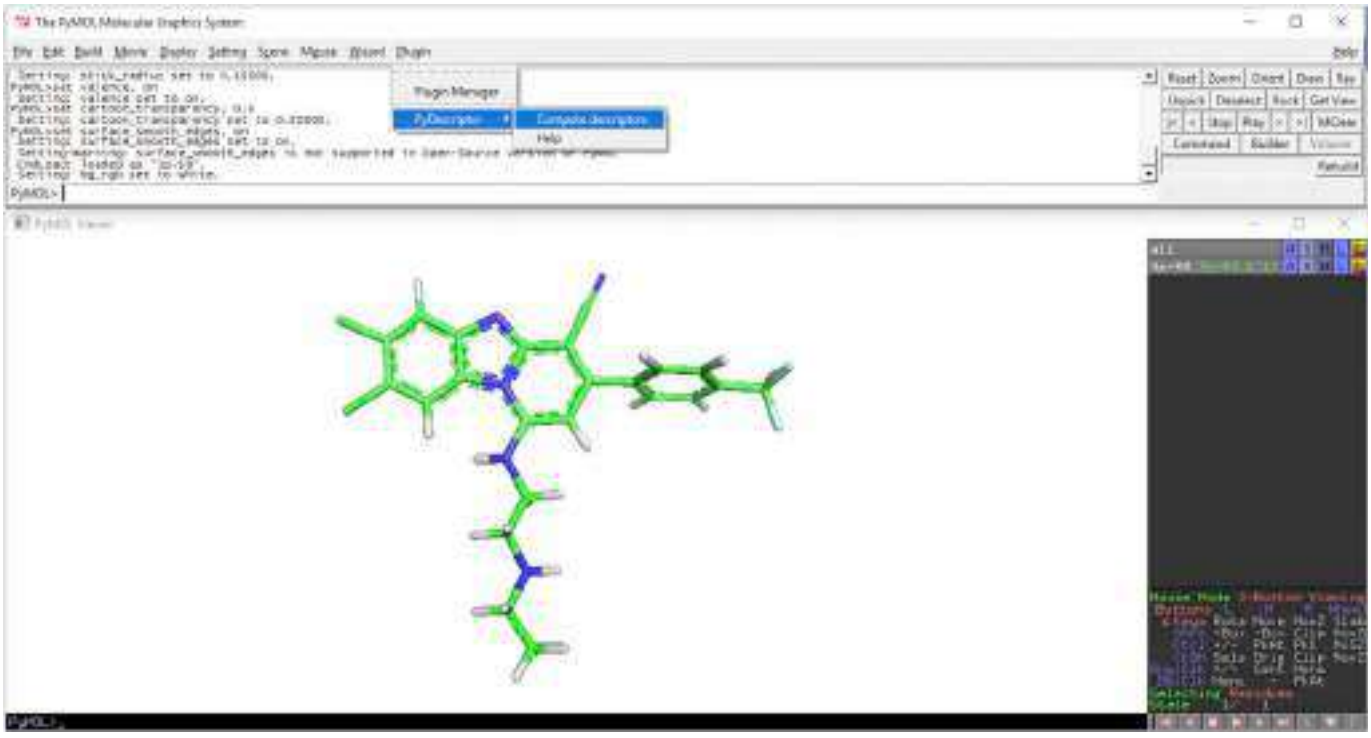


Fig. 1. GUI for *PyDescriptor* plugin loaded with a 3D molecule.

2.3.1. Descriptors calculation speed experiments

A straightforward comparison of the descriptor calculation speed of different softwares in a strict way is hard as the number and types of descriptors calculated by each software are different [19]. Therefore, all experiments for calculating the speed of descriptor calculations were accomplished only for *PyDescriptor* using Windows 7 (64 bit) on two different computers with varying architectures. Each experiment was repeated five times and the average of the total time needed to complete the calculation has been reported. Python's "timeit" module was employed for the measurement of calculation time. The details of computers and data set are as following:

1. Computer-1: Windows 7 (64 bit) operating system installed on a Lenovo G560 system with Intel® Pentium® P6100 2.00 GHz processor with 3 GB RAM.

2. Computer-2: Windows 7 (64 bit) operating system installed on a Dell system with Intel i7 2.00 GHz processor with 8 GB RAM.

Data set: The data set contains a diverse set of 1290 molecules as reported by Xu et al. [32]. The data set was converted from the SMILES flat file representation to individual MOL2 file using OpenBabel 2.4.0 using MMFF94 for structure optimization.

2.3.2. Derivation of interpretable QSAR

As the present plugin calculates 11,145 molecular descriptors, a very logical question can arise about the possibility of using these descriptors for developing scientifically interesting new, better and interpretable models as well as about the diversity of pool of descriptors calculated by *PyDescriptor*.

In majority of situations, a small dataset is available to a QSAR researcher for building the models. Hence, to address these issues, new QSAR models were built and statistically compared for two datasets of small size using the molecular descriptors calculated by *PyDescriptor*.

Dataset 1. It comprises a small dataset of sixty phosphoramidate and phosphorothioamidate analogues of amiprophos methyl reported as antimalarial [33].

Dataset 2. This dataset encompasses ninety-seven substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates exhibiting antiproliferative activity [4].

2.3.3. Procedure for QSAR model development

For QSAR model development, OECD guidelines were followed to ensure internal and external predictive ability with mechanistic interpretation. The procedure mentioned in development of QSAR model for dataset 1 and 2 has been followed to assure reproducibility of results and fair comparison [4,33]. That is, the training and prediction sets were kept identical with the training and prediction sets as in the respective original publication [4,33]. In addition, statistically robust multiple QSAR models were also developed by changing the composition of training and prediction sets. These multiple models are available in supporting information. In general, the structures were drawn and optimized using MMFF94, followed by calculation of molecular descriptors using PaDEL, e-Dragon and *PyDescriptor*. The next step comprises elimination of highly correlated ($|R| > 0.90$) and constant variables (>95%). Subjective feature selection was used to build the statistically robust OLS QSAR models using genetic algorithm (GA) in QSARINS-Chem 2.2.1 [34,35] using Q^2_{LOO} as the fitness function. The exhaustive search of optimum number and set of descriptors was performed till there was improvement in the value of Q^2_{LOO}. Th e GA module of QSARINS-Chem 2.2.1 does not require a prior knowledge of important descriptors, that is, an important descriptor may or may not be in the final QSAR model [34,35]. Exhaustive internal as well as external validation along with Y-scrambling and analysis of Applicability Domain (AD) by Williams plot [34,35] for all the developed models were performed using QSARINS-Chem 2.2.1 to reject over-fitting and spurious models. Various parameters for internal and external validation includes: determination coefficient R^2, leave-one-out (LOO) cross-validation Q^2, leave-many-out (LMO) Q^2_{LMO}, coefficient of determination for Y-scrambling R^2_{Yscr}, root mean squared error (RMSE), $RMSE_{ex}$, MAE_{ex}, R^2_{ex}, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, and CCC_{ex}. The mean value of Q^2_{LMO} has been reported.

3. Results and discussion

Molecular descriptors occupy a unique place in QSAR. The success of

QSAR models not only lies on accurate set and number of descriptors with proper validation but on correct correlation and interpretation of molecular descriptors in terms of structural features also [5]. Many a time, the QSAR models are derived using a set of esoteric descriptors only [5,7,33,36,37]. This substantially limits the use of a properly validated QSAR model by synthetic chemists, to whom the descriptor calculating software is not available, or he/she is unable to correlate structural feature with a specific descriptor, or has little knowledge of QSAR field [5,7,33,36,37]. Therefore, the molecular descriptors involved in an appropriately validated QSAR model must be understandable in terms of structural features and the descriptor calculating software must be available either free or at very low cost. To address this crucial issue, we have developed *PyDescriptor*. The sole purpose of *PyDescriptor* is to facilitate calculation of easily understandable molecular descriptors.

This PyMOL plugin possesses following merits: easy to operate, reproducible results, calculates thousands of molecular descriptors (11,145 descriptors), calculates unique molecular descriptors which are either available in commercial or operating system dependent free softwares, the results are directly saved in a CSV file, and free for academia. In addition, molecular descriptors are easily and rapidly calculated with no missing values, a common difficulty with many existing commercial systems.

3.1. PyDescriptor descriptors

PyDescriptor computes 11,145 easily understandable molecular descriptors using conventions and idioms used in PyMOL. The molecular descriptors that are calculated using this plugin possess a value that is independent of the particular characteristics of the molecular representation, such as atom numbering or labelling, spatial reference frame, translational invariance and rotational invariance, etc. The descriptors possess following additional advantages: easy interpretation in terms of structural moieties, applicable for representing local environment or structure, simple to understand, independent of experimental properties, efficient construction possible, use of familiar structural concepts, conformation dependent, and change according to continuing modification in structures. A majority of descriptors calculated by the present plugin are information-based descriptors i.e. encode the information stored in molecular structures. It can calculate 1D- descriptors like molecular weight, number of atoms, etc., 2D- descriptors like charge descriptors, H-bond donor acceptors, 2D- fingerprint, etc. and 3D-descriptors like charged partial surface area, three-dimensional autocorrelation (3DA) descriptors, etc. A majority of 2D- and 3D- descriptors calculated by *PyDescriptor* represent the relative position of atoms or atom properties by calculating the separation between atom pairs in terms of number of bonds (2DA) or Euclidean distance (3DA) [38].

A very important feature of *PyDescriptor* is its ability to calculate a good number of circular fingerprints (CFP) [39], extended connectivity fingerprints (ECFP) [40], and their variants. These fingerprints are extensively used in high-throughput screening (HTS), similarity searching, including chemical clustering and compound library analysis, etc. [39] [40] These fingerprints can capture rich local structural information available in a molecule. For example, *O_N_5A* is a circular fingerprint descriptor calculated by *PyDescriptor*. *O_N_5A*, which stands for the presence of N atoms within a spatial distance of 5 Å from O atom, looks for the N atom(s) within the radius of 5 Å whose center is O atom. *PyDescriptor* not only counts ECFP/FCFP/CFP but it can calculate several ECFP/PFP/Circular fingerprints inspired 'specific' descriptors containing additional features such as partial charges, frequency of connected or non-connected atoms or functional groups, etc. For example, *O_N_5Ac* stands for sum of partial charges on N atoms which are within 5 Å from O atom. Another example is *O_N_7Bc* which corresponds to sum of partial charges on N atoms which are within seven bonds from O atom.

As *PyDescriptor* is a software plugin dedicated for molecular descriptor calculations only, henceforth its comparisons shall only be made with other similar dedicated software instead of comparing it with general QSAR software. For comparison purpose, molecular weight, average molecular weight and number of atoms for simple organic molecules calculated by PaDEL, e-Dragon and *PyDescriptor* have been tabulated in Table 1. From Table 1, it is clear that the values of molecular descriptors calculated by *PyDescriptor* are in good agreement with the values for same descriptors calculated by PaDEL and e-Dragon.

PyDescriptor has numerous benefits that are generally associated with existing open and free dedicated molecular descriptor calculation software. Being free will broaden the easy availability of the software to a good number of users and open source will permit users to easily check the code and amend it to suit their requirements. This could possibly help in the recognition of errors/bugs and increase the number of molecular descriptor calculation abilities. Since *PyDescriptor* is a plugin built within the framework of PyMOL, the users of *PyDescriptor* must also agree with the respective licenses of PyMOL and Python. Another important advantage of *PyDescriptor* is that it can work on any platform on which PyMOL 1.8.2 and Python 2.7 have been installed. This allows it to run on the three major platforms, Windows, Linux, and MacOS.

In addition, *PyDescriptor* can be used not only through GUI but using command line (via PyMOL) also. Having both GUI and command line options for running *PyDescriptor* is important, as the GUI will cater the need of a large number of users while the command line is useful for those who need to run *PyDescriptor* in computer clusters for big databases.

At present, a major caveat of *PyDescriptor* is its inefficiency to calculate graph-based topological descriptors; work is in progress to overcome this limitation. However, to our knowledge, no simple, freely available Python and PyMOL tool is available that can easily perform molecular descriptor calculation using PyMOL (see Table 2).

3.2. Descriptor calculating speed

For a data set of 1290 molecules, computer-1 and computer-2 took 19406.00 (15.04 s per molecule) and 8845.56 (6.86 s per molecule) seconds, respectively. Thus, it is clear that *PyDescriptor* works well on a computer with high computational abilities. We clarify that *PyDescriptor* has not been optimized for speed. As *PyDescriptor* is open source, users can modify it for speed and their specific use.

3.3. Developing new QSAR models

According to OECD guideline, “mechanistic interpretations of (Q) SARs begin with the number and the nature of the molecular descriptors used in the model”. According to Johnson [41,42], a QSAR modeler must always keep in mind that mechanistically interpretable models are more likely to define causative relationships and are less liable to be the result of chance correlations. Therefore, understanding of the meaning of descriptors is very important during QSAR interpretation step. The mechanistic interpretation of a QSAR model helps to develop “action plan” by a decision maker, for example a medicinal chemist [43]. Since, many easily understandable descriptors calculated by *PyDescriptors* are able to provide useful information about local environment in the molecule and capture specific pharmacophoric patterns, deriving new QSAR models using descriptors calculated by *PyDescriptors* will be beneficial in mechanistic interpretation of QSAR model and in decision making.

1. **QSAR modelling for anti-malarial activity of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl** [33]

Recently, our group published [33] multiple properly validated QSAR models for anti-malarial activity of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl using understandable molecular descriptors for the best model (termed as Old Model 1 in the present work).

Table 1
Comparison of different molecular descriptors calculated by PaDEL, e-Dragon and *PyDescriptor*.

S.N.	Molecule	Molecular Weight			Number of rings			Number of Atoms		
		PaDEL	e-Dragon	*PyDescriptor*	PaDEL	e-Dragon	*PyDescriptor*	PaDEL	e-Dragon	*PyDescriptor*
1	Acetylene	26.01565	26.04	26.03728	0	0	0	4	4	4
2	Aniline	93.05785	93.14	93.12648	1	1	1	14	14	14
3	Benzene	78.04695	78.12	78.11184	1	1	1	12	12	12
4	Benzimidazole	117.04530	118.15	118.13590	2	2	2	14	15	15
5	Cyclohexane	84.09390	84.18	84.15948	1	1	1	18	18	18
6	Cyclopropane	42.04695	42.09	42.07974	1	1	1	9	9	9
7	Ethane	30.04695	30.08	30.06904	0	0	0	8	8	8
8	Ethene	28.03130	28.06	28.05316	0	0	0	6	6	6
9	Naphthalene	128.06260	128.18	128.1705	2	2	2	18	18	18
10	Phenol	94.04186	94.12	94.11124	1	1	1	13	13	13
11	Propane	44.06260	44.11	44.09562	0	0	0	11	11	11
12	Pyridine	80.05002	79.11	79.09990	1	1	1	12	11	11

Table 2
A representative list of different types of molecular descriptors calculated by *PyDescriptor* (see supporting information for complete list).

S.N.	Type of Molecular Descriptor	Some examples of Molecular Descriptor	Total Number
1	Constitutional • Functional groups • Molecular weight • Simple Atom counts • Ratio of various types of atoms	Molecular weight, Average Molecular weight, -OH, 3° Amine, number of atoms, total number of bonds, total number of rings, etc.	235
2	Geometric • Molecular surface area (MSA) • Solvent accessible molecular surface area (SASA) • Ratio of MSA and SASA of various types of atoms	Molecular Surface area and Solvent accessible molecular surface area of molecule, positively/negatively/neutral atoms, etc. Absolute Surface Area, MSA of C atoms, MSA of N atoms, SASA of C atoms, SASA of F atoms, etc.	212
3	Circular fingerprint • Presence/Absence of different types of atom pairs at specific spatial distance	Number of C atoms within 5 Å from ring atoms, etc.	2650
4	Quantum chemical • Charges	Sum of partial charges of C atoms within 4 bonds from O atoms, Sum of partial charges of C atoms within 4 Å from O atoms, etc.	3548
5	Topological • Atom-pairs	Number of C atoms within 9 bonds from O atoms, Number of N atoms within 5 bonds from Cl atoms, etc.	4500

Old Model-1: pIC_{50} = 2.3367 (±0.7641) + 1.5695 (±1.7697) *R6p* − 0.0306 (±0.0254) *nBT* + 0.4084 (±0.1941) *nN* + 0.6338 (±0.1605) ALogP
R^2_{tr} = 0.79, Q^2 = 0.72, MAE_{cv} = 0.27, R^2_{ex} = 0.81 and CCC_{ex} = 0.89

In the present work, the same dataset (Keto form) was used for developing new QSAR model using the molecular descriptors calculated by *PyDescriptor*, e-dragon and PaDEL with identical training and prediction sets as mentioned in our previous publication. The newly derived best four parametric QSAR model built for anti-malarial activity of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl is as following:

New Model-1: pIC_{50} = +2.682 (±0.411) − 0.104 (±0.071) * *N_O_3A* − 13.310 (±9.785) * *all_O_8Ac* + 0.422 (±0.168) * *plus_N_2A* + 0.434 (±0.091) * *ALOGP*
R^2_{tr} = 0.83, $RMSE_{tr}$ = 0.25, MAE_{tr} = 0.19, CCC_{tr} = 0.91, Q^2_{loo} = 0.79, $RMSE_{cv}$ = 0.28, MAE_{cv} = 0.21, CCC_{cv} = 0.89, $RMSE_{ex}$ = 0.32, MAE_{ex} = 0.28, Q^2_{F1} = 0.75, Q^2_{F2} = 0.73, Q^2_{F3} = 0.72, CCC_{ex} = 0.89, R^2_{ex} = 0.81

The symbols used for various statistical parameters have their usual meaning and available in supporting information [34,35]. The descriptor ALOGP represents lipophilicity of the molecule. The descriptors *N_O_3A* stands for the presence of oxygen atom within a spatial distance of 3 Å from nitrogen atom. The descriptor *all_O_8Ac* corresponds to sum of partial charges of all atoms within 8 Å from oxygen atom. The descriptor *plus_N_2A* corresponds to the number of nitrogen atom present within 2 Å from positively charged atoms. The descriptors *N_O_3A*, *all_O_8Ac* and *plus_N_2A* have been calculated by *PyDescriptor* and represent local environment inside the molecule, while *ALOGP* is a property of whole molecule.

A simple comparison of statistical parameters of model-1 and old model-1 reveals that the new model has improved performance not only with respect to fitting but for cross-validation parameters like Q^2, MAE_{cv}, etc. also.

In addition, another adequately validated QSAR model was built using molecular descriptors calculated by *PyDescriptor* only (neither PaDEL nor e-Dragon descriptors were used) with identical training and prediction sets as stated in our previous publication. The newly derived best four parametric QSAR model is as following:

New Model-2: pIC_{50} = +3.333 (±0.356) + 5.159 (±1.351) * *H_S_4Ac* − 0.123 (±0.046) * *byring all_S_4A* + 0.096 (±0.062) * *fHS6B* + 0.099 (±0.038) * *C_don_6A*
R^2_{tr} = 0.82, $RMSE_{tr}$ = 0.26, MAE_{tr} = 0.22, CCC_{tr} = 0.90, Q^2_{loo} = 0.75, $RMSE_{cv}$ = 0.30, MAE_{cv} = 0.26, CCC_{cv} = 0.86, $RMSE_{ex}$ = 0.33, MAE_{ex} = 0.27, Q^2_{F1} = 0.74, Q^2_{F2} = 0.72, Q^2_{F3} = 0.71, CCC_{ex} = 0.88, R^2_{ex} = 0.81

The symbols used for various statistical parameters have their usual meaning and available in supporting information also [34,35]. The descriptor *H_S_4Ac* indicates sum of partial charges of sulphur atoms which are at a spatial distance of 4 Å from hydrogen atom. The descriptor *byring all_S_4A* stands for the presence of sulphur atoms which are at a spatial distance of 4 Å from ring atoms. The descriptor *fHS6B* corresponds to frequency of occurrence of hydrogen and sulphur atoms separated by six bonds. The descriptor *C_don_6A* resembles the number of

presence of donor atom or group at a distance of 6 Å from carbon atom.

A comparison of statistical measures of model-2 with old model-1 indicates that the model-2 has outperformed the previously reported model. From model-2, it is clear that the model, derived using molecular descriptors calculated by *PyDescriptor* only, has better statistical performance and high degree of correlation of molecular descriptors with structure feature than the old model-1. This indicates that the molecular descriptors calculated by *PyDescriptor* could result in useful augmentation of statistical performance of the model and increase in mechanistic interpretation as well. It also indicates that scientifically interesting new and improved models could be built using descriptors calculated by *PyDescriptor*. In addition, the diversity of pool of descriptors calculated by *PyDescriptor* is also reflected.

A comparison of statistical parameters of model-1 and 2, derived in the present work, reveals that model-1 has better statistical performance than model-2. This indicates that a combination of molecular descriptors calculated by *PyDescriptor* with different types of descriptors generates a thriving QSAR model with easy interpretation and statistical robustness. Therefore, it is logical to use molecular descriptors calculated by *PyDescriptor* with different types of descriptors calculated by other softwares.

2. **QSAR modelling for anti-proliferative activity of substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates** [4]

An appropriately validated QSAR model for undivided dataset of ninety-seven substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates for anti-proliferative activity using three molecular descriptors was published by our group [24].

Old model-1b: $\log IC_{50} = -8.5590\ (\pm 4.0430) + 55.8097\ (\pm 23.1356)$ * Xt – 71.0572 (±18.4287) * VEA2 + 0.7420 (±0.2572) * nHDon.
$R^2_{tr} = 0.87$, $Q^2 = 0.85$, $RMSE_{tr} = 0.50$, $RMSE_{cv} = 0.52$, $F = 205.12$, $CCC_{tr} = 0.93$, $CCC_{cv} = 0.92$

In the present work, the same dataset was used for developing new QSAR model using the molecular descriptors calculated by *PyDescriptor*, e-dragon and PaDEL. The newly constructed best three parametric QSAR model built for anti-proliferative activity of substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates is as following:

New Model-1b: $\log IC_{50} = -29.646\ (\pm 3.549) + 1.043\ (\pm 0.135)$ * *lipo_N_2B* + 0.649 (±0.206) * *all_N_6Ac* + 115.995 (±19.541) * *X3A*
$R^2_{tr} = 0.93$, $Q^2 = 0.92$, $RMSE_{tr} = 0.36$, $RMSE_{cv} = 0.38$, $F = 409.17$, $CCC_{tr} = 0.96$ and $CCC_{cv} = 0.96$

The descriptor *X3A* accounts for the multiplicity of the bond and for the presence of hetero atoms in the molecule, especially the hydrogen bond donor/acceptor atoms. The descriptor *lipo_N_2B* stands for number of lipophilic atoms separated by two bonds from nitrogen atoms. The third descriptor *all_N_6Ac* corresponds to sum of partial charges of all atoms present within a spatial distance of 6 Å from nitrogen atom. The descriptors *lipo_N_2B* and *all_N_6Ac* have been calculated by *PyDescriptor* and represent local environment of the molecule, whereas *X3A* is a property of whole molecule.

It is evident from the statistical parameters of **old model-1b** and **new model-1b** that the new model has superior statistical robustness not only with respect to fitting but also for cross-validation parameters like R^2, $RMSE_{cv}$, etc. Additionally, a different statistically validated QSAR model was built using molecular descriptors calculated by *PyDescriptor* only (neither PaDEL nor e-Dragon descriptors were used) with identical training set as specified in our previous publication. The newly derived best three parametric QSAR model is as following:

Model-2: $\log IC_{50} = -3.471\ (\pm 0.852) - 1.223\ (\pm 0.265)$ * *N_lipo_3Bc* – 5.082 (±2.065) * *S_all_8Bc* − 0.250 (±0.049) * *S_byring all_9B*
$R^2_{tr} = 0.90$, $Q^2 = 0.89$, $RMSE_{tr} = 0.43$, $RMSE_{cv} = 0.45$, $F = 285.36$, $CCC_{tr} = 0.95$ and $CCC_{cv} = 0.94$

The descriptor *N_lipo_3Bc* corresponds to sum of partial charges of all lipophilic atoms which are separated from nitrogen atoms by three bonds. The descriptor *S_all_8Bc* represents sum of partial charges of all atoms separated from sulphur atom by eight bonds. The third descriptor *S_byring all_9B* stands for number of ring atoms which are separated from sulphur atom by nine bonds.

It is clear from the statistical measures of **model-2** that it has better statistical performance when compared with **old model 1b**. Thus, this again confirms that the molecular descriptors calculated by *PyDescriptor* are advantageous for increasing the statistical robustness of the model and mechanistic interpretation of the model in terms of structural features.

3.4. General comparison of newly developed models with old models

A comparison of newly developed models with the old models points out that the new QSAR models have better statistical performance and greater number of easily understandable molecular descriptors. The molecular descriptors used in the present models not only represent the local environment of the molecule but complete molecule also. This would have been difficult without the incorporation of new descriptors calculated by *PyDescriptor*. It appears that the use of esoteric descriptors along with the descriptors calculated by *PyDescriptor* significantly augment the statistical performance and mechanistic interpretation of the QSAR model. Therefore, a combination of e-Dragon, PaDEL and descriptors from *PyDescriptor* is useful for deriving quantitative and qualitative QSAR models with high statistical performance and mechanistic interpretation. A statistically best QSAR equation may have only complex descriptors which cannot be easily interpretable at the level of substructures of the molecules. In our opinion, a QSAR model should be selected which should be statistically sound and easier to relate to the structural features of the molecules under study.

4. Conclusions

The use of esoteric descriptors along with easily understandable descriptors provided models with better accuracy, fidelity and easy physical clarification in a biological perspective which, in turn, could yield perceptions of a causal mechanism of action, ways of decreasing a drug's toxicity or increasing its efficacy. In the present work, a PyMOL plugin *PyDescriptor* molecular descriptor calculator has been reported which possesses a good number of advantages. The plugin can be used on all the popular platforms (Windows, Linux, MacOS). The 11,145 *PyDescriptor* descriptors calculated here consists of 1D- to 3D- molecular descriptor. For QSAR community, it provides a zero-cost option for calculating a good number of easily understandable and informative molecular descriptors with broad applicability to various types of problems. To summarize, *PyDescriptor* is a useful addition to the currently existing molecular descriptor calculation software.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemolab.2017.08.003.

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An Analytical Study of Cloud Computing: IT Opportunity and Challenges

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Abstract---**Cloud Computing is a new technology that provides us all the services and resources for retrieving our data globally. Now a days IT industry is standing at the threshold of a new era in the technological field. Cloud computing is everything that could answer the problems of IT companies. Cloud computing has the ability to make IT resources more cost-effective and it gives businesses a great flexibility to expand.**

There are several fields including business, e-governance, utility computing, military, and healthcare where computer system play a vital role. All the fields include the sharing of data among each other's. So if we want a channel through which we will have easy way to communicate and share the data then cloud computing provides us a very seamless way to communicate. But as the time is growing cloud computing should also have to enhance its performance. Many big companies are not adopting this technology till now because of many challenges. The different types of challenges are:

1. Performance
2. Security and privacy
3. Bandwidth cost

In this paper we have tried to summarize the uses ,opportunity and challenges of cloud computing and we also have tried to explain how the cloud computing can help in business in today's scenario.

Keywords—**Cloud computing, Utility computing, E-Governance, Internet, Security.**

I. INTRODUCTION

Cloud computing is the use of computing resources both hardware as well as software that are delivered as a service over a network typically the Internet. As the name suggests clouds means that the network is of the cloud type as the clouds spreads in the sky as a network. In cloud computing we may access our data globally via the use of internet. Internet plays a vital role while sharing of data in between various networks. We run many applications via the use of a cloud and Cloud providers manage the infrastructure and platforms that run the applications.

Day by day, big companies spend millions of dollars on their IT infrastructure that consist of hardware, system software, applications, networks, people, and other organizational assets. Now a day's computing is becoming as import part of our life as the importance of water in human life. So we will also have to change our mind as per the technology is changing. The cloud is simply a service where all the data saves but when it combines with computing then it became very complex and fuzzy. Here different services- such as servers, storage and applications are delivered to an organization's computers and devices through the Internet.

II. HOW CLOUD WORKS

The main goal of cloud computing is to apply supercomputing or high-performance computing power to the organizations such as military, healthcare, utility computing and all to perform trillions of computations per second to provide a very large data storage.





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Suppose we have an organization. In that organization we will also have to provide all the facilities to all of the employees of that organization like right hardware and software they need to do their jobs. We will buy the computers for each and every employee of the organization but that is not enough we will also have to provide the software and tools required for the job. Whenever we have a new hire, we have to buy more software or make sure our current software license allows another user. That is a very long lasting process so the solution of the problem is cloud computing. In which we will have a centralize server which will provide all the services to the employees as well as to the customers.

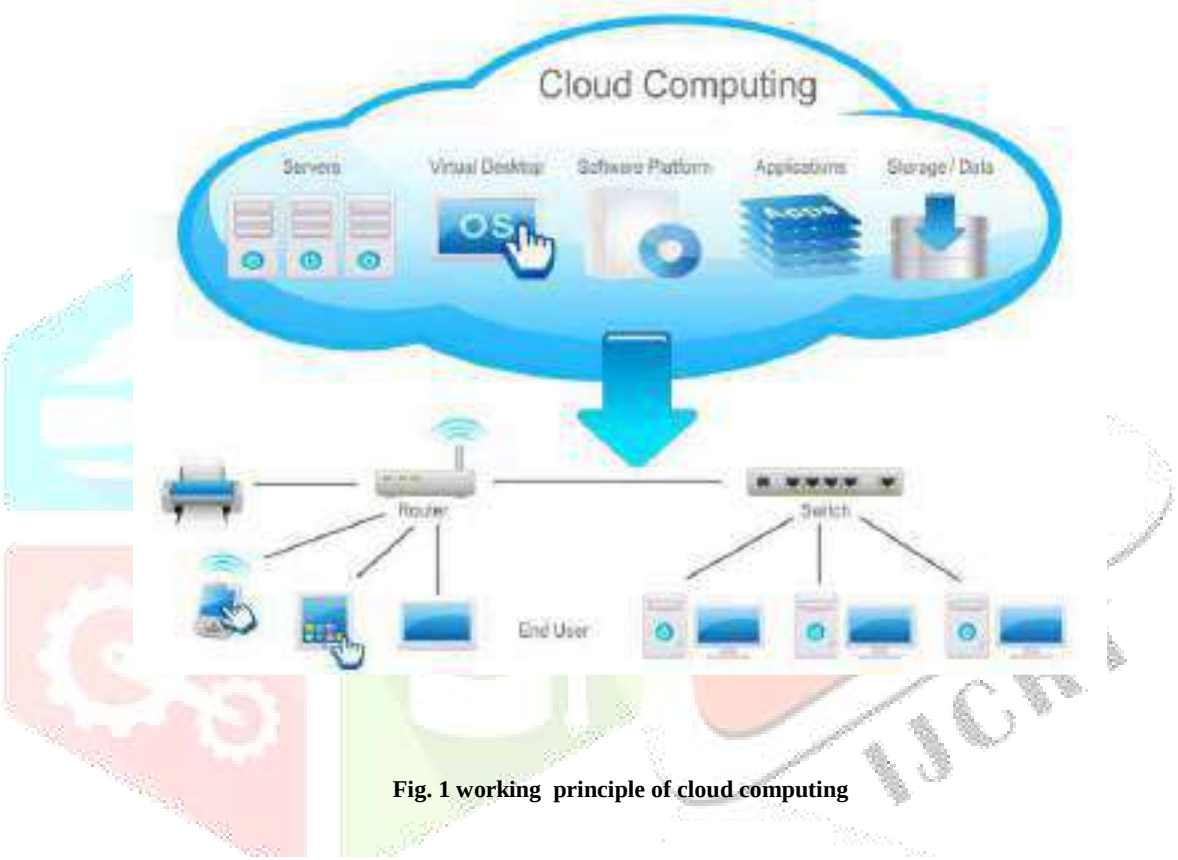


Fig. 1 working principle of cloud computing

The total workload of the local computers shifted to server computers by using cloud computing technology. Local computers no longer have to do all the heavy lifting of data and all when it comes to running applications. The network of computers that make up the "cloud" handles them. We have a very good example of cloud computing that is the E-mail which most of us have used many times but we did not notice that where our data actually saved, that is in the cloud and we access our data whenever we want to access.

III. SECURITY ISSUES AND CHALLAGES

Everywhere you turn these days "the cloud" is being talked about. This ambiguous term seems to encompass almost everything about us. While "the cloud" is just a metaphor for the internet, cloud computing is what people are really talking about these days. Cloud computing is the delivery of hosted services over the internet, through a network of remote servers. These remote servers are busy storing, managing, and processing data.

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Cloud computing comes into focus when you think about IT. If we are using this technique in our business applications then we will also have to make our business more secure. There are mainly three models of cloud computing IaaS (Infrastructure as a Service), PaaS (Platform as a Service), SaaS (Software as a Service) and Utility Computing.. These three models have different impact on different types of applications. Two main questions arise while using these models that are: –
-How secure is the Data?
-How secure is the Code?

The capabilities and breadth of cloud computing are enormous. The IT industry broke it into three categories to help better define use cases.

A. Software as a Service (SaaS) – Software is owned, delivered and managed remotely by one or more providers. To start, Software-as-a-Service, or SaaS, is a popular way of accessing and paying for software. Instead of installing software on your own servers, SaaS companies enable you to rent software that's hosted, this is typically the case for a monthly or yearly subscription fee. More and more CRM, marketing, finance, and business intelligence and even Adobe's Creative Suite has adopted the model.

B. Infrastructure as a Service (IaaS) – Compute resources, complemented by storage and networking capabilities are owned and hosted by providers and available to customers on-demand.

C. Platform as a Service (Paas) – The broad collection of application infrastructure (middleware) services. These services include application platform, integration, business process management and database services.

D. Utility computing- Utility computing is mainly a business model which provides services as per the demand. As the name suggest "utility computing" which generally means that any service which is mostly needed by any customer? Better economic is the main benefit of utility computing.

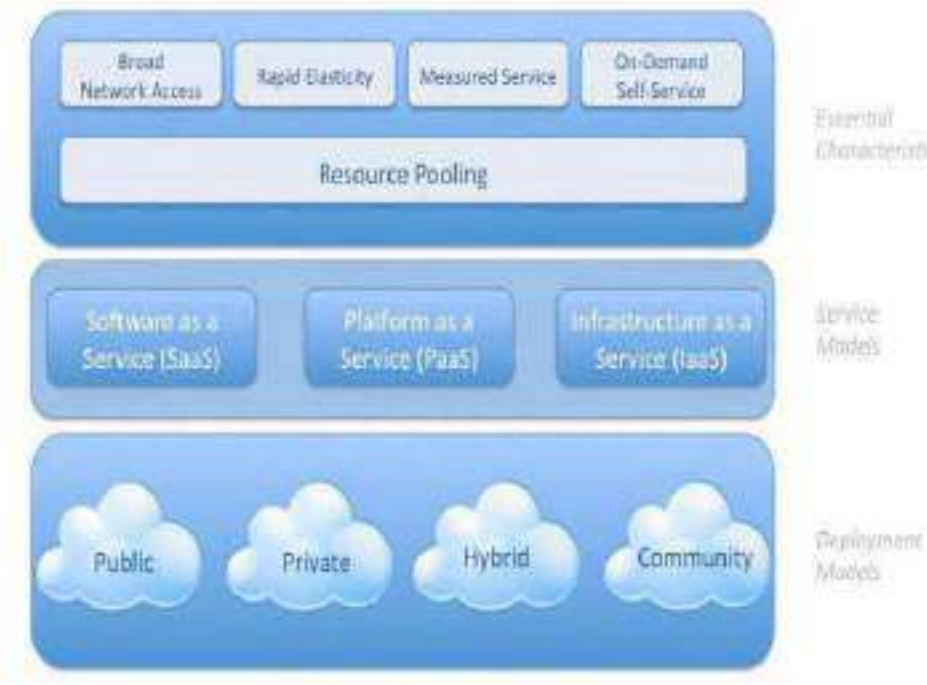


Fig. 2 Visual model of cloud computing definition

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All of this is a deviation from traditional on-premise computing which is done via a local server or personal computer. These traditional methods are increasingly being left behind. In fact, IDG's recently published Enterprise Cloud Computing Survey (2016) found that by 2018 the typical IT department will have the majority of their apps and platforms (60%) residing in the cloud.

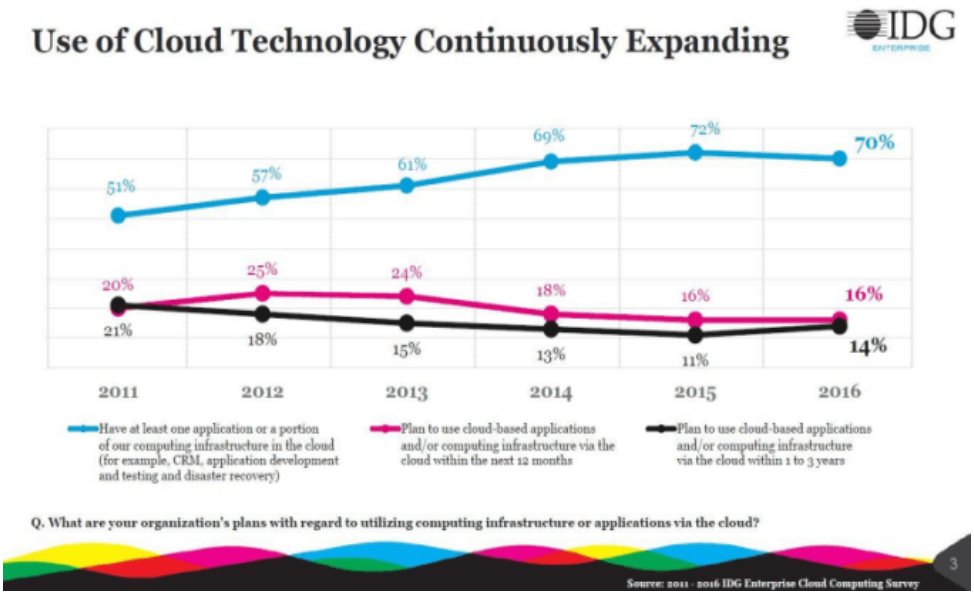


Fig. 3 Graphical Representation: Growth Of Cloud Computing Technology

In an effort to do everything from offer better in-store customer service to fully leverage advances in manufacturing, companies from even most traditional and change-resistant sectors are seeing the writing on the wall: Cloud technology strategies cut cost and risk.

Though the opportunities are great, the cloud computing explosion hasn't come without challenges. Now let's go over more of those challenges organizations are facing, and how they are being addressed.

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IV. CURRENT CLOUD COMPUTING CHALLENGES

Below, we have expanded upon some of additional cloud computing problems that businesses may need to address.

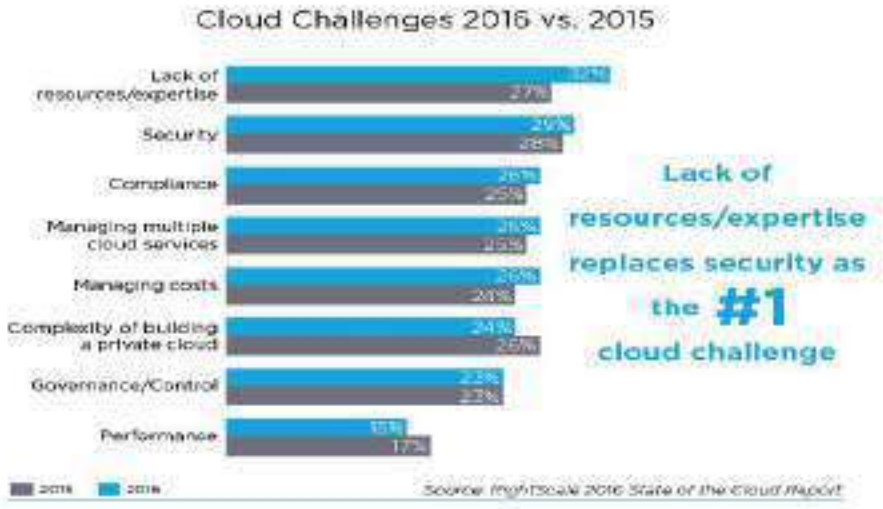


Fig. 4 Comparison Of Challenges For The Year 2015-16

A. Lack of resources/expertise

For the longest time, security was the number one voiced cloud challenge. In 2016 however, lack of resources/expertise inched ahead. Organizations are increasingly placing more workloads in the cloud while cloud technologies continue to rapidly advance. Due to these factors organizations are having a hard time keeping up with the tools. Also, the need for expertise continues to grow. These challenges can be minimized through additional training of IT and development staff.

B. Security issues

Resource/expertise concerns slightly passed security cloud computing problems in 2016. Security has indeed been a primary, and valid, concern from the start of cloud computing technology: you are unable to see the exact location where your data is stored or being processed. Headlines highlighting data breaches, compromised credentials and broken authentication, hacked interfaces and APIs, account hijacking haven't helped alleviate concerns. All of this makes trusting sensitive and proprietary data to a third party hard to stomach for some. Luckily as cloud providers and users, mature security capabilities are constantly improving. To ensure your organization's privacy and security is intact, verify the SaaS provider has secure user identity management, authentication and access control mechanisms in place

While you are auditing a provider's security and privacy laws, make sure to also confirm the third biggest issue is taken care of compliance. Your organization needs to be able to comply with regulations and standards, no matter where your data is stored. Speaking of storage, also ensure the provider has strict data recovery policies in place.

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C. Cost management and containment

For the most part cloud computing can save businesses money. In the cloud, an organization can easily ramp up its processing capabilities without making large investments in new hardware. Businesses can instead access extra processing through pay-as-you go models from public cloud providers. However, the on-demand and scalable nature of cloud computing services makes it some times difficult to define and project quantities and costs.

D. Governance/Control

Proper IT governance should ensure IT assets are implemented and used according to agreed-upon policies and procedures; ensure that these assets are properly controlled and maintained; and ensure that these assets are supporting your organization's strategy and business goals. In today's cloud based world, IT does not always have full control over the provisioning, de-provisioning and operations of infrastructure. This has increased the difficulty for IT to provide the governance, compliance and risk management required. To mitigate the various risks and uncertainties in transitioning to the cloud, IT must adapt its traditional IT governance and control processes to include the cloud. To this effect the role of central IT teams in cloud has been evolving over the last few years. Along with business units, central IT is increasingly playing a role in selecting, brokering, and governing cloud services. On top of this third party cloud computing/management providers are progressively providing governance support and best practices.

E.. *Performance*

When a business moves to the cloud it becomes dependent on the service providers. This partnership often provides businesses with innovative technologies they wouldn't otherwise be able to access. On the other hand the performance of the organization's BI and other cloud based systems is also tied to the performance of the cloud provider when it falters. When your provider is down, you are also down.

This isn't uncommon, over the past couple of years all the big cloud players have experienced outages. Make sure your provider has the right processes in place and that they will alert you if there is ever an issue.

For the data driven organization real time data is imperative. With an inherent lack of control that comes with cloud computing, companies may run into real time monitoring issues. Make sure your SaaS provider has real time monitoring policies in place to help mitigate these issues.

F. Segmented usage and adoption

Most organizations did not have a robust cloud adoption strategy in place when they started to move to the cloud. Instead, ad-hoc strategies sprouted, fueled by several components. One of them was the speed of cloud adoption. Another one was the staggered expiration of data centre contracts/equipment, which led to intermittent cloud migration. Finally, there also were individual development teams using public cloud for specific applications or projects. These bootstrap environments have fostered full integration and maturation issues including:

1) *Isolated cloud projects lacking shared standards*
2) *Ad hoc security configurations*
3) *Lack of cross-team shared resources and learnings*

V. CONCLUSION

In an emerging discipline of cloud computing, security is the main issue that should have to be provided by big companies who are providing the service of clouds. So we may say that cloud computing brings both opportunities as well as challenges for us. In this paper we mainly focus on the services provided by cloud and new opportunities and challenges in the IT industries by using cloud computing. We have three models of cloud computing that are IaaS, PaaS and SaaS and utility computing. All the three models are important because all have different impact on implementation of the services.

While cloud computing challenges do exist, if properly addressed these 6 issues don't mean your IT roadmap has to remain anchored on-premise. Business intelligence (BI) and cloud computing are an ideal match, as the first one provides the right information to the right people while the latter is an agile way to access BI applications

So we may say that cloud computing is a leading technology worldwide. If security, authentication and authorization will be provided effectively then this will be one of the most promising technologies

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Study of Relation between Big Data & Cloud Computing: Big Data Challenges & Issues

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Abstract

The amount of data in world is growing day by day. Data is growing because of use of internet, smart phone and social network. Big data is a collection of data sets which is very large in size as well as complex. Now a days, Big data is one of the most talked topic in IT industry. It is going to play important role in future. Big data changes the way that data is managed and used. Communicating by using information technology in various ways produces big amounts of data. Such data requires processing and storage. The cloud is an online storage model where data is stored on multiple virtual servers. Big data processing represents a new challenge in computing, especially in cloud computing. Data processing involves data acquisition, storage and analysis. In this respect, there are many questions including, what is the relationship between big data and cloud computing? The answer to this question will be discussed in this paper, where the big data and cloud computing will be studied, in addition to getting acquainted with the relationship between them in terms of safety and challenges. I have suggested a term for big data, and a model that illustrates the relationship between big data and cloud computing.

Keywords: **Big Data; security; systematic mapping study, cloud, resources, 'five Vs'.**

I. INTRODUCTION

Data is the raw material for information before sorting, arranging and processing. It cannot be used in its primary form prior to processing. Information represents data after processing and analysis. The technology has been developed and used in all aspects of life, increasing the demand for storing and processing more data. As a result, several systems have been developed including cloud computing that support big data. While big data is responsible for data storage and processing, the cloud provides a reliable, accessible, and scalable environment for big data systems to function. Big data is defined as the quantity of digital data produced from different sources of technology for example, sensors, digitizers, scanners, numerical modeling, mobile phones, Internet, videos, e-mails and social networks. The data types include texts, geometries, images, videos, sounds and combinations of each. Such data can be directly or indirectly related to geospatial information.

Cloud computing refers to on-demand computer resources and systems available across the network that can provide a number of integrated computing services without local resources to facilitate user access. These resources include data storage capacity, backup and self-synchronization. Most IT Infrastructure computing consists of services that are provided and delivered through public centers and servers based on them. Here, clouds appear as individual access points for the computing needs of the consumer. They are an online storage model where data are stored on multiple virtual servers, rather than being hosted on a specific server, and are usually provided by a third party. The hosting companies, which have advanced data centers, rent spaces that are stored in a cloud to their customers in line with their needs.

The relationship between big data and the cloud computing is based on integration in that the cloud represents the storehouse and the big data represents the product that will be stored in the storehouse, since it is not possible to create storehouses without storing any product in them. The traditional databases known as 'relational' are no longer sufficient to process multiple-source data. For example, how can these traditional methods deal with data such as record of transactions, customer behavior, mobile phone and GPS navigation, and others. Here comes the role of cloud computing. At this





point, a relationship between big data and the cloud will arise. In this paper, the relationship between them will be discussed, in addition to the challenges and issues that Big Data may encounter.

II. BIG DATA

Big data comes and is composed through electronics operations from multiple sources. It requires proper processing power and high capabilities for analysis. The importance of big data lies in the analytical use which can help generate an informed decision to provide better and faster services.

The term big data is called on the huge amount of high-speed big data of different types; this data cannot be processed and stored in regular computers. The main characteristics of big data known as 'five Vs', are as follows:

1. Volume: It represents the amount of data produced from multiple sources which show the huge data in numbers by zeta bytes. The volume is most evident dimension in what concerns to big data.
2. Variety: It represents data types, with, increasing the number of Internet users everywhere, smart phones and social networks users, the familiar form of data has changed from structured data in databases to unstructured data that includes a large number of formats such as images, audio and video clips, SMS, and GPS data.
3. Velocity: It represents the speed of data frequency from different sources, that is, the speed of data production such as Twitter and Facebook. The huge increase in data volume and their frequency dictates the need for a system that ensures super-speed data analysis.
4. Veracity: It represents the quality of the data, it shows the accuracy of the data and the confidence in the data content. The quality of the data captured can vary greatly, which affects the accuracy of analysis. Although there is wide agreement on the potential value of big data, the data is almost worthless if it is not accurate.
5. Value: It represents the value of big data, i.e. it shows the importance of data after analysis. This is due to the fact that the data on its own is almost worthless. The value lies in careful analysis of the exact data, the information and ideas it provides. The value is the final stage that comes after processing volume, velocity, variety, contrast, validity and visualization .

III. CLOUD COMPUTING

It is a term that refers to on-demand computer resources and systems that can provide a number of integrated computer services without being bound by local resources to facilitate user access. These resources include data storage, backup and self-synchronization, as well as software processing and scheduling tasks. Cloud computing is a shared resource system that can offer a variety of online services such as virtual server storage, and applications and licensing for desktop applications. By leveraging common resources, cloud computing is able to achieve expansion and provide volume.

A. *Characteristics of cloud computing*

That cloud computing is one of the distributed systems that represents a sophisticated model. NIST has identified important aspects of the cloud, as it shortened the concept of cloud computing in five characteristics as follows:

1) *On-demand self-service*: Cloud services provide computer resources such as storage and processing as needed and without any human intervention.

2) Broad network access: cloud computing resources are accessible over the network , mobile and smart devices even sensors can access computing resources on the cloud.

3) Resource Pooling: Cloud platform users share a vast array of computing resources; users can determine the nature of resources and the geographic location they prefer but cannot determine the exact physical location of these resources.

4) Rapid Elasticity: Resources from storage media, network, processing units and applications are always available and can be increased or decreased in an almost instantaneous fashion, allowing for high scalability to ensure optimal use of resources.

5) Measured service: Cloud systems can measure the processes and consumption of resources as well as surveillance, control and reporting in a completely transparent manner.

B. Cloud computing service models.

Cloud computing types are classified on the basis of following models:

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1) *Software as a service (SAAS)*: Cloud service providers provide various software applications to users who can use them without installing them on their computer. The user is not responsible for anything other than adjusting the settings and customizing the service as appropriate to his needs. SAAS helps big-data clients to perform data.
2) *Platform as a service (PAAS)*: Cloud service providers provide platforms, tools and other services to users, where the cloud service provider manages everything else, including the operating system and middleware., with resources that enable you to deliver everything from simple cloud-based apps to sophisticated.
3) *Infrastructure as a service (IAAS)*: Cloud service providers provide infrastructure such as storage, computing capacity, etc. is a form of cloud computing that provides virtualized computing resources over the Internet , In an IaaS model, a third-party provider hosts hardware, software, servers, storage and other infrastructure components on behalf of its users.
4) *DaaS* : It is the alternative cloud computing model, as it differs from traditional models like (SAAS, IAAS, PAAS) in providing data to users through the network, as data is considered the value of this model in conjunction with cloud computing based on solving some of the challenges in managing a huge amount of data. For these reasons, DaaS is closely related to big data whose technologies must be utilized. DaaS provides highly efficient methods of data distribution and processing. DaaS is closely related to SaaS (storage as a service) and SaaS (software as a service) which can be combined with one of these models or both of them.

IV. THE RELATIONSHIP BETWEEN THE CLOUD AND BIG DATA

Cloud computing is a trend in the development of technology, as the development of technology has led to the rapid development of electronic information society. This leads to the phenomenon of big data and the rapid increase in big data is a problem that may face the development of electronic information society. Cloud computing and big data go together, as big data is concerned with storage capacity in the cloud system, cloud computing uses huge computing and storage resources. Thus, by providing big data application with computing capability, big data stimulate and accelerate the development of cloud computing. The distributed storage technology in environmental computing helps to manage big data.

Cloud computing and big data are complementary to each other. Rapid growth in big data is regarded a problem. Clouds are evolving and providing solutions for the appropriate environment of big data while traditional storage cannot meet the requirements for dealing with big data, in addition to the need for data exchange between various distributed storage locations. Cloud computing provides solutions and addresses problems with big data. The cloud computing environment is expanding to be able to absorb big amounts of data as it follows the policy of data splitting, that is, to store data in more than one location or availability area. Cloud computing environments are built for general purpose workloads and resource pooling is used to provide flexibility on demand. Therefore, the cloud computing environment seems to be well suited for big data.

Big data processing and storage require expansion as the cloud provides expansion through virtual machines and helps big data evolve and become accessible. This is a consistent relationship between them. Google, IBM, Amazon and Microsoft are examples of the success in using big data in the cloud environment. In order for the cloud environment to fit with big data the cloud computing environment must be modified to suit data and cloud work together. Many changes are needed to be made on the cloud: CPUs to handle big data and others.

V. CHALLENGES IN BIG DATA AND CLOUD COMPUTING

The security challenges in cloud computing environments fall under several levels: the network level which includes dealing with network protocols and network security such as distributed nodes, distributed data, and communications between the nodes; authentication level where the user handles encryption / decryption techniques, authentication methods such as contract administrative rights, authentication of applications and nodes, and logging entry; the data level which is concerned with data integrity and availability as well as data protection and data distribution. Cloud computing follows the policy of shared resources, where the privacy of data is very important because it faces some challenges like integrity, authorized access, and availability of (backup / replication). Data integrity ensures that data is not corrupted or tampered with during communication. Authorized access prevents data from infiltration attacks while backups and replicas allow access to data efficiently even in case of technical error or disaster in some cloud location .

Big data face some challenges as they can be classified into groups: data sets, processing and management challenges. When dealing with big amounts of data we face challenges such as volume, variety, velocity and verification which are also known as 5V of big data . Also, in the field of computer networks the

cost of communications is a major concern compared to the cost of processing the same data, as the challenge is to reduce the cost of communications to the minimum while meeting the requirements of storage and additional data from the general cloud to handle big data . Among the factors and challenges that affect the processing of big data in a timely manner is The bandwidth and latency . Where several challenges can be summarized in the relationship between big data and cloud computing.

i) Data Storage: The storage of big data through traditional storage is problematic because hard drives often fail, data protection mechanisms are not effective, and the speed of big data requires storage systems in order to expand rapidly, which is difficult to achieve with conventional storage systems. Cloud storage services offer almost unlimited storage with a great deal of error tolerance, which offers potential solutions to address the challenges of big data storage.

ii) Variety of data: Big data naturally grow, increase and vary, which is the result of the growth of almost unlimited sources of data. This growth leads to the heterogeneous nature of big data. Generally speaking, data from multiple sources of different types and representations are highly interrelated. They have incompatible shapes and are inconsistent. A user can store data in structured, semi-structured, or unstructured formats. Structured data format is suitable for today's database systems, while semi- structured data formats are only fairly suitable. Unstructured data is inappropriate because it contains a complex format that is difficult to represent in rows and columns.

iii) Data transfer: The data goes through several stages: data collection, input, processing, and output. Big data transfer is a challenge, so data compression techniques need to be reduced to reduce the volume, where data volume is a hindrance to transfer speed. It also affects the cost, while cloud computing provides distributed storage resources and data transfer on high-speed lines, reducing costs through virtual resources and resource use at user's request.

iv) Privacy and data ownership: The cloud environment is an open environment and the user's role in monitoring is limited. Privacy and security are an important challenge for big data. Big data and cloud computing come together in practice. According to (IDC) estimates, by 2020, around 40% of global data will be accessed by cloud computing. Cloud computing provides strong storage, calculation and distribution capability to support big data processing. As such, there is a strong demand to investigate the privacy of information and security challenges in both cloud computing and big data.

VI. BIG DATA TECHNICAL ISSUES AND CHALLENGES

A. *Fault Tolerance*: With the advent of technologies like cloud computing the aim must remain such that whenever failure occurs the damage done must occur within acceptable threshold rather than the entire work requiring to be redone. Fault-tolerant computing is tedious and requires extremely complex algorithms. A foolproof, cent percent reliable fault tolerant machine or software is simply a far-fetched idea. To reduce the probability of failure to an acceptable level we can do.

B. *Divide the entire computation to be done into tasks* and assign these tasks to different nodes for computation.

C. *Keep a node as a supervising node* and look over all the other assigned nodes as to whether they are working properly or not. If a glitch occurs the particular task is restarted. There are however certain scenario where the entire computation can't be divided into separate tasks as a task can be recursive in nature and requires the output of the previous computation to find the present result. These tasks can't be restated in case of an error. Here checkpoints are applied to keep the state of the system at certain intervals of time so that computation can restart from the last checkpoint so recorded.

D. *Data Heterogeneity***:** 80% of data in today's world are unstructured data. It encompassed almost every kind of data we produce on a daily basis like social media interaction, document sharing, fax transfers, emails, messages and a lot more. Working with unstructured data is inconvenient and expensive too. Converting these to structured data is unfeasible as well.

E. *Data Quality***:** As has been mentioned earlier, storage of big data is very expensive and there is always a tiff between business leaders and IT professionals regarding the amount of data the company or the organization is storing. The quality of data is an important factor to be looked into here. There is no point in storing very large data sets that are irrelevant as better result and conclusions can't be drawn from them. Ensuring whether the amount of data is enough for a particular conclusion to be drawn or whether the data is relevant at all are further queries.

F. *Scalability***:** The challenge in scalability of big data has led to cloud computing. It is capable of aggregating multiple different workloads with different performance goals into very large clusters. This needs high level of sharing of resources that is quite expensive and brings along with it various challenges like executing various jobs so that the goal of every workload is met successfully. It also has to deal with system failures in an efficient manner as it is quite common when working with large clusters. Hard disk drives being replaced by solid state drives and phase change technology do not have the same performance between sequential and random data transfer. The kind of storage device to be used is thus a large question looming around big data storage issue.

VII. BIG DATA PROCESSING ISSUES AND CHALLENGES

Effective processing of big data requires immense parallel processing and new analytics algorithms so as to provide rapid information. Often it may be unknown how to deal with a very large and varied volume of data and whether all of it needs to be analyzed. Challenges also include finding out data points that are really of importance and how to utilize the data to extract maximum benefit from it.

VIII. BIG DATA PRIVACY AND SECURITY ISSUES AND CHALLENGES

Often in big data analysis, the personal information of people from a database or from social networking sites need to be combined with external large data sets. Thus facts about anyone which might have been confidential become open to the world. Often it leads to taking insights in people's lives of which they are unaware of. Often it happens that a more educated person having better knowledge and concepts about big data analysis takes advantage of predictive analysis over a person who is less educated than him.

IX. CONCLUSION

Big data and cloud computing have been studied from several important aspects, and we have concluded that the relationship between them is complementary. Big data and cloud computing constitute an integrated model in the world of distributed network technology. The development of big data and their requirements is a factor that motivates service providers in the cloud for continuous development.

Cloud computing represents an environment of flexible distributed resources that uses high techniques in the processing and management of data and yet reduces the cost. All these characteristics show that cloud computing has an integrated relationship with big data. Both are moving towards rapid progress to keep pace with progress in technology requirements and users.

To handle big data and to work with it and obtaining benefits from it a branch of science has come up and is evolving, called Data Science. Data Science is the branch of science that deals with discovering knowledge from huge sets of data, mostly unstructured and semi structured, by virtue of data inference and exploration. It's a revolution that's changing the world and finds application across various industries like finance, retail, healthcare, manufacturing, sports and communication. As far as security is concerned the existing technologies are promising to evolve as newer vulnerabilities to big data arise and the need for securing them increases.

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Discrimination at working place

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What is Discrimination?

"Treating one or more members of a specified group unfairly as compared with other people. Discrimination may be illegal on the ground of sex, sexual orientation, race, religion, disability, or nationality." The term *discriminate* appeared in the early 17th century in the English language. "Discrimination" derives from Latin, where the verb *discrimire* means "to separate, to distinguish, to make a distinction". Discriminatory traditions, policies, ideas, practices and laws exist in many countries and institutions in every part of the world, including in territories where discrimination is generally looked down upon.

What is sex or gender discrimination?

Sex or gender discrimination is treating individuals differently in their employment specifically because an individual is a woman or a man. If you have been rejected for employment, fired, or otherwise harmed in employment because of your sex or gender, then you may have suffered sex or gender discrimination.

Discrimination in working places can be in different form. According to a survey made by TEAMLEASE, 48% of Indian has faced same kind of discrimination or the other discrimination at workplace. Most of the biases are based on Gender (25%), Age (22%) and Cast and Religion (18%).Amongst the cities employees in Delhi, Pune and Chennai faced the highest rate of discrimination, while employees in Ahmadabad faced the lowest amount of discrimination. While certain type of discrimination are illegal in India like equal remuneration, sexual harassment, discrimination due to pregnancy and disability.

Legal Protections: The Constitution of India has several provisions which grant certain fundamental rights to its citizen, which includes right to equality.

Article 14 guarantees Equality before Law.

Article 15 prohibits state from discrimination on the grounds of religion, race, caste, sex and place of birth.

Article 16 empowers the state to make reservations with respect to appointment for posts in favour of backward classes of citizens if in the opinion of state such classes are under-privileged.

However, these protections can only be opted when the discrimination has been made by the State or any Governmental bodies, including Government offices of both Central and State Governments. In case of discrimination on any of the grounds mentioned in Article 15, i.e, religion, race, caste, sex and place of birth by the Government through its policies, or regulations, or otherwise, including recruitment, promotions, transfers, demotions and removals, the affected person can file a writ before the concerned High Court of the State or the Supreme Court.

The Constitution further lays down certain fundamental duties, which though cannot be challenged before a Court of law; the duties should ideally be implemented by the Government. **Article 39** in part IV of the constitution urges state to ensure that citizens ,men and women equally have the right to an adequate means of livelihood, right to shelter ,food, education and work.

Below is a list of federal laws that prohibit discrimination based on gender in a number of settings.

- **Civil Rights Act of 1964: Title VII (Equal Employment Opportunities)** the Civil Rights Act of 1964 protects individuals against discrimination in many different areas. Title VII prohibits employee discrimination or harassment based on sex, race, color, religion, and national origin (including limited English proficiency).
- **The Equal Credit Opportunity Act** (ECOA) ECOA guarantees an equal opportunity to obtain credit and prohibits creditors from discriminating against credit applicants on the basis of sex, familial status, race, color, religion, national origin, age, or because an applicant receives income from a public assistance program.
- **Fair Housing Act** (FHA) The FHA prohibits discrimination in the sale, rental, and financing of housing based on sex, familial status, race, color, national origin, religion, and disability.
- **Equal Pay Act of 1963** (EPA) The EPA requires that employers pay all employees equally for equal work, regardless of whether the employees are male or female.
- **Family and Medical Leave Act** (FMLA) The FMLA gives employees the right to take time off

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from work in order to care for a newborn (or recently adopted) child, or to look after an ill family member.

- **Pregnancy Discrimination Act** The Pregnancy Discrimination Act prohibits employment discrimination against female workers who are (or intend to become) pregnant - including discrimination in hiring, failure to promote, and wrongful termination.
- **Title IX of the Education Amendments of 1972** Title IX prohibits sex discrimination in education programs that receive federal funds, to increase educational and athletic opportunities for females in schools and colleges nationwide.
- **U.S. Code Title 42, Chapter 21 - Civil Rights** Title 42, Chapter 21 of the U.S. Code prohibits discrimination against persons based on gender, age, disability, race, national origin, and religion (among other things) in a number of settings including: education, employment, access to businesses and buildings, federal services, and more. Chapter 21 is where a number of federal acts related to civil rights have been codified including: the Civil Rights Act of 1866, Civil Rights Act of 1964, and the Civil Rights of Institutionalized Persons Act.

Conclusion: If we considering gender equality in all fields it is necessary to create work environment that discourage discrimination and encourage employees to treat each other with respect. There are many benefits to employers for creating a work environment free of discrimination and harassment such as a harmonious work environment, increased productivity, reduced absenteeism, decreased turnover, an environment of trust, collaboration and cooperation between employees and increased employee and customer/client satisfaction.

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06

E-Commerce In India: "Role Of Online Payment System"

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Introduction:

In many respects, online payment is the foundation of systems for e-commerce. The ability to take payment distinguishes an e-commerce system. Must be sufficient to protect the system. From one that provides only advertising or other communications capabilities. Incorporating payment abilities, however, adds considerable complexity to a system first, the security of both the payment mechanism and the overall system must be sufficient to protect the system. Second, the system must provide a high degree of integrity for transactions the system must not lose or inadvertently change a payment transaction.

Online payment system is a back bone of e-commerce in India. All transaction depends on e-commerce in online payment system. Increasingly business potential timely and accurately captured and efficiently e-business data. Interchange, is the key to any business success.

In e-commerce, every transaction is done electronically due to this system is important in online payment system in India. Many types are available in e-commerce for online payment system and some models are available depend on e-commerce

1) Business to Business
2) Business to consumer
3) Consumer to consumer
4) Business to Government

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5) Government to Business

6) Government to Citizen.

This model depend on 92% and Government sector depend on 90% on online payment system. The Impact of e-commerce all sector due to consumer social and economical status up-lifment and consumer improve has living standard.

E-Commerce:

The word "Commerce" is the concept for electronic commerce or e-commerce, pertaining to the buying and selling of goods. While commercial "denotes business practice and activities intended to make profit E-commerce like any other business, deals, with the exchange of money for soft or hard goods and services.

In other words substantial commerce is a process of distribution of goods form the place where they are produced and found in plenty to a place where the goods are short supply or scarce and hence in demand. The concept of commerce is a very comprehensive and complex organism and includes all the necessary functions involved in buying and selling. It consists of all persons. Organizations and institutions engaged in the distribution of goods. They include railways, road transport, shipping, merchants, Bank, Insurance, Companies, brokers whole sellers, retailers, stock market, distributors, agents, service, providers etc.

E-commerce is a selling and transfer process requiring several institutes. It is a systematic and organized network for the exchange of goods between producers and consumer directly and in this the net embraces all those related activities which are indispensable for maintaining a continuous, free and uninterrupted distribution and transfer of goods.

Role of Electronic Payment System:

Electronic payment system is essential part of between consumer and Business. Traditional Commerce's in use cash but not use cash in e-commerce. Nevertheless now in India 65% transaction is depend on online payment system. The payment mechanism which constitutes the core of e-commerce process has become on important business strategy. It is simply because the payment mechanism has the potential to change the very essence of commercial transaction, business and industry models throughout the world. Payment processing system play a critical role in e-business and any company considering launching its business must have chalked out plans well in advance. It is strategic business needs.

There are a number of payment options available. They are broadly classified as offline payment option and online payment system.

1: Offline Payment System.

These systems mostly related to the conventional payment methods. Under this method An individual may use.

1)A phone

2. Drop a cheque into the postal head box

3. Earn and we discounts

4. Bills

5. Drafts

6. Money order

7. Cash on delivery.

2. Online Payment System.

Doing business online is an innovative strategy and the payback or payment through the e-shop is one of the most critical and challenging issues for any such business. Haw to make payment for online buying is a frequently asked question.

Electronic Payment via the web is catching up gradually. Even today, many customers prefer using the traditional payment methods such as cash on delivery. This system divided in to three stages.

A) Bank and financial organization Payment:

1. Large scale on payment: Bank to Bank transfer

2. Small and medium scale on payment: Automated trailer machine (ATM) or by cash Payment.

B) Retail Payment:

1) Credit card

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TO MEASURE THE IMPACT OF GLOBAL ECONOMIC RECESSION ON THE FINANCIAL PERFORMANCE OF SELECTED INDUSTRIES IN VIDARBHA

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ABSTRACT

The purpose of this research was to evaluate the changing dynamics during recession and recovery with reference to its effect on industry in Vidarbha.

The focus of empirical study has been on recession and to a lesser extent on recovery, and its impact on industry. Hardly any in-depth research on the critical evaluation of the changing dynamics during recession and recovery with reference to its effect on industry has been conducted in the Vidarbha context. A few of the doctoral studies have been completed on changing dynamics during recession and recovery in Vidarbha and even fewer have focused particularly on the changing dynamics during recession and recovery with reference to its effect on industry in Vidarbha.

INTRODUCTION

Due to substantial increase in financial globalization the recessionary cycles not only made deeper impact on the real economies of advanced countries, but doomed emerging market economies as well. As this crisis unfolded, credit markets appeared to be drying up in the developing economies along with the developed world. The Keynesian economics substantiates that demand-driven theories were at the root of recession as once panic and deflation set in, many people avoided further losses by keeping clear of the markets, resulting in falling investment & aggregate demand. On the other hand the monetarists believe that the recession started due to significant policy mistakes by monetary authorities especially the Federal Reserve's expansionary monetary policy and the Community Reinvestment Act. Along with it Government's inability to evaluate counter-party risk due to opaque financial statements and the unpredictable nature of government's response germinated the present crisis. The end result was internal as well as external instability in the economies of the world, that needs an appropriate use of 'Monetary and Fiscal Policy' to combat such situations. MUNDELL Model explains that 'Internal balance in an economy is achieved by reducing inflation and unemployment to zero whereas external balance is achieved by reducing balance of payments deficits and surpluses to zero' through expansionary monetary policy and expansionary fiscal policy. Expansionary fiscal and monetary policies constitute expenditure increasing policy measures, whereas contractionary monetary and fiscal policies constitute expenditure reducing policy measures. To maintain internal balance as well as external balance during recession a mixed package of various fiscal & monetary measures used by the Government of India has been studied through this model in this study.

OVERVIEW OF ECONOMIC SITUATION

Theoretical work in earlier chapters is much in needed to calculate with current data enabling to understand the current situation of the World, nation, markets leading to the analysis of situation of the organisation and industry sectors.

Table no. 1

Effects of recession on loss of sales volume

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	No.of Respondents	Percentage of Respondents
	18	11%
	0	0%
	93	56%
	18	11%
	37	22%
	166	100%

56% of the respondents reported a moderate loss of sales volumes,

11% reported some loss of sales and

11%of the respondents reported much loss of sales

22% reported more sales volume loss.

Table 2:

Effects of recession on loss of Customer / market share

	No.of Respondents	Percentage of Respondents
	73	44%
	18	11%
	55	33%
	20	12%
	0	0%
	166	100%

Some 44% of the interviewed respondents reported least loss of customer base or market share.

11% reported some loss of customer base

11% of the respondents reported much loss of market share.

33% reported moderate market share loss

None lost most or total market share.

Table 3 :

Effects of recession on other factors .-like Reduction in customer orders, extended Business Cycle, Market Competition, Price Competition, Extent of Sales Cost

Effect on other factors	No.of Respondents	Percentage of Respondents (out of 166)
Reduction in customer orders	73	44%
extended Business Cycle	18	11%
Market Competition	129	78%
Price Competition	166	100%
Extent of Sales Cost	73	44%

Only 44% of the respondents' companies lost the least number of customers or market share,

11% of the respondents reported to have been faced with the challenge extended Business Cycle

All 100% of the respondents reported to have been faced with the challenge of fierce price competition.

44% of the respondents reported to have been faced with the challenge of market competition.

78% of the respondents reported to have been faced with the challenge of extent of sales cost.

Table 4:

Strategies adopted for recovery purpose

Effect on other factors	No.of Respondents	Percentage of Respondents (out of 166)
Adjust company goals	166	100%
Asking support from Government	97	60%
Kept regular contact with Market	133	80%
Smart Management Techniques	166	100%
Used loyalty Programmes	116	70%

All of the representatives interviewed reported that their companies had adjusted their sales volumes down in response to the phenomenon.

60% devoted their efforts to ask support from government

80% reported that it was good to keep regular contact with market situation.

100% of the respondent reported to have improvised on use of their smart management

techniques.

In their endeavors to keep the customer base and market share, loyal customers, employees, supplies were rewarded, overall 70% of respondents claim to have used this strategy.

CONCLUSION

Many of the companies have had to make large scale organisational changes to deal with the impact of recession and have had to make changes (sometimes substantial) to their existing business strategies. They recognise that in the 'good times' prior to recession there was some degree of loss of focus on certain aspects of management and financial management but remedial action has been taken to alleviate these problems.

India has been hit by the global meltdown, it is clearly due to India's integration into the global economy. The strategy to counter these effects of the global crisis on the Indian economy. The strategy to counter these effects of the global crisis on the Indian economy and prevent the latter from any further collapse would require an effective departure from the dominant economic philosophy of the neo-liberalism.

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Gender Inequality In Education

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Introduction: We proud Indians of 21st century rejoice in celebrations when a boy is born, and if it is a girl, a muted or no celebrations is the norm. Love for a male child is so much so that from the times immemorial we are killing our daughters at birth or before birth, and if, fortunately, she is not killed we find various ways to discriminate against her throughout her life. Though our religious beliefs make women a goddess but we fail to recognize her as a human being first; we worship goddesses but we exploit girls. We are a society of people with double-standards as far as our attitude towards women is concerned; our thoughts and preaching are different than our actions.

Definition And Concept Of Gender Inequality: 'Gender' is a socio-cultural term referring socially defined roles and behaviors assigned to 'males' and 'females' in a given society; whereas, the term 'sex' is a biological and physiological phenomenon which defines man and woman. In its social, historical and cultural aspects, gender is a function of power-relationship between men and women where men are considered superior to women. Therefore, gender may be understood as a man-made concept, while 'sex' is natural or biological characteristics of human beings.

Gender Inequality, in simple words, may be defined as discrimination against women based on their sex. Women are traditionally considered by the society as weaker sex. She has been accorded a subordinate position to men. She is exploited, degraded, violated and discriminated both in our homes and in outside world. This peculiar type of discrimination against women is prevalent everywhere in the world and more so in Indian society.

Journey from Ancient to Present : In the ancient India women were held in high esteem and the the position of a woman in the Vedas and the Upanishads was that of a mother (maata) or goddess (Devi). In the Manusmriti, woman was considered as a precious being and in the early Vedic age, girls were looked after with care. Then practice of polygamy deteriorated the status of woman and in the medieval period, the practices of purdha system, dowry and sati came into being. With the passage of time, the status of woman was lowered. After the development of science and technology, female foeticide is being practiced on a large scale. This has led to a drop in the female ratio. And then dowry have become common and started female infanticide practices in few areas.

In many parts of India, women are viewed as an economic liability despite contribution in several ways to our society and economy. The crime graph against women is increasing at an alarming rate. The condition of an Indian widow is quite deplorable. At home, the woman's contribution towards home as a housewife is not recognized. Domestic Violence, Rape, Sexual Exploitation, molestation, eve-teasing, forced prostitution, sexual harassment at work places etc are a common affair today and in some cases its too tragic that it gets the global attention. The major reasons for this inequality are identified as the need of a male heir for the family, huge dowry, continued financial support to girl child, poverty, domestic violence, farming as major job for poor and the caste system.

Gender Inequality In India: Important Data: Global Indices: Gender Inequality is also reflected in India's poor ranking in various global gender indices.

- **UNDP's Gender Inequality Index- 2014:** India's ranking is 127 out of 152 countries in the List. This ranking is only above Afghanistan as far as SAARC countries are concerned.
- **World Economic Forum's Global Gender Gap Index- 2014:** India's ranks at 114 in the list of 142 countries of the world. This Index examines gender gap in four major areas:
- Economic participation and opportunity.
- Educational achievements.
- Health and life expectancy.
- Political empowerment.

India's position on these indicators was as follows:

- Economic participation and opportunity: 134th
- Educational achievements: 126th
- Health and Life expectancy: 141st
- Political empowerment: 15th

These two important Global Indices show the sorry state of affairs in India as far as gender equality is concerned. Only in case of 'Political Empowerment' India is doing fine which is a welcome sign. But other indices are very poor and a lot need to be done to improve the same.

Gender Inequality And Significance Of Education: Education is a gate way of all the values, sincerity, equality and character. It is a best weapon to fight all challenges related with human society. The gender inequality can be handled with the help of promoting gender equality through education. The school, classroom and teachers are all part and parcel of a society. In a society people are suffering from various problems related with gender such as gender discrimination, oppression, inequalities, biasedness and various other issues. Therefore, by keeping in mind to all these issues, government of India time to time has worked on the education for women equality and has launched various scheme as;-SarvaShikshaAbhiyan; Kasturba Gandhi BalikaVidyalya Scheme (KGBVS); District Primary Education Programme (DPEP); MahilaSamakhy a (MS);Mid-day Meal Scheme (MDMS); The Total Literacy Campaign (TLC); Non formal Education System etc. Moreover, in India gender equality issues in education have been studied for several decades. But, gender equality in education based on systematic research is necessary precondition forformulation of inclusive educational policies that would not leave out a single girl or boy. It is therefore important to gain insight into the overall situation of teachers as well as their behaviour and attitudes towards their pupils. (NarayanraoandGingine; 2016).

Thus, the above mention scheme helps the girl children to access education on priority bases. With the help of education, genderequality in educational institutes can create awareness among the children, parents and other members of the community about their roles in future as the men and women in the society. Although presently,gender has been accepted as a main category in the formulation of policy and curricula framework in India. Moreover, women and gender studies also becomes the main subject and a stream to study at higher level of education.

Gender Inequality And Educational Institutes: This is the responsibility of educational institutes to ensure that all the students should be sensitized to gender and learned to respect each-other without gender bias. Children in a school come from such types of societies where there is a male dominate societies. Usually father is head of the family; male child is given more freedom rather than girl child. There may be possibilities of gender discrimination within the school premises between peer groups or by teachers. Thus, with the help of educational institutes can create awareness towards gender equality in schools and make the children to understandable their roles for presentand future about as the men and women in the society. The main concern of educational institutes should be to increase the sensitivity of people at large towardswomen equality and their problems, so that students can develop right perception about women who have equal role, rights, status and significance in decision making at every field of life. Overall stereotypical image related with women should not be seen longer in the mind-set of men. Gender sensitization is first instance, tends to change the perception that men and women have equal to each other. Education institutes should also promote leadership qualities among the girls so that they can get strengthen to fight with every challenge in their life.

A comprehensive school programmes should be introduced that address to thegender issues and can make a constructive impact on the minds of the studentsregarding gender equality. The various co-cerricular activities like discussion, seminar, plays, slogan writing, fancy dress competitions, elocution, debate,essay writing, story writing, poem writing, workshops and campaigns, clubs activates focus related issues on current women problems & gender sensitization issues & introduced self defence lessons etc. should be organized on the possiblethemes and related activities to promote gender sensitivity and also complementto co-existence of men and women.

As well as educational institutes shouldorganize some community based activities and programmes on gender equalitywithin the institutes and also outside of the institutes that involve the parents, stakeholders and teachers. Thus, both kinds of activities inside and outsideof institutes can play a significance role for gender equality. Moreover, the Education institutes should involve the media in sensitizing gender based issues sothe awareness can be created in among the masses. In the same line, Gingine andNarayanrao (2016), described that "gender sensitivity in early childhood education-equal encounter in nursery schools to plan and implement training for kin-dergarten professionals about equality education. The goal was the promote gender equality in the pedagogical work in finish speaking kindergartens throughresearch, education and engagement in the debates of educational policy."To sensitize the people towards gender, all of the educational institutes' administrations, teaching and other staff and also students should treat with dignity andequality to men and women both. The institutes should also arrange discussionson the all concerns related with female rights and their roles in the society duringthe parents' teacher meetings. Thus, if all educational institutes take care of theseactivities then gender inequality will not be an issue to think and work for along time. Moreover, this is the power of education that can make a great socialchange in the society at large. Presently, a gender and women study has become amain subject of study at higher level of education. It is also included in the syllabus of teacher education, so that pupil teacher can learn how to deal with issuesrelated with gender inequality in a smooth manner. Thus, all the possible concerns should be made by the educational institutions to promote the genderequality in education access, learning process and educational outcomes.

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Conclusion: India needs to deactivate the gender inequality. The needs of the day are trends where women are able notonly to break out of the culturally determined patterns of employment but also to offer advice about careerpossibilities that look beyond the traditional list of jobs. It is surprising that in spite of so many laws, womenstill continue to live under stress and strain. According to Baredia (2015) that "gender sensitization through education can be as a forceful, effective and primary tool to bringchange in the thought process of students through formal school education. Themain focus should be on breaking the stereotypes and set patriarchal notions prevalent in the society. The time has come for women to rise up and force the patriarchal society to underline the importance and necessity of the role played bywomen in cultivating a strong, rational and progressive society."To ensure equality of status for our women we still have miles to go.Man and Woman are like two wheels of a carriage. The life of one without the other is incomplete.

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g) Promote basic and applied researches on Ecosystems and Biodiversity Conservation and help the institutions through guiding information to conserve ecosystems, biodiversity and mobilize its benefits.

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BIODIVERSITY IN BUSINESS AND ENTERPRISES

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Introduction

All companies can have an impact on biodiversity in the course of their business because they use natural resources, produce or consume products, own and manage areas of land, or finance other activities which have direct and indirect impacts. Biodiversity is recognized as being key in ensuring a stable environment for businesses to operate in. All business depends on biodiversity and ecosystem services, directly or indirectly; most businesses also have impacts on nature, positive or negative. Some business like forestry, fishing, agriculture, ecotourism, and pharmaceuticals are direct dependants whereas there are sectors which have a direct impact on ecosystems and biodiversity through their operations, such as mining, construction, and energy. In our country India, the lives and livelihoods of a large number of rural poor people is dependent on the sustainable use of biological resources. The business case for biodiversity management is strong and so are the challenges.

Dependence on Biodiversity and Ecosystem Services

The links between business, biodiversity and ecosystem services vary across sectors and even within sectors. These links depend on the location of the business, the source of its raw materials, in some cases the location of its

customers, and the production technology employed. Broadly, these links can be grouped into business impacts on biodiversity, on the one hand, and business dependence on ecosystem services on the other. In each case it is important to look beyond direct impacts and dependence, to consider the indirect links arising through business value chains. This section provides an overview and some concrete examples of business impacts and dependence on biodiversity and ecosystem services, across a range of sectors.

• **Agriculture**

The agriculture sector faces a growing dilemma: it needs to feed a rapidly growing and increasingly comfortable global population while also conserving biodiversity and sustainably managing natural resources on an increasingly exhausted planet. The need for increased food production is meanwhile constrained by poor land management and lack of means, financial and technological to maintain, let alone enhance productivity. Agriculture as a sector is the biggest land manager in the world and provides important habitats for many wild plant and animal species. At the same time, extensive land clearing for farming, and especially for large-scale intensive crop production and livestock, is one of the main drivers of biodiversity loss. Agricultural productivity is heavily dependent on numerous species and ecosystem services, including soil micro-organisms, natural and domesticated pollinators and pest predators, the genetic diversity of crops and livestock, as well as freshwater supplies, climate regulation and nutrient cycling.

• **Forestry**

Forest ecosystems are important habitats for many wild plant and animal species, and the forestry industry depends on numerous ecosystem services, including freshwater supply, climate regulation and nutrient cycling. Sustainable forest management has a large role to play in biodiversity conservation and mitigating climate change. On the latter point, not only do forests and wood products act as carbon sinks, but the main industrial outputs of the forest products industry timber and pulp are renewable if managed sustainably. In addition, compared to other common building materials like cement, steel and aluminum, wood-based building materials require less energy for production, have higher thermal efficiency, and can be reused, recycled, or used as bio-mass for energy. While forest loss is primarily driven by expanding agriculture, unsustainable commercial logging activities are nevertheless a significant contributor to forest and biodiversity loss around the world. Both legal and illegal logging activities can also indirectly affect biodiversity through the construction of logging roads habitat fragmentation, which can facilitate small-scale mining, hunting, illegal logging, fishing and settlement within previously untouched forests. The forestry industry, especially the pulp and paper sector, is relatively energy intensive. However, wood-based biomass is often used as a fuel that, if sourced from a sustainably managed forest, is carbon neutral or near carbon neutral. Overall, production processes in the forest products industry make a relatively small contribution to climate change.

• **Mining and Quarrying**

With the exception of supplies of freshwater for mineral processing, the mining industry is not directly dependent on biodiversity or ecosystem services. However, it has a number of significant direct and indirect impacts on BES which if ignored can create major risks to mining operations. One of the main direct impacts comes from surface mining, whereby overlying habitats and geological features are removed during the extraction of minerals. Other disturbances to plants and animals during the quarrying process include noise, dust, pollution and removal and storage of waste. While the

process of quarrying itself is mainly associated with negative impacts, a growing number of companies are beginning to use biodiversity offsets to compensate for residual impacts that cannot be mitigated onsite, while also investing in ecological restoration and rehabilitation on former mine sites.

The indirect impacts of mining on biodiversity and ecosystems include pollution and water used during refining and smelting processes. Mining operations can also have significant indirect impacts on biodiversity sensitive areas by developing roads that provide access to areas that were previously underdeveloped and inaccessible, leading to immigration and accelerated conversion of habitat.

• **Oil and Gas**

The oil and gas sector delivers a range of products to end users, including fuel, electricity and derivatives of oil-like plastics and lubricants. Like the mining sector, most parts of the oil and gas sector are not directly dependent on biodiversity and ecosystems services except for supplies of freshwater. In terms of direct biodiversity impacts, the industry can be split between upstream exploration, production, downstream, marketing and distribution activities. The most obvious impacts on biodiversity are from upstream activities seismic studies, drilling, construction, production, maintenance and transportation. Although significant progress has been made to reduce these impacts, environmental gains have been overwhelmed by increased consumption and demand for energy, and increasing exploration and production in sensitive environments, such as deep water drilling, oil sands and the arctic. The industry also has significant indirect impacts on biodiversity due to the emission of greenhouse gases from upstream and downstream activities, and from the consumption of oil and gas products.

• **Cosmetics**

The cosmetics sector relies on biodiversity for many natural ingredients. As the variety of species and habitats continue to decline, both the quality and quantity of these natural ingredients may be jeopardized. This example illustrates that compensation for adverse environmental impacts is not only an important means for companies to maintain their license to operate, but can deliver overall improvements in ecosystem services with substantial economic benefits at modest expense. A renewed focus on natural ingredients is apparent throughout the food and cosmetics sectors. Consumer concerns about health and adoption of more 'wholesome' lifestyles are important market drivers, as affluent consumers are keen to buy products that enhance or are perceived to enhance their well-being.

• **Water Supply and Sanitation**

The water sector is highly dependent on ecosystems for sustainable and cost-effective operations. The quantity and quality of water depends on functioning aquatic ecosystems, including lakes, rivers, streams and wetlands, as well as local bio-physical processes and land-use practices. Ecosystem services important to water utilities include:

- Protection of water quality and quantity through the water cycle and hydrological processes throughout a catchment area
- Riparian vegetation filtering water, removing impurities and reducing erosion
- Catchment rehabilitation processes following natural events such as flood and fire Flood protection
- Assimilative capacity of large waterways and the ocean for waste water discharge and treatment
- Microbiological purification of wastewater
- Other ecosystem services associated with intact watershed catchments e.g., carbon sequestration, pollination, bio-banking and

biodiversity offset value, recreational and cultural values.

• **Transport**

Transport within business comprises specialist transport and logistics companies as well as distribution, logistics and transport departments within larger companies. Covering air, road, rail and sea transport, this sector is characterized more by its impacts on biodiversity than by its dependence on ecosystem services. Typical risks to biodiversity relate to transport infrastructure e.g. land take and pollution associated with developing and operating roads, ports and depots, incidents such as ship groundings on corals and oil spills, and operational externalities such as emissions of carbon and particulates.

• **Manufacturing**

The impacts of manufacturing industry on biodiversity are both direct and indirect, reflecting the footprint of facilities and the pollution arising from production processes, as well as the impacts of suppliers of raw materials or semi-finished goods.

• **Finance**

The impacts of the financial services industry on biodiversity are indirect but nevertheless can be very significant. While financial institutions are not directly dependent on ecosystem services, they are exposed to BES risks through the loans, investments and insurance cover they provide to companies and projects. The banking sector uses at least four strategies to manage biodiversity risks: 1) 'Red-lining' investments in areas of high biodiversity; 2) Developing sector guidelines for environmentally sensitive sectors; 3) Refraining from financing sectors in which a bank lacks specialist knowledge; and 4) Working together with borrowers to improve their environmental performance and mitigate harm through an engagement policy.

Conclusion

The conservation community should work to improve techniques for monitoring conservation outcomes of specific measures, and should remain vigilant about the quality of impact assessments and subsequent implementation of mitigation actions. The biodiversity and impact assessment community should seek opportunities to work with those companies within the private sector that are positioned to take action in integrating biodiversity into impact assessment practices and guidance. This can benefit the conservation community both by delivering conservation outcomes on the ground around the projects that develop under this improved planning process, and by gaining access to more and better information about the status and trends of biodiversity. At the same time, the biodiversity and impact assessment community should be looking to work with governments to establish stronger regulatory frameworks that require biodiversity to be integrated into all impact assessments, regardless of which company is implementing the project.

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THE CONCEPT OF 'CLOUD COMPUTING'

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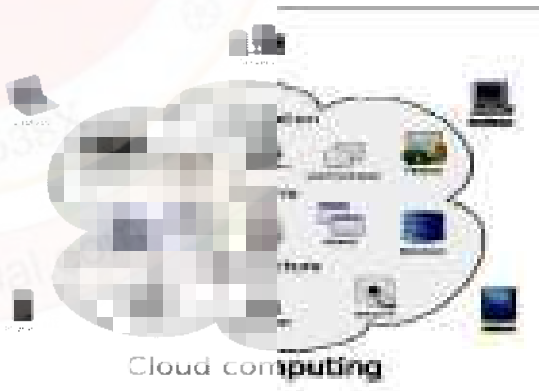
ABSTRACT

In the field of computing, a lot of changes have been observed due to the increased use and popularity of the Internet and the availability of high-speed networks.
Resource sharing in a pure plug and play model that dramatically simplifies infrastructure planning is the promise of "Cloud computing".
Cloud computing is becoming an increasingly popular enterprise model in which computing resources are made available on-demand to the user as needed.
Cloud computing[1] is the development of parallel computing, distributed computing, grid computing and virtualization technologies which define the shape of a new era. Cloud computing is an emerging model of business computing.
The paper aims to provide a means of understanding the model and exploring options available for complementing your technology and infrastructure needs. Also explore some of the basics of cloud computing with the aim of introducing aspects such as:
Realities and risks of the model
Components in the model
Characteristics and Usage of the model.
This work aims to provide the ways to reduce security risk & also promotes the performance of cloud computing

Keywords: *Cloud computing, architecture, Cloud systems, SLA, SaaS, Paas, Iaas, daas, Cloud Service Provider, Cloud computing metaphor.*

INTRODUCTION

The term "Cloud Computing" [2] is everywhere. Simply put, cloud computing is computing based on the Internet. In the past, people would run application or programs from software downloaded on a physical computer or server in their building. Cloud computing allows access from the same kinds of applications through the internet on a virtual server.
It is the new computing example which provides large pool of dynamical scalable and virtual resources as a service on demand. Cloud computing is a complete new technology. It is the development of parallel computing, distributed computing
grid computing, and is the combination and evolution of Virtualization, Utility computing. The main principle of cloud computing representation is to offer computing, storage, and software as a service,(SaaS), Platform as a Service (PaaS), Infrastructure as a Service (IaaS),) or as a utility, Data as a Service(Daas). We just by using the need internet.



Cloud computing metaphor: Cloud is a metaphor[9] to describe web as a space where computing has been pre installed and exist as a service; data, operating systems, applications, storage and processing power exist on the web ready to be shared. the group of networked elements providing services need not be individually addressed or managed by users; instead, the entire provider-managed suite of hardware and software can be thought of as an amorphous cloud.

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AMRAVATI

"Cloud is a parallel and distributed computing system consisting of a collection of inter-connected and virtualized computers based on service-level agreements (SLA) which established through cooperation between the service provider and consumers."

Cloud computing is a computing example, where a large pool of systems are connected in private or public networks which provide dynamically scalable infrastructure for application, data and file storage.

Cloud computing is a practical approach for to experience direct cost benefits and it has the potential to transform a data center from a capital-intensive set up.

The idea is based on a very fundamental principal of reusability of IT capabilities'. The difference is that to bring compared to traditional concepts of "grid computing", "distributed computing", "utility computing", or "autonomic computing".



Fig. 1: Cloud computing concept

Fig. 1 shows [8] that how users can connect to the cloud services which are provided by cloud service provider by using any device over the internet. It includes scalable resources in storage, network, and compute & also contain virtualized infrastructure and provide that services to the users.

Forrester defines cloud computing as:

"A pool of abstracted, highly scalable, and managed compute infrastructure capable of hosting end-customer
applications and billed by consumption."



It cuts the operational and capital costs and permits the IT departments to focus on strategic projects instead of keeping the datacenter running. It provides the services on Infrastructure level, Platform level, and Software level, many features such as speed, scalability of resources, parallel processing, to choose another technology at any time to further work like 24/7 availability of services, device and location independent and security etc. Cloud computing has five essential features such as rapid elasticity, measured services, on-demand self-service, resource pooling, and board network access. as shown in Fig. 2.



Fig. 2: Five features of cloud computing

CLOUD COMPUTING MODELS

Cloud service Providers [4] following 4 types of Models:-

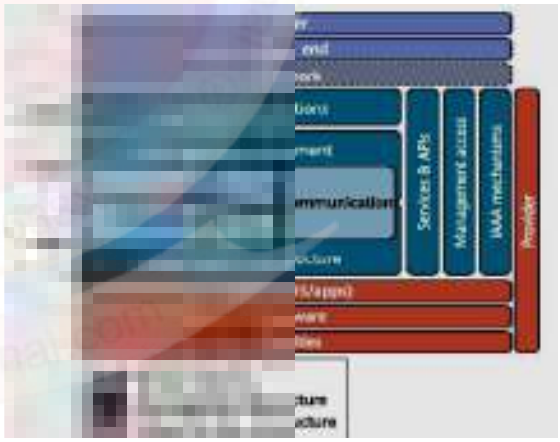


Fig.3: The Cloud reference architecture

Cloud reference architecture [11] that makes the most important security-relevant cloud components explicit and provides an abstract overview of cloud computing for security issue analysis.

1. Software as a Service (SaaS): In this model,[12] a complete application is offered to the customer, as a service on demand. A single instance of the service runs on the cloud & multiple end users are serviced. Today SaaS is offered by companies

such as Googlemail, Salesforce.com, Microsoft, Zoho, etc.

2. Platform as a Service (Paas): a layer of software or development environment is encapsulate & offered as a service, upon which other higher levels of service can be built. In this model The customer has the freedom to build his own applications, which run on the provider‟s infrastructure. PaaS providers offer a predefined combination of OS and application servers, such as LAMP platform (Linux, Apache, MySql and PHP), classified J2EE, Ruby etc. Google's App Engine, Force.com, etc

3. Infrastructure as a Service (Iaas): IaaS provides basic storage and computing capabilities as standardized services over the network. The basic strategy of virtualization is to set up independent virtual machines (VM) that are isolated from both the underlying hardware and other VMs. Servers, storage systems, networking equipment, data centre space etc. The customer would typically deploy his own software on the infrastructure. Some common examples are Amazon'EC2, GoGrid, 3 Tera, etc.

DATA AS A SERVICE (DAAS): DAAS

Delivery of virtualized storage on demand becomes a separate Cloud service - data storage service. Notice that DaaS could be seen as a special type IaaS. DaaS allows consumers to pay for what they are actually using rather than the site license for the entire database. In addition to traditional storage interfaces such as RDBMS and file systems.

Some common examples are Amazon S3, Google BigTable, and Apache HBase, etc.



Public, Private & Hybrid Cloud:-

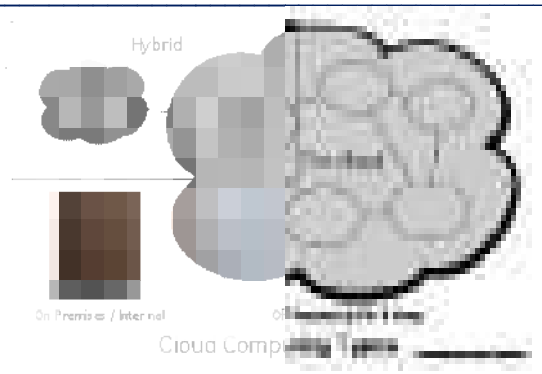


Fig. 3: Types of Cloud Deployment Model

Public Cloud

Public clouds are owned and operated by third parties; they deliver better economies of scale to customers, as the infrastructure costs are spread among a mix of users, giving each individual client an attractive low-cost, "Pay-as-you-go" model. One of the advantages of a Public cloud is that they may be larger than an enterprises cloud, thus providing the ability to scale seamlessly, on demand.

Private Cloud

Private clouds are built exclusively for a single enterprise. They aim of Private Cloud is to address concerns on data security.

There are two variations to a private cloud:-

- On-premise Private Cloud: also known as internal clouds are hosted within one own data center.
- Externally hosted Private Cloud: This type of private cloud is hosted externally with a cloud provider.

Hybrid Cloud

Hybrid Clouds combine both public and private cloud models.. The Hybrid cloud environment is capable of providing on-demand, externally provisioned scale.

Cloud Computing Characteristic:-

1: Dynamic computing infrastructure
2: IT service-centric approach
3: Self-service based usage model
4: Minimally or self-managed platform
5: Consumption-based billing
6. Reduced Cost
7. Increased Storage
8. Flexibility
9. Data Protection
10 Data Recovery and Availability
11. Management Capabilities
12. Disaster Recovery
13. Automatic Software updates
14. Free Capital- expenditure
15. Work from anywhere

16. Document control
17. Security

ADVANTAGES OF CLOUD COMPUTING

(1) Shared Resources:
it shares resources to provide the services to multiple users.
(2) Pay-As-You-Go:
Users only need to pay those resources which are used by them. They can demand for more resources if they required
(3) Better Hardware Management:
It is easy for cloud service provider (CSP)[4] to manage the hardware easily because all computers run the same hardware.

Area of Cloud Computing:
1. Banking
2. Insurance
3. Weather Forecasting
4. Space Exploration
5. Software as a service
6. Platform as a Service
7. Infrastructure- as -a-Service
8. Data-as-a-service

MOTIVATING FACTORS AND CHALLENGES

Cloud systems [15] are not just another form of supply provisioning transportation and in fact, have multiple opportunities from the principles for cloud infrastructures that will enable further types of applications, compact development and provisioning time of different services.

APPLICATIONS

There are a few applications of cloud computing [6] as follows:
1) Cloud computing provides dependable and secure data storage center.
2) Cloud computing can realize data sharing between different equipments.
3) The cloud provides nearly infinite possibility for users to use the internet.
4) Cloud computing does not need high quality equipment for the user and it is easy to use.
Scope:-
Cloud computing is a tremendous innovation in the digital landscape that has changed the way IT solution are delivered and how end-users put them tom use. The cloud computing aspect is growing and will continue to do so.

CONCLUSION

Cloud computing is a new technology of computer network, providing the web services at lower cost comparing to normal technique. It contribute to improve the service in other related technologies like,
Grid Computing, Cluster Computing,
Utility Computing / Automatic Computing
Distributed Computing
With cloud computing, to the interface between service suppliers and multiple groups of service consumers. Cloud services will demand expertise in distributed services, procurement, risk assessment and service negotiation — these are the areas that many enterprises are only modestly equipped to handle.

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FIDOOP ALGORITHM : DATA HIERARCHY AND PARALLEL MINING OF FREQUENT ITEMSETS USING MAP REDUCE

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ABSTRACT

In Existing parallel mining algorithms are deficient in some of the features like parallelization of sequential code, distribution of data over computers in a cluster and balancing load over cluster of computers. To overcome these problems, FIDoop uses parallel mining algorithms on the basis of I/O overhead, data distribution, storage, scalability, load balancing, automatic parallelization and fault tolerance. FiDoop algorithm uses the ultrametric tree pattern for storage of data. This technique incorporates three MapReduce job to mine the large amount of data conventionally and economically.
In first MapReduce job , it minimizes I/O overhead by scanning the database twice ,all frequent itemsets are discovered.
In second MapReduce job is FIU-tree an improved way to partition a database, which results from clustering transactions, and significantly reduces the search space, it removes infrequent itemstes.
Third MapReduce is most important, it construct small ultrametric trees which is helpful to mine the frequent data conventionally and economically which significantly reduces computing time.
FiDoop algorithm is implemented in Hadoop cluster. For high dimensional data, FiDoop-HD is used, it is an improved version of FiDoop. FiDoop using FIUT and Map Reduce programming model

Key words: *Automatic parallelization, Scalability , Frequent item sets, frequent items ultrametric tree (FUIT), Map Reduce, FiDoop,load balance.*

INTRODUCTION

The existing mining algorithm lacks in some areas like it is expensive to mine the required data, the time required to mine the data is more, it require more storage while processing the data. The existing system uses the FIUT(frequent itemset ultrametric tree), but it lacks some of the features like parallelizing the data. To overcome this problem FiDoop algorithm is introduced.
FiDoop algorithm overcomes these problems. In FiDoop algorithm the data is decomposed and with the help of ultrametric tree the data is stored. With ultrametric tree we can mine our data or we can FIU-tree is a tree structure constructed as follows, the FIU-tree to enhance the efficiency of mining frequent itemsets.
After the root is labeled as null, an itemset p1, p2, . . . , pm of frequent items is inserted as a path connected by edges (p1, p2), (p2, p3), . . . , (pm−1, pm) without repeating nodes, beginning with child p1 of the root and ending with leaf pm in the tree. An FIU-tree is constructed by inserting all itemsets as its paths, each itemset contains the same number of frequent items. Thus, all of the FIU-tree leaves are identical height. Each leaf in the FIU-tree is composed of two fields: named item-name and count. The count of an item-name is the number of transactions containing the itemset that is the sequence in a path ending with the item name. Non leaf nodes in the FIU-tree contains two fields: named item-name and node-link. A node-link is a pointer linking to child nodes in the FIU-tree.
get our data very easily, we do not have to scan the tree again and again to get our data. FiDoop uses some special scheme to distribute the data over nodes of the cluster. For high-dimentional data, FiDoop-HD is used. The FiDoop has some special features like parallization of sequential data which improve the performance of data mining.
To distribute the data over nodes so that it does not degrade the performance by over loading the data at one node in a cluster.
The three Map Reduce jobs are performed in FiDoop.

FIUT

The FIUT algorithm consists of two key phases. The first phase involves two rounds of scanning a database. The first scan generates frequent one-itemsets by computing the support of all items, whereas the second scan results in k-itemsets by pruning all infrequent items in each transaction record. Note that, k denotes the number of frequent items in a transaction. In phase two, a k-FIU-tree is repeatedly constructed by decomposing each h-itemset into k-itemsets, where $k + 1 \leq h \leq M$ (M is the maximal value of k), and unioning original k-itemsets. Then, phase two

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starts mining all frequent *k*-itemsets based on the leaves of *k*-FIU-tree without recursively traversing the tree. Compared with the FP-growth method, FIUT significantly reduces the computing time and storage space by averting overhead of recursively searching and traversing conditional FP trees.

Scan results in *k*-itemsets by pruning all infrequent items in each transaction record. Note that, *k* denotes the number of frequent items in a transaction. In phase two, a *k*-FIU-tree is repeatedly constructed by decomposing each *h*-itemset into *k*-itemsets, where $k + 1 \leq h \leq M$ (*M* is the maximal value of *k*), and unioning original *k*-itemsets. Then, phase two starts mining all frequent *k*-itemsets based on the leaves of *k*-FIU-tree without recursively traversing the tree. Compared with the FP-growth method, FIUT significantly reduces the computing time and storage space by averting overhead of recursively searching and traversing conditional FP trees.

MAPREDUCE FRAMEWORK

MapReduce is a promising parallel and scalable programming model for data-intensive applications and scientific analysis. A MapReduce program expresses a large distributed computation as a sequence of parallel operations on datasets of key/value pairs. A MapReduce computation has two phases, namely, the Map and Reduce phases. The Map phase splits the input data into a large number of fragments, which are evenly distributed to Map tasks across the nodes of a cluster to process. Each Map task takes in a key-value pair and then generates a set of intermediate key-value pairs. After the MapReduce runtime system groups and sorts all the intermediate values associated with the same intermediate key, the runtime system delivers the intermediate values to Reduce tasks. Each Reduce task takes in all intermediate pairs associated with a particular key and emits a final set of keyvalue pairs. Both input pairs of Map and the output pairs of Reduce are managed by an underlying distributed file system. MapReduce greatly improves programmability by offering automatic data management, highly scalable, and transparent fault-tolerant processing. Also, MapReduce is running on clusters of cheap commodity servers—an increasingly attractive alternative to expensive computing platforms. Thanks to the aforementioned advantages, MapReduce has been widely adopted by companies like Google, Yahoo, Microsoft, and Facebook.

Hadoop—one of the most popular MapReduce implementations—is running on clusters where Hadoop distributed file system (HDFS) stores data to provide high aggregate I/O bandwidth. At the heart of HDFS is a single Name Node—a master server that manages the file system namespace and regulates access to files. The Hadoop runtime system establishes two processes called Job Tracker and Task Tracker. Job Tracker is responsible for assigning and scheduling tasks; each Task Tracker handles Map or Reduce

FIDOOP

In light of the MapReduce programming model, we design a parallel frequent itemsets mining algorithm called FiDoop. The design goal of FiDoop is to build a mechanism that enables automatic parallelization, data distribution and load balancing for parallel mining of frequent itemsets on large clusters. To facilitate the presentation of FiDoop. Aiming to improve data storage efficiency and to avert building conditional pattern bases, FiDoop incorporates the concept of FIU-tree .

1. METHODOLOGY

first MapReduce job is responsible for creating all frequent one-itemsets. A transaction database is partitioned into multiple input files stored by the HDFS over data nodes of a Hadoop cluster. Each mapper sequentially reads each transaction from its local input split, where each transaction is stored in the format of pair. Then, mappers compute the frequencies of items and generate local one-itemsets.

Second MapReduce Job: Given frequent one-itemsets generated by the first MapReduce job, the second subsequent MapReduce job applies a second round of scanning on the database to prune infrequent items from each transaction record. The second job marks an itemset as a k-itemset if it contains k frequent items ($2 \leq k \leq M$, where M is the maximal value of k in the pruned transactions).

Third MapReduce Job: The third MapReduce job,a computationally expensive phase is dedicated to: decomposing itemsets; constructing k-FIU trees; mining frequent itemsets. The main goal of each mapper is twofold: 1) To decompose each k-itemset obtained by the second MapReduce job into a list of small-sized sets, where the number of each set is anywhere between 2 to $k - 1$ and 2)to construct an FIU-tree

by merging local decomposition results with the same length.

6. LOAD BALANCE

The *decompose*() function of the third MapReduce job accomplishes the decomposition process. If the length of an itemset is *m*, the time complexity of decomposing the itemset is *O(2m)*. Thus, the decomposition cost is exponentially proportional to the itemset's length. In other words, when the itemset length is going up, the decomposition overhead will dramatically enlarge. The data skewness problem is mainly induced by the decomposition operation, which in turn has a significant performance impact on FiDoop. The first step toward balancing load among data nodes of a Hadoop cluster is to quantitatively measure the total computing load of processing local itemsets. We achieve this first step by developing a workload-balance metric to quantify load balance among the data nodes.

7. PERFORMANCE ANALYSIS

The efficiency of the system can be analyzed in terms of time taken by the FP-Tree and FIU-Tree algorithms in generating the Frequent Itemsets. We compare the performance of the system with the Fidoop system.

In Table 7.1 shows the time taken to create the Frequent Itemsets of different transactions size. From the Table, it is clear that the amount of time taken to generate frequent itemsetsby FP-Tree algorithm is around 1.5 times slower than the FIU-Tree for the same input.

FP-Growth Tree				FIU- Tree			
S. No	No. of Records	Support Value	Time	S. No	No. of Records	Support Value	Time
1.	10	0.1	10.002	1.	10	0.1	1.31
2.	20	0.1	20.00	2.	20	0.1	2.44
3.	50	0.1	100.05	3.	50	0.1	6.54
4.	100	0.1	212.04	4.	100	0.1	14.98

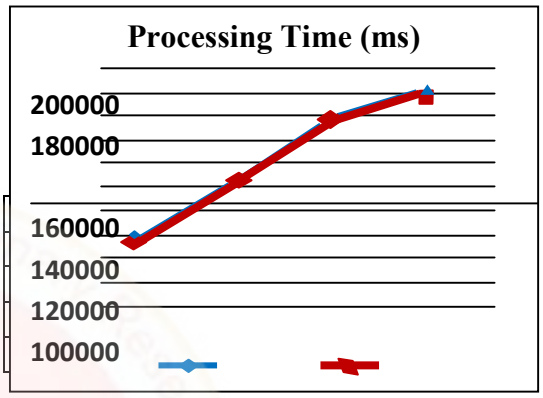
Table :7.1

8. ADVANTAGES

8.1 Processing time

Processing time is defined as the time it takes to complete a prescribed procedure.

This graph shows the processing time. When compared to the existing method, there is less processing time in the proposed method.



9. CONCLUSION

This paper, proposed the FiDoop based parallel mining of frequent item set using map reduce. To solve the scalability and load balancing challenges in the existing parallel mining algorithms for frequent itemsets,the MapReduce programming model to develop a parallel frequent itemsets mining algorithm called FiDoop. FiDoop incorporates the frequent items ultrametric tree or FIU-tree rather than conventional FP trees, thereby achieving compressed storage and avoiding the necessity to build conditional pattern bases. FiDoop seamlessly integrates three MapReduce jobs to accomplish parallel mining of frequent itemsets.

An important role of the third MapReduce job plays in parallel mining; its mappers independently decompose itemsets whereas its reducers construct small ultrametric trees to be separately mined. We improve the performance of FiDoop by balancing I/O load across data nodes of a cluster. We enhance the execution of FiDoop by adjusting I/O load crosswise over information hubs of a group.

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How to Raise Kids who will Believe in Gender Equality

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Introduction: *As we all are aware of a well known quote by Simone de Beauvoir from her book 'The Second Sex' is " One is not born but becomes a woman". With this famous phrase Beauvoir first articulated what has come to be known as the sex-gender distinction, that is, the distinction between biological sex and the social and historical construction of gender and its attendant stereotypes. The fundamental source of woman's oppression, Beauvoir notes its historical and social construction as the quintessential Other. De Beauvoir defines women as the " second sex" because women are defined in relation to men, In other words sex is determined by nature but gender is determined by society. Thus in modern time awareness for gender equality in society is going to start in various ways. Among them there is a stream of thought that achieving gender equality through art of parenting i.e. to raise kids who believe in gender equality. We all want our children to grow up to be caring, thoughtful and socially conscious people. Part of this means raising them to believe in and stand up for gender equality.*

There are number of stages of upbringing of kids in natural way and as a parent these stages can be used for the kids to become more humane socially . A gist of the present paper is that how parents can give their children both girls and boys the solid foundation they need to become the feminists of tomorrow.

Learning through observation: Social learning science teaches us that children's development happens through observation and imitation. Modeling parents own feminism can mean anything from showing love for their body to filing a complaint with a local retailer for running a sexist ad campaign. No matter where parents are on the activist spectrum. Let your kids see your feminism in action.

Find everyday opportunities to walk your talk. A parent can raise their kids in a household where there always use gender neutral pronouns . For example in Marathi language " aag tikde ja" instead of using "aag" we as a parent can use " tu tikde ja" . Instead of buying doll as a toy for girls and plane or helicopter for boys as a parent we must buy any toys whatever girls like rather we should promote them to buy plane, car, etc.

Acknowledge the parenting power of fathers: Break the biological determinism that says women means parenting and men means working out. Today's dads come in many forms : they can be single or married ; externally employed or stay at home gay or straight; adoptive or step-parents. What do we know is that dad's affection and increased family involvement help promote children's social and emotional development.

Start early: It is never too early to start talking about equality with your children. Find opportunities in everyday life for teachable moments.

Teach them that gender is fluid: Gender is one of the first social categories children become aware of . By the time they are 3 years old, they have formed their gender identity. So much of what limits boys and girls is rooted in socially constructed ideas about what one is or isn't permitted to do within their gender. Let your children take the lead and experience their gender with as much fluidity as they wish.

Teach them about healthy sexuality: Teaching your kids about healthy sexuality is as important as teaching them about safety, nutrition and acceptable social behaviour. It's important to be both helpful and approachable as a parent .

- *Start conversations about sexuality rather than waiting to be asked.
- *Give them real names for their body parts.
- *Give honest answers about sex and sexuality.
- *Assure them that you will answer any question about sex no matter how awkward or uncomfortable the topic might be.

Teach them about body autonomy and how to exercise their own consent.

Body autonomy is the right control over own body and to decide what happens to it. Allowing your kids to exercise their own consent (in ways that are age appropriate) ensures that they grant the same body autonomy to others. Some ways to empower your kids to practice body autonomy include:

- *Giving them a say when it comes to when they eat or sleep (within reason)
- *Telling them they have right to say stop when they feel uncomfortable, regardless of who the person is .
- *Giving them real names for body parts.
- *Never forcing them to hug or kiss people (including grown- up and family members)

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*Teach them to respect others when they say no or stop .

*Trusting their abilities in age-appropriate ways.

Teach them emotional intelligence: According to psychology today emotional intelligence is the ability to be aware of, control and express one's emotions. Children with high EQ become empathetic, engaged and nurturing adults who respect and value others.

Parent can teach their son empathy by making gender equality issues personal to them by asking such type of questions " How would you feel if that happened to him\ his mom \dad and their family members".

Encourage them to celebrate diversity: " kids don't come with instructions but they do come with open minds " said Dr. Christopher Metzler. As parents, we are positioned to guide our children to appreciate the differences that make each of us unique. Explaining diversity in a way that is understandable to kids can be challenging, but is integral to raising kids who treats others fairly.

Conclusion: Here are a few tips to get started:

- Recognize that you may hold your own conscious or unconscious biased and work on addressing them.
- Talk to your kids about stereotypes : how they can be divisive and don't always tell the whole story.
- Find age appropriate ways to bring diversity into your children's lives. And not just of thought, experience, socio-economic status, sexual orientation and identity- etc.

Thus through above mentioned ways, we, as parents can raise our children with the basic ideals of gender equality. Welcoming, adopting and practicing such patterns of behaviour has become must today. In the globalized world, things are changing in a fast rate. The age old norms, definitions and codes of behaviour are changing with a fast rate. In order to keep a pace with the changing time, we need to nurture these ideologies for the betterment of future generation. After all it is well said, "Charity Begins at Home".

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Changing Language Teaching Methodologies: The Need of the Day

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Abstract:

Language is a complex specialized proficiency which gets developed spontaneously without conscious effort or formal instruction without awareness of its underlying logic. So language teachers need to use some strategies to teach effectively. Apart from it, English language teachers need to utilize innovative ideas in their teaching because in our country English is learnt as a second language. This paper analyses the innovative and quite interesting methods we have in teaching English language. We may have a number of teaching methods in between traditional and modern. Everybody has his own understanding and conclusions on teaching English language. But this paper portrays combining this two types how we can make our teaching very effective. We have been completely bounded with traditional methods of teaching and understanding where the present day learners felt uncomfortable a bit. Learner's mind will never be static it is ever growing and ever changing. The study is based on secondary data.

Keywords: Language, strategies, innovative, portrays, traditional, growing, changing,

1.1 Introduction:

The importance of language cannot be underestimated, because it is the vehicle of thought and communication. The English language is a national and international medium of communication. By so doing, it has led to the exchange of feelings and effects which has contributed tremendously to the socio-economical and political development of any state. The poor performances in English language in most schools/colleges are due to the fact that the teaching is textbook-based. Teachers do not have regular supply of the teaching aids and where they are available they are inadequate and obsolete. This paper stresses the need for making English language lessons easy and enjoyable through the use of instructional aids/ improvisations. It presents innovative methods and techniques to teach English language by using various teaching aids. It also aims to make English teachers aware of the strategies to use it in an effective manner.

1.2 Advantages of Using Innovative Methods:

" Adds interest, involvement and brings the world into the classroom;
" Makes learning permanent;
" Develops greater understanding;
" Stimulates self-activity;
" Fosters continuity of thought;
" Makes teaching effective;
" Helps in overcoming language barriers; and
" Provides a great variety of methods.

1.3 Problems with Current Methodologies:

It is of paramount importance that the teacher should know what his/her task is and what he/she is trying to achieve by teaching English. They go on with their job of teaching without knowing the difficulties of the learner. The teacher should be fully aware of the fact that his student's proficiency in English is not up to mark owing to the deteriorating standard of teaching in
is taught in a
teaching is ne

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the formation of the words is essential and a must. But there is something that is even more important. The student must be able to speak the words and understand their meaning before writing them down. The foundation to teach English can only be taught using the orthodox methods of teaching the alphabets and the words and the rules. But then teaching only the grammatical rules is found to be boring by most students and it is because of this that they lose interest in learning the language. Although there is no way other than the traditional one to teach the basics of the language these methods must be tweaked a bit so as to appeal to the students. When it comes to teaching English to students of higher classes who are supposed to have the basics the traditional methods generally tend to yield poorer results that innovative methods. This has already been proven by methods implemented like use of stories, poems, movies, books and newspapers etc. These methods help the students learn the language better without them actually realizing and also it keeps their interest. This paper will provide a few of such methods to teach English Language.

1.4 Use of Innovative Methods, Materials and Practices in ELT

Innovative teaching is necessary for the present and future of education to help students to reach their full potential. In most of the class rooms in India conventional teaching methods, materials and teaching techniques based on prescribed texts and syllabus are used homogeneously in spite of vast differences in class rooms and level of students. The traditional methods which largely depend on lecturing and rote learning reduce English language learning to mechanical memorization and miserably fail in developing language competency among the students. These stereotyped methods and teaching material makes the learning a monotonous activity and creates distaste among the students by reducing them to mere passive receptors of language and not active participants in the learning process.

1.4.1 Task-based teaching/Activity-centered teaching:

Students always look for opportunities to be active participants in tasks which is required to practice language in communication with their teacher, their peers, and others. It is adventurous for them by using projects and everyday materials to teach English. It involves shared experiences in a particular situation. Through active discussion, students discover language principles at work in the situation. Through debriefing, students are able to sort and order the information gathered and relate it to the lesson. The teacher guides the students but it is the students who actually discover for themselves what is being taught.

1.4.2 Transactional reading

Transactional reading strategies can be used at specific intervals during or between other activities in order to encourage students to read a wider range of sources rather than just one textbook. It will help students to make the transition from passive listener to active reader.

1.4.3 By Using Language Laboratory:

Technological aids in language teaching are a major force today, and among these aids, the language laboratory occupies the most prominent place. The language laboratory is very useful for assessing students' speech. It provides students with the technical tools to get the best samples of pronunciation of the language.

1.4.4 Teaching through word games:

It is one of the interesting method of teaching. Traditional methods dictated for study and games to be separate but the fact remains that the students tend to be more interested in playing games rather than using traditional method for study. Any logical reasoning would dictate us to combine the two aspects to solve the problem. The most important part of any language is the vocabulary. To understand the meaning of the words and to use them in day to day life is a very difficult task and games can

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help the students overcome this difficulty. Games like scrabble, housie etc. have been designed for this specific purpose. These games are just based on words and help the students develop their vocabulary.

1.4.4 Teaching through arranging various competitions:

Most of the times competitions like debates and elocutions, group discussions, role playing also help the students a lot in learning the language as the aspect of the competitions keep them at the best in conversations. It forces them to use the best possible construction of sentences to put forward their opinions and to use good vocabulary

1.4.5 Teaching through various multimedia sources:

Multimedia sources like songs, movies, TV series, magazines, newspapers play a very vital role in improving our language. Such sources can be used to help the students improve their language. This is something that the students will do in their spare time. Traditional methods of reading newspapers and books, novels are also very good methods to teach the language. When the traditional methods are modified along with some innovative ideas the entire learning and the teaching process is enriched and guarantees a success in efficient learning.

CONCLUSION:

Since English is the official language of this world it has to be taught in such a way that it will help us not just to speak and write and listen but to communicate. That is the purpose of the language and that is what it must be used for. Hence innovative methods help in bringing a change and most of the times for the better. So, innovative methods help in bringing a change which helps the students to learn in an efficient, interesting and an interactive manner. And it is responsibility of teacher not only to use traditional methods but for using new and better methods for the students benefit. This can bring a much awaited and much required change in teaching techniques.

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How to Raise Kids who will Believe in Gender Equality

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Introduction: *As we all are aware of a well known quote by Simone de Beauvoir from her book 'The Second Sex' is " One is not born but becomes a woman". With this famous phrase Beauvoir first articulated what has come to be known as the sex-gender distinction, that is, the distinction between biological sex and the social and historical construction of gender and its attendant stereotypes. The fundamental source of woman's oppression, Beauvoir notes its historical and social construction as the quintessential Other. De Beauvoir defines women as the " second sex" because women are defined in relation to men. In other words sex is determined by nature but gender is determined by society. Thus in modern time awareness for gender equality in society is going to start in various ways. Among them there is a stream of thought that achieving gender equality through art of parenting i.e. to raise kids who believe in gender equality. We all want our children to grow up to be caring, thoughtful and socially conscious people. Part of this means raising them to believe in and stand up for gender equality.*

There are number of stages of upbringing of kids in natural way and as a parent these stages can be used for the kids to become more humane socially . A gist of the present paper is that how parents can give their children both girls and boys- the solid foundation they need to become the feminists of tomorrow.

Learning through observation: Social learning science teaches us that children's divelopment happens through observation and imitation. Modeling parents own feminism can mean anything from showing love for their body to filing a complaint with a local retailer for running a sexist ad compaign. No matter where parents are on the activist spectrum. Let your kids see your feminism in action.

Find everyday opportunities to walk your talk. A parent can raise their kids in a household where there always use gender neutral pronouns . For example in Marathi language " aag tikde ja" instead of using "aag" we as a parent can use " tu tikde ja" . Instead of buying doll as a toy for girls and plane or helicoptor for boys as a parent we must buy any toys whatever girls like rather we should promote them to buy plane, car, etc.

Acknowledge the parenting power of fathers: Break the biological determinism that says women means parenting and men means working out. Today's dads come in many forms : they can be single or married ; externally employed or stay at home gay or straight; adoptive or step-parents. What do we know is that dad's affection and increased family involvment help promote children's social and emotional development.

Start early: It is never too early to start talking about equality with your children. Find opportunities in everyday life for teachable moments.

Teach them that gender is fluid: Gender is one of the first social categories children become aware of . By the time they are 3 years old, they have formed their gender identity. So much of what limits boys and girls is rooted in socially constructed ideas about what one is or isn't permitted to do within their gender. Let your children take the lead and experience their gender with as much fluidity as they wish.

Teach them about healthy sexuality: Teaching your kids about healthy sexuality is as important as teaching them about safety, nutrition and acceptable social behaviour. It's important to be both helpful and approachable as a parent .

*Start conversations about sexuality rather than waiting to be asked.

*Give them real names for their body parts.

*Give honest answers about sex and sexuality.

*Assure them that you will answer any question about sex no matter how awkward or uncomfortable the topic might be.

Teach them about body autonomy and how to exercise their own consent.

Body autonomy is the right control over own body and to decide what happens to it. Allowing your kids to exercise their own consent (in ways that are age appropriate) ensures that they grant the same body autonomy to others. Some ways to empower your kids to practice body autonomy include:

*Giving them a say when it comes to when they eat or sleep (within reason)

*Telling them they have right to say stop when they feel uncomfortable, regardless of who the person is .

*Giving them real names for body parts.

*Never forcing them to hug or kiss people (including grown- up and family members)

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*Teach them to respect others when they say no or stop .

*Trusting their abilities in age-appropriate ways.

Teach them emotional intelligence: According to psychology today emotional intelligence is the ability to be aware of, control and express one's emotions. Children with high EQ become empathetic, engaged and nurturing adults who respect and value others.

Parent can teach their son empathy by making gender equality issues personal to them by asking such type of questions " How would you feel if that happened to him\ his mom \ dad and their family members".

Encourage them to celebrate diversity: " kids don't come with instructions but they do come with open minds " said Dr. Christopher Metzler. As parents, we are positioned to guide our children to appreciate the differences that make each of us unique. Explaining diversity in a way that is understandable to kids can be challenging, but is integral to raising kids who treats others fairly.

Conclusion: Here are a few tips to get started:

- Recognize that you may hold your own conscious or unconscious biased and work on addressing them.
- Talk to your kids about stereotypes : how they can be divisive and don't always tell the whole story
- Find age appropriate ways to bring diversity into your children's lives. And not just of thought, experience, socio-economic status, sexual orientation and identity- etc.

Thus through above mentioned ways, we, as parents can raise our children with the basic ideals of gender equality. Welcoming, adopting and practicing such patterns of behaviour has become must today. In the globalized world, things are changing in a fast rate. The age old norms, definitions and codes of behaviour are changing with a fast rate. In order to keep a pace with the changing time, we need to nurture these ideologies for the betterment of future generation. After all it is well said, "Charity Begins at Home".

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BABY HALDER'S "A LIFE LESS ORDINARY": AN EXTRAORDINARY AUTOBIOGRAPHY

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ABSTRACT

Baby Halder, formerly a domestic worker and now a writer, is the author of three memoirs. Her first book, Aalo Aandhare (2002), written in Bengali, is the first account of a domestic help from India. It has been translated into 25 languages. Baby Halder's story is extraordinary precisely because domestic workers' realities are so invisible in middle and upper-class peoples' everyday consciousness. Halder battled enormous odds, a single mother of three, at the age of 25. Her autobiography, written alongside her job as a domestic worker, is a bestseller and has been translated into twenty-one languages. Written without a trace of self-pity, A Life Less Ordinary is a shocking look deep inside a world of poverty and subjugation that few outsiders know about—and an inspiring true story of one remarkable woman's strength, courage, and determination to soar above her circumstances. The present paper reveals the courageous character of Baby Halder , the champion who comes out with triumph.

INTRODUCTION

Article 2 of the universal declaration of Human rights states: " Everyone is entitled to all the rights and freedom set forth in this declaration, without distinction of any kind, such as race, color, sex, language, religion, political or other opinion, national or social origin, birth or other status"

India, as an ancient country has seen many upheavals both natural and man- made. In early Vedic era, equal opportunities s of education for women is mentioned. But later on Manu openly played a degenerating role in lowering women's status. In addition to this, frequent invasions from the other parts of the world also kept changing the position of women in Indian society. They were considered as a commodity or a prize of war. They were deprived of the changes in the society. On the emergence of women like Meerabai from Bhakti Movement, general position of women's education was restricted only to listening to Kathas and kirtans.

During the Mughal empire, nothing much has been done in this field except to provide access to education to women of elite class. Whenever the society was in flux, the most affected and suppressed class was the women. The social norms and prejudices became more tenacious against the women. But with the advent of British people, some changes were being brought from the West. Some literate Englishmen and enlightened Indians like Raja Rammohan Roy, Ishwarchand Vidyasagar, Mahtma Jotiba Fule worked very hard to start educational institutions for girls. Mahatma Jyotiba Fule an ardent lover of humanity started first girls school in the house of Mr. Bhide in 1848 in Pune. This school was meant for girls from the poor as well as rich classes. Girls from untouchable classes were also admitted and education was imparted to them. This rumor of girls school spread all over Pune and some parts of the country too. In the later half of the 19th century the efforts of these philanthropists resulted in the realization by the emergent Bengali " Bhadralok" to impart a certain measure to educate their women folk. The heroine of this article Baby Halder is the outcome of such a long lasted strife against the existing social systems.

The story of Baby Halder's life is an extraordinary lesson in courage and survival. It is a story of a young domestic worker who has battled poverty, hardship and violence. A strenuous life story with storms and woos. She only used to sob and go ahead with courage and strength. Nobody, even her father, step mothers, brothers and relatives helped her to come out of the miseries and agony in her life. The sufferings which are found in her story are beyond imaginations and tolerance.

A small girl of hardly eleven years leaves her home with her small brother from Dhanbad to Durgapur to her Jetha (Brother of her father). Stayed there and joined school. She wants to learn. She joins school. No books and other aids for learning but an utter desire and urge for education

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pushed her upto higher class in school. Her father was in army once upon a time, after his retirement came back and joined some other jobs. He could not provide financial support to family. He did not take care of his wife and children. Finally his wife along with his younger son, a child of 3 years leaves his house without telling anyone around her. In this situation Baby's elder sister (Didi), Baby and one younger brother literary became like orphans.

Baby's story is a story of hardships and acute poverty. Story begins from her childhood. Her father got her elder sister (Didi) married with a person who was a bad man. He used to beat her often. Her Didi could not resist much and finally one fine morning committed suicide. Being a paternal society nobody in the family could oppose him. Baby was left alone with her brother for further suffering. After going through a lot of hardships with two steps mothers who ill treated Baby. No good food and sufficient clothes were served to her. But still baby continued to learn.

One day Baby was in her Mashi's house she found her bed and clothes wet with blood. She started weeping. She didn't understand what was happening to her. She was very much frightened and started weeping. Pishi Mashi convinced her and added one more burden that now she was no more a small girl. But as Baby was very courageous she used to play with boys. She loved to play all the boys games. She used to run very fast, swim very swiftly and so on.

The tragic story of her life has taken a second bad turn when she was eleven and half years. Her father got her married to a man of twenty six years. As her father and other relatives were negotiating her marriage, Baby was unable to understand the situation. She anyhow was not prepared for the marriage. Her marriage was settled with a man named Shankar, a son of a potter.

Shankar who was a mere worker having a small house of mud. He spoke lie while fixing the marriage that he has no father or mother and he is all alone. But he has a family at a small village. As per nature's law Baby became pregnant and conceived a son in the hospital. Despite pains and labor for three to four days her husband did not turn up to see her or did not care for her at all. He used to come from work, used to eat and go to sleep. He was very cruel and selfish. For him a woman was only a means of enjoyment. He never used to give her money for home expenses. On top of it he was very much suspicious about his wife and never allowed her to speak to neighbors like Shasti and her sisters who were kind enough to her. Actually Baby liked to see cinemas, jatras and participate in the pooja of Kali but Shankar always forbidden her from all these activities. If she failed to obey him, he would beat her like animal. He never pitied her. Once when she was carrying four months child in her womb, Shankar beat her so brutally that she got aborted. She went to her father's house with the determination of not going back to Shankar's house ever but she was helpless. As her stepmother didn't like her staying in the house. So her father insisted her to go back to her house.

Baby comes to her husband's house to live together, but her husband was very much reserved type of a man. They did not have any cordial relations. He never used to give her money. She was totally dependent on him. This dependency and despondency made her a slave of Shankar. She remained pregnant again and gave birth to a son. Still she had to survive in the same hopeless conditions. There was no improvement in the relations of husband and wife.

Baby, as a woman, a wife and as a mother had tried to resist and revolt against the situation many times. Her struggle for searching her identity, for her freedom and liberty was going on relentlessly. But Shankar had no sympathy for her. When she quarreled for justice, he used to beat her cruelly. She became desperate and left all hopes of cordial relations with her husband. She conceived one more daughter in such a tense relations. Living with such an inhuman and callous man was getting critical day by day. One day Shankar fought with her very badly and beat her horribly before her children. Children were terribly frightened to see this. Baby decided to stop the farce.

On the next morning, with an air of finality, Baby went to her father's house along with her children and declared that she will never go back to her husband's house. Her father didn't like this. He tried to explain to her that her husband's house is the only destination for her. She demanded few money to her father and address of her brother and got the railway tickets. With all sorts trouble she reached Faridabad to her brother's house. Baby's sister-in-law didn't like this addition to her family. She along with her three children had her dinner and next morning went in search of another room which was near her brother's house. She requested him to search for some work for her so that she can pull on her expenses. Moreover she wanted her children to learn. It had been her dream that

the children should go to a school. After two days she found a work. She requested a small place to live with her children. Memsab was very unsympathetic with her all the times. She used to keep her busy for the whole day. Baby hardly got any time to spare with her children. Memsab used to love her dog' more than maid servant. Baby felt very bad and left her job.

Baby Halder started working in the house of Dr. Prabodhkumar Shrivastav. He used to give her Rs. 500 per month. He was very kind hearted man. He used to give her fatherly and brotherly treatment in the house. He never treated her like a servant. He asked her to bring her children there in his house only. He gave one room for them. As her school going children were small he used to ask Baby to take milk for her children. He was living there with his sons. One day she went up-stairs which happened to be a study room of Dr. Prabodhkumar. She started cleaning the bookshelves and books very carefully and neatly. Her busy hands would go slow as she dusted the books. During this she picked up one book and started reading it. She didn't know Dr. Prabodhkumar was also present in the study room at that time. He was very much surprised to see her reading a book. He asked, "Do you read?" and she kept quiet for a while. She looked so guilty as if he had caught her hand in the biscuit tin. Thereafter Dr. Prabodhkumar encouraged her to read and write at her leisure time. One day he asked her to show what she wrote. She handed over the papers to him. He read all those papers and sent to his friend to go through. His friend liked the story very much and asked Dr. Prabodhkumar to publish it. Dr. Prabodhkumar belonged to a literary family. His grandfather Munshi Premchand was one of India's best known writers whose novels and short stories brought out a social reform in the early 20th century.

Here Dr. Prabodhkumar, her dada, worked as a source of inspiration in Baby Halder's life. He encouraged her to read and write. As a servant Baby entered his house, he treated her sympathetically like his daughter and behaved like a good human being, a true Samaritan. As the days passed the result came out in the form of a book, "A life less Ordinary " (Published in Hindi and Bengali as 'Aalo Andhari', from which means 'darkness to light')

During an interview 'If You will.....U Can.....Baby Halder proved it' which was telecasted on Delhi Doordarshan in a programme called 'Stree Shakti', Baby Halder shared one incident in which she said when she used to clean the bookshelf at her dada's house she came across a book written by Mahashweta Devi which depicted a pathetic story of a suppressed woman who undergoes the ordeal of life, wins in life by creating her own identity. Baby was overwhelmed to read this experience. She was also highly inspired by these words of encouragement. Coincidentally Mahashweta Devi, the great Champion of Women's Freedom Movement in India read Baby Halder's Autobiography and wrote her comment," A story of courage and grace.....a book worth waiting for."

Our Former Prime Minister, Pandit Jawaharlal Nehru said that until and unless our male and female are suppressed under the dominance of some power they cannot find themselves independent and free by any law or rule. Economic dependence is the main reason of backwardness of Indian women. They are never free as long as they are not economically self- reliant.

CONCLUSION

Baby Halder's book is miraculous and an inspiration to all of us. It gives the message to the reader's that Education brings rays of happiness and prosperity in one's life. She is a woman with perseverance, self respect and resilience. She showed the courage to fight against all odds in life and worked as a torch bearer, bringing light of hopes and spirit not only for herself but also for all the women folk in India who are fighting the battles of life, searching for their own identity in the darkness. She underwent the ordeal of life only to prove herself. Of course in this rigorous journey of adversity Mr. Prabodhkumar, her dada, played the role of a lighthouse which stands firm to show light and gives right direction to the ship that loses path during the voyage.

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TRAINING ENGLISH LANGUAGES TEACHERS: A NEED BASED APPROACH (PROBLEMS & REMEDIES)

ASHWINI N. TONDRE, DR. PRADNYA S. YENKAR

Abstract: Today's economy is globalized; it means many of us are interacting across cultures. The importance of learning English as a second language becomes self-evident. Learning a second language helps you to communicate across world, where you may never have previously considered potential reach. Here trained teachers play a crucial role. It is said that, "Great teachers help create great students" In fact, an inspiring and informed teacher is the most important school-related factor influencing student achievements, so it is essential to pay close attention to how we train and support both new and experienced educators. The research paper focuses on the need of trained teachers to teach the second language. It also briefly discusses the problems faced teachers. And attempt has been made to provide remedies to the problems.

Keywords: Globalization, culture, learning, teacher, problems, remedies

Introduction: University courses prepare students to become academically eligible for the labour market. In higher education language teaching has a huge share to achieve this goal. Increasing internationalization and developments in technology, societies and working life have changed the environment to such an extent that English language learning has become the need of the day. The primary aim of language and communication studies is to enable students and staff to become convincingly communicating experts in their own fields and to be able to cope with international; in other words and intercultural contexts. And for this purpose the demand of the trained and efficient language teachers need to be satisfied. Considering this the researcher has used the following research methodology for the research purpose

1.1 **Research methodology:**The study is based on secondary data which is collected from various books, National and International journals and publication from various websites which focused on importance of language teaching teachers. Descriptive Research was used for the research purpose

1.3 **Teacher training:**The best teacher-preparation programs highlight subject-matter mastery and provide many opportunities for student teachers to spend time in real classrooms under the supervision of an experienced mentor. Just as professionals in medicine, architecture, and law have opportunities to learn through examining case studies, learning best practices, and participating in internships, such teacher-preparation programs allow teacher to apply their learning in the context of practical teaching in a real classroom sessions.

1.4 **Importance of Language Teacher training:**

Teacher training is an important aspect in the dome of English Language Teaching. Teachers need to be trained to improvise their knowledge on the professional ground and enhance their teaching capabilities. Training is, even, more important when curriculum, teaching approach or methods or course books are changed or modified as teachers need to cope up with the changes and to apply new approach effectively in the classroom. Teacher training programmes are always aimed at the improvement of the quality of teaching and learning and developing the ability in teachers to teach effectively. With a view to enhancing the quality of English language teaching and learning, Communicative approach was introduced. Accordingly English teachers have been trained to equip them with the new approach. But question is about the implementation of the training in the classroom. This study aims to find out the rate of implementation as well as spotting different kinds of problems that may hinder the implementation of training in the classroom with a view to suggest possible ways to overcome from them.

Non trained teachers are often assigned to the most challenging schools and classes with little supervision and support. Most of the teachers are dissatisfied with their jobs and couldn't perform at the expected level, so more attention should be paid to provide them with early and adequate support, especially if they are assigned to demanding school environments. Mentoring and coaching from veteran colleagues is necessary to the successful development of a new

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teacher. Great induction programs create opportunities for beginner teachers to learn from best practices and analyze on their teaching.

1.5 English as a Lingua Franca: The world has become a global village. English has become necessary for mobility and social and economic success in the world today. The approach of the people towards English language has changed now. There is a great demand of education of English in English and through English throughout the country. English the same time it has become a status symbol. English has become a status symbol and a student without a reasonable command over English is perhaps not very comfortable with attainment of any educational goal. Similarly, teaching of English holds the key position in the entire curriculum of education. Teachers of English, in this context, take the responsibility to enable the learners to achieve the educational goals in general and language aim in particular. Hence the teaching of English language is required to be strengthened and problems need to be reduced with the best efforts of government and educationists and researchers. For this purpose teacher must be well trained but on the contrary this question remains unanswered, **Are our English teachers adequately trained to face this challenge and make the students competent enough to face the world?**

Let's look at the problems in teaching and learning English language.

1.6 Problems in Teaching and Learning English Language: Around the world and in the country like India, many people learn English. While some could get the fluency within a few years, lots of students encounter problems and challenges along the way. Some of these pertain to learning English in particular, due to the language's diverse roots, large amount of irregular verbs and profound regional variations. Some of the common problems in learning are as stated below.

1.6.1. Pronunciation, Vocabulary and Grammar:

Almost all English learners encounter following problems:

1) Challenges with pronunciation
2) Issues with vocabulary
3) Grammar

1.6.2Selection of Appropriate Techniques: earning English requires different techniques for different types of learners. Some people require more time to reflect on concepts before diving into dialogs and presentations. Others need to speak to reinforce new information. Music, rhymes, chants, poems and games provide additional reinforcement

1.7 Conventional English Language Teaching: In the past, students were introduced to English only in their fifth or sixth standard. Students learned English just as another subject like Physics and Mathematics with lot of burden and used to get little opportunities to use it within as well as outside the school premises. Only in convent schools students used to get the opportunities to use this language. Fortunately well trained teachers were available in such premises. But in other schools there has always been a scarcity of such well trained language teachers. They used inappropriate methods to teach English as a second language.

The above context was appropriate for the use of methods that did not focus much on communicative competence. Language teachers usually adopted and followed different methodologies such as

1. Grammar Translation Method:

2. Bilingual Method:

3. Direct Method:

But use of such methods was not of that much use to check the communicative status of candidate. Because teaching of English subject was treated like other subjects and the importance of this was always neglected.

1.8 English is simply treated as a subject: Students learned English only as a subject rather than as language. They are unable to put their learning into practice due to lack of a favorable environment. In addition to the given constraints, teachers have to manage with the limited teaching hours which is not enough to teach the language in detail.

Another limitation seen in Indian teachers is that some of the English teachers are not familiar with the latest developments in ELT pedagogy. The situation is no better even at the college level as Robert Bellarmine observes, "The most serious problem in the teaching of English in our country is the appallingly small quantity and atrociously poor quality of English to which our learners are exposed." Teaching of English in India is examination-oriented only.

1.9 Challenges in Teaching English Today: Challenges before the English Language teachers in India are huge and obvious. They should be able to provide to the practical needs of learners, to make them competent enough to interact with one another and also to retrieve information all over the world.

English has a base in several countries and is considered as the most suitable and convenient tool for International Communication. The people who

have proficiency in this language could access large number of jobs and also were seen holding high positions in many National and International Organizations.

In the earlier days English was just like a Library language, but now that notion has changed totally. At present the challenges visible before the English language teachers in India are diverse and it is necessary for them to shape up accordingly to meet the demands of the day.

1.10 Methods to be Adopted to Improve Spoken Skills:

1. **Group Discussions:** Due to the world wide growing trend in English, teachers give more emphasis to communicative approach rather than the lecture mode. Their main goal is to make the students communicative in English language.

To achieve this, they involve the students to participate more in classroom activities so that they will acquire adequate command over speaking skills. To create this environment, teachers can conduct group discussions, where students are supposed to speak only in English. Here, they can give their views, ideas and thoughts in English due to which they develop the habit of speaking fluently in English like they do in their mother tongue.

Various types of discussions also help students to improve their general awareness and understanding about current affairs. It gives a lot of scope for good imagination and deep thoughts. This type of discussions help the students to listen to the views of fellow students which in turn helps them to gain knowledge and enrich the vocabulary also.

2. **Debates:** Debates too play an important role to improve the speaking ability of the students both at school and at higher level. Debates not only make the students to speak boldly and fluently but also help them to take one stand and be firm and consistent on that. Along with this advantage of reasoning, it gives students some experience to control their emotions without losing their temper. This also helps them to organize their thoughts and ideas in a specific way while speaking.

3. **Role Plays:** Role-plays are another important task that can improve the basic colloquial English of the learners. In role plays, the students assume themselves as one of the characters and behave and speak accordingly involving in the given character completely. In these types of activities teachers have to play a vital role as instructors and guide the students properly so that they can act appropriately to meet the situation. They should help the students now and then to understand and take up the role given to get a grip on the tone of voice.

4. **Language Lab Learning:** Now-a-days computer has become a part and parcel of our day to day life. It plays a vital role in the process of teaching and learning. It can be used to learn a foreign language like English. Language lab software has made language learning easy and also made the language learning process interesting and enjoyable for both teacher and student in this technical world.

1.10 English for Specific Purposes: As English has emerged as a global language, it also plays a vital part in every profession with respect its importance and demand. Every profession has its own professional terminology which is used frequently in that particular profession. For example, certain terms used by the doctors, lawyers, et al. are quite different from those of other professionals. So, to benefit these professionals, English for specific purposes is introduced so that specific English words related to that particular profession can be taught by those professionals. Jargon related to one profession is different from the other. Hence every professional is taught in a particular manner that fits in well with his professional demands.

1.11 Teaching Language through Visual Aids: One of the innovative methods used by the teacher to teach language in class room is visual aids. The teacher distributes visual aids to students by dividing them into various groups. The students are then given stipulated time to extract relevant information on the given aids. After that, those learners are supposed to speak about the visual aids given to them. This method expands the analyzing capacity of the students. By looking at the picture, the learner should think and come out with innovative thoughts which also help in learning language by creating fun-filled environment around them. The teacher acts as facilitator who motivates the students to talk freely. As each person gets their own unique thinking it helps to sharpen their thinking process.

1.12 Conclusion: The goal of this paper was to convey the importance of teacher training which is the need of the day. As the complexities of living conditions demand skilled persons in various dimensions of life. All the skills have their own significance so is the teaching of English as a language. Hence, the teaching of English language is required to be strengthened and problems need to be reduced with the best efforts of government and educationists and researchers. Instead of conventional language teaching new technical methods need to be adopted for the better result of language learning and teaching. Teaching English language is a challenge today especially before non trained teachers so they should be properly trained to get the positive result. Use of new technology changes the class room environment from a boring one to a positive environment where students would be concentrating and participating in various activities selected by teachers. Trained teachers of English, in this context, should take the responsibility to enable the learners

to achieve the educational goals in general and language aim in particular.

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HEMOGLOBIN STATUS OBSERVED IN WOMEN OF AMRAVATI (MS) INDIA BY USING ANOVA TEST

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ABSTRACT

In the present study examined the hemoglobin status in women of Amravati region and its statistical analysis by using ANOVA test. Total 298 women were tested for hemoglobin status. The one way ANOVA test was used to compare population groups, and analyzed hemoglobin %. The normal values of hemoglobin % were not observed in any age groups of total survey of women of Amravati region.

Keywords: Hemoglobin, Women, ANOVA test

INTRODUCTION

Hemoglobin an iron bearing protein molecule containing within red blood cells. It performs major function which is essential to life that is 'tissue oxygen buffer' that means hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure in the tissues. It picks up oxygen from the lungs and delivers it to the body's tissue to maintain the good condition of cells. Although hemoglobin functions primarily as an oxygen carrier, it is also important in the transport of carbon dioxide and in the maintenance of the acid-base balance of the body tissues. When hemoglobin level decreases that time obesity increases in the patients and obesity decreases when hemoglobin level increases (Yong Zhang *et al.*, 2010).

Now a day a common factor affecting today's girls is the problem of dark circles below the eyes, the patchy type of skin, one of the main reason behind this is the low hemoglobin level. People do not take proper diet; illiteracy may also be the cause. Socially somewhere women are more prone so it because of Indian tradition (about eating habits). Low hemoglobin or anemia is a common condition. Among older adults, with prevalence increasing with age (Buzzle Com, 2010). Anemia is associated with increased mortality (Zakai *et al.*, 2005, Penninx *et al.*, 2006, Culleton *et al.*, 2006, Dong *et al.*, 2008) disability, and poorer physical performance (Penninx *et al.*, 2004) regardless of the underlying cause of the low hemoglobin.

High hemoglobin level is seen in smokers and in people living in high altitudes area (Right health.com, 2000). Dehydration can also cause high hemoglobin level; it can be corrected as soon as normal proper fluid balance is restored. Other causes include; bone marrow problem and excessive intake of drug erythropoietin (Epogen) by athletes for blood doping purposes. Anemia in pregnancy remains one of the most intractable public health problems in developing countries. It is extremely common and although not always shown to have a causal link, severe anemia contributes to maternal morbidity and mortality (Usanga *et al.*, 1994, Shulman *et al.*, 1996; WHO, 2001; Crawley, 2004). Anemia, even when mild to moderate affects the sense of well-being resulting in fatigue, stress and reduced work productivity (Haas and Brownlie, 2001). Hemoglobin levels, In each milliliter of blood there are approximately 4.5 billion red cells and 150 milligrams of hemoglobin. The normal ranges for hemoglobin depend on the age and sex of the person.

Newborns hemoglobin level is 17-22 grams/ 100ml of blood
One month baby is 11-15 grams/ 100ml of blood
Normal hemoglobin level for men is 14-18 grams/100ml of blood.
Normal hemoglobin level for women and children is 12-16 grams/100ml of blood.
Men after middle age is 12-16 grams/ 100ml of blood
Women after middle age is 11.7-13.8 grams/100ml of blood
The aim of the study was to detect anemia especially in women of Amravati region.

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MATERIALS AND METHODS

A cross sectional study was performed. To evaluate hemoglobin status, under guidance of Doctor and medical technician, blood samples were collected from women's and hemoglobin percentage were observed with the help of haemocytometer. On the basis of three years data (2009-10, 2010-11, 2011-12), the women distributed in average age groups wise. The average age groups distributed into 20-30, 30-40, 40-50, 50-60, 60-70, 70-80 (Table 1). The one way ANOVA test was used to compare population groups. The Null hypothesis was also used to evaluate the statistical analysis of the test.

RESULTS AND DISCUSSION

Result of the experiment showed that, total no. of individuals is 15. And $\sum X$ = 125.2. The common mean X of all the sample is 8.346 where as mean of sample T1 (i.e. X1) is 846, of sample T 2 (i.e. X2) is 8.57 and mean of sample T3 (i.e. X3) is 8.1(Table 2).

We have to see whether levels of 3 different samples in comparisons to common mean X show significant varience using Null hypothesis.

Table 1: Hemoglobin status of the women population in Amravati region (M.S)

sr. no.	Age range	Hb% (gm) 2009-10	X_1	$(X_1)^2$	Hb% (gm) 2010-11	X_2	$(X_2)^2$	Hb% (gm) 2011-12	X_3	$(X_3)^2$
1	20-30	6.3-9.8	8.5	72.25	6.2-10.0	8.1	65.61	6.0-9.7	7.8	60.84
2	30-40	7.2-10.0	8.6	73.96	6.6-10.2	8.4	70.56	5.9-10.1	8.0	64.00
3	40-50	5.8-10.4	8.1	65.61	7.2-9.9	8.5	72.25	7.0-10.0	8.5	72.25
4	50-60	8.4-10.0	9.2	84.64	8.6-10.0	9.3	86.49	8.0-9.9	8.9	79.21
5	60-70	8.0-7.8	7.9	62.41				6.9-8.5	7.7	59.29
6	70-80							7.3-8.1	7.7	59.29

Table 2: Statistical analysis of Hemoglobin levels in three different groups

Group I	Group II	Group III
$n_1 = 5$	$n_2 = 4$	$n_3 = 5$
$t_1 = 42.3$	$t_2 = 34.3$	$t_3 = 48.6$
$x_1 = 8.46$	$x_2 = 8.57$	$x_3 = 8.1$
$S_1^2 = 357.85$	$S_2^2 = 293.95$	$S_3^2 = 393$

Calculate three sum of square

1) Sum of observations from all individuals from all three groups
   $\sum x = 8.5+8.6+\text{----------}+7.7+7.7=125.1$
2) Sum of sqare of all 15 observations
   $\sum X^2 = (8.5)^2+(8.6)^2+\text{----------}+(7.7)^2+(7.7)^2$
3) Correction term $\sum X^2/n = (125.1)2/15 = 1043.33$
4) Total sum of squares= $S(X-X^2) = 5.34$
5) Sum of square between groups is 1043.33
6) sum of square within group is 3.09

-Total sum of square = No. of observation = 15-1
The degree of freedom (df) = 14

-Sum of squares between groups = No. of groups = 3-1
The degree of freedom (df) =2
-Sum of squares within groups = Total sum of squares- sum of squares between groups = 12
Mean square = Sum of squares between the groups/Degree of freedom
= 1.125

a) Variance (sum of squares) between the groups
b) Varience (sum of squares) within the groups= 0.2575

The results are represented in the table 3

Table 3: Hemoglobin status for the Analysis of variance observed in women was of Amravati region.

sr. no.	Variation	Sum of Squares	Degree of freedom	Mean square
1	Between the groups	2.25	2	1.125
2	Within the groups	3.09	12	0.2575
Total		5.34	14	

Varience Ratio,

F_{obs} = Mean square between groups (M.S.)/ Mean square within groups (residual)

$F_{obs} = 4.368$

ANOVA results indicated that individuals in age groups 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, years of age were all significantly low in served groups.

From the above result it is evident that between groups and variability is greater than the within group variability. Also all the three groups are not from population having identical means. All the data were presented as mean ± and standard deviation (X ± S).

Women health hygiene is the main problem of our society .From babies to adult women they do not attention properly to their health .the basic needs does not fulfill by families .In the present study all the age groups women showed anemic condition similar finding by Barrett –connor *et al.*,1987 , Joan Prat 1989.

Iron deficiency is the main reason of lower hemoglobin in women. About the balanced diet unconsciousness among women is another reason. Similar investigation by Kiwanuka *et al.*,1999, Nils milman *et al.*, 2000.

Also observed that lack of scientific knowledge about Hemoglobin. Nutritional problems observed in each age group of total women are served. Nutritional deficiency were indicates Anemia in all surved groups.

From the above results , we focus in future research is needed to determine the effectiveness of educational programmed involving all age women ,children and parents. Also the distribution of multivitamin for the low in come populations. Similarly awareness programs arrange in economically backward areas.

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(Christian 1985:176).Despite its limitation, it contributes in shaping the image of African-American woman.

With PauleMarshell new period of female characters in African-American letters emerged.It shows her desire for self-understanding.In her first novel BrowngirlBrownstones (1959), Marshell portrays a woman caught between her own desire and life imposed upon her.InThe Chosen Place Timeless People (1969) Marshellrepresents the shared life and communal responsibility.In The Praisesong for the Widow (1970), she represents complex women characters.

Alice Walkers works changed the scenario OF African-American women's literature.She represents woman as a creator.Her first novel Third Life of a Grage Copeland represents struggle for wish to change.Social dimensions are mentioned in The Merridian(1976).The Color Purple(1982) is written in the series of letters.

Toni Morrison is one of the eminent African-American women writers. She has won the Nobel Prize for literature.With her works, she fills the literary corpus with varied colours.Her first novel The Bluest Eye (1970) is a story of African-American girl striving for blue eyes and measuring herself with the white beauty standards.Her Second novel Sula (1973) marked her as a significant voice in America.Her Song of Solomon (1977) is a folkloric novel, where she celebrates African culture.Her Tar Baby (1981) reflects cultural conflict.Beloved (1987) is a story of live experience of former slave Sethe, who kills her daughter in fear of slavery.Then her novels Jazz and Paradiseappeared. She wrote Love (2000) with a religious theme.

There are many other African-American women writers who are coming forward and blossomming their literary tradition. To sum up the African-American women writers are standing at the top of the literary world with their talent, skill, and capacity of resistance. Their work is a celebration of African-American culture, folklore, community, sisterhood and the strength to live and teach the human values.

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BREAKING THE SILENCE: A NEW FEMINISTIC APPROACH REVEALED IN SHASHI DESHPANDE'S "THAT LONG SILENCE"

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Abstract

Shashi Deshpande's novel "That Long Silence" reveals the plight of women, their quest for self, an exploration into the female psyche and an awareness of the mysteries of life and the place of protagonist in it. A woman has to go beyond the society's ordained roles of mother, sister, wife , daughter etc., she has to find out who she is ? This paper presents the feministic approach of Shashi Deshpande's "That Long Silence." The word "silence" is the key metaphor in this novel. At last the patience of silence and endurance of Jaya, the protagonist, is broken and its outcome is a **New Woman** with Self affirmations and emotional explosions.

Shashi Deshpande's 'That Long Silence', a Sahitya Akadami Award winner novel published in 1988 looks at social history from the perspective of the family. It explores man-woman relationship in Indian society. Deshpande, in this novel offers readers an intimate and domestic chronicle of the subtle tyrannies suffered by women and the pain of coming to self-knowledge. The title of the novel, 'That Long Silence' suggests a belated reaction, a postponement of offensive behaviour for long till the postponement cannot be made anymore. In this novel Shashi Deshpande deals mainly with the silence of an Indian house-wife. She shows her

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protagonist 'Jaya' to be in a great inner conflict and a quest for her identity.

The entire novel is written in the mode of retrospective narration. Jaya, the narrator and the protagonist of the novel speaks about her childhood as well as her marital life. The first person narration makes the novel 'an intense one'. Jaya's consciousness becomes the central pivot of the novel.

Jaya's silence is similar to the fate suffered by a majority of women the world over. Silence is a suppressive device, it signifies death. It also means long, untold suffering, mostly mental, which ultimately overcomes the need to express one's thoughts as an individual. It negates the self. The metaphor suggests withdrawal. That Long Silence reverberates with many silences some imposed on the characters and others embarked upon willingly.

The title also suggests the female psyche during the quest of the protagonist for 'self. 'That Long Silence' is the period of self introspection of the woman to explore her true identity. The protagonist Jaya is caught in the midst of a domestic storm. Her husband, Mohan is accused of corrupt practices at office and the couple leaves their posh flat at Bombay's Churchgate to an old Dadar flat of theirs. The children go out for a holiday. That gives space to Jaya for self-interrogation. Traditionally, a woman has an identity only as 'husband's wife or father's daughter or son's mother'. She can never have her own identity. Ten different mirrors show ten different faces. Thus the individuality of Jaya cannot be defined. She can be defined only in relation to others.

Jaya is a conservative, educated middle class "Smiling, placid motherly woman" who learns to suppress her own wishes and acts according to her husband's. She cannot dare to protest. Mohan is an engineer who cares for money, status and material comforts. Working in the purchase section of his office, he prospers well, looks arrogant and brash. Unfortunately, he is caught taking commission and an enquiry is on. He has to take refuge in their Dadar flat. He takes Jaya for so much granted that she is not consulted about shifting. Yet she quietly accepts his decision and follows him. However, Jaya seems to have gained confidence as he begins to lose it, being in trouble, When Mohan demands the key, Jaya refuses to hand it over to him. She opens the door herself symbolizing her refusal to be servile.

Her Dadar flat is in no way comparable to her elegant, well furnished Churchgate home. Yet, she is perfectly at ease here, relating herself easily to her neighbours and servants. Away from the routine, she is now prepared to look at herself with utmost objectively and examines her relationship with her husband. Emulating Mohan's mother and sister, she tries to adjust and compromise with her lot though every compromise shatters her individuality. She surrenders herself so totally that she is afraid of expressing her likes and dislikes. Now she is a stereotyped housewife who is "nervous, incompetent, needing male help and support."

Outwardly, she is a satisfied housewife married to an apparently caring man with a comfortable home, with no dearth of material comfort, But on scrutiny, it is revealed that to achieve this stage of fulfillment as a wife. Jaya has systematically suppressed even-aspect of her personality that refuses to fit in with her image as a wife and mother besides a failed writer.

Ruminating on the past, Jaya sees how her marriage has reduced her to a mere automation. She realizes how she wasted away the most valuable time of her life in arranging and re-arranging things, dusting, polishing, washing, ironing, cleaning the fridge and changing the sheet She is bewildered to find in her dairies that she had spent her life engrossed in such trivialities as what she bought, how much she paid for it, the dates the children's schools had begun, the servant's absence, the advance they had taken etc.

Jaya, as a girl, was taught by her father to have confidence in herself. He named her Jaya which stands for **victory** and has encouraged her to be resilient and courageous. He has made her feel that she is someone special, and someone different from the other girls who would normally end up becoming house wives. He would dream that Jaya either bags an international award or goes to Oxford. However, his untimely death shatters her dreams and makes her to face the reality that she is after all like any other middle class girl destined to be a wife and a mother. As a child she was chided by her grandmother for asking too many questions and was told that no husband could be comfortable with a woman who asked questions and retorts. Her early training at home has made her obedient and submissive towards her husband. Her relatives taught her the importance of being with a husband, "a husband is like a sheltering tree." After so many years, the words came back to her. A sheltering tree, without the tree, you are dangerously

unprotected and vulnerable." And Jaya proceeds to "Keep the tree alive and flourishing, even if you have to water it with deceit and lies" And since a husband is the protector, a woman should never complain or protest. Mohan's mother does not, though his father piles humiliations upon her. Mohan had given the description of his mother's endurance. All the children would have their food, except their mother, who would always wait for her husband to return, though he never gave the intimation of when he would come back. She would finish off the children's dinner and again cook rice for him as he had made it clear to her, that he would not eat what he called "Your children's disgusting leavings". He always wanted fresh and hot rice from the untouched vessel. She had just finished her cooking and was waiting for her husband, hoping that he would not be late, because lighting the fire again, "that was unthinkable." When he returned back and sat for the dinner, he questioned, 'why is there no fresh chutney today?', when she mumbled something, the next moment he picked up his heavy brass plate and threw it, not at her but deliberately at the wall and jerking his shirt off the peg walked out of the house. Mohan" s mother then silently cleared the mess and asked Mohan to get some chilies from next door." She lit the fire again and put rice to cook. She began grinding the chutney and also hushed and breast fed the baby. When the baby was asleep, "she was still sitting there in front of the fire, silent, motionless." Mohan saw strength in the woman sitting silently in front of the fire, but Jaya saw 'despair'. She saw despair so great that it would not voice itself. She writes. "I saw a struggle so bitter that silence was the only weapon. Silence and surrender" The pathetic end of Awa, Mohan's mother, about which Vimala had told secretly to Jaya, also speaks of the trauma and suffering of a housewife. "Strange isn't it? Vimala had said to Jaya, 'how different I am from my mother? Five years married now - I have no children, while Awa almost all my childhood I remember her as being pregnant. She didn't want that last child. She'd lost four or five babies by then, and she was desperate."

Vimala clearly remembers the day when the mother began hitting herself on the face. Her hands were all floury. Soon there were red patches as she went on and on hurting herself. Vimala recalls: "I tried to stop her, I tried to stop her screams, I tried to hold her hands, but I could do nothing. Her hands were like steel." She just went on saying that, she couldn't bear it all now. She lay stiff near the fire moaning. A week later she died as she had gone to a midwife and tried to get herself aborted. Thus there was the end of her silence, her long endurance and struggle.

Though Vimala is quite different from her mother 'Awa', Jaya finds something common in them, 'some thing that links the destinies of the two the "silence" in which they died'.

The sufferings of women are put forward again through the character of Vimala. When she was taken to the doctor by Mohan and Jaya, the doctor had asked: "You mean to say, she didn't tell anyone about her illness? When she was suffering so much?"

When Vimala had been in bed over for a month her mother-in-law had complained, that she had never seen women taken to doctors for such a thing. As if other women don't have heavy periods, she had grumbled. The doctors had pronounced that it was too late for a surgery. Vimala sank into coma and died a week later, 'her silence intact'. Here, ends the silent fate of another woman who struggled to death, keeping intact the silence, tradition bound and imbibed in them since childhood. Jaya, since, her childhood, has designed her life in according to her family members' desires. She marries Mohan not out of choice but out of convenience. As he is from the same caste, decent, good looking and had a good job. Jaya had no reason to reject him. After marriage, Jaya also seeks to conform to the pattern the other women in Mohan's house do. She learns to suppress her own wishes and act according to her husband's. She, for example, likes to see advertisements that precede a movie show, for they give her "the illusion of happiness" within the wall of the home. Over the years, she shapes herself "so resolutely to his desires" that in the end she is left with no identity of her own, "just emptiness and silence "Deshpande brings the picture of enduring women who bear all tortures silently.

Jaya remembers how Jeeja came to work bruised and hurt, but she never complained. Jeeja silently faced all the problems, and there seemed to be no anger behind her silence. Jeeja represents those suffering lot of the lower class women, who bear all the traumas inflicted upon them by their husbands silently and worn themselves out to earn their livelihood. The fate of Jeeja is the fate of many women, who have a drunkard husband but they still endure all the pains and sufferings just because a

husband holds a superior position and after all he is the Kumkum for a woman. The same is the fate of her daughter - in - law Tara. as Rajaram. Jeeja's Stepson is also a drunkard and beats up his wife Tara.

Tara had none of Jeeja's reticence or stoicism. She cursed and reviled her husband and sobbing loudly, moaned her fate. When once Tara cursed Rajaram and wished death for him. Jeeja stemly shuts her up saying that a woman is nothing without a husband.

Thus through Jaya, the protagonist and other female characters like, Vanitamami, Kusum, Jeeja, Tara, Vimala, the novelist presents the plight of women. Deshpande gives minute details from the protagonist's personal life. Like other women novelists, Shashi Deshpande also has chosen a woman narrator. The novel gives the details of a predicament, anguish, sufferings of women, some of them belonging to the middleclass, some are illiterate and rural and some are servants. Deshpande gives their different life pattern.

Through the character of Jaya, Shashi Deshpande has thus expressed the ambivalence attitude of contemporary educated women in India who can neither reconcile themselves to a new situation, when their husbands ignore them and crush their ambition in life nor cast off their husbands simply because a husband is 'like a sheltering tree', they cannot afford to live without. In a way, Jaya is a representative figure of the modern woman who resents her husband's callousness. By implications attitude, the character of Jaya represents modern women's ambivalent and becomes the victim of circumstances. By implicating the attitude, the character of Jaya represents modern women's ambivalence to married life.

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CONTEXTUALIZING LITERATURE: TEACHING AND LEARNING

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Abstract

In order to make the study of literature effective and to make it as a special form of knowledge with imaginative sensibility, it is necessary that the classroom teaching should reach to the effect of literary comprehension. The text as another name for literature must be analysed in terms of its relative areas and theme. There are three worlds in the understanding of the text- the world of the writer, the world of the text itself and the world of the reader. The intentions and the perceptions of the writer need to be taken into consideration while studying any work of art. It is the responsibility of a teacher to bridge the writer with his reader to bring the text towards his students.

From centuries the study of literature has been shifting in the manner of its definitions and approaches. The term 'literature' is constantly modifying and evolving. The definition of Aristotle about what is literature is no more static. It undergoes such tremendous changes that litterateure and thinkers don't look at it as merely imitation of life. According to some writers literature is the work of excellence, beauty and art. Literature should illuminate some particular predicament of a man. This definition denotes that literature should reflect the gaiety and the grief of life. On the other hand, it should give pleasure to its reader. Scholars have talked about different aspect and functions of literature. 'Literature is the language well used.' According to Ezra Pound, 'Great literature is simply language charged with meaning to the utmost degree." While Channing relates literature to the socio-political context while he says, 'literature is the expression of the

PORTRAYAL OF BILLY AS DISTRESSED SELF IN ARUN JOSHI'S ''THE STRANGE CASE OF BILLY BISWAS'

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Abstract

In the modern era a man is always under the pressure of social taboo to maintain dignity and social prestige. As a result his inner urge is suppressed and self distressed is created in his mind. Arun Joshi is one of the dittinguished Indian novelists who explore the innermost depths of human psyche and the chaotic underworld of human mind through their novels. All his protagonists are mostly men for whom self distressed is the sole natural condition.In all his novels Arun Joshi is more concerned with thought, emotion, sensation than with action. His protagonists emotional traumas sometimes lead to violent death in the end of the novel. A certain awareness of man's restlessness and the consequential estrangement from the society and self is the keynote of Arun Joshi's unique vision of predicament of modern man in contemporary Indian English fiction. According to G.S. Amur ''his novels take us to the heart of darkness- one of the most favourite metaphores is the Labyrinth - but he is not a prophet of despair. All his novels hold out promise of regeneration and redemption''.[1] In research paper an attempt has been made to explore distressed of the modern man in Arun Joshi's novel '' The Strange Case Of Billy Biswas'' on the basis of the portrayal of characters and situations. The strange Case of Billy Biswas is a story of inner psyche of the protagonist Billy who is unable to survive in civilized façade of modern life. The story is unfolded from the witness narrator point of view. The first part of the novel gives us the glimpses of the restlessness of Billy's soul in the midst of the upper class Indian society, which is lost in superficialities of life.

The narrator Romesh Sahai is a friend of Billy. Despite being a concerned friend in Billy's life, Rimi finds Billy's character to be enigma. Billy has an impressive though a strange personality. What one strikes about him not only his aristocratic background but also his elegant demeanor: '' he was one of these rare men who have poise without that pose''.[2] One would never fail to notice'' the strong, rather British accent of his speech'' [3]with ''words had a cadence, a compulsive quality engaged you in spite of yourself. ''[4]

He has a strong fascination for the tribal life. Its beginning when he is fourteen years old at Bhubaneswar. His visit to the sculpture at Konark sun temple urged him on to think of his own identity. He is fascinated by the imagery of the sculptare. For the first time he feels that the true beauty of imagination is appreciated only by the Adivasis. Also that spirit may be very old, older than human existence itself, yet the knowledge of truth is embedded with the tribal behind dark in securable faces. His visits to the tribal village with the chauffer proves to be a turning point in the life of Billy Biswas as he is for the first time ,overwhelmed by erotic energy in the tone and tune of the folk music while dancing and celebrating life. The young Billy feels: Something has gone wrong with my life. This is where I belong. This is what I always dreamt of.

His interest in primitive is continues even when he goes to America for further study. Despite his father's unwillingness he studies anthropology. During his stay in America he prefers to live in Harlem, the black ghetto of America. He thinks it '' the most human place.''[5]White America is too much civilised for him. It is his urge for the primitive that he plays the pair of banjo drums creating a strange hush on the scene in a music party in George's apartment. Billy's friend Tuula, the Swedish researcher and Romi, the narrator '' who had any clue to what went on it dark, inscrutable, unsmiling eyes of Bimal Biswas.''[6] Tula informs Romi that ''a great force ukraft a----------a primitive force'' [7]lying suppressed in the personality of Bimal Biswas.Billy stays in America for a long but does not suffer much except some passing spell of loneliness. He is not bothered about cultural alienation, what teases him is the superficialities of a grossly materialistic civilization. The elite foreign society is not congenial to the quest of identity for Billy and he returns to India .During his stay in India he finds Delhi is not different from American society. Further he feels that all the rich societies all over the world are superficial. His inherent

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protest against mechanized dehumanized civilized world i reflected in his letters to Tuula.

He writes: 'I see a roomful of finely dressed men and women seated on the downy sofas and while I am looking at them under my very nose , they turn into a kennelof dogs yawning (their large teeth showing) or snuggling against each other or holding whisky glasses in their furred paws''[8]

The imagery of dogs with large teeth and furred paws reveals the hatred of Billy and the character he thinks they bear. He has no love for the modern civilization. Billy feels that civilization is a monster. It is not civilization ,but degradation'' . He says :'' I some times wonder whether civilization is anything more than the making and spending money.''[9]

Due to his search for the viable alternatives he gets a job as a lecture at Delhi University. In order to study the life of primitive communities in hills and forests he undertakes numerous expeditions. But he remains very upset by his hallucinations. They reduce him to such panic condition. As a result he feels marriage is only remedy to stop them. He marries Meena Chatterjee , a sensuous ,gorgeous and good looking woman.

With passing of days in conjugal life , Billy realizes his blunder that hurried marriage is not a solution for his perennial problems. His wife fails to satisfy his inner urge and their conjugal life turns to be the most precarious of battlefield . For Meena ''Billy is getting stranger and stranger with every passing day ''.[10]She is unable to give him peace and satisfaction that he badly requires. Billy hates the worldly pleasures, but Meena is fond of money, market and the materialism, supposedly true identity of the elite society.As a result Billy starts getting estranged from his wife and family.

Whatever may be the psychological reason for the separation between Meena and Billy, it can be aptly concluded that the step Billy taken to start his new identity is a complete failure. Arun Joshi reveals the fact here that his protagonists is not an abnormal person. Rather he also takes efforts to integrate with the society and find out the meaning to life by establishing a family. But Billy is destined by his very nature for some other person and places .It can be concluded that Billy's character is the character of destiny.

Marriage fiasco has the negative impact upon psyche and personality of Billy. He feels in civilised society like pinned down there like a dead butterfly. He starts to take wine and to lie and sham. Even in his family, he feels alone and alienated like Camus's outsider.

His trauma is reflected in a letter written to Tuula : '' It seems , my dear Tuula that we are softly losing what is known as one's grip on life .Why else this constant blurring of reality ? Who am I? Who are my parents? My wife? my child ? At times I look at them, sitting at the dinner table, and for a passing moment I cannot decide who they are or what acident of creation has brought us together''.[11]

The aforementioned statements make it amply clear that he is in conflict with his identity. His exploration of the real inner being makes him an existentialist being, estranged and alienated. He never feels himself at home because one thing is clear to him that he is not the man of civilized society and his real destination is some other places. His health fails and his intellectual understanding starts declining. It is during his degradation he seduces Rima Kaul, an innocent girl in Bombay . The seduction of Rima Kaul is the evidence of his estrangement not only from his family and society but also from his true self. He comes extremely irritable with his behavior. Seduction of Rima Kaul is the last warning signal to Billy which gives him a preview of the corrupting force which awaits him if he continues to defy what his soul longed for.

In reality, Billy is a misfit in both the societies : of the twilight city of charm in America and elite like socializing society of Delhi, both of which have gone barren and spiritually bankrupt, madly comforts pursuing physical. They are appropriately materialistic and money doubles the centric worlds of technology. His hatred for the civilised world is so intense that he blindly supports the superstitions and the blind rituals of the primitive society in the case of child sacrifice by a clerk. His study of anthropology becomes the tool to justify the same by giving examples world around from Africa, Indonesia, Japan and many reports about the same happening in the rural parts of India when his father against him.

Despite being a member of the aristocratic heritage he longs for unlimited freedom of choice that awaits him in the primitive life.The very epigraph of the novel is from Arnold's ''Thyrisis'' :It irked him to be here ,he could not rest.'' make thematic direction of the novel clear. Like Arnold's scholar Gipsy, Billy too flees from the so-called civilized society and seeks shelter in the idyllic Maikala hills.

Conclusion

Billy has a family, a tradition, a set of values. Even though he ''considers himself a misfit, misplaced and does not enjoy the role he has carved for himself by

virtue of his qualification. He finds contentment neither in family nor in teaching. He seems to be misgotten in a world which he does not seem to fit in.''[12] Thus Arun Joshi's the second novel 'The Strange Case Of Billy Biswas' is a study of the total estrangement of the protagonist from upper-upper crust of society and his resultant quest for meaningful life. Billy realises that the meaning of life ''lies not in glossy surfaces of our pretensions, but in those dark mossy labyrinths of the soul that languish forever, hidden from the dazzling light of the sun''.[13] Through this novel Arun Joshi seems to give massage that parents should not suppress inner urge of children otherwise they will have to pay heavy prize for that. At last Billy realises that all his efforts to integrate with the society are fatile. He is so much mentally tortured that he dislikes the civilised and wants to get away from the greedy, avaricious and hypocritical world of the civilized. Therefore, he decides to listen his inner self and joins the tribal world.

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PROBLEMS OF IMMIGRANTS IN DIVAKARUNI'S *'THE MISTRESS OF SPICES'*

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Abstract

Chitra Banerjee Divakaruni is an Indo-American immigrant author. She investigates through her novels the issues of immigrants who have been getting by in the clash of conventional Indian identity, inalienable as a part of their identity and their fascination for westernization. She fits in with post-modern group of Indian authors who have been writing in English. Her written work fundamentally has managed the encounters of the immigrant women. In her novel, Mistress of Spices Divakaruni depicts that women break the hindrances of exhausted customary values and live free lives. Tilotamma (past name Nayantara) is the hero of the novel, Mistress of Spices. Her guardians consider her as the load however she has the ability to anticipate what's to come. Her magical powers and acclaim spread all around. The old lady told Tilotamma that she ought to stay secluded and ought not get to be excessively included in anybody's life. It implies that she ought not utilize the spices for her own particular purposes. Tilotamma opens a little spice store in Oakland, California. The clients of Tilotamma speak to the concealment and difficulty of women in an alien land. Tilotamma cures the mental anguish of the woman clients with the assistance of her spice. This paper intends to depict the issues of immigrants in her novel Mistress of Spices.

Women compositions and its assessment have pulled in an extensive number of women and commentators in the course of the most recent two decades and have procured a significant space in the historical backdrop of Indian writing in English. In spite of the fact that India has a history of old development, the surfacing of the first composed record of women's writing in India has been followed back to the approach of Buddhism in the early sixteenth century. Then again, in the eighteenth century women's written work declined

There are many other landmarks created by the diasporic literature. It has helped to understand and form potentials and core competencies. Access made available to educational, social, professional opportunities and political empowerment. It has made possible the removal of all kinds of limitations and barriers- traditional, cultural, linguistic etc. It ignites and synergies common and shared values in addition to coalition building among the social and political Diaspora. In addition to strengthening, it also enhances ties and bonds with others countries. To mention a few are the neighbouring countries including Pakistan, China, Bangladesh and other Asian Countries. Diaspora literature also helps countries to bring about a strategic partnership based on prosperity, security and commitment to freedom and peace. These are actually a very few features to name. If planned and monitored positively, Diaspora literature can also aid to fight larger evils such as terrorism, drug trafficking, environment degradation, combating the spread of contagious disease and actually fighting many other common political and social hurdles. Looking at it optimistically, Diaspora literature also helps in creating good will, a cordial relationship and in spreading values, virtues and universal peace.

Shri A. B. Vajpayee speaking on his expectations from the Pravasi Bharatis i.e. N.R.I's said

"What we seek is a broader relationship, in fact a partnership among all children of Mother India, so that our country can emerge as a major global player. We value the role of people of Indian origin as unofficial ambassadors providing a link between India and the rest of the world". No doubt, many of the Indians have left their motherland to seek anchor in various other countries. The reason for this movement ranges from indentured labour to seeking better prospects. No matter where we all are scattered across the globe, we are brought closer through the medium of films, songs, concerts and of course the Diaspora literature. This literature has helped in providing a link between India and the rest of the world. And this coming together and closer has helped creating tremendous self confidence with a combative spirit. The awareness that they are articulate, artistic, talented, creative, practical and adaptable has also dawned upon them. In the past, the Indians were intellectually fed on the thoughts of Dickens, Scott and the likes. Today, people all over the world are being nourished by the writers of the Indian Diaspora namely V.S. Naipaul, Rushdie, Mistry, Vikram Seth, Mukherjee, Vassanji etc. The European voyagers, travelers, traders and the orientalists rediscovered the cosmopolitan culture of India. The writers of the Indian Diaspora, through their literary contributions have greatly enriched the English literature. They have been aiming at re-inventing India through the rhythms of ancient legends, the cadences of mythology, the complexities of another civilization, cultural assimilation and nostalgia. They dive deep into the realms of imaginations and the ocean of memory to paint something quite different and distinct from that portrayed by fellow novelists. The writers of the Indian Diaspora write about India painting the vastness and the complexities of the home country which contains everything in multitudes – multiple truths, multiple crisis, multiple realities and this diversity is portrayed for the world wide reading public.

Conclusion

Diaspora is therefore, a scattering of the seed in the wind, the fruits of which are a new creation and a fight to survive. Every Diaspora movement holds a historical significance, as it carries within itself the kernel of the nations' history. Diaspora is a journey towards self-realization, self-recognition, self-knowledge and self-definition. There is an element of creativity present in the Diaspora writings and this creation stands as a compensation for the many losses suffered.

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THE TRIALS OF BROTHER JERO OF WOLE SOYINKA

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Abstract

This research paper focuses on the social ills prevalent in the African societies with the view of correcting them in order to make the contemporary society a better place to live. Drama is called as a mirror of a society. By using drama as an effective tool, the renowned Nigerian writer Wole Soyinka depicts the socio-economic evils prevailing

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in the society. These evils are being satirized to bring about a social reformation. Through this drama a sociological approach is employed by the play Wright in order to bring out the religious hypocrisy, moral decadence, and marital imbalance in the society. This research paper brings out the evils inherent in African social system and how the dramatist makes an effective use of **Satire** as a corrective measure social change especially in the prevailing society.

Soyinka captures worldwide issues by using a West African setting .The satirical message in the text is conveyed through redialing of the vices and follies of the contemporary Nigerian society via religious institution. His fictive output belongs to the Horatian mode of satire which ridicules the follies with the intention of reformation in the society.

Through satire and humor, the aberrant and corrupt nature of our religious leaders are exposed. Moral decadence, prevalent in the society is also dealt with. The text centers around a bar beach prophet Jero who pretends to be a true prophet but in the actual sense, he is cheat , a rogue, and in fact the devil's incarnate. As the play unfolds Soyinka presents prophet Jero as a representative of hypocritical religious person. He presents him in a humorous and comical way that we see through the front of the holy hermit which he puts on for the benefit of his deluded worshippers.

The wrong mentality or orientation of some so called prophets is brought to the core. Prophet hood ought to be a call to selfless and sacrificial living towards God and mankind. However prophets like Jero don't have this mental set-up. For Jero it's a business, a profit making venture, the easiest way to meet one's material needs. In one word its a trade, just as he calls it. To present it in his own words, Jero says, "I am glad here before any customers- I mean worshippers well, customers if you like. I always get that feeling every morning that I am a shopkeeper waiting for customers," (p 20)

There is a clear picture about how Brother Jero views the divine call, his prophethood. This is not far- fetched from what is obtainable in the contemporary Nigerian society. A lot of pastors or men of God have this mentality just like Jero. Since their orientation is wrong, there is bound to be the abuse of the religion. This is exposed and justified by Soyinka.

Furthermore, the character or attitude of some religious leaders negates what they preach. The exploitative nature of prophet Jero is exposed: how he chats on other to achieve his selfish interest. One of the victims of this bad attitude of his is the old prophet, prophet Jero grew up under his tutelage. He pretends to be working together with his master to acquire a piece of land. Again, Brother Jero's exploitative and pretentious attitude is seen in his relationship with his worshippers whom he calls customers. Brother Jero likes keeping his members unhappy. He believes that as long as men are unhappy and dissatisfied, they will seek the prophet.

Prophet Jero keeps his worshipers in bondage which is contradictory to the message of freedom that Christianity as a religion spells. The whole idea of keeping people dissatisfied and helpless is baseless in Christian ethics. It is simply exploitation in its highest order.

Chime is another victim of Brother Jero's exploitative character. Soyinka satirizes religious leaders and how they work on the ignorance or gullibility of their worshippers to achieve self – convenience and accumulate wealth.

Amope who is the wife of Chime, doubles as Brother Jero's creditor. Unknowing to prophet Jero, he discourages Chime from beating his wife in a bid to keep him dissatisfied.

Jero's weakness is not a hidden thing. It is obvious that he has passion for women. We begin to wonder what is divine in lustfully looking at a woman who has just had her bath. Prophet Jero's divine transformation is not achieved from studying the world of God but from lusting after a woman. After all a woman is his weakness. In another instance, we see prophet Jero being carried away with a woman's naked wombs instead of blessing the water for his worshippers. Many religious leaders who profess to be holy are the false victims of one type of weakness or the other. We hear of great men of God having extra marital affairs. This is highly wrong not only morally but also religiously. A man of God is supposed to be a virtuous, morally upgraded as he is works as a Torch – Bearer for others in Justifying the Ways of God to Men.

There is a deliberate commercialization of religion by the so called custodians of sacred institution. In this case it is not only Christianity; Brother Jero represents, religious practices observed all over the world.

Soyinka very boldly satirizes such ill practices existing on a large scale in Nigerian society."The Trials of Brother Jero" is a satiric comedy which aims of correcting the evil in leading social institutions from society.

Conclusion

An attempt has been made to examine the social issues existing in the contemporary Nigerian society by Wole Soyinka. The playwright has made use of the popular technique of satire in order to bring about an re-orientation of the Nigeria citizens.

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R.K. NARAYAN'S 'THE FINANCIAL EXPERT' A PORTRAIT OF SOCIAL AND FAMILIAL INDIAN MIDDLE CLASS

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Abstract

Primarily, R.K. Narayan is a writer of social and familial novels. His novels revolve round the family and the society, the society in which he inhabites. His remarkable grasp of the social structure and his concern towards middle class life enables him to delineate Indian middle class social life with perfection. "His dispassionate social detachment suggests a personal endeavour to attain an equation with life to overcome and rationalize the profound and unmitigated loneliness of life. He does not keep only to surface reality. His vision is truly comprehensive." Narayan's social vision is marked by a greater degree of affirmation and optimism. "It has been cliche to regard Narayan as a delineator of middleclass people. Since the typical middle-class milieu constitutes the matrix of all the Malgudi novels. Its significance may hardly be exaggerated."

The middle class provides him desiered material to dramatize his conception of humanity and the notion of man's existence. What in fact the middle class milieu brings into light is that although Narayan is "fully immersed in his material", and his confined to his South India middle class, he seems to have acquired the representative in his regional world and thus, in the final analysis, seems to touch the chord of universality, dealing with the tale of the common man." It is through the human spectacle of the middle class that Narayan seems to the dramatize theatre of the absurd. The typology also notes the reflection of the novelist autobiographical elements, the clear indication of his sacrosanct tradition and his faith in the internal spirit of India, through the middle class portrayal.

Right from *Swami and Friends* Narayan has peopled his fiction with the Indian middle class- a class close to him as palm skin. "His strict confinement to the portrayal of the middle class milieu often finds Narayan bracketed with Jane Austen (in the context of her 'two inch ivory tower')". Significantly, all typological frames underline the average and the ordinary middle class protagonist as he plays the central consciousness and dramatizes the theme of illusion versus reality. In fact, the middle class portrayal seems to have become Narayan's strategy to project several issues.

Fundamentally, Narayan's fiction is Indian in the sense that they explicitly exhibit the social pattern of life existing in India. *The Financial Expert*, is an excellent example of his keen ears and observation of Indian middle class social life. Its protagonist Morgayya, rises before as from a very humble position to be a very big banking magnet. We are not only witness of his rise but also beholder of his down fall. Accumulation of money and more money, by hook and by crook is his only obsession. Lakshmi the Goddess of

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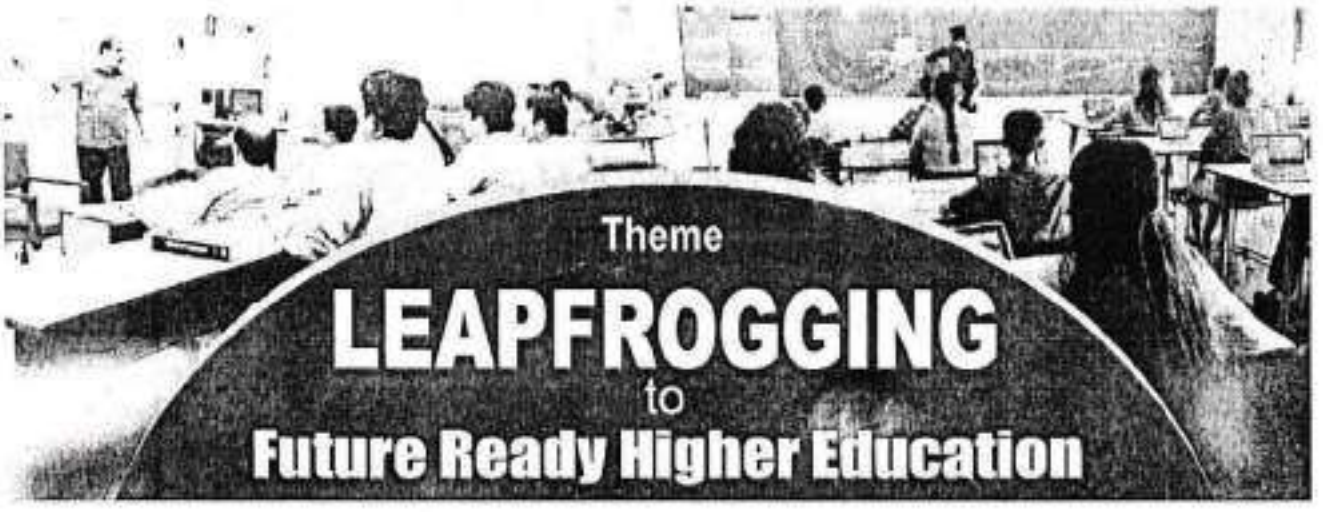
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CONQUERING ANGLOPHOBIA: SOME REMEDIES

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ABSTRACT:

In this modern era, English has become a universal language that is widely spread and spoken by many people across the world. Ithas been accepted as the official language. The world is shrinking fast into a global village and English has become the most important language for India as for other countries. It has emerged as an important component in all spheres of human life; politics, press, advertising, broadcasting, transport, Information Communication Technology & Science. With the sophistication that has developed in Science& Technology, it has come to hold preponderant position amongst languages in the world. Consequently, the demand of English has been far-reaching almost in all the fields like politics, international relations, media, communication, travels and education.

Etymologically, Anglophobiameans the hatred or fear of England and anything English. A large majority of students suffer from Anglophobia. There is a great need for finding cure or remedy for the Anglophobia, here in simple words, the fear of English Language. This research paper proposes to throw light upon somefeasible remedies to acquire a comfortable level to communicate in English. It deals with the effective methods which can be employed in teaching English to the students for their enhancement in language proficiencies.

Keywords: *Anglophobia, Communicating through English, Fear of English*

Introduction:

The advancements in the field of science and technology have shown an instant impact on the language. There has been a dramatic enhancement in the expository material available in the English language. Access to new knowledge is possible only through English. The English language has been an important medium of the press for nearly 400 years. Literary reviews, hobby journal reviews, children story books, scholarly journals etc., are published primarily in English. Unfortunately it is seen that the students, to a large extent and the teachers to some extent are not able to communicate comfortably or effortlessly in the existing scenario. It is said," If a language makes you a Human being, knowing more languages makes you Superhuman." The motive to learn any language is to communicate efficiently. Any communication is impossible if one doesn't get a chance to communicate with the people. "Though human society has progressed with remarkable speed, the use of language for communication is still not free from ignorance, prejudice and superstition". It is natural that the demand for communication is high in this ever-changing world. Language plays an important role in communication and English is

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no doubt the foremost and most important tool of communication in every field all over the world. Individually every man should strive hard to acquire good communication skills in English which is the most important prerequisite to excel in one's life, at personal level as well as professional level.

Status of Students in Rural and Urban Areas

In comparison to the rural, urban students get an opportunity to learn through lot of modules. They have a wider exposure of learning English through diverse methods. Specialized training programmes are available in the urban schools to improve the students' LSRW skills, whereas the rural students get limited exposure to improve their English language skills. The language training provided in rural schools, is purely theoretical and bookish. English is taught considering only examination point of view. Hence, even after learning English since an early age of education or entry level, students are hesitant to communicate in English language. To some extent same is applicable to urban students also. Many of them are good in English but when it comes to communicate in English hesitation prevails among students. It is high time to motivate the students, right from their school by creating an awareness regarding the importance of English language. It is necessary that the teachers who teach English in rural areas should be trained enough and should have an open approach to prepare the students in language skills. The available resources should be completely tapped so as to provide an encouraging atmosphere for learning and practicing the language. Today, conventional teaching methods are being replaced with modern techniques which rely hugely upon media resources. Teaching English with the help of such modern techniques fosters a positive attitude among the rural students to learn the language which would enable them to meet the demands of the day in a creative way.

Problems faced by the rural students:

To begin with, the first and the foremost factor is the Socio-Cultural background and financial conditions of the family. Most of the illiterate or less educated parents are not able to guide their wards as educated and cosmopolitan parents can do. Therefore, the students' growths towards education require parental supervision and guidance. The illiterate or less educated parents are unaware of the importance of education so they do not understand the value of communication skills which plays a crucial role in their ward's career. The children from rural areas who attend the school in their nearby city areas are not much exposed to the same type of facilities and motivated as the urban children.

In cities, the children get motivated through two ways: Instrumental and Integrative motivation. Learning a language only for rewards is instrumental motivation, on the other hand integrative motivation includes the urge to be part of the community which is so strong that drives the child to pick up the language with perfection. Regarding the syllabus, the most important point is in most of the schools English is taught as any other subject. One should not forget the fact that it is a language and not any theoretical subject with its own concepts based on theories. The importance of English as a communicative tool is not realized. So the existing methods followed

at rural schools are not enough to train the students to communicate effectively in English. There is a departure from conventional teaching which was mostly teacher centred. One has to adopt a learner-centred approach.

The students belonging to rural area are not given the required training to develop their LSRW skills at different stages of learning. These students somehow manage to pass in the examinations at their X or XII levels but when they take up professional courses at the later stage, they face a lot of difficulties. Since they are not good enough to communicate in English, they miss many opportunities. Their *Anglophobia* does not allow them to move on comfortably in their professional life and ultimately they fail to fulfil their aspirations. As there is an increase in the ratio of rural students preferring for professional courses, the above facts should be considered and those students should be trained to meet the need of the hour.

Challenges of teaching English Language in the rural areas:

Need of competent teachers:

One of the problems of teaching language in rural areas is the unavailability of competent teachers. Most of the schools employ teachers for teaching English subject and that too without training. Therefore there is a need of regular B.Ed., D.Ed colleges where teacher training courses are offered, proper training should be provided, so that they would be able to teach English in more methodical or systematic way to the students in rural areas. There are some institutions which provide training to the English teachers, but still, a serious attitude towards improving standard of English couldn't set in.

Need of suitable teaching aids and materials:

Teaching a language requires good teaching material, work books, hand books for teachers, audio-visual material like charts, pictures, radio, computers & TV. Unfortunately, teachers and students are not benefited with these materials and therefore teaching has become monotonous and tedious activity due to lack of insufficient teaching aids and material for learning language. It is an irony of the situation that today we live in an Information Communication Technology (ICT) world but the ICT tools have notyet been devised and used so effectively as expected. Even though the government has been initiating to provide digitalised classrooms &teaching aids, the internet connectivity and regular power supply refrains the effective use of these technologies.

Need of exposure to the language:

This is yet another problem faced in teaching and learning English language all over. English language is getting taught with translation method. Only convent students are privileged of having such environment and getting command over English language and being presentable. The learners get little or no exposure to the language outside the classroom. So, there is little scope for the learners to learn the language beyond a certain limit. As a consequences, the entire burden of teaching the language falls on the teacher. Only CBSE, ICSE Board students are seen to be benefited of such exposure.

Large Number of students in Classes:

Large number of students in a class has become a severe problem in the Indian class rooms for years. Classrooms are diverse in socio-economic, cultural and geographical levels. There's no extra special time or attention paid for the weak student. There's no scope for individual attention and thereby no proper intellectual growth seen among students.

Lack of Practical Sessions:

The numbers of periods allotted to English are specifically theory sessions. Which need to cut down and few practical sessions need to be added for more practical exposure to make them comfortable and more used to with the language.

Suggestions:

It must be remembered that language is not just a means of communication. It is also a vehicle of culture of the community that speaks the language.

I) The teacher must be trained systematically as per the needs of that language. The basic requirements of the students to acquire English language must be researched, studied and analysed first.

II) The teaching process be reformed or modified to achieve the targets of the learners. The curriculum from the basic to advanced levels be framed catering to the needs of the learners at every level.

III) The overall process of language learning at an early stage be made more entertaining so that the learners will develop interest in the process. The number of students in language class be reduced so that every learner will get an opportunity to practice and develop LSRW skills at their own pace. Ideally speaking the class should consist of 20-25 students so that the teacher can attend each student personally.

IV) The class should be conducted in more participative and inclusive manner. Exercise in loud reading, effective group discussion, personal interviews, role-playing, telephonic conversations, extempore, paper reading, paper presentation, elocution competition, quiz, debate, mock interviews, seminars etc. should be incorporated in in the process of teaching learning.

V) There should be an optimum use of ICT tools. The use of audio-visual aids in teaching-learning of language makes the whole process not only effective but also entertaining. Screening of films, cartoon shows, documentaries, classical films, sci-fi films occasionally will have a positive impact upon the learners.

VI) Teachers should widen their teaching resources by referring to ICT tools such as MOOC, Swayam or educational programmes on you-tubes and other e-resources available on Internet today.

VII) Language laboratory can also be one of the effective measures to make teaching, learning and evaluative process more result oriented.

Conclusion:

The purpose of education today is not just making students literate but add rationale thinking, making him more knowledgeable and self- sufficient. When there is a willingness to change, there is a hope for progress in any field. Creativity and

innovations be developed and appreciated as they benefit both teachers and students. As Albert Einstein once said, "I never teach my pupils. I provide the conditions in which they can learn". So let us make sincere attempts to evolve or create conducive conditions for the learners in such a manner that they will never develop Anglophobia in life.

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Attaining Good Governance in Higher Education Institution through Technology

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Abstract:

Higher Education plays a pivotal role in nation building. It is one of the most powerful means to create knowledge based society. Historically, India was knowledge centre in the world attracting pupil from Europe and South East Asia by its well established universities like Nalanda and Takshashila which were the centres of disciplines such as Mathematics, Physics, Astronomy, Numerology, Economics and Philosophy. But in the course of time India lost its glory in higher educationfor well-known historical and political reasons especially, due to foreign evasions. Recently, higher education imparted through the universities in India is facing challenges in terms of quality and access. There has been a constant transformation in HE in India. There has been an expansion of education in all spheres of knowledge. Today's competitive world demands good quality education. In other words it needs good academic environment, teaching – learning process, research facilities, healthy campus life, digitalized classrooms, support services, infrastructure, modernization or digitalization of library, updating of library books, journals and reference material in the form of database.Hence improving the quality of education and campus life is the major concern of HE. As everyone knows quality of a nation depends upon the quality of its citizens and quality of citizens in turn depends on the quality of their education. In order to compete with the world economy, India needs to develop quality manpower with modern outlook.

The present paper discusses the necessity androle of E Governance in higher education.Benefits of e-Governance to various stakeholders of higher education andKey Challenges of implanting e-Governance in higher education are also briefly discussed. The paper concludes with the suggestions & recommendations for attaining good governance in higher education institution through technology

1. Introduction:

The 21st Century has witnessed tremendous advancements in technology which has led to far-reaching developments in administrative system.Cost-effective technology combined with the flexibility in learning and administrative activities is essential to enhance efficiency. Computers can be used extensively for educational administration. There are some of the areas where computers can be used for effective educational administration (Ben-Zion Barta et. al. 1995):

- General Administration
- Pay Roll and Financial Accounting
- Administration of Student Data
- Inventory Management
- Personnel Records Maintenance
- Library System

Information and Communication Technology (ICT) plays a vital role in supporting powerful, efficient management and administration in education sector. It is specified that technology can be used right from student administration to various resource administration in an education institution (Christiana Maki 2008).

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Moreover many studies revealed the need for ICT integration into administrative activities of higher education institutions. The various ways of introducing technology in education institution administration are the following (Caroline Salerno 2009):

- Sending e-mail notices and agendas to staff, rather than printing and distributing them
- Submission of lesson plans through e-mail
- Foster technology growth by asking parents to write e-mail addresses on medical forms.
- Insist that all teachers create a class Web page
- Attend technology conferences to see what other colleges are doing, what other teachers are doing to integrate technology, and what principals are doing to encourage the use of technology in their schools and classrooms.
- Admissions through web-enabled services.
- All day-to-day activities of the institution(General Administration)
- Staff administration
- Single Window System for students.

2. Role of Higher Education in Society:

Higher education is generally understood to cover teaching, research and extension. If critically analyze the different concept of higher education it can list the various roles higher education plays in the society. Higher education is the source or feeder system in all walks of life and therefore supplies the much-needed human resources in management, planning, design, teaching, and research. Scientific and technological advancement and economic growth of a country are as dependent on the higher education system as they are on the working class. Development of indigenous technology and capabilities in agriculture, food security and other industrial areas are possible because of our world- class higher education infrastructure. Higher education also provides opportunities for lifelong learning, allowing people to upgrade their knowledge and skills from timeto time based on the societal needs.

3. Necessity of e- Governance in Higher Education:

If the quality of our higher education system has to be improved to make these institutes really world class, then there is no alternative to the introduction of e-governance in this sphere at the fastest possible pace. Implementation of e-governance in technical and vocational institutes will enable their effective & real time monitoring by Government/the regulatory bodied & other stakeholders their own managements, parents of the students & the society, thereby forcing them to maintain quality & become more responsible. E-governance process brings transparency in the system, so e-governance initiatives in the field of higher education will help reduce the corruption up to a large extent. The introduction of e-governance in higher education is one such concept that can empower the governing bodies to administer the progress of the education plan in the whole country and serves various stakeholders in a much better ways. E-Governance is becoming a global phenomenon that is increasingly attracting the attention of community citizens including politicians, economists, decision and policy makers amongst others (Naheed et al., 2009).

3.1 Role of e-Governance in Higher Education

We are living in constantly rising new era of digital world. ICT and e-Governance has an impact on nearly every aspect of our lives – from working to socializing, learning to playing. The digital age has transformed the way youthful people communicate, network, seek help, access information and learn. We must know that three billion young populations all over the world are now on-line and access information through a variety of means such as Cell Phones, Tablets, Laptops or Computers and through TV.

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As technology becomes more and more implanted now-a-days in our culture, we must provide our learners with relevant and contemporary experiences that allow them successfully to engage with modern technology and prepare them for life after education.
In general, educators, researchers and policy makers all will agree on the potential of ICT and for administration through e-Governance which has a significant and positive impact on higher education.

3.2 Benefits of e-Governance in Higher Education:

E-Governance offers various benefits and advantages for the government, corporate sector and society. E-Governance helps better delivery of academic services to citizens, improved interactions with business and industry, citizen including student, faculties" empowerment through access to information, or more efficient administrative management. The benefits of e-governance in an educational sector are improved efficiency, increase in transparency and accountability of educational administrative activities convenient and faster access to services, and lower costs for administrative services. It streamlines internal operations and improves performance of educational departments while helping all sections of educational stakeholders to avail e-governance.
The multi-faceted benefits of e-governance can be summarised in a tabular form as shown below:

Benefits of e-Governance to the various stakeholders of higher education

Stakeholders of Higher Education	Benefits of e-Governance to stakeholders
1) University	a. Centralized information access from anywhere. b. Monitoring academic performance of colleges c. Increase in student enrolment ratio. d. Provide quality e-services, e-participation. e. Increase transparency. f. Introduction of innovative teaching tools (Video Conferencing, Live Demo etc.) g. Improved decision making, Private Public Participation. h. Less corruption, less paper work. i. Reduction of load on campus administration. j. On schedule, hassle free cycle from admission to result. k. Optimized and re-engineering process. l. Lifelong electronic data for instant retrieval.
2) Students	a. Increase participation in education affairs. b. Better access to information and quality services for student. c. Personalized login and Password for each student. d. Substantial saving in time, cost and efforts. e. Better Job opportunities and career advancement opportunities for good students. f. Social connectivity for collaboration. g. Students can access virtual lectures and webinars. h. Students can solve their problems on-line like- examination queries, result verification etc. i. Students can submit their feedbacks to university. j. Improve means of education not only urban but rural student as well.
3) Colleges	a. Improved Quality of service to students. b. Transparency in operations.

	c. Increased efficiency of faculties and of administration processes. d. Data can be accessed easily. e. Integrated e-Governance in education sector. f. Saving of hidden operational cost. g. Instant statistical report generation. h. Students" data can be captured at source. i. Helpful for NBA or NAAC accreditation.
4) Faculties	a. To know the latest syllabi. b. Communication to the business community for syllabi development. c. On-line appointment of examination. d. Minimum faculties can set on line examination paper. e. Sharing new concepts and ideas with faculties and business community. f. To get on line help for certain topics with experts. g. Improve quality of services from Universities. h. To get latest GR and Notification from Universities.
5) Sansthas / Institutions	a. On-line connectivity's for various Governments agencies. b. To get latest GR. c. On-line connectivity for all colleges within organization (Extranet). d. To know up-to-date admission Status College wise, course wise. e. To know the present status of staff at various department. f. Improving services to people and students. g. Staff attendance. h. Grievance Handling.
6)Government /other statuary bodies	a. Simplicity, efficiency and accountability in the government functioning. b. Online feedback system. c. Centralized system of checking and monitoring. d. To know the latest trends of education. e. To know the present enrollment for higher education. f. To know the University wise, college wise, Course wise enrollment status. g. To know the geographical, gender wise enrollment status. h. To know the scholarship budget for the financial year. i. Fund utilization and budget allocation. j. To get University, Staff and Student progress in terms of global scenario. k. Make future plan for higher education.
7) Industry or Business	a. Improved interactions with business and education. b. To get quality and skilled employee. c. Set syllabus as per industry needs. d. Helps for better industry related research. e. Recruitment with good performing colleges / Institutes.
8) Overall education system	a. Long term impact on organization goals. b. Improve education system. c. Empowerment of faculties, students and encouragement of their participation in governance.

(Courtesy:shodhganga.inflibnet.ac.in/jspui/bitstream/10603/198980/17/4- Role of e-Governance in Higher Education)

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3.3Key Challenges of implanting e-Governance in higher education:

1. *Less Bureaucracy* – As digital information can move rapidly from liable office to another, without the need to wait for paper documents.
2. *Cyber Crime* – Despite the efforts of government agencies to ensure the safety of citizens; personal data, e-governance websites are still liable to attack from hackers.
3. *Infrastructure Cost* - An efficient e-Governance system requires all stakeholders or at least the vast majority to have access to the Internet. Therefore, Internet-enabled devices are essential to connect to government websites. In addition, universities / institutions need advanced servers and security systems to cope with vast amount of information and complex cyber threats. All these requirements constitute a costly investment.
4. *Inaccessibility* - An e-Governance site that provides web based access and support often does not offer the potential to reach many users including those who live in the remote areas, have low literacy levels and exist on poverty line income.
5. *Lack of Human interaction between Students and Staff* - They will miss out on the discussion and instructor feedback that characterized for credit classes and that makes such classes useful and valuable.
6. *Technological Issues* - Some students may have trouble using e-Governance, if they have slow or erratic internet connection. Others may not have infrastructure as well they are not able to afford it. Students in urban and remote areas find it very difficult to access these facilities.
7. *Language and/or Cultural Barriers* - Although efforts are being made to make websites available in multiple languages, many are only available in English, limiting their usefulness to Non-English knowledge stakeholders. Additionally, not all resources are culturally appropriate for all stakeholders.

4. Suggestions and Recommendations:

The online methods enable more effective education and offer significant advantages over traditional services.

Provide E Services– After the implementation e-governance, we improve the delivery of services to students, faculty by providing services like enrolment, examination, result, feedback, requests for documents, requests for certificates, issuing admit cards and ID cards, employment etc.. The system provide timely alert to colleges through SMS /Emails. E-governance in education provides new ways of communicating to the students, imparting education and organizing and delivering information and services.

Improved education system - E-governance in education sectors allows use of information and communication technologies with the aim of improving education, improve information, service delivery, encourage student participation in the decision making process, making administration transparent and effective and give universities a new channel of educational unemployment. Also, the system can obtain feedback from industry and students to modify course curriculum if deemed appropriate by the authorities. This will allow all the lesser performing colleges to reduce the gap with better performing institutes. It will be help in the betterment of the higher education in the country and increase the number of employable students.

Innovative Teaching Tools – The new technologies offer vast opportunities for progress in all walks of life with the introduction of new technological initiatives the structure of higher educational institutions has changed. The changing role of lecturers, the changeable learning environment and the design of e-

Learning facilities all contribute to a potentially more flexible organizational structure of higher education in rural area. The future delivery of education will be based through eLearning technology providing lecturers with superior teaching tools. This has been possible by technological implementation based environments such as bulletin boards, virtual lectures and e Libraries and video conferencing. In e learning environment can support communication with classmates and lecturers.

Private Public Participation – almost all e-government projects have found it convenient to involve different private agencies for different tasks through public-private-partnership (PPP) arrangements. These tasks include design and development of application software, population of data and content in the regional language, procurement and installation of networking and computer systems, deployment of software and delivery of services.

Centralized Information - E-Governance has provided electronic information infrastructure to simplify service delivery, reduce duplication, and improve the level and speed of service at a lower cost. The centralized information approach of e-Governance keeps all information at one place in electronic form. This approach of making information secure prevents it against any theft or leakage.

Use of intranet - Intranet-based training provides a low cost and knock-on savings, is that it can be a virtual two-way system, with students connected to mentors and teachers receiving real-time feedback and support. Managers with employees scattered among sites and locations, particularly if they are so far flung that they are in different areas, need a cheap and effective way to communicate them. ICT is already proven as the way to access knowledge based information from anywhere to anytime but a limitation of the university that they can't communicate with other colleges.

With the help of above benefits and suggestions it is possible to design a system that is student centric and can provide a variety of services—informative, interactive, and transactional and integrated system across the entire spectrum of the education sector. Central Universities, State Universities, Autonomous Institute, Deemed and Private universities and affiliated colleges will enter the data and caters the need of MIS of regulating and coordinating bodies. Users can tap the system and find out the related information needed. The higher education coordinating and regulating bodies could obtain the reports on various issues about future planning like budget, demand of courses etc.

5. Conclusion:

In this 21st century, for our survival and development, we need an education system which would be suitable to our existing personal, professional and social situations. Hence the nature of our existing higher education system needs to be transformed into a better and distinct one than the previous education system. In this context, the planning for efficient administration of higher educational institutions, to achieve the world class standard it is necessary to have an improved collaboration and access to information available in all the parts of the world. Itis possible only by introducing IT in Educational Sector with e-governancemechanism. The e-governance is neededfor smooth information flow, best practice database and enhanced capacity for information analysis etc. It requires completely new infrastructure, procedures, policies and working skills for producing and collecting online information. With the advent of ICT, electronic governance is an emerging trend to re-invent the way the Higher Education system works. This can be a new model of governance. Such a comprehensive and integrated system can also enable authorities to analyze the performance of one of the best performing institutes and compare it with other Institutes of Higher Education to identify the gaps and bridge them efficiently in order to bring uniformity in the smooth functioning of Higher Education. Through e-governance we can improve the quality of higher education system in India. E-governance can create the

transparency between the universities, colleges and students. According to Nobel Prize winner and ex-president of South Africa, Nelson Mandela ***"Education is the most powerful weapon we can use to change the world".***

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The Plight of a Woman delineated in Mahasweta Devi's "Draupadi"

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Abstract: Mahasweta Devi basically belongs to the Reformer's Family. Being a social activist Mahasweta Devi wrote about the lives of ordinary men, women, particularly Adivasi(tribal) people like the Santhals, Lodhas, Shabars, and Mundas, and other topics of social and political relevance. In "Draupadi", the story is set in a realistically delineated forest background in Southern Bengal. Draupadi Mejhen is the name of the central character who was brutally raped in police custody. Despite the torment, she resists against the male dominance and faces the ordeal boldly. This research paper is an attempt to reveal the misery and plight of the Dalit women depicted by Mahasweta Devi.

Introduction

Mahasweta Devi was was born in Dhaka (now in Bangladesh) in 1926. Like Devi herself, her family members were both literary and civic-minded; her grandparents had taken part in Rammohan Roy's movement that promoted Western education and social reform in India. Devi's father was a well-known Bengali writer whose stories address slum life, and her mother was a writer and social worker who promoted literacy among underprivileged children. As a child, Devi studied at Shantiniketan, a school founded by Rabindranath Tagore. After finishing her Master of Arts in English at Calcutta University, Devi began teaching and working as a journalist. Mahasweta Devi, always wrote for deprived section of people. She was a loving daughter, a clerk, a lecturer, a journalist, an editor, a novelist, a dramatist and above all an ardent social activist. Her stories brought to the surface not only the plight of the completely ignored tribal people, but also articulated the oppression of women in the society. Being a social activist Mahasweta Devi wrote about the lives of ordinary men, women, particularly Adivasi(tribal) people like the Santhals, Lodhas, Shabars, and Mundas, and other topics of social and political relevance. She also had spent many years crusading for the rights of the tribal. Devi as a writer handled many forms such as short story, short fiction, novel, drama, essay and article. Her short fiction "Draupadi" is primarily the story of a Santhal tribal woman raped by men in power. This is the story of a woman who was tortured sexually in police custody. The purpose of presenting this research paper is to show how a woman is being tortured as a subaltern.

Woman as a subaltern:

Mahasweta Devi has been considered to be a spokesperson of tribal and dalit communities. Devi is also concerned with the peripheral existence of women of Bengal within social, political and economic nexus. Woman has always been dominated by man, be it in matters of socio-economic issues, and cultural rights. She is victim of a wicked sexual politics. Simon de Beauvoir wrote in the introduction to her famous book "The Second Sex", "Woman is defined and differentiated with reference to man and not man with reference to woman; she is the incidental, the inessential as opposed to the essential. He is the Subject. He is the Absolute – she is the Other". Woman is the "Other", that is, she does not have primacy in society, politics, culture, and not even on her own self. The value of woman is judged in accordance with men – woman only makes sense when placed against man. Woman is traditionally considered to be inferior to man; she is emotional, unintelligent, and vulnerable. Woman is customarily taught to find her fulfilment in relation with man where she is but slave to his desires.

Draupadi as a Woman:

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"Draupadi" as a text first appeared in Agnigarbha ("Womb of Fire"), a collection of loosely connected, short political narratives. Later on it was translated by Gayatri Spivak in 1981. In "Draupadi", the story is set in a realistically delineated forest background in Southern Bengal. Draupadi Mejhen is the name of the central character. Dopdi(Draupadi) Mejhen is a tribal woman who is twenty-seven years old. She is a wife of DulnaMajhi in the story.Draupadi is a tribal reincarnation of mythical Draupadi from Mahabharata. The tale of Draupadi is a tale of 'rape-murder-lockup torture' in police custody. It expresses the torturing experience of Santhal tribe. As a tribal she cannot pronounce her own Sanskrit name Draupadi. She cannot pronounce even her name because of the underprivileged background. The tale exposes the dalit feminist consciousness in its initial exposition itself: "What's this, a tribal called Dopdi? The list of names I brought has nothing like it! How can anyone have an unlisted name?" Dopdi and Dulna are married couple, active workers in Naxalbari movement and fights for their prime necessities. After Dulna's murder, Draupadi is brutally molested by the policemen in their attempts to extract information about the fugitives. Senanayak, the army chief torments Dopdi (Draupadi).she was brutally raped in police custody. Her character in a story explicitly and implicitly is a subaltern itself. Her status in custody becomes even more subordinated as a woman.

Draupadi as a symbol of struggle:

Draupadi has to face so much torture but she come up as symbol of struggle. She refusesage old man dominated social norms. She was offered a piece of cloth to hide her shame after multiple-rape on her chastity throughout the night. Draupadi pours down the water, tears the cloth to pieces and refuses to cover herself up with the male –defined notions. According to Spivak, the effectiveness of Draupadi's resistance is not the refusal to act, but the redefinition of construction of "sexual honour" of a woman when she comes out naked and confronts Senanayak. Unlike the mythological Draupadi, Dopdi challenges the brutalizer. Instead of lamenting at the loss of the supposed "respectability", she goes forward to question the masculinity of her "maker". As a counter-offense, she tears her clothes and makes herself naked as a figure of refusal in front of Police authorities, displaying her crushed body. As Draupadi's revenge excerpts: "What's the use of clothes? You can strip me, but how can you clothe me again? Are you a man?" (37). She looks around and says, there isn't a man here that I should be ashamed. I will not let you put my cloth on me. What more can you do? This is the sardonic reality of India whose futile promise of an integrated nation, equality and justice are fully exposed in this story.

Conclusion:

Mahasweta Devi's stories deal with the lower stratum of life in Bengal. Her stories bear the mark of her acute sensibility to history because she feels that a historical sense is essential for Literature. Her famous story "Draupadi" manifests the oppression on the tribal Santali community through the persona of Dopdi Mejhen, who resembles the Draupadi of Mahabharata bearing the brunt of oppression of men around her. The life of the tribal Dopdi and the mythic Draupadi of the Mahabharata as both seem to have struggled for their legitimate rights, snatched by the establishment throughout their life.

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Giovanni Boccaccio's "The Decameron" A Harbinger of Renaissance

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Introduction:

The Decameron attained enormous popularity among the literary class when it first appeared in manuscript form in 1370. The renaissance brought a rebirth of learning. It began in Italy about 1300 and spread throughout Europe in 1400's and 1500's, scholars rediscovered Greek and Roman Classics. Renaissance men turned away from medieval ideas and ideals. They started finding inspirations in classical models and attitudes. A balanced development of mind and body was emphasized. This period was marked by a surge of creative activities in art and literature. Philosophers became curious about the nature of human knowledge. Writers needed new literary forms to express the vitality of times.

The Italian writers Giovanni Boccaccio and Petrarch were among the first to study ancient literature. Petrarch mastered the Sonnet, a poetic form and later became popular in all parts of Europe. Boccaccio's fame rests on his Decameron, a collection of a hundred short stories. He was one of the earliest authors to work in the vernacular language, as opposed to Latin. He created realistic characters. He broke away from many medieval conventions. In France, the new thirst for knowledge produced essays of Michel De Montaigne and the rollicking tales of Franois Rabelais. Boccaccio's narrative poems and romances influenced Geoffery Chaucer.

The word Decameron is based on a Greek word for "Ten Days". The hundred stories are distributed over 10 days. They are arranged in a progression of themes. The themes are designed to show the complexity of human relationships and their happiness before the terrible and mysterious forces of nature. It centers around 10 people hoping to escape the black plague of 1348. They retreat to the hills of Fiesole above Florence. For ten days they candidly tell each other stories dealing with topics such as love, intelligence, human will or desire before returning to the city. Although the one hundred novellas comprise numerous themes and characters, critics have observed that Boccaccio's use of framing structures and narrative devices, his introduction to the first and fourth days and his epilogue lend a sense of thematic and stylistic unity to a work which otherwise would have appeared disordered or fragmented.

Depiction of women characters in Boccaccio's work:

In The Decameron, Boccaccio is much in sympathy with women and supportive to them. Boccaccio does portray women with more realistic colours. When examining stories where Boccaccio gives in detail the male-female relationships, it emerges that women are stronger, more lustful and more cunning. When he compares men and women, it appears that he favours women as the better sex in terms of both good and evil. Overall, it is fair to say that Boccaccio does portray women as outshining men in many respects. Boccaccio demonstrates that women tolerate more adversity than men. This increased tolerance for adversity may stem from the basic lack of options. If women face any problem, they have no power to eliminate or escape the problem. As a result women endure large amount of hardships. Why did Boccaccio as a male writer take such a rational and positive

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attitude towards women in a male-dominated society? We can say that his own life experience and the social background partially attribute to this.

Attitude towards Women:

The role of women was a very scarce role during renaissance. Women were supposed to be seen and not heard. Women were to be prim and proper, the ideal women. Females were able to speak their minds but their thoughts and ideas were shaped by men. Mostly everything women did had input given by men. A Woman was controlled by her parents from the day she is born until the day she is married, then she would be handed directly to her husband so he could take over that role. In the time of the renaissance women were considered to legally belong to their husbands. Women were supposed to be typical 'housewives.' In this research paper the researcher has selected the work of Giovanni Boccaccio's The Decameron , where women generally are held in a lower social standing than men. As with most societies until relatively recently in history, women were not allowed to have a significant role in society, other than that of a wife and mother.

The most amazing part is that seven out of ten story tellers are female, but what makes it even more valuable is that these female characters in the work are quite different from those in other European literature works. However, in The Decameron, Boccaccio's portraits of women are quite different. Instead of being made fun of, women in the tales are given intelligence and thought. They often made their husbands laugh stocks instead of they themselves becoming a butt of laughter. For example, the tales in the Seventh day are mainly about how women play tricks on their husbands to successfully have love affairs.

Feudalism is a combined economic and social system that defined the Middle Ages. Under feudalism, social classes were highly hierarchical. In this society, arranged marriage prevailed. Love and Marriage was not simply an individual act but a political activity aiming to expand one's power. As a representative of a newly rising bourgeois class, Boccaccio was strongly against arranged marriage and advocated for free love and marriage for women. In The Decameron, Boccaccio claimed for this wish for women by creating many tragic love stories.

It is generally accepted that The Decameron is the first work publicly and directly defending female sex in European literature. Female sex is an opposite concept to male sex. In The Decameron, Boccaccio defends boldly for female sex by portraying several female characters who are bold, brave, and enthusiastic enough in pursuing and satisfying their sex desire. Instead of being shameful, they dare to speak out their need in front of the fathers and public, which shows the awaking of female consciousness. The Decameron demonstrates the subtler powers of women; though they do not enjoy any real power in the social hierarchy of the 14th Century , they do possess a considerable amount of power over the other sex because of their superiority over men.

Conclusion:

In The Decameron, Boccaccio employed his pen to speak for women to express what exactly women want to say but dared not and could not say at that time. The Decameron is the first literary work in European literature which speaks for women, and Boccaccio is thus the first male writer serving as a spokesman for women by writing this work mainly for women, defending women for having the rights to enjoy sexual pleasure, asking for the equal rights shared by men and women both at home and in society, and claiming for free love for women. Although there is still some dross in The Decameron, it is still regarded as a classic work in European literature in the depiction of modern women during renaissance.

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"We Are Home!" A Call of Triumph
Betti Mehmoody's Journey against the Fundamentalists

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Introduction: Women writers in America, Iran, Pakistan and Afghan, who suffered from harassment, challenge those orthodox concepts of religious fundamentalism which they find to be unbearable in the modern context. In fact they consider all religious scriptures including the Quran, the Bible and the Vedas out of place and out of time as they project women physically and mentally inferior and thus are oppressive in nature. To their horror, any religion does not consider woman even as a separate human entity. The increasing influence of religion in a male dominated society and the inferior position accorded to woman forced these writers to reject all orthodox rites and rituals as dead wood. They find that the concept of marriage is based on patriarchy and religion is a mere construction in their fiction, they endeavor to expose the ugly face of a society that hold woman in a perpetual subjugation. This serious issue of women identity, their suppression and oppression by male dominated society is being portrayed in many years through feminists' movements all over the world. Numerous western as well as eastern feminists, philosophers and theorist like Mary Wollstonecraft, J.S. Mill, Virginia Woolf, Simone de Beauvoir; Gayatry Spivak etc. also have talked on this issue. All over the Asian world, there is a patriarchy, and lots of importance is given to a man. Woman is given secondary status. She, has always been remaining inferior, even in the 21st century. So far, a number of problems have been taken into consideration and solved in time, but the problems and issues related to equality and identity of women are still continued from the ancient times to the present date. Issues such as deliberately detaining a woman in house, banning to learn, ruling as to be in veil as the fundamentalist detains them under the name of religion, women are deprived of their rights and they are given treatment like slaves. Betti Mehmudy's novel "Not without My Daughter" highlights the problems of women's life, the reality between fundamentalists and rationalists. The novel also exposes the justice and oppression against women, which will aid to find out remedy to stop the unbearable sorrows in their life as well as to make them free from the detained life as a free bird.

The present research paper explores post-colonial, transnational, feminist discourses in the context of religious fundamentalism, communalism and feminist issues in South Asia, particularly in Iran. It argues that despite living in patriarchal and conservative society, women writers have successfully asserted their right to be heard and they write to define the totality of their world on their own terms.

Betti Mehmoody is an American writer who wrote about the plight of Muslim women suffering the same in Iran. She was born on June 9, 1945 in Alpena, Michigan, is an American author and public speaker best known for her book, *Not Without My Daughter*, which was subsequently made into a film of the same name. She is the President and co-founder of *One World: for Children*, an organization that promotes understanding between cultures and strives to offer security and protection to children of bi-cultural marriages.

Her book, '*Not without My Daughter*', is an account of experiences in her own life during 1984–86.It is also the "story of a woman's courage and total devotion to her child", which "would give any loving mother nightmare". When she left Alpena, Michigan, to go to Iran with her husband and daughter for what she was promised would be a short visit. Once there, she and her daughter were held against their will. According to the book, she and her husband, Sayed Bozorg Mahmoody, and her daughter, Mahtob, traveled to Iran August 1984 for what her husband said would be a two-week visit with his family in Tehran. Once the two weeks were over, however, he refused to allow his wife and child to leave. Mahmoody became trapped in a nation that was hostile to Americans, a family hostile to her, and an abusive husband. According to the book, Mahmoody's husband separated her from her daughter for weeks on end. He also assaulted her and threatened to kill her if she tried to leave. She eventually fled with her daughter. The novel gives detail information about her 500 mile (800 km)

escape to Turkey. She received help from many Iranians. Upon returning to America in 1986, Betty filed for divorce in US court, whereas, Sayd Bozorg Mahmoody had no voice since he was not present in the US.

An Iranian physician, Sayed Bozorg "Moody" Mahmoody wants to visit Iran with his American family. He claims that his Iranian family wants to meet his wife Betty and daughter Mahtob, and asks them to come with him for a two-week visit. Despite her deep fears about visiting Iran, particularly due to the Iranian Hostage Crisis, Betty reluctantly agrees. Upon their arrival, they are all greeted warmly by Moody's family, but shortly before their flight back to America, Moody announces to his wife that he wishes for them to stay in Iran. Betty realises that she has been deceived by her husband, even though Moody took an oath that they would return to America, "swearing" on the sacred Quran. When she protests, Moody strikes her, and nobody in Moody's family sympathises with her.

Moody becomes more hostile and abusive, preventing her from leaving the house or using the telephone. Betty briefly manages to visit the American Interests Section of the Swiss Embassy, but is told that she is now an Iranian citizen since she is married to an Iranian, and as long as she lives in Iran, she cannot leave the country without her husband's written consent and has no parental rights over her daughter. Moody learns of Betty's meeting and threatens to kill her if she tries anything again.

Knowing that her chances of escape are very scarce, Betty conforms to her husband's wishes in order to gain the trust of Moody and his family. By chance, during a trip to the marketplace, she meets a sympathetic shopkeeper who overhears her telephone conversations with the Swiss Embassy and puts her in contact with a humanitarian Iranian, Hossein, who offers to help Betty and Mahtob in their passage back to America. The plan becomes complicated when Betty receives news from America that her father is seriously ill and may be dying. Moody approves of Betty returning to see her dying father, but will not let Mahtob go with her. Betty decides to wait to return to America with Mahtob, but Moody unknowingly foils her by having her booked on a flight several days early thanks to his relatives' contacts in the airport.

Betty eventually gets what seems to be her last chance to escape when Moody is suddenly called to the clinic for an emergency. On the pretense of going to buy presents for her father, Betty takes Mahtob and they contact Hossein, who manages to send Betty and Mahtob off with some Iranian smugglers, and using fake identity documents, they make their way past the checkpoints. Despite the difficult and very dangerous journey, Betty and Mahtob are dropped off in a street in Turkey, where they see the American Embassy in the distance. "We're home," says Betty.

Conclusion: During the last few centuries women writers with their sharp feminine sensitivities and perceptions have considerably widened and deepened the areas of human experience, transmuted into the verbal artifact, with new vitality and purpose. The world body of literature in English would have been much poorer without the contribution of women writers. These writers have been raising questions, opening perspectives, challenging, illuminating and explaining life as they see to it. It is indeed striking when we consider the fact that so many great writers of modern times have been women. Betti Mehmoodi's novel is another significant mile stone in this journey of freedom of women.

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English Today: "Nvr 2 L8 2 Learn"

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Language is being used as the most effective means of communication by human beings today. It has enabled man to interact with the environment. It regulates human social behavior. It is the most sophisticated system of symbols used by man. The sophistication which has been attained in devising this complex system of "meaning – sharing" activity is a result of experiments of so many centuries. The language which we have today is the most prized possession of man. It is a propeller for the advancement of knowledge and a telescope to view the vision of the future. Ever since the dawn of civilization, man has been trying to exploit the dynamism of language for the conduct of his day-to-day affairs. With the advancement in technology, human life is changing and so is the language. If we could talk to the English speakers a hundred years ago, they would say we have already ruined English. The English language as well as the other languages is moving right along with the times and recording and taking part in innovations and change. With all our new ways of communicating, we've constantly been evolving the language.

The human language has been greatly influenced by changing technologies throughout the last several centuries. Today the modern trend of communications has made a direct attack on the Written Discourse. The texters have begun changing words, appearing as phonetically transcribed sounds to shorten the language. Before studying the pros and cons of the text messaging and its impact, both, in terms of positive and negative, on English language, it becomes necessary to see how and why text messaging has become such a popular mode of communication. Text messaging or texting is a colloquial term referring to the exchange of brief written messages between mobile phones. While the term most often refers to the messages sent using the short message service (SMS). Today it has been extended to include messages containing image, video and sound contents such as MMS messages. Individual messages are referred to as 'text messages' or 'texts'.

The first big revolution of technology affecting language was the invention of the printing press. As a result of the printing press, language became more standardized. It became possible to print in mass and make copies available to the public. As a result of which regulation of spelling and grammar became a concern among academics. The great English lexicographer, Samuel Johnson, undertook the important prescriptive task of regulating spelling by creating the first dictionary in the English language. The most significant technology in the 16th century, the printing press, caused a transitional shift in the English language and though many technological advances have been made since then, none has affected language beyond the creation of new words and redefining old words until recently. The digital technology in the 21st century is causing another transitional shift in language moving beyond naming and redefining to creating a shortened language system with accompanying rules. Both Samuel Johnson, a revered scholar of the 18th century, and the average Internet and phone user in the 21st century, attempt to prescribe rules of the language to work with the technology of the time.

Today text messaging is the most widely used mobile data service; with 35% of all mobile phone users worldwide or 4.2 million out of 7.3 million phone subscribers at end of 2003 being active users of the Short Message Service. In countries like Finland, Sweden and Norway over 72% of the population use SMS. The European average is about 85% and North America is rapidly catching up with over 40% active users of SMS by end of 2006. The largest average usage of the service by mobile phone subscribers is in the Philippines with an average of 15 texts sent per day by subscriber. In Singapore the average is 12 and in South Korea 10. [1]

Text messaging was reported by the Global Messaging Survey by Nokia in 2001 to have addictive tendencies. This addiction was confirmed by the study at the Catholic University of Leuven in Belgium in 2004. Since then the study at the University of Queensland in Australia found that text messaging is the most addictive digital service on mobile or internet, and is equivalent in addictiveness to cigarette smoking. The text reception habit introduces a need to remain connected, called "Reachability"[2].

The people sending text messages, texters, are experimenting with written language, manipulating it to fit the technological limitations of space and style. Many of the abbreviations originated in chat rooms to allow for faster response time and texters expanded the abbreviations to create a writing system that contains new prescriptive rules and reflects a better phoneme-grapheme match in spelling than traditional English spelling.

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Today, networked computer-mediated communication technologies are the latest ways to communicate quickly since the invention of the telephone. In Hale's (1996) "Guide to Computers and Computer Language", she questions the recent semantic changes. "Writers today must navigate the shifting verbal currents of the post-Gutenberg era. When does jargon end and a new vernacular begin? Where's the line between neologism and hype? What's the language of the global village? How can we keep pace with technology without getting bogged down in buzzwords?" [3]. Although there are no easy answers, users are changing written discourse to work with the technology, changing the language first in the chat rooms and making even greater changes when using text messaging. Traditional prescriptivism, grammatical rules about written language, originating with Samuel Johnson and others, does not exist in the digital world; users attempt to define themselves stylistically to their groups by playing with the language and creating new prescriptive rules for written language in the process. Scholars do not make the rules any longer; our language is distinctively being changed by technologically savvy users who are primarily young adults.

Many people understand that written English differs greatly from spoken English, even within a specific dialect or pidgin. Language is used (and some would say abused) in many different ways, relating to the medium of expression. For example, those who write newspaper reports use the English language in a very different way to those who write poetry or who speak as a radio announcer. The style of English is adapted to fit the mode of delivery.

The ability to send short messages in an abbreviated format that are still understood is an evolution of *the first telegram message*. It was sent on 24 May 1844 by Samuel L Morse. The last telegram sent by Western Union was on 2 February 2006, marking the end of an era that undoubtedly spawned the Internet as we know it today along with emails and text messages. Just as the telegram did not destroy the English language, neither do emails or text messaging.

The invention of the computer does not belong to one person; rather it belongs to various individuals who contributed toward technological advances in creating "machines" that aide in the computation of numbers. Not until the 1980s did companies build computers available for the public that did not require a punch card. The invention of the desktop computer and the software that utilizes the computer is the cause of a language revolution creating new prescriptive rules. The pc (personal computer) not only caused significant semantic changes in English by adding new vocabulary and expanding/generalizing existing vocabulary, but also delivered the capability to retrieve information as well as communicate remotely through the Internet. The Internet soon became a medium for a select group of people to communicate. As more citizens connected to the Internet, these newbies either had to learn the new prescriptive rules created by the original users created to communicate selectively with one another or forfeit an understanding the new modes of communication. The Internet allowed users to create something similar to a new dialect or vernacular only people using this technology would understand, often called "netspeak", "netlish", "weblish", "cyberspeak", "electronic discourse", "electronic language", and "computer-mediated communication (CMC)" [4].

Seeing a language in its written form is important to the individual's ability to understand sentence structure and grammatical use. Written English when used correctly, even in an abbreviated form, strips away all the vocal inflections of accent. It is a standard language, and as such is used in the Medical arena and by many other professions as an internationally-used language of communication. The merging of the sound of some English words with the written form that produces text messaging has never been intended to replace the formal language. It is simply a means to an end, a form of digital graffiti that is quick and temporary in nature.

Today's age is the age of information. Things are changing instantly. The networked computer- mediated communication technologies are the latest ways to communicate quickly. The World Wide Web (WWW) has brought the world very close today. With the help of these advanced means of communication, one can very easily get connected with any part of the world. This fast and easy access to information has been made possible by means of Internet, email, chat rooms, handheld computers and phone cables of multiple medium formats. The latest trend in this technologically advanced communications is text messaging i.e. short messaging system (SMS) which is also popularly known as texting. On the one hand the world is enjoying the golden fruits of technological advancement in communication today; on the other hand one needs to think seriously over the emerging language problems today. It is true that language changes with changes in the technologies. The language is abbreviated due to the limitations in the number of characters allowed per message. The examples given below will prove the state of affairs in the written discourse today.

"cu@coll" Replying "cnt cu cos im sik" which means 'can't see you because I am sick.' Another message says, "Il b bk 2 wrk b4 wknd" meaning 'I'll be back to work before weekend.' "kcw 2 cu" which means 'can't wait to see you' which replies "cu2moro" meaning 'see you tomorrow.' In English language today the texters started using four distinct numbers to the sounds in a word. The number 8 replaces the sound /et/, 4 replaces /f^{TM} r/, 2 replaces /to͞o /, 1replaces/ won /. "3 some" means 'threesome.' If 'cr8' means 'create'; 'db8' means 'debate' and 'f2f' means 'face to face' and the most commonly used one is '143' means 'I love you' and so on. Similar to aforementioned style, dropping vowels from a word is another quick way to shorten the language. The consonants are retained for word recognition. Some of the examples are fwd –forward, btr-better, chln-chilling, emsg- email message, sry-sorry, txt-text, etc.

Using acronyms is the most common way texters have shortened the language through the text messaging. It is true that the acronyms allow a texter to write more in a condensed space; however, there are many drawbacks too in using them. The use of acronym is growing so rapidly that it is becoming a complete long system. But many texters are unable to decipher the acronyms because more often they are not familiar with the acronym or the definitions. The acronyms are often imprecise. It can be seen from the following examples. " wywh" stands for ' wish you were here.' "uw" or " yw" for ' your welcome'. "ttul8r" or " tlk2ul8r" stands for 'talk to you later.' " wfw" means 'work for me', etc. Condensing of language to such an extent certainly give rise to ambiguity. If the same acronyms are not shared by the sender as well as the receiver, there will be utter confusion. *Intelligibility* is one of the primary features of language, if it is lost, the very purpose of communication will not be served. Contraction is another way to condense the language. It is seen that the texters have started dropping the middle part of the word or phrase - such as " bday" for birthday, "wassup" means 'what's up', "werru" means where are you? etc. The most confusing of all is the use of abbreviated phrases. These phrases are very harmful to use unless the meaning is shared by both the parties. Many such phrases are region or group dependent.

The real problem in written discourse emerged when these texters crossed their limits and started using this mode of writing in the classroom. *The chatroom language has started affecting the classroom language.* Teachers became the immediate victims of this mode of writing. The time has come for the teachers to learn the language of abbreviations and translate the text messages. One teacher from Britain asked her students to write about their summer and received the following essay: "my smmr hols wr CWOT. B4, we used 2go2 NY 2C my bro, his GF & thr 3 :- kids FTF. ILNY, it's a gr8 plc." The translation for those of you who are not text message savvy: "My summer holidays were a complete waste of time. Before, we used to go to New York to see my brother, his girlfriend and their three screaming kids face to face. I love New York. It's a great place"[5]. Educators will need to address this issue of separating conversational text from formal writing if our language goal is to continue using traditional prescriptive rules to communicate written discourse. Another concern for educators when teaching students writing and communication skills is how the postmodern tendencies appearing in the changing language will affect? How can we communicate when there is so much lack of depth, ambiguity, and fragmentation?

One needs to ponder on the following point:

i) Do people really need to manipulate written discourse to fit their need for communication to such an extent?

ii) If communication means to share information between two or among many and if this 'sharing-activity' is being held successfully through texting, then should that be openly accepted as a means of communication?

iii) As it is known to all that youngsters who are the new-learners of English, and who occupy the majority of the class using texting so freely, these young learners who use English as L_1or L_2 orL_3 are highly influenced by this shortened means of communication.

The emergence of mobile phone and the rise of text messaging as a means of communication appear to have influenced the standards of writing. No doubt it has brought a great deal of convenience, quickness and a new language to our society. Technology is the hallmark of our innovative world today. Many benefits have emerged from text messaging, however many problems have risen with the development and prevalence of text messaging. One cannot deny the fact that it has very badly affected the grammar and writing of the students all over the world. Text messaging, with its use of phonetic spelling and little or no punctuation seems to have posed a threat to traditional conventions in writing. In many cases, users seemed unnecessarily reliant on short sentences, simple

tenses and a limited vocabulary. The frequency of errors in grammar and punctuation has become a matter of serious concern today. It can rightly be called as a 'Global' problem today. Prior to text messaging, adolescents in most countries used slang to define their specific group, but language used in text messages goes beyond the creation of new words. They began redefining the rules for the language.

Postmodern scenario:

In a postmodern society, contradictions define our lives. Linguists Aitchison and Lewis discuss these contradictions in the introduction of a collection of articles from a Conference on Media and International Communication [6]. The first contradiction they discuss is ***globalization versus fragmentation***. In a world where technology allows us to connect to the world through instantaneous news and *communication*, the world has thus become smaller to us than it was to our forbears, even our parents. The Internet, especially, connects us to the world and others, making us feel as though many people surround us, but according to Wilbur, "the physical isolation of sitting in front of a computer fragments our experience because it is nothing more than a virtual reality" [7]. Also, digital technology has fragmented the audience because a homogenous mass audience does not exist anymore, but rather small communities of niche market [3]. The users who belong to these small communities are the ones shaping and defining communication changes including, but not limited to, written language.

Aitchison and Lewis discuss a second contradiction of postmodern society, ***linguistic expansion versus language compression.*** "The television and the Internet can be accessed for news around the clock, news reports for "special events" are extended, websites provide links for more information; however, the information we receive is compressed as well. Although we know more, we compress the language into headlines in newspapers that provide a summary of the article in a few short words and tickers in news shows with brief updates flashing across the bottom of the television screen" [6]. Other technologies, such as the Internet and mobile phone, have expanded the ways in which we can communicate with others across time and space; however, the users must compress the information due to the formatting of certain mediums of communication. For example, people in chat rooms must shorten language because of the required quick response and text messages can only have 140-160 characters due to the limitations of the technology. Scholars have also noticed trends that support postmodern tendencies in the information society; Green compares characteristics of modern and postmodern societies and lists the following as postmodern characteristics in an information society: ambiguity, chaos, random, no certainty, surface (lack of depth), niche market, overlapping layers, shifting meanings, fragmentation [7]. Text messaging reflects these postmodern problems because the language is fragmented, text is abbreviated and words often left out.

Impact of texting on the young Learners:

Just as the Internet is a communicative tool utilized globally, so is text messaging. Text messaging is far more popular in Europe and Asia than it is in the United States. Due to the popularity of text messaging in other countries that speak English as well as other languages, English is not the only language affected by text messaging shaping the language.

Within each country, adolescents make up the primary group utilizing text messaging and are therefore often responsible for changing the language. In 2001 the BBC reported that 90 percent of 11-16 year olds in England have a mobile phone and the top reasons to text someone include sending a greeting like happy birthday and arranging or canceling a date[8]. By 2003, adolescents made up 43 percent of those sending messages, as opposed to 25 percent of those 30-34 [9]. Kesseler and Bergs suggest in their study that text messages are replacing love letters between adolescents and even though text messages are simplified, the love mail still contains the same images, metaphors, and codes [10]. Prior to text messaging, adolescents in most countries used slang to define their specific group, but language used in text messages goes beyond the creation of new words to redefining the rules for the language.

The emergence of the mobile phone and the rise of text messaging as a popular means of communication has had an impact on standards of writing. There are several evidences in the responses of candidates. This method is most popular among teenagers. A study by Upoc found 43% of cellular phone users ages 12 to 17 used text messaging, compared with 25% of those 30 to 34.Those teenagers, hampered by limited space and the difficulty of writing words on numeric phone keypads, have helped create the text-messaging lingo. Jesse

Sheidlower, Principal Editor of the U.S. office of the Oxford English Dictionary said, "Text messaging is going through the natural progression of language. Much of the text-messaging lingo was first used in instant-messaging programs on personal computers."[11]

Even though text messaging is another example of an established trend in written communication, it has certainly bothered many linguists today. The actual problems arise when people use the quick, casual language in other forms of written communication, such as e-mail, in which the sender may not receive the message for some time, or writings in which the reader may not even know the author. Text and instant messaging are negatively affecting students' writing quality on a daily basis, as they bring their abbreviated language into the classroom. As a result of their electronic chatting, kids are making countless syntax, subject verb agreement and spelling mistakes in writing assignments. The text message writing style aims at getting as much said with as few words as possible. This rushed form of writing neglects to consider the audience or appropriate voice. The shorthand style is not suitable in formal or classroom writing, and the fact that it has become the students' primary form of writing, is a serious problem. As we constantly see the shortened words, terms and contractions typically found in text messaging dialogue used in students' formal writing assignments. It is found that students' overall quality of work suffers because their attitude toward writing has changed. Much like texting, students want to get everything written as fast as possible. They do not want to be bothered with the writing process-drafting, revising and editing. Student writing is not up to par. Poor grammar, punctuation and spelling mistakes appear in everything students write, from classroom assignments and e-mails for teachers, and then to the written exams. As teachers, we have to believe that students' wide use of "text speak" is a key factor in their negative performance.

Communication is never a bad thing, and having students text one another is great. It will not be an exaggeration to say that it is our job as educators to prepare our students for the real world and instill in them the formal writing skills they need to succeed. As more and more students immerse themselves in Textspeak over their cell phones and computers, it has become a matter of worry for many educators that their writing skills are suffering. After all, the short-message format routinely sacrifices grammar, syntax, and punctuation for the sake of slang and brevity. There is concern that students who frequently express themselves in abbreviations and smiley faces may lose the capacity for more nuanced, grammatically correct writing. When communicating through text rather than speech, paralinguistic communication is lost, such as facial expressions, gestures, and body language critical for determining meaning in context. First appearing in email and chatrooms, texters borrowed smileys (also spelled smilies) and emoticons; both are modern forms of ideograms designed to show emotional and facial expression. Smileys and emoticons use letters and symbols on the keyboard to create the appropriate emotion. Specific abbreviations may not stay because language changes over time; however, text messaging will affect how we communicate with one another. The general populace will be more exact with words because the discourse used in everyday communication like email, IRC, chat room, and text messaging is compressed; however, the brevity of words will cause more ambiguity and the loss of paralinguistic features of communication. No longer can a person easily distinguish emotions when communicating. A gap has always existed between scholars and the common people, but the gap has decreased in the last few centuries as more people have access to education. However, as more people turn to technology to assist them in communication, the further the gap will once again grow between scholars and everyday users of technology as the idea of written discourse changes."Language and languages change," said Carolyn Adger, Director of the Language in Society Division of the Center for Applied Linguistics in Washington. "Innovating with language isn't dangerous" [12].

Language is ambiguous due to the elimination of words or letters in a word, as well as removing paralinguistic communication like facial expressions and hand movement from a conversation; lastly, communication lacks depth when language is stripped to the basic element. Still, with English as a first language of around 400 million individuals and a second language of somewhere between 500 and 1000 million more, the English language is in no danger of being destroyed by text messaging or any other new fad that arrives via modern technology. Indeed, the advent of mass mobile communications may even increase the use of the English language still further, in all its variations. The English language as it is used today is not at all the same as it was 50, 100 or 1000 years ago. It is continually evolving, taking on words from other languages and developing new meanings for existing words within English. It is a fluid and beautiful language with so much variety and scope, which can prove confusing at times for those trying to learn it but ultimately provides as wonderful means of expression for many millions of people around the world. Text messaging is just another development along the language's path; ***nvr 2 L8 2 learn. i.e. it's never too late to learn.***

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Approaches and Methodologies of Receptive Skills in English Language

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Abstract:

The basic skills of learning a language are listening, speaking, reading, and writing (LRSW). In order to acquire any language perfectly, a learner needs to be given a proper training in all these four skills. One fails to acquire the comfortable level of speech or comprehension unless properly trained in these skills. Majority of students offering traditional as well non-traditional courses such as BCA, MCA, MCM, B Pharm. or other technical courses are not in a position to use English language comfortably; even though they are exposed to English (SL or F L) for such a long time. It may be due to lack of proper training in receptive skills at the proper stage.

If speaking and writing are considered [illegible] skills. But the relationship between these two sets of skills is very much supporting each other. Developing perfect listening or reading skills further leads to developing perfect writing skills. The main objective of developing receptive skills need not be teaching of more grammar or vocabulary, but developing learners' ability to understand and interpret using the existing knowledge of language.

This paper deals with the basic Receptive Skills; Listening and Reading, whereby the listener or reader receives information. It will also discuss the different approaches of receptive skills, the methodologies, common drawbacks in the process of developing these skills and the remedies to deal with them. An attempt will also be made to explore the process of assessing learner's ability so that the process of teaching and learning English Language becomes more effective.

Introduction

Today, communication in English has become an important aspect of our life. It is not just a means of sending or receiving messages from one person to another, it is much more than that. In last four to five decades, it has been refined and strengthened by contributions from a variety of disciplines. It is central to everything that we do. We live and act in our organizations, our family, school or college, office, hobby places, community groups, our city, town etc. Our activities succeed or fail, and our goals are achieved or not achieved, according to our ability to communicate effectively with others. After independence, though the British people left India, English language remained behind. It will not be an exaggeration to call English as the 'lingua franca' of the country. Due to globalization of economy, today English has become functional language in the professional world. Even though India is a land of contradictions and paradoxes, people of different castes, creeds and different ethnic groups speak different regional languages. Under such circumstances, English language enjoys considerable importance in India. So, it becomes our primary responsibility to develop and improve the basic skills of communication among the students so that they will be able to accomplish their goals in life. The paper follows with the explanation of basic receptive Skills, necessity to develop receptive skills, problems in the process of developing receptive skills and explores the method for assessing learner's abilities.

I. Receptive Skills

As the famous saying goes, 'Practice makes a man perfect'. If a person wants to be perfect in some skill, he has to make certain deliberate efforts to achieve proficiency in that skill. One needs to acquire all the linguistic skills to use the language efficiently. Listening, Speaking, Reading and Writing (LSRW) are the four basic linguistic skills through which a speaker has to undergo to acquire a language. Out of these four skills listening and reading are called **Receptive Skills**. While acquiring them, a learner merely receives and understands it. He does not have to produce it. These skills are also known as passive skills. Whereas speaking and writing are considered as active skills. Generally it is observed that learners begin with receptive understanding of a language and later they move on to productive use. The relationship between receptive and productive skills is not only inter- dependent but also supporting to

each other.[1] Therefore, for a learner of English (as L_2 or L_3), systematic exercise in receptive skills becomes essential to develop the productive skills.

Listening Skills: In communication, effective speech is only one side of the coin. The other side of the coin is listening. It is observed that listening is the most neglected area in the process of communication in India. Basically we need to inculcate the habit of listening among the learners of English. This skill needs to be developed at the very initial stage. As quoted in the Holy Bible:

"Listen to counsel and receive instruction,
That you may be wiser in your latter days.
Cease listening to instructions, my son,
And you will stray from the words of knowledge."[2]

Listening is a fine art; it can be mastered by cultivation, consciously, carefully and systematically. When a child learns, L_1, his mother tongue, he gets rich exposure of listening since his birth. As he grows, he gets a lot of opportunities to practise his L_1. But the need of training arises when one has to learn L_2 ie. Second language. As a systematic exercise of speech organs is essential to attain proficiency in speech, a systematic exercise in ear-training is indispensable. One needs to be very attentive while listening to some speech or conversation in English. Proper ear training could be provided by taking some special efforts. There are modern scientific techniques available today. The schools and colleges must facilitate the learners with all the facilities. The electronic media such as radio, television, various news channels etc. may help in creating that language environment which is required in for the ear-training.

In the elementary classes learners of English are not provided with sufficient opportunities to listen to good English. There are no systematic or deliberate efforts made either by the teachers or the learners.

There are two types of listening:

*i **Passive listening:*** The listener is unable to comprehend the speaker. The mind fails to perceive any message so there is no communication.

*ii. **Active Listening:*** In this, the listener is involved actively and enthusiastically in the speech.[3]

In our schools, every child can not avail of this facility to get exposed to English at an initial stage. In the vernacular schools, the teaching of English as L_2 or L_3 begins only after the 5th class. Another important aspect is the lack of 'Trained Teachers'. In order to provide successful ear training programme we need to have trained teachers to undertake it. The empathy towards English initiates at this level. The problems of comprehension keep multiplying as a learner shifts from the elementary level to the intermediate level. This is a very common experience of all the teachers that after crossing the 10+2 level or even at the graduation levels, students are reluctant to take assignments in dictation. When a teacher dictates, it is common to hear "yes!", "can you repeat that please?", "Sorry we didn't understand", "what did you say?"etc. This is undoubtedly a common experience of teachers in most of the classes. If you use videos, CDs or audio cassette tapes, learners interrupt repeatedly. I would like to mention observation of a personal experience. G. B. Shaw's 'Pygmalion', the classical play was prescribed for a literature class. In order to make learning experience more interesting and effective for the students, the film 'My Fair Lady', which is an adaption of the play was shown in the college. The story line of the film was already provided to the viewers so that they shouldn't miss the gist of it. Unfortunately very few could enjoy the film. The most discouraging part was that the majority of students could not comprehend it. They had no patience to listen carefully they did not show any interest to make it understand from their side, it is only because they are not skilled in listening.

According to Prof. Larry M. Lynch, there are seven factors which directly or indirectly contribute to learners' listening comprehension skills: **Vocabulary, Rhyming Sounds, Idioms and Expressions, Pronunciation, Regional or National Accents, Grammar in Context, Language Rhythms.**[4]

Reading Skills: In olden days, knowledge was transmitted from teacher to taught through a speech. When man grew civilized, he gradually developed a language which became a mean of communication. He developed certain oral and visual symbols. He started recording his experiences of knowledge. Today all the knowledge has been treasured in books, whose reading makes man wise and learned. So it is very essential to inculcate reading habits among the learners of English. This habit must be developed at an early stage. It is observed that majority of students learning English language read the texts only for the sake of passing the examination. As the education system is exam-oriented, not only a student but also a teacher is bound to finish the prescribed syllabi in given period of time. A teacher, like a task master, has to do his duty of finishing the syllabi in order to prepare students for the examination. In this whole process of teaching and learning, training in linguistic skills is neglected completely. Students are not exposed to good reading. They read only exam-oriented material (readymade notes) as word symbols without grasping the meaning. In order to develop good reading comprehension, a reader needs to adopt some measures. The reading material should be of reader's choice. The teachers should see to it that the selection of reading material should be in accordance with the reader's field of interest, his background and past knowledge. The learners should be taught the scientific procedure of reading. in order to grasp the meaning clearly, a reader must be taught to take efforts to understand the reading material on his own.

There are two popular methods of reading:

i. Scanning: It means reading the text quickly to look for specific bits of information. The reader is required to read a passage carefully but quickly to grasp the meaning.

ii. Skimming: It means to read superficially or look over curiously and gather salient facts in it.[3]

Majority of readers read quickly but carelessly. If they are asked to put down briefly the substance or gist of what they have just read, they fail to do so. It is because their attention was not fully centered on the passage. A proper practice in skimming method enables the reader to comprehend the passage with brevity and in logical order.

II. Necessity to Develop Receptive Skills

In India, it is necessary to focus on developing proper receptive skills, at a proper stage. It will be more beneficial if systematic exercises are provided at the beginning or elementary level. On this issue Costas Gabrielatons opines, "My survey of EFL course books, as well as my observations of lessons and discussions with teachers indicate that courses for early learners at the elementary levels usually concentrate on grammar and vocabulary teaching. Texts are normally used as vehicles of the presentation of a new language. Whereas systematic receptive skills development is reserved for intermediate levels. Teaching materials may involve some comprehension tasks, but this alone cannot seem to constitute systematic skills development".[5] The main objective of a receptive skills programme is not the teaching of more grammar and vocabulary, but the development of learner's ability to understand and interpret texts using their existing knowledge of language. The programme of receptive skills development should go hand in hand. Care should be taken that the language component should not cancel the skills.

III. Problems in the process of Developing Receptive skills:

In India, teaching or learning English as a L2 or L3 is all together a different experience. When working through a lesson in a class, we should take up all four linguistic skills (LSRW), so that the process of learning will be recycled during the teaching of the lesson. It is true that learning rules of grammar is important; but practice of language is even more important. Bringing all these aspects into teaching a lesson will help developing the basic linguistic skills, which is very necessary at the early stage of learning. There are many learners who can very well solve the questions based on grammar without any mistake. But when asked, "How do you do? or Could you introduce yourself?" They are in trouble. This is only because there is no proper exercise in receptive skills which leads to failure in presenting productive skills.

Secondly, there is no proper exposure to the L2 or L3. Learners are not effectively and sufficiently exposed to the language. They listen or read for words and not for the meaning. They get easily discouraged by unknown words. They do not make conscious use of their background knowledge and experience. When systematic receptive skills development starts at intermediate level, the learners' reading or listening becomes problematic. They are asked to read or listen to much longer and more complex texts. They are asked to perform higher activities such as reading selectively, extracting gist, locating specific information and finding meaning of unknown words.

One of the reasons behind these problems seems to be the habit of explaining all unknown lexes and translating texts. Research findings have suggested that teachers are more keen at explaining or translating all the words first. Then the meaning of the text is explained. The learners also get into the habit of doing the same, because for a learner or a tutor a teacher's behavior in the classroom is an ideal one. They also apply the same methodology of translation of the texts. As a result of which they think that the meaning is strictly in the words. They do not bother to utilize their background knowledge and that is how they fail in comprehension.

IV. Assessing Learner's Abilities

Assessment is an important part of teaching learning process. It is a way of checking the progress of the students and identifying problems to work on them. Teachers are often found doing the test items throughout the year instead of developing the skills which are to be tested. The main difficulty with teaching any class where exams play a vital role, is how to stop the exams from taking over everything. Luke Prodromon ad Lindsay Clanfield says, 'As a teacher, I'd like to do more fun activities in class, but I have to prepare them for the test'.[6] Unfortunately, only test items related to examinations are practiced more, where as development of the basic linguistic skills is totally neglected. To make the matter worse, if a teacher deals with language, particularly, vocabulary and structure, the basic skills are neglected. In such circumstances there are very few opportunities for developing the linguistic skills.

Assessment of learner should be decided on following factors:
i. Learner's previous knowledge/ knowledge of the past.
ii. Learner's present level of comprehension.
iii. Learner's proficiency in the language.
iv. Various levels of the linguistic skills achieved by the learner so far.
v. Impact of learner's L_1 over L_2.
vi. Learner's purpose behind learning the language.
vii. Motivational factors behind learning the language.
viii Socio-psychological impact over the learner's ability in learning the language.

V. Conclusion:

Language is learnt through practising the linguistic skills and not by learning only grammatical rules. Process of learning a new language becomes successful if learners begin with **receptive** skills for understanding the new items and then move on to **productive** use. The learners should be taught the scientific procedure of listening and reading. Receptive skills development should be combined with language input in such a harmonious way that the language component should not overshadow the basic linguistic skills.

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Role of Dr. Babasaheb Ambedkar in Women Empowerment

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Introduction:

Right from the Vedic period, women were deprived from the right of freedom, gender equality, education and social status in the society. Religion, tradition, taboos were of prime importance and they rule the society. Manusmrity, Yadnyavalkasmrity, Shruti-smrity, Ramayana, Mahabharata and Epics were required to be observed by the society. Depressed class people and women were suppressed under these ethos. They were not allowed to learn or hear religious epics. They had no freedom. They were treated like slaves in the prevailing social system.

It was Lord Gautm Budhha who brought light in the life of women for the first time in the history. Before 2500 years, was Bhagwan Budhha who allowed women to talk "Pravajya" and availed the freedom of education, thought and equality with men irrespective of gender.

Women were allowed to go in for higher education, seek knowledge and explore their own thoughts. In this way Lord Budhha was 'Adya Praneta of Stree Mukti'. In his regime women like Kshema, Kundalesha, Mahaprajapati Gautami, Patachara, Amrapali, Sanghamitra enjoyed the freedom of placing themselves on on equal footage with men. After that, during the regime of Mourya Dynasty freedom of women was in existence. Later on during the period of Guptas restriction on women's liberty were leveled up. Before Manu, women like Gargi, Maitreyi, Sulesha, Vidyadhari were enjoying all privileges in society.

Black Period:

History reveals that later on the right of education, freedom of thought is found denied by the so called courtiers and preachers of religion under the pretext that it is given in the Holy books of religion. Women were restrained from the right of studying Vedas. Unfortunately all those books were written by the 'then men'. Women were given secondary importance and were treated as the slaves of men because of the patriarchal system.

If Winter Comes; Can Spring Be Far Behind?:

Dr.Babasaheb Ambedkar, a Gospel of women upliftment came to the help of women in 20th century. He offered them a weapon of education, by liberating women the social and their own psychological constraints. The education contributes to a better self image; liberates one from a sense of dependency and despondency, inhibition and powerlessness. It helps to break the physical and psychological isolation of women. It helps them to face and overcome the negative impact that the culture and the religion, caste and class determined factors have generated. In those days women of upper and lower society were oppressed and suppressed through many ways and means. The condition of women from the downtrodden strata was more pathetic.

The poverty and illiteracy had chained them. For removing this bad tradition people like Mahatma Jyotiba Fule sacrificed their life. Dr Babasaheb took inspiration from Mahatma Fule and went one step ahead. He prepared 'Hindu Code Bill' and liberated women from the slavery. Women were offered equal status with men by law. In the bill it is given that women are entitled for an equal share in the parental property as that of a son.

There can be an adoption of a woman. In this way a woman was given an equal status, same respect and self prestige. Unfortunately this dream of Dr Babasaheb did not materialized completely and therefore he resigned from the law ministry. Women of India today must respect and honor this sacrifice of Dr Ambedkar.

Doors of knowledge are opened:

During the regime of 'Peshwas', women were oppressed like anything. They were exploited physically and mentally and were reduced to a miserable status. During the British regime things have started improving. For the upliftment and empowerment of women special efforts were being made. Along with Dr Babsaheb eminent persons like Mahatma Gandhi, Raja Ram Mohan Rai, Gopal Ganesh Agarkar, Gokhale and Justice Ranade also worked hard for the cause of women liberation but Dr Ambedkar, a man with a Reformer's Zeal, paid special attention toward the depressed conditions of untouchables and women in particular. Simultaneously he focused on the annihilation of caste system, religious tradition. He was a bold and learned leader.

It was his dream to free the depressed class people and women from the existing oppressive tradition. In order to fulfill these goals, he started women liberation movement. He gave a direct fight against the existing system. He believed that socio-cultural forces artificially construct gender relations.. As Simone De Beauvoir observed, "Women are made, they are not born", Ambedkar also raised the question, "Why Manu degraded her (woman)?"

In his The Riddle of the Woman, The Woman And the Counter Revolution, The Rise and Fall of Hindu Woman, Castes in India Their Mechanism Genesis and Development and through the issues of his journals Mooknayak (1920) and Bahishkrit Bharat (1927), Dr. Ambedkar tries to show how the gender relations and

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differences are constructed by Hindu Brahminical order, which conditions women to conform a stereotype femini behavior, requiring them to be passive and submissive, suited only to a life of domestic and family responsibilities.

Contribution toward Woman's Emancipation:

Dr Ambedkar started his movement in 1920. He started fierce propaganda against the Hindu social order an launched journals Mook Nayak in 1920 and Bahishkrit Bharat in 1927 for this purpose. Through its issues he put du stress on the gender equality and the need for education, and exposed the problems of the depressed as well a women. He pursued his higher studies abroad. His exposure to the West has influenced his perception on feminis issues. It was a time when first wave feminism had been coming to an end with the achievements of franchise righ for women in Britain in 1918, and America in 1920 and Dr. Ambedkar's perception of the women question emphasizing their right to education, equal treatment with men, right to property and involvement in the politica process resembled the global feminist demands.

His reading habits helped him to understand the feminist developments in different cultures and countrie around the world. As J.S.Mill expressed in the Subjection of Women, the legal subordination of one sex to the othe is wrong in itself and one of the chief hindrances to human development; and ought to be replaced by a principle of perfect equality, admitting no privilege or power on the one side, nor disability on the other, Ambedkar also holds th same views on work for the untouchables and women.

After returning to India he devoted his life fully to work for the depressed classes including women. I Ambedkar's movement launched from 1920 onwards, women actively participated and acquired the confidence to voice their issues on various platforms. Venubai Bhatkar and Renubai Shambharakar are worth mentioning. In 1924, Bahishkrit Hitakarni Sabha was formed to work for the socio-political equality of depressed people and promoting their economic interests.

Women started participating in satyagrahas and also launched women's associations for untouchable women for spreading education and awareness among them. In the Mahad Satyagraha for temple entry in 1927, even caste Hindus participated. Shandabai Shinde was one such participant. In the Satyagraha it was decided to burn the Manusmriti, which humiliated women, and shudras. In the demonstration after the bonfire of the Manusmriti more than fifty women participated. Ambedkar addressed the meeting thereafter and advised women to change their style of wearing saree, wear lightweight ornaments, not to eat meat of dead animals. It was upper caste women like Tipnis who taught them proper way of wearing sarees.

In January 1928, a women's association was founded in Bombay with Ramabai, Ambedkar's wife, as its president. Along with the Depressed Classes Conference in Nagpur in 1930, women also had their separate conference. In the Kalaram Temple Entry Satyagraha at Nasik in 1930 five hundred women participated and many of them were arrested along with men and ill treated in jails. To face tortures along with their men, women also organized their Samata Sainik Dal. When Ambedkar returned to India after attending the round table conference in 1932, hundreds of women were present for the committee meetings. At various places depressed classes women's conferences were held and they began to present their demands assertively.

The encouragement of Ambedkar empowered women to speak out boldly their feelings. He said in his speech delivered in the Constituent Assembly on 25th November 1949, "Political democracy cannot last unless there lies at the base of it social democracy." By social democracy he means a way of life, which recognizes liberty, equality and fraternity as principles of life. He further said: "On 26th January 1950, we are going to enter into a life of contradictions. In politics we will have equality and in social and economic life we will have inequality. In politics we will be recognizing the principle of one man one vote and one vote one value. In our social and economic life, we shall, by reason of our social and economic structure, continue to deny the principle of one man one value.

How long shall we continue this life of contradictions? How long shall we continue to deny equality in our social and economic life? If we continue to deny it for long, we will do so only by putting our political democracy in peril. We must remove this contradiction at the earliest possible moment or else those who suffer from inequality will blow up the structure of political democracy which this Assembly has so laboriously built up."

The new social movements emerged especially from Dalits, women and peasants, to assert democratic rights and urged for a new path of development which legitimizes this warning of the Father of the Indian Constitution, when he submitted it to the nation.In this way Dr Babaseb Ambedkar undertook the movement of public awareness. He wanted to make the people aware of their legitimate rights. Movements like Mahad, Kalaram Mandir etc. exclusively talk about his humanistic approach.

Women also came forward and participated in these movements in large numbers. They spontaneously campaigned to fight the injustice and are still doing that. Thousands of women have strived hard and have been doing so against the exploitation of women as a class.

Women have been aggressively and committedly took part in this movement. Dr Ambedkar has been a strong inspiration in this awakening among women. Women, inspired by his ideologies have played a significant role in various struggles, ranging from struggle against untouchabilitty to the fight for women's dignity that rejects patriarchal domination in the contemporary society. She is a part of struggle for a self respect and dignity.

Conclusion:

Dr Babasaheb Ambedkar proved himself to be a genius and was known as a great thinker, philosopher, revolutionary, jurist-par excellence, prolific writer, social activist and critic and strode like a colossus in the Indian socio-political scene unto his death. The credit for self-respect and firm determination of women goes to Dr Ambedkar. The Writings and Speeches of Dr Babasaheb show what values India should develop and how they would modernize its social and political institutions. He was firmly committed to the ideals of equality, liberty and fraternity.

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THE ROLE OF DR. AMBEDKAR IN WOMEN EMPOWERMENT AND DIGNITY OF LABOUR.

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INTRODUCTION :-

Women, a word which when strikes one's ears gives a sad feeling of a class of human livings horribly suppressed, exploited, used for pleasure by the other class, that is man, and sums up a long history of dependence subordination. In ancient law women are used by the man for their pelasure. Manu the father of Hindu Dharma Sutra says about woman-

A woman is under the subjection of her father when a child, when married, under that of her husband, after her husband under her sons, and if she was no sons then to her agnostic relation, beacuse there is no woman whatsoever who is fit to independent.

The subordination and dependance of woman particulary in socio-economy life continued till independance as they were not at par with their male companions in socio-economic and political-cultural life. Dr.Ambedkar was one of the very important political thinkers, philosopher, revolutionaries, jurist, writer, social activist and social revolutionaries that modern India has produced. He was the Chief Architect of the Constitut ion of republic of India.

EMPOWERMENT OF WOMAN :-

Emporment is an active multidimentional process, which should enable women to relise their full identity and powers on all sphre of life. For Indian Women's movement Ambedkar provides a powerfull source of inspiration to formulate a feminist political agenda which simulteniously addresses the issues of class, caste and

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Emerging Portrait of 'New Woman' in the Victorian Era in English Literature

Dr. Pradnya S. Yenkar
Vidyabharati Mahavidyalaya, AMRAVATI (M S)-444602

Introduction:

The period extending from 1890 to the outbreak of the First World War seems to have a fairly unique character. It transformed the whole fabric of private and social life bringing in a profound change in the thought and outlook of English nation. It gave birth to a new spirit. People started speaking enthusiastically or scornfully about things like 'New Morality' 'New [illegible]' characterized by an extraordinary social and intellectual ferment. In social relations and domestic life people grew contemptuous of old ideals. There was no political principle, no theological dogma, no social tradition or moral sentiment that was not challenged. The old restraints and taboos were repudiated and the new generation claimed unfettered freedom of thought and action. But it was also a period of deeply serious enquiry, of impatient debate over central questions of moral and social behavior which created acute anxiety especially among those who felt themselves to be witnessing the breakdown of the rules traditionally thought to hold society together. The froth and ferment gave birth to new social ideals. It was widely believed that society was sick probably with an infection spread from Europe through the translations of Ibsen and Zola.

Emergence of 'New Woman' in Literature:

Woman always held to delicate, had succumbed more severely than most. Violently abused by many, ridiculed by the rest hysterical and championed by a select few, the New Woman became a focal point for a variety of the controversies which rocked the Nineties.

She flouts Love's Caresses Reforms ladies' dresses
And scorns the Man-Mother's tirade;
She seems scarcely human This mannish New Woman
This Queen of the Blushless Brigade (1).

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In the comparatively permissive atmosphere of the time, feminist thinkers were provided with a unique opportunity for a radical investigation of the female role. Highly qualified women were emerging as a result of concessions given in the educational establishments. It was a time to find suitable work and social status for them. The financial independence and personal fulfillment gained through work began to seem attractive alternative too marriage. The writers and reformers clearly pointed out that women were likely to remain the weaker sex as long as they are encased in an ivory tower. Their existence should not be confined to their physical activity to the decorous movements of the ballroom. The new 'Doctrine of Hygiene' as it was coyly termed advocated sports for women and Rational Dress. Many young women could enjoy the undreamt-of-freedom on various horizons. But these things alone could not account for the elevation of the New Woman in to a symbol of all that was most challenging and dangerous in advanced thinking. The crucial factor inevitably was to have an equal footage with men in society.

Feminist Movement (1875 -1918):

The question of the proper position of women in society, the function they might legitimately endeavor to discharge and the education which would fit them for those functions were beginning to be agitated in this period. They were to be considered as the offspring of the democratic development which had won its earliest triumphs in 1832 (Reform Act). Many of the earliest champions of women were found among the

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Utilitarian. John Stuart Mill was one of the greatest supporters of women's suffrage. His feminist views inspired his essay 'On the Subjection of Women (1869)'. Though many of his points had been made earlier by Mary Wollstonecraft in 'A Vindication of the Rights of Women (1792)'. She was practically far ahead of her time. In this essay he showed that the principle of liberty and representation were applicable to women as to men. He provided the new path of Political Emancipation of Women. In this way, after having undergone a lots of ups and downs, in 1918 the Representation of the People Act gave the power to vote to women over thirty giving rise to a new era in women's emancipation.

New Women Sketched in the Novels of Thomas Hardy, Gissing and George Meredith:

Thomas Hardy's last three major novels embody ideas of central interest to the New Woman. In 'The Woodlanders' a great deal is said in favour of divorce and against the discriminatory marriage laws. 'Tess of D'Urbervilles' is a powerful indictment of the double moral standards. The heroine of this novel pre-dates the New Woman of the popular fiction of the modern age. Whereas Sue Bridehead, the central figure of 'Jude the Obscure', with her quivering nerves and anti-marriage sentiments represents typical New Woman of the Neurotic school. This apparent development towards a strong feminist position, coinciding with the widespread discussion of similar views by other writers and thinkers of the age is significantly reflected in Hardy's novels. This issue was partly of public debate of that time. A close study of Hardy's heroines shows that Hardy projected his portraits of advanced womanhood in a slightly different manner than the committed feminist writers of the day. Another virtue that attributes to his heroines is that all his women have a good formal education as well as a quick native intelligence.

George Meredith can truly be called as the 'Champion of Women'. He reached his height of feminist conviction during the years of the New Woman novel's popularity. Meredith's novels were widely read and it seems greatly appreciated by contemporary women of advanced views. Edith Slater, who dismissed Hardy's heroines as "Men's Women", had nothing but praise for Meredith, "he, better than any man, feels for the sufferings and limitations of sex"[5]

Conclusion:

Literature is a mirror to society. The struggle of freedom of women since the last two centuries has been clearly noted in English literature. As it is based on the views shared by readers and writers; it comes alive, reflecting the realities of life. It is a true source of cultural, political, economical and social awakening in the hands of writers who are sensitive and sensible towards such issues. Today woman has achieved success in every sphere of life. But the credit of the success of the modern woman lies in thousands of known and unknown writers who showed the courage to improve the status of a woman by fighting against the prevailing social conditions of their time.

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Exploitation: A Significant Feature Revealed in Amitav Ghosh's Sea of Poppies

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Introduction: The renaissance in modern Indian literature begins with the writings of Raja Rammohan Roy, Michael Dutta, Manmohan Ghoshand his brother Sir Aurobindo, Sarojini Naidu, the first female contributor who served Indo-Anglian

Gandhian era Jawaharlal Nehru, Mulk Raj Anand, R.K. Narayan and Raja Rao. Most of their novels dealt with the theme of exploitation of British in India Postcolonial literature developed during the imperial period.. As stated by an eminent critic "Post-colonial situation has given us confidence to write creative literature in English and it would be good for us to gain confidence to write literary criticism in our own way – then only 'post-colonial' will redeem the 'colonial'."1

Features of Postcolonial Novels: During this period novelists mainly wrote on postcolonial situations in India. Their writing reflects the true picture of colonization. The history of the nineteenth century and a few decades of the early twentieth century can be conveniently summed up by the word 'Colonialism'. A generation of post-colonial Indian writers has brought a larger world a teeming, myth-infused, gaudy, exuberant, many-hued and restless world and past the immigration inspectors of English literature. We must be grateful to all the postcolonial novelist as well as Indo-Anglian novelists for reminding us that the colonized likewise has his secret. Above all the great writers work is the main place that we are witnessing the infamous death-struggle of colonialism. The long list of all the postcolonial novelists has given the precious contribution to post-colonial literature but the major contribution of Amitav Ghosh to Indian Writing in English on colonialism is unforgettable.

Amitav Ghosh as a Novelist: Over the last two decades, the Indian author Amitav Ghosh has established himself as a writer of uncommon talent who combines literary flair with a rare seriousness of purpose. He includes different themes on different issues in his novels and tries to articulate Indian life. His novels show political and social picture by giving a new face to the Indian English fiction. He has won

of the most lyrical an insightful work on the effect of colonialism. He is an innovative writer. At the same time he is a great experimentalist who extensively experimented with forms as well as ideas. An acclaimed critic, Suzeene Keen, rightly says, "Amitav Ghosh re-envisions the romance of the archive for an interconnected global future."2 He has been glorified with many awards and prizes.

His famous novel **'Sea of Poppies'**, an epic saga was shortlisted for the 'Man Booker Prize' in 2008. 'This new prize will reward high international achievement, but unlike other global prizes, it will target fiction in English, or translated into English, and so will celebrate English-language fiction as a major cultural force in the modern world.'3 This novel is based on physical, economical; psychological, and environmental exploitation. The story is set prior to the Opium Wars on the banks of the holy river Ganges and in Calcutta. The characters are just as diverse as the British Empire itself, each with their own dialects and idiosyncrasies. His topics are unique and personal; some of his appeal lies in his ability to weave the flow of the theme of exploitation.

In 'Sea of Poppies' Amitav Ghosh assembles from different corners of the world sailors, marines and passengers for the Ibis, a slaving schooner now converted to the transport of coolies and opium. In bringing his troupe of characters to Calcutta and into the open water, Ghosh provides the reader with all manner of stories, and equips himself with the personnel to man and navigate an old-fashioned literary three-decker. In his novel he draws heavily upon the character, traditions, and dichotomies of

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his native land. His protagonists and themes often extend beyond India's actual boundaries, most notably toward the Middle East and Great Britain. Through his discourse, Ghosh's works expose the cross-cultural ties between India and its former colonial ruler as well as with its kindred neighbours. Thus this novel crashed the theme of exploitation. Ghosh has been hailed by critics as one of a new generation of cosmopolitan Indian intellectuals writing in English.

'Sea of Poppies' primarily reveals the physical, economical, psychological, religious and environmental exploitation. It is a combination of three short stories. The main characters include Deeti, an ordinary village woman, a mulatto American sailor named Zachary Reid, an Indian Raja called Neel Ratan Halder, and Benjamin Burnham, an evangelist opium trader all these characters made novel interesting and bring out a theme of exploitation. The author compares the Ganges to the Nile, the lifeline of the Egyptian civilization, attributing the provenance and growth of these civilizations to these selfless, ever-flowing bodies. He portrays the characters as poppy seeds emanating in large numbers from the field to form a sea, where every single seed is uncertain about its future. It is rightly said by Toby Lichtig in 'New Statesman', Sea of Poppies is bathed in a rich vernacular. It is a thoroughly readable romp of a novel, filled with excellent set pieces, comic digressions, love interest, subterfuge and betrayal. We are left thirsty for more."4

Exploitation: A significant Feature

This novel deals with various types of exploitation like physical, economical, psychological and religious. All characters in this novel are badly exploited. Mr. Shashi Tharoor has described the novel in such words in 'The Washington Post.' "His descriptions bring a lost world to life....At times, Sea of Poppies reads like a cross between an Indian one with the Wind and a Victorian novel of manners...his novel is also a delight."5

Physical Exploitation:

Physical exploitation of the natives is very effectively and boldly described in this novel. Exploitation of the Black natives by Burnham, exploitation of Kalua by Ghazipur's young Thakur and in Alipore jail Bhyrosingh's shocking treatment to Jael, or for instance Munia's tragedy all events boldly speak of physical exploitation. Though the novel is full of such shocking episodes, here are a few examples:

In the beginning of the novel Mr.Burnham has given the horrifying treatment to the 'Black' natives. Mr.Burnham was in hurry to get his new schooner to India. It had a crew of nineteen and a 'Black' including Zachary. The ibis was carrying a cargo of cotton, to defray the costs of journey. In that ship they had given half rations eating maggoty hard, tack and rotten beef, to the crew. There was an outbreak of dysentery. On the ship three men were dead and two of the black crewmen were in chains. They were refusing the given food.

Ghazipur's Thakur family is the core of exploitation. They exploited the Kalua physically. The three young scions thakur sahibs arranged the wrestling matches. They had called Kalua in the wrestling match. He had won, defeating the local pehlwans and strongmen. The young landlords earned a good profit and had gained his ox-cart as a reward prize. By this work he had become famous and that news goes to the Maharaja of Benares. He expressed the desire to see the strongman of Ghazipur pitted against the champion of his own court.He had suffered his first defeat in front of the Ramgarh palace. All Ghazipur was humbled and came home in disgrace. The three young landlords of city had decided to be excellent sport to couple with a woman. In the night they do harm to Kalua very badly. That night Deeti saw three horse men and one was following on foot. She saw that the fourth man had a halter around the neck and was being led like a horse. She saw that he was Kalua. The three horse men were the sport-loving landowners. Deeti heard a whimpering, sobbing sound as Kalua fell suddenly to his knees. He had clutching at the thakur's feet.

One of them had struck his whip into the fold of Kalua's cotton langot and whisked it off with a flick of his wrist. Kalua cried. All the landlords went away and only Kalua living unconscious in the sand, naked and sun eared in dung. In this way the physical exploitation of Kalua is very tragic. They used the power to harm to poor person.

Burnham had been successful in transportation of convicts. Calcutta was made the principal conduct through which Indian prisoners were stepped to the British Empire's network of island

prisons, like Penang, Bencoolen, Port Blair and Mauritius. Thousands of Pindaris, Thugs, dacoits, rebels, head-hunters and hooligans were carried away for the muddy waters of the Hooghly to be dispersed around like Indian Ocean. The British had incarcerated their enemies in the various islands jails. Mr. Burnham had turned his attention to the correspondence that had accumulated over the course of voyage.

Raja Neel Ratan Halder is another example who was badly exploited by Mr. Burnham. He was the King of Raskhali also known as Raja Neel Ratan Halder, the head of an old Bengali family in Calcutta. He is also being forced to consider life's radically altered circumstances. He started his opium business with Mr. Burnham and finds himself the victim of a shady conspiracy to rid him of family lands and brand him a criminal. After court's last justification, he had been sent to jail and his worst days started. His food continued to come from the Raskhali Palace. He sank helplessly on his string bed and holding his son by the shoulders.

The prisons at Lalbazar and Alipore were both known as jails. The Lalbazar was surrounded by the noise and bustle of Calcutta's busiest streets and Alipore lay at edge of a deserted stretch of land on the city's outskirts. Neel had passed into the custody of new set of jailers. In the jail the prisoners were given the horrifying treatment. The sepoys responded by pinning Neel's arms to his side. After a long practice they had made expert in stripping the clothes from convicts. In that process many gladly have died or killed themselves rather than be subjected to the shame of having their nakedness exposed. Neel's struggles presented no challenge to them and they quickly tore off the remnants of his clothing his limbs and vastly exposed his naked body to his fingertips. It was as if his body had passed into the possession of new owner who was taking stock of it as a man might inspect a house. Thus the novel is full of such incidents which reveal the hair raising experiences of exploitation.

Economical Exploitation:

Amitav Ghosh has given the detail description about British monopoly in opium trade and economic exploitation of natives. British Empire stands on the place of economic strength and always searching a new way of gaining wealth. Opium trade is one of the findings of the British for economic growth. Opium was the exclusive monopoly of the British. They produced and packaged entirely under the supervisions of the East India Company. Burnham had paid the Halder estate a ten percent dasturi on the profit. After some months British and American traders had got the Chinese market in large scale for opium and growing the Business as well as profits..

"As Mr. Ghosh puts it, this came as a shocking surprise that India under British was the biggest exporter of Opium till recent time. In India there is no awareness at all about this aspect. West before lecturing Indians / Developing Countries should look into their past. I feel that with so much prosperity before British came to India, we would have modern institution even without them stepping into ruling role." -Said S. S. Pande, India (7).

Psychological Exploitation:

Psychological exploitation is another example of exploitation depicted in this novel. Some characters are badly exploited. They lose their human existence. The novel focuses on many scene of psychological exploitation. Mr. Burnham is mostly psychologically exploited character. Chandan Singh was the brother of Hukam Singh. He was never before shown any interest in Hukam Singh's condition. He now began to insist on his rights to enter the house in order to sit beside his brother's bed. He thinks that Hukam Singh's land was passed to him and no one will have the right to dispute it.After few days Hukum Singh's condition grows steadily worse and he dies. This position shows that brother's brotherhood changes into selfishness. The evil of individuality comes in his mind and he forgets his duty towards his brother. This is obviously an instance of psychological exploitation.

Political Exploitation:

Political exploitation is a special quality of post-colonial novels. Amitav Ghosh has given the King and his kingdom's exploitation in this novel. British entered the colonies for their economic gains and interfered in natives political policies. They used their power for own purpose and lastly created a problem before natives. Raja Neel Ratan Halder is example of political exploitation.Burnham told Neel that he was very glad to have this opportunity to speak with him. It was an unexpected pleasure. Neel told Burnham

that he could not restore his funds and it was impossible for him to entertain his proposal. Mr. Burnham was interested in the zemindary of Raskhali but Neel was by heart associated to Raskhali. Neel required funds but Burnham's proposal was not good for Neel.

Religious Exploitation:

Religious exploitation usually occurs due to lack of education, poverty, and attraction of new religion. Indian society had been a victim of such notions and accepted the new religion. Converting people of other religions into their own religion this policy of British is not new. Amitav Ghosh gave the example of such things in this novel.

Kalua saw many frightened things in 'Black water.' The Black water was the dangerous place. They sweated in the steamy heat of the jungle. Their fears and apprehensions were not fine. The pulwar became a cauldron of rumours. It began to be whispered that their ration on the Black water ship would consist of beef. Those person refused to eat would be whipped and the meats would be thrust down their throats. On reacting Marrech, they would be forced to convert to Christianity. They would be made to consume all kinds of forbidden foods from the sea and the jungle. After they die, their bodies would be ploughed into the soil like manure. There was no provision for cremation on that Island.

"A wonderful book, a large ambitious novel in which extraordinary people come to life and vibrant, exotic places are memorably depicted." 8

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Fiminism in Amitav Ghosh's novel The Glass Palace

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Abstract: Women's role in Pre-colonial social structures reveals that feminism was theorized differently in India than in the West. Historical circumstances and values in India have caused feminists to develop a feminism that differs from Western feminism. Indian writing in English has been highly influenced by this movement. The values and practices of this movement are clearly reflected in their writings. A host of prominent Indian writers have made use of their pen for the cause of Women's Emancipation. They were true reformers. Their writings have helped in spreading this message more effectively .Amitav Ghosh, the acclaimed novelist of modern India,also has made great contribution in this respect through his novels. He has created many women characters in his novels who are strong, bold, courageous and truly Indians. This research paper deals with the feministic approach in Amitav Ghosh's novel 'The Glass Palace'.

Introduction: The terms "feminism" or "feminist" first appeared in France and The Netherlands in 1872 (as *les féministes*), Great Britain in the 1890s, and the United States in 1910. The *Oxford English Dictionary* lists 1894 for the first appearance of "feminist" and 1895 for "feminism".The UK *Daily News* first introduced "feminist" to the English language, importing it from France and branding it as dangerous. "What our Paris Correspondent describes as a 'Feminist' group... in the French Chamber of Deputies". Prior to that time, "Woman's Rights" was probably the term used most commonly, hence Queen Victoria's description of this "mad, wicked folly of 'Woman's Rights' [1]. Defining feminism can be challenging, but a broad understanding of it includes the acting, speaking, writing, and advocating on behalf of women's issues and rights and identifying injustice to females in the social status quo.

Feminism in Indian Context: In India, women's issues first began to be addressed when the state commissioned a report on the status of women to a group of feminist researchers and activists. The report recognized the fact that in India, women were oppressed under a system of structural hierarchies and injustices. During this period, Indian feminists were influenced by the Western debates being conducted about violence against women. However, due to the difference in the historical and social culture of India, the debate in favor of Indian women had to be conducted creatively and certain Western ideas had to be rejected. Women's issues began to gain an international prominence when the decade of 1975-1985 was declared the United Nations Decade for Women.

Historical circumstances and values in India have caused feminists to develop a feminism that differs from Western feminism. For example, the idea of women as "powerful" is accommodated into patriarchal culture through religion, which has retained visibility in all sections of society. This has provided women with traditional "cultural spaces." Furthermore, in the West the notion of "self" rests in competitive individualism where people are described as "born free yet everywhere in chains." In India the individual is usually considered to be just one part of the larger social collective. Survival of the individual is dependent upon cooperation, and self-denial for the greater good is valued.[2]

Feminism in Post-Independent India: Post independence feminists began to redefine the extent to which women were allowed to engage in the workforce. Prior to independence, most feminists accepted the sexual divide within the labor force. However, feminists in the 1970s challenged the inequalities that had been established and fought to reverse them. These inequalities included unequal wages for women, relegation of women to 'unskilled' spheres of work, and restricting women as a reserve army for labor. In other words, the feminists' aim was to abolish the free service of women who were essentially being used as cheap capital. Feminist class-consciousness also came into focus in the 1970s, with feminists

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recognizing the inequalities not just between men and women but also within power structures such as caste, tribe, language, religion, region, class etc. This also posed as a challenge for feminists while shaping their overreaching campaigns as there had to be a focus within efforts to ensure that fulfilling the demands of one group would not create further inequalities for another. Now, in the early twenty-first century, the focus of the Indian feminist movement has gone beyond treating women as useful members of society and a right to parity, but also having the power to decide the course of their personal lives and the right of self-determination.[4]

Feminism in Amitav Ghosh's Novel 'The Glass Palace': Amitav Ghosh has established himself as one of the finest prose writes of his generation of Indian writing in English. Over the last two decades, the Indian author Amitav Ghosh has established himself as a writer of uncommon talent who combines literary flair with a rare seriousness of purpose. He includes different themes on different issues in his novels and tries to articulate Indian life. His novels show political and social picture by giving a new face to the Indian English fiction.

Brilliant and impassioned, 'The Glass Palace' is a masterly novel by Amitav Ghosh. It is a detail account of journey, displacement, war, mixing of the human races, sex movement and the human relations. Ghosh's novel 'The Glass Palace' has been noted as the masterpiece because of his brilliant expression of the different scenes, expressions of love and the innermost themes of life. The story of the novel seems to be a superb saga of the love, war, displacement, business, colonizing ideas and many other things. It is an epic journey of three generation (King, Rajkumar and Dinu) set in Burma, India and Malaya.

'The Glass Palace' was the Eurasian regional winner in the "Best Book" category of the 2001 'Commonwealth Writers' Prize, but Amitav Ghosh was not aware that his publishers had submitted his book, and he withdrew it upon learning that he had won the regional round. It is also winner of 'Grand Prize' for Fiction, Frankfurt e-Book Award, 2001 and New York Times Notable Books of 2001.

> *'Amitav Ghosh's novel The Glass Palace is an epic journey through three generations, set in Burma, India and Malaya. The characters encapsulate the pain of colonialisation and come to terms with the violence and destructive energy of empire on their ... ' by Kim Balmanno* [5]

This novel depicts the story of the British Empire in Asia, but it embraces this expansive world differently than most. It is a rare and imaginative telling in which the colonized – their life experiences, voices, and formative moments – figure prominently, where so many other telling put the colonial rulers at the centre. It comprises of historically, culturally, and linguistically located details. 'The Glass Palace' renders the complex response of the colonized to the hurried modernity enforced by the colonizer.

> *"Ghosh's narrative cools as he depicts the family's interwoven stories, his fervent opening chapters giving way to a more objective sensibility. The historical forces that served as the love story's lush background begin to overcome the characters." - Stephen Amidon, The Atlantic Monthly* [5]

The Glass Palace of his title as it turns out, indicates both the magnificent hall of mirrors which forms the centerpiece of the Mandalay residence of Burmese Kings and the name of a small photo studio where the book's action approximately ends.

Amitav Ghosh has given most importance to female characters. This novel is an epic journey of three generation. Firstly the King Thebaw and the Queen Supalayat, second Rajkumar and Dolly and third Dinu and Alison, this is generation appeared in this novel. The King Thebaw and the Queen Supalayat, second Rajkumar and Dolly and third Dinu and Alison all these main chararcters play a super role in this novel but other characters like Jaya, Elsa,Uma, Manju and four Princess named Hteiksu Myatpayagyi , Hteiksu Myatpayalat, Hteiksu Myatpaya aka, Hteiksu Myatpayalay taking a colour in this novel. But

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Amitav Ghosh has made Queen Supayalat is a strong character in all characters. It is different character than any other.

The Queen Supayalat : The King fell in love with the Queen Supayalat. His middle Queen was by far the fiercest and most willful. The Queen was a woman of quiet and determination. It was she who had roused the great cone of the land when the British began to issue their ultimatum from Rangoon. The banishment of the King and the pregnant Queen from Mandalay to distant Rantagiri in the west coast of India the reverse movement of Bahadur Shah Zafar's deportation to Rangoon a generation ago was an astute move by the British successful in the public humiliation of the royal couple and drawing them from public memory at home. The abandoned King and Queen led a life of oblivion and obscurity in an unknown territory while their homeland was robbed of its precious natural resources teak, ivory and petroleum.

The King Thebaw had three wives but only the Queen Supayalat was loveable for him. She fell long in love with her husband, the King. In order to protect him from her family, she stripped her mother of her powers and banished her to a corner of the palace, along with her sisters or co-wives. Next thing is that she ordered the killing of every member of the royal family who might ever be considered a threat to her husband. By his order seventy- nine Princesses were slaughtered. It is difficult to imagine that a woman can do that type of work.

The KingThebaw was defeated in the Third Anglo-Burmese War and forced to abdicate by the British. They were taken away in a covered carriage, leaving Mandalay Palace. The Queen Supayalat never lost her composure, and was said to have asked a British tommy by the wayside for a light to smoke a Burmese cheroot. She was pregnant and accompanied by her husband, their two daughters, her two sisters, and her mother; the rest of their party followed on foot. the next year they were moved to Ratnagiri on the west coast where they could no longer look across the Bay of Bengal. Lastly the King and Queen were going by bullock carts from his kingdom. This pathetic transformation of kingdom is the economical.

In another incident the Queen Supayalat's behavior with maids is a part of physical exploitation. The Queen's two maids began to make sarcastic comments on the Queen's hearing. The Queen came to know about it. She told to Padein Win and he took them into a locked room, he beat them and pulled their hair. Cause of such thing made the girls even more resentful. The Queen was angry on Evelyn and Mary because they slept beside her bed. Evelyn was very upset. According to Mr. Cox they were slaves on Mandalay but Evelyn lastly thinks that 'the princesses are prisoners too.[6]

After coming in Ratnagiri, she met the Collector. She informed that his eldest daughter Princess Ashin Hteik Su Myat Phaya Lat is pregnant. She requested him that he would convey the good news to their superiors in the Government of India. The Collector asked about the name of husband. At that time, after a long discussion, she has given the name of their coachman –Mohan Sawant.

The Collector Said – "that your Highness should choose to make light of such a scandal."[7]

The Queen was angry on the Collector. She told him that they should have to spend their lives in this prison. She clearly told about matter. She said that they had heard so many lectures from their colleagues on the subject of the barbarity of the King of Burma and the humanity of the Angrez. Lastly Queen used her words to focus on limitless exploitation.

> *"we were tyrants, you said, enemies of freedom, murderers. The English alone understand liberty. we were told; they do not put kings and princes to death; they rule though laws..... Would the English not do the same?"*[8]

Such things occurred in the Queen's life, it is the tragic things about women. In another way the Queen also thinks about county's condition.The world's richest gem mines lay in the Burma and many fine stones had passed into the possession of the ruling family. Most valuable ruby ever mined in Burma. His

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ancestors had provided himself and his family in exile. The British occupation had changed everything. Burma had been quickly integrated into the Empire, forcibly converted into a province of British India The Queen thinks about the position of poor country and Europeans greed, after coming in India. They had taken their kingdom, promising roads, railways and ports for their greed. She had never regarded herself as beholden to the British who she believed robbed her of her kingdom with all the wealth and riches therein.

"In a few decades the wealth will be gone- all the gems,
the timber and the oil – and then they too will leave."[9]

In the past in golden Burma where no one ever went hungry and no one was too poor to write and read. Now the entire picture was changed. Following words of the Queen Supayalat focus on the true condition. The convert of rich Kingdom in to poor as well as Queen and Kings changed position is real tragic event in the life of these people.

"We were the first to be imprisoned in the name of their progress, millions more will follow."[10]

Burma becomes the mine of wealth for the British. The King and Queen thinks that in a few decades the wealth will be gone, all the gems, the timber and the oil and then they too will leave. That all things comes in true and it is dark future of Burma.

That's all changes comes in Queen Supayalat's life. After many years Rajkumar came to Ratnagiri, he saw the Queen Supayalat. She had changed a lot. She was small on slight of figure and even though that he had never seen her before. He knew at once that she was the Queen Supayalat. The greatest change in the Queen Supayalat is the reflection of change of kingdom. The political exploitation of Burma made the change in the Queen Supayalat's living style and existence.

When the King Thebaw died at the age of 58 after 30 years in exile, Supayalat fought in vain for the right to take her husband's body back to be buried with proper funeral rites in Burma. She refused to give up the bodies of both her sister and her husband, buried in the grounds of their palace, to the authorities who eventually took them by force to be buried in Ratnagiri. The queen did not attend the funeral although she did send two of the royal princesses to the ceremony. She died six years later and the colonial government declared the day of her funeral a national holiday, the royal family's request for her to be buried in Mandalay was also refused.

Conclusion: To sum up, women live in any condition, they change by position and live a life. The character of Queen Supayalat is tyrant, loyal, proud about country and also good nature. She chose the how to live a life but she is character of different colour. Amitav Ghosh, the gifted novelist Peter Matthiessen has called "an exceptional writer". Truly he is a sage of human relations and this present novel is the proof of his different writing style. Will Rogers says,

"Women are not the weak, frail little flowers that they are advertised. There has never been anything invented yet, including war, that a man would enter into, that a woman wouldn't, too." [11]

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स्त्री शिक्षण : एक प्रवास

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प्रस्तावना :-

वैदिक काळामध्ये स्त्रिया स्वातंत्र्य, शिक्षण ह्या सर्वांपासून वंचित होत्या. धर्म, परंपरा, रुढीवाद ह्या सगळ्या सामाजिक बंधनांमध्ये त्या अडकून होत्या. समाजाची रचनाच मूळी मनुस्मृति, याज्ञवाल्क्यस्मृति, श्रृति-स्मृति या आणि तत्सम ग्रंथांमधून निर्माण झालेल्या तत्वांवर आधारित होती. स्त्री आणि शूद्र दोघेही ह्या समाजबंधनाच्या बेड्यांमध्ये गुरफटलेले आढळतात. जिथे जगण्याचेच स्वातंत्र्य नाही, तिथे शिक्षण घेऊन स्वत:ची ओळख निर्माण करणे केवळ अशक्य होते. अज्ञानाच्या अथांग सागरामध्ये संपूर्ण स्त्री जात बुडालेली होती. सुमारे २५०० वर्षांपूर्वी इतिहासामध्ये भगवान बुध्द नावाचा एक 'मसिहा' जन्माला आला ज्याने सर्वप्रथम स्त्रियांना शिक्षणाची, वैचारिक स्वातंत्र्याची आणि समानतेची दालनं खुली करुन दिली. स्त्री शिक्षणाची पहिली सुवर्ण किरणं ह्याच काळात प्रथमच अनुभवली गेलीत. ह्या अर्थाने भगवान बुध्द हे 'स्त्री मुक्तीचे वा स्त्री शिक्षणाचे आद्य प्रणेता' होत. ह्याच काळात क्षेमा, कुंडलेशा, महाप्रजापती गौतमी, पातचार, आम्रपाली, संघमित्रा सारख्या विभुतिंनी भारतीय समाज मना समोर एक नविन पायंडा घातला. त्यांनी सिध्द करुन दिले की स्त्रिया निसर्गत:च इतक्या सक्षम आहेत की त्यांना कुठे ही कमी लेखता कामा नये. त्यानंतर मौर्य काळात ही स्त्री शिक्षण आणि स्त्री स्वातंत्र्य अस्तित्वात असल्याचे पुरावे इतिहासात आहेत. त्यानंतर गुप्त काळातही ह्याचे पडसाद आपल्याला दिसतात. गार्गी, मैत्रेयी, सुलेषा, विद्याधारी ह्या सारख्या आणि अनेक विरांगणांचे अस्तित्व प्रखरपणे जाणवते. ह्यानंतरच्या काळात इतिहासाच्या आलेखाचा वक्र बदललेला दिसतो. ह्यानंतरच्या काळात मात्र स्त्रीच समाजामधील स्थान, तिचा दर्जा हळूहळू घसरायला लागला आणि बघता-बघता स्त्री पुरुष प्रधान संस्कृतीच्या अत्याचार आणि अन्यायाला बळी पडली. अशाप्रकारे स्त्री शिक्षणाचा हा प्रवास हजारो वर्षांपासून कूस पालटत, अनेक उतार-चढावांचे प्रवाह ओलांडत आज २१ व्या शतकातील दुसऱ्या दशकामध्ये प्रवेशित झाला आहे. आज भारतीय स्त्रीयांनी पुरुषांच्या खाद्याला खांदा लावून समाजातील प्रगतीचे सर्व मार्ग पादाक्रांत केले आहेत. निसर्गानेग सोपवलेली **मानवी वंश वृध्दीची** अत्यंत महत्वाची जबाबदारी अगदी लिलया सांभाळत ती आज सर्व क्षेत्रांमध्ये खूप पुढे गेली आहे. स्त्री शिक्षणाचे पोवाडे जितके गावेत तेवढे कमीच पण खरचं तिला हवं ते सर्व तिला मिळाले का ? भारतामध्ये मोठ्या प्रमाणात स्त्रिया आजही अगदी मुलभूत अधिकारांपासून वंचित आहेत. आजही शोध चाललाय त्यांच्या 'छोटाशा विश्वाचा .....' खरंच ते सगळ्यांना गवसेल का ? ज्या दिवशी त्यांच्या हाताला लागेल कदाचित स्त्री शिक्षणाचा हा जीवघेणा प्रवास सुखदायी होईल .... आनंदी होईल.

भारतीय समाज हा पुरुष प्रधान समाज, त्यामुळे शतकानुशतके पुरुष श्रेष्ठ आणि स्त्री कनिष्ठ अशी धारणा रुढ होती. इतकेच नव्हे तर एखाद्या स्त्रीचे त्या समाजातील तिचे स्थान पुरुषाच्या दर्जा व त्याचे शिक्षण, त्याचे समाजातील प्रतिष्ठा यावरुन ठरवायची. कालांतराने हळूहळू हे चित्र बदलू लागले. स्त्री आणि पुरुष हे समाजरथाची दोन सारख्याच ताकदीची चाके आहेत असा विचार रुढ होऊ लागला. स्त्री चा दर्जा हा पुरुषा समान आहे आता मान्य होऊ लागले. स्वतंत्र भारताचे पहिले पंतप्रधान पं. जवाहरलाल नेहरु असे म्हणायचे की, ''जोपर्यंत पुरुष आणि स्त्री परस्परांच्या आर्थिक प्रभुत्वाखाली दबुन असतात तोपर्यंत कोणत्याही कायद्याने स्त्री किंवा पुरुष स्वतंत्र होऊ शकत नाही. आर्थिक परावलंबन हेच भारतीय स्त्रियांच्या समस्येचे मुळ कारण आहे.''

ह्या उलट परंपरावादी भारतीयांचा मनुस्मृतीत सांगीतल्या प्रमाणे ह्या गोष्टीवर ठाम विश्वास होता,

''पिता रक्षती कौमारे, भर्ता रक्षति यौवने ।
रक्षिन्ता, स्थविरे पुत्र:, न स्त्री स्वातंत्र्य महंति''

अर्थात स्त्रीचे संरक्षण व पालन पोषण लहानवयात तिचा पिता, तरुण वयात तिचा पती व म्हातारपणी तिचा पुत्र करतो तेंव्हा तिला स्वातंत्र्य देण्याची गरज ती काय ? 'न स्त्री स्वातंत्र्यमर्हति' हाच समाजाचा आदर्श होता. धर्माची ह्याला पृष्ठी असल्याचे भासविण्यात येत होते. स्त्रियांनी चुल आणि मूल सांभाळावे स्त्री व शुद्रांना शिक्षणाचा अधिकार नाही. प्रसवणे, रांधणे, कांडणे, दळणे व घरातील पुरुषांच्या आदेशाचे त्यांच्याशी एकनिष्ठ राहून पालन करणे एवढेच त्यांचे काम हेच त्यांचे विश्व, हीच तिची बांधीलकी.

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स्त्री शिक्षणाबद्दल अनास्था :

थोड्या फार फरकाने जगभरातील स्त्रियांच्या वाट्याला हेच दास्थ, हीच गुलामी, हाच छळ, हीच कुचंबना, हेच आर्थिक परावलंबित्व होते. स्त्री शिक्षणाला प्रखर विरोध होता. शिकलेल्या बाईला धर्म बुडवी, कुळाला कलंक लावणारी म्हणून संबोधण्यात येत होतं. गुलामीचे हे कवच स्त्रीयांना फोडता येईना, मनातील भाव भावनांना मोकळी वाट करुन देता येईना. एकीकडे ''जिच्या हाती पाळण्याची दोरी ती जगाने उध्दारी'' असे म्हणून स्त्रियांचा उदो उदो करायचा आणि दुसरीकडे स्त्रीयांना शिक्षणाचे, समतेचे, स्वातंत्र्याचे सर्व मार्ग बंद करायचे असे एकंदर षडयंत्र सुरु होते. त्यामुळे स्त्रियांना एकंदर सामाजिक वातावरणात वावरतांना घुसमटल्या सारखे व्हायचे. सामाजिक अवंडबरांच्या ओझ्याखाली त्या विव्हळत, खितपत पडलेल्या असायच्या, सामाजिक, आर्थिक, धार्मिक स्वातंत्र्याच्या अभावी बाल विवाह, केशवपन, सति प्रथा, जन्मास आल्यात. धार्मिक दडपणाखाली मुकाटपणे हया कुप्रथांचा त्यांना स्विकार करावा लागायचा. आयुष्यभर उपेक्षित, अवमानित, दुय्यम दर्जाचे जीवन जगावे लागे असा होता स्त्रियांचा 'काल' महिलांना कुठलेही सुरक्षा कवच नव्हते.

स्त्री उध्दाराचा उषःकाल अर्थात, स्त्री उध्दाराच्या संकल्पनेचा उदय

'कालाय तस्मै नमः' या उक्तीप्रमाणे कळाकळांनी काळ कुस पालटत होता. अवहेलना व कुचंबनेचा ही काळरात्र प्रहरा प्रहराने संपत होती आणि एक दिवस स्त्री स्वातंत्र्याच्या, स्त्री उध्दाराच्या विचारांची पहाट दृष्टीपथात आली. स्त्री शिक्षणाची कोयळी किरणे, हळुवार कवळसे आता स्त्रियांचे भाग्य उजळून टाकणार ही काय असे वाटायला लागले. आशियाखंडातील सर्वच देशात स्त्री विकासाचे वारे वाहू लागले.

स्त्रियांच्या स्वातंत्र्याचा प्रथम पुरस्कर्ता :

सामाजिक, राजकीय, आर्थिक, धार्मिक व सांस्कृतिक अशा सर्वच क्षेत्रात स्त्रियांना दुय्यम प्रतिचा दर्जा असतांना कुठल्याही प्रकारच्या स्वातंत्र्यांची वाणवा असतांना स्त्रियांच्या उध्दाराचा पहिला टाहो भगवान गौतम बुध्दांनी फोडला. स्त्रियांच्या उन्नती व मुक्तीसाठी लढणारे अनेक योध्दे आता पुढे येवू लागलेत. त्यांनी समाजातील पाखंडी वृत्तीचे परंपरावादी व दुरसटलेल्या तत्वज्ञानाची लक्तरे समाज मनाच्या वेशीवर टांगलीत. महात्मा ज्योतीराव फुले, सावित्रीबाई फुले, डॉ. बाबासाहेब आंबेडकर, राजर्षि शाहु महाराज, राजाराम मोहन रॉय, ईश्वरचंद्र विद्यासागर, महादेव गोविंद रानडे, विठ्ठल रामजी शिंदे, धोंडो केशव कर्वे या व समविचाराने पछाडलेल्या विभुतींनी अथकपणे समाज मन ढवळून काढले.

शिवरायांचे स्त्री विषयक विचार :

ज्या काळात शिवबा जन्मले तो सरंजामशाहीचा काळ होता. या काळात स्त्रिया माणूस म्हणून जगणे केवळ अशक्य होते. या काळात सर्व सामान्य जनतेपैकी कुणाचीच संपत्ती व स्त्री सुरक्षित नव्हती. शिवबांनी केवळ भारतीय नव्हे तर परकीय स्त्री यांचाही सन्मान केला हे इतिहास कधीही विसरणार नाही. शिवबानंतर मात्र हया विचारांचा विसर पडला आणि १८१८ साली शेवटच्या उचक्या देत देत हा दिव्य वारसाही मावळला.

स्त्री शिक्षणाचा उदयकाल :

महात्मा ज्योतीराव फुलेंनी स्त्री शिक्षणाचा अहोरात्र ध्यास घेतला. स्वतःची अशिक्षित पत्नी सावित्रीबाई यांना प्रथम शिकविले व भारतातील पहिली स्त्री शिक्षिका म्हणून स्त्रियांच्या शैक्षणिक, सामाजिक, आर्थिक उध्दाराचे त्यांना बाळकडू पाजले. हे काम अवघड असले तरी हा शिवधनुष्य अनेक अपमान, कुचंबना, हाल अपेष्टांना सोसत लिलया पेलला. महात्मा फुले म्हणायचे –

''विद्ये विना मति गेली, मति विना निती गेली ।
निती विना गती गेली, गति विना वित्त गेले, वित्त विना शुद्र खचले
इतके सारे अनर्थ एका अविद्येने केले''

स्वातंत्र्योत्तर काळात स्त्री शिक्षणावर भर देण्यात आला. १९४० साली या देशातील केवळ १४% लोकसंख्या सुशिक्षित होती यांत स्त्रियांचा वाटा केवळ ६% टक्के होता. स्वातंत्र्योत्तर काळात चित्र बदलले. केंद्र व राज्य सरकारांना स्त्रियांच्या सर्वांगीन विकासाशी, स्त्री शिक्षणासाठी निरनिराळ्या उपायांचे आयोजन केले आणि पाहता पाहता आपणास स्त्री शिक्षणाच्या क्षेत्रात संख्यात्मक तसेच गुणात्मक सुधारणा आढळूत येत आहे. सामाजिक सुधारणा, आर्थिक स्वावलंबन राजकीय सुधारणा हया केवळ शिक्षणाद्वारेच येवू शकतात हे आज सिध्द झाले. शिक्षण स्त्रियांना आर्थिकदृष्टया स्वावलंबी करते, त्यांच्या जीवनातील नैराश्य घालवून आशावाद निर्माण

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करते. त्यांच्यातील मानसिक व शारीरिक हिनत्वाची भावना नष्ट करते. आत्मविश्वास निर्माण करते. जात, धर्म, लिंग आदी सामाजिक बंधने झुगारुन देण्यास मदत करते. शेवटी काय तर शिक्षणामुळे स्त्रियांना आत्मसन्मान मिळतो. शिक्षण हे स्त्री उत्थानाचे अत्यंत प्रभावी माध्यम आहे.

स्त्रियांनी यांत्रिकी व तांत्रिकी शिक्षण घ्यावे काय ?

अर्थातच उत्तर होय असे राहील. आज स्त्री यांनी शिक्षणाची सर्व क्षेत्रे पादाक्रांत केली आहेत. शिक्षण, उद्योग, नोकरी, नौदल, वैमानिकदल अशा संरक्षणाच्या तीनही फळ्यात मुसंडी मारली आहे. अत्यंत प्रभावी अशा पोलीस अधिकारी म्हणून त्यांनी मान्यता प्राप्त केली आहे. अवकाशयाना सारख्या जोखमीच्या क्षेत्रात ही स्त्रियांनी प्रवेश केला आहे. रेल्वे, राज्य परिवहन सेवा, आदिक्षेत्रात शिरुन त्यांनी आपली पात्रता सिध्द केली आहे. व्यावसायिक क्षेत्रात, वैद्यकीय क्षेत्रात त्या तसुभरही मागे नाहीत.

तथापी आजही आमच्या मनावरील बुरसटलेल्या पारंपारिक विचारांची पकड पुरेशी निघालेली दिसत नाही. कुठल्याही क्षेत्रात पुरुषापेक्षा आम्ही सुतभरही कमी नाही हे सिध्द करुन ही त्यांना कमी लेखण्याचे अनेकदा आढळून येते. स्त्रियांच्या कामाच्या जागांवर, कारखान्यात, कार्यालयात त्यांना सापेक्ष वागणूक दिल्या जाते. अनेकदा त्या मानसिक व लैंगिक छळाला बळी पडल्याचे ऐकिवात आहे. सरकारला त्यासाठी कायदे करुन स्त्रियांना सुरक्षाप्रदान करावी लागते ही निश्चितच खेदाची बाब आहे. आमची मानसिक गुलामगिरी अजूनही संपलेली दिसत नाही. भारताची 'राजधानी' दिल्ली जिची गौरवशाली परंपरा, जिचा वैभवशाली इतिहास आणि आजचा नयनरम्य डोलारा बघून संपूर्ण जगभरातील भारतीयांना अभिमान वाटावा. परंतू अलीकडच्या काळात तरुण मुलीवर होणारे अत्याचार एवढे वाढले की चक्क संध्याकाळी तरुण मुलींचे घराबाहेर पडणे बंद करावे लागले. त्यांच्यासाठी संध्याकाळी आठ वाजल्यापासून कर्फ्यु ! केवढा हा दैवदूर्विलास !

ग्रामीण भागातही वेगळा अनुभव नाही. एकाच दर्जाच्या कामाबद्दल स्त्री आणि पुरुष यांना समान मोबदला दिला जात नाही. त्यांना दुय्यम दर्जा दिला जात आहे. आज खुप कायदे झाले आहेत. कागदोपत्री स्त्री पुरुष समानता दिसते परंतु ही समानता अनेकदा उधारीची वाटते व स्त्री पुरुष भेद मात्र नगदीचा वाटतो.

राष्ट्रीय शिक्षण विषयक धोरण १९८६ मध्ये स्पष्टपणे नमूद करण्यात आले की, स्त्री पुरुष समानता निर्माण करण्यातील अडचणी शिक्षणाने मध्यस्थी करुन दुर करावयात इतकेच नव्हे तर Education for Women's Equality (Part IV 4.2 and 3) हा स्वतंत्र भाग त्यात समाविष्ट करण्यात आला आहे. यात असे नमुद करण्यात आले की, "Education will be used as an agent of basic change in the status of women. Inorder to neutralize the accumulated distortion of the past, there will be a well conceived edge in favour of women. The National education system will play a positive, interventionist role in the empowerment of women. It will foster the development of new values through designed curricula, text books, the training and orientation of teachers, decision makers and administrators and its active envolvement of educational institutions this will be an act of faith and social engineering. Women's studies will be promoted as a part of various courses and educational institution encouraged to take up active programmes to further womens develoment. "

भारत सरकारने स्त्री शिक्षणाचा प्रचार, प्रसार करण्यासाठी नि:संदेहपणे अनेक मार्गांचा अवलंब केला आहे, वेगवेगळे कायदे केले आहे, कायद्याचे पालन न केल्यास दंड व शिक्षेची तरतुद केली आहे. परंतु अजूनही स्त्री पुरुष भेदाच्या हीन भावनेतून आमची मने शंभर टक्के मुक्त झालेली अनेकदा दिसत नाहीत. असुया, असुरक्षितता, पुरुष प्रधानतेचा नाग अजूनही फना काढून फुत्कारतांना दिसतो आहे, हे सामाजिक परिवर्तन निव्वळ कायदे करुन होणार नाही, मन:परिवर्तन हाच त्यावरील एकमेव उपाय आहे.

स्त्रीयांचे संघटन, प्रबोधन करुन स्त्री अस्मिता जागण्याची अत्यंत महत्त्वाची जबाबदारी आज आपल्या सारख्या सुशिक्षित स्त्रीयांवर आलेली आहे. जोपर्यंत आपण सगळ्या सुशिक्षित स्त्रीया हया सामाजिक उपक्रमामध्ये हिरारीने व निस्वार्थपणे भाग घेणार नाही तोपर्यंत स्त्री शिक्षणाचा हा प्रवाह, हा प्रवास असाच अर्धवट आणि निरर्थक राहील. भगिरथाने महतप्रयासाने पृथ्वीवर जीवनदायीनी गंगा आणली आणि त्या पृथ्वीचे नंदनवन झाले. आज हीच जीवनदायानी गंगा जशी मृत्युशय्येवर आहे. अर्थात तिचा विनाश म्हणजे पृथ्वीचा विनाश ठरेल. त्याप्रमाणेच स्त्री शिक्षणाची ही गंगा अविरतपणे भारताच्या कानाकोपऱ्यातून भरुन भरुन न वाहील्यास भारतीय समाज ही लोप पावेल की काय ? अशी भिती निर्माण होत आहे.

संदर्भ : National Policy on Education 1986 (Part IV 4.2 and 3)

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Role of Multimedia Technology in Language Teaching & Learning

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Abstract: As the use of English has increased in popularity so has the need for qualified teachers to instruct students in the language. English Language Teaching has been with us for many years and its significance with

and technology, the emerging and developing of multimedia technology and its application to teaching, featuring audio, visual, animation effects comes into full play in English class teaching and sets a favorable platform for reform and exploration on English teaching model in the new era.

The present paper discusses the role of multimedia technology in English language teaching & learning. It also explains various problems arising from application for multimedia technology to English teaching.

Introduction:

At present, the status of English is that it is the language of social context, political, sociocultural, business, education, industries, media, library, communication across borders. It is the key subject in curriculum and language of imparting education. It is also a crucial determinant for university entrance and processing well paid jobs in the commercial sector. Since there are more and more English learners in India, different teaching methods have been implemented to test the effectiveness of the teaching process. One method involves multimedia in ELT in order to create English contexts. This helps students to get involved and learn according to their interests. It has been tested effectively and is widely accepted for teaching English in modern world.

With the rapid development of science and technology, the emerging and developing of multimedia technology and its application to teaching, featuring audio, visual, animation effects comes into full play in English class teaching and sets a favorable platform for reform and exploration on English teaching model in the new era. It's proved that multimedia technology plays a positive role in promoting activities and initiatives of student and teaching effect in English class.Technological innovations have gone hand –in hand with the growth of English and are changing the way in which we communicate..

Teachers can use Multimedia Technology to give more colorful, stimulating lectures. There are many techniques applicable in various degrees to language learning situation. Some are useful for testing and distance education, and some for teaching business English, spoken English, reading, listening or interpreting. There are various reasons why all language learners and teachers must know how to make use of the new technology. Here we also need to emphasize that the new technologies develop and disseminate so quickly that we cannot avoid their attraction and influence in any form.

Advantages of Using MMT in Class room Teaching & Learning a Language:

Vidya Bharati Mahavidyalaya College Amravati

Yenkar
PRINCIPAL
VIDYA BHARATI MAHAVIDYALAYA
AMRAVATI

In spite of advantages of application of multimedia technology to English class teaching has to improve teaching effect and university students' overall capacities, there are many problems existing in practical teaching, such as:

No Technology can completely Replace Man: Serves an assisting Instrument:

Application of multimedia technology is and assisting instrument to achieve the projected teaching effect, While if totally dependent on, multimedia devices during teaching, the teachers may be turned into slaves to the multimedia and cannot play the leading role in teaching, It is observed in practice that a lot of teachers are active in multimedia technology application but not proficient enough to handle it confidently. In class, they are standing by the computer and students are fixing their attention only on the screen, and therefore, there is no eye contact between teachers and students. Hence, the notion of Creative Education is to be fully comprehended that modern educational techniques serves as a [illegible] target: and that should not dominate class. They are substitutes to effective teaching and learning

Sometimes May increase Lack of communication between teachers and students

English language and English analysis by the teachers are effective in conveying knowledge to the students from English pronunciation to comprehension. It improves students' English thought patterns and oral expression, Whereas, the introduction of multimedia technology featuring audio, visual, textual effect fully meets audio and visual requirements of the students and enhance their interest, but it also results in lack of communication between teachers and students, replacement of teachers' voice by computer sound, and teachers' analysis by visual image and students have' few chances for speaking communication.

Suggestions to the Existing Problems

In practical teaching, it is improper to duplicate the textual material simply to the screen so that the teacher's position is ignored In order to ensure the function of, multimedia in teaching. It is proved through practice that adequate application of multimedia technology to teaching can make breakthroughs in class teaching. That is to say, during multimedia assisting teaching, teachers still play the leading role that their position could never be replaced by the computer. For instance, the introduction to each lesson and speaking communication are good way to improve students' listening and speaking which the computer cannot fulfill, Therefore, teachers' interpretation shall not be overlooked.

Screen can't Substitute the Blackboard

Some teachers take the computer screen as the blackboard, They have input exercises, questions, answers and teaching plans into the computer and display them piece by piece, without taking down anything on the blackboard or even the title of a lesson. It is known that teachers are supposed to simulate situations based on teaching and guide the students to communicate in English. Beside traditional writing on blackboard is concise and teachers can make adjustment and amendment to it if necessary.

Avoid overusing of Multimedia Technology

Some teachers may totally apply multimedia technology in their teaching. It is also believed that the more utilization of multimedia technology, the better class atmosphere may grow, the more actively the students get involved in class participation, the more easily the material access to the students. Apparently, the students show some interest in leaning, but actually, they feel like looking on. In practice, the more unconscious attention the students pay. It is impossible to effectively train the students' language expression in class time. It is clear that in spite of advantages of application of multimedia technology, it assists in teaching.

It is important for language teachers to be aware of the latest and best equipment and to have a full knowledge of what is available in any given situation. There are many aspects and the reasons to use multimedia technology in class room teaching & learning a Language.

1)Motivate the students for language learning:

Nowadays, the stereotyped traditional teaching methods and environment are unpopular while multimedia technology featuring audio, visual animation effects naturally and humanely makes us more access to information besides, with such characteristics as abundant-information and crossing time and space, multimedia technology offers a sense of reality and functions very well, which greatly cultivates students' interest and motivation in study and their involvement in class activities.

2)Promoting to improve Communication skills:

Traditional teaching has hampered students' capacity to comprehend certain language and also understanding to structure, meaning and function of the language. It makes the students passive recipients of knowledge, So it is hard to achieve the target of communication. With teachers' instructions leading students' thought patterns and motivating students' emotions, the multimedia technology seeks integration of teaching and learning and provides the students greater incentives, The PPT courseware activate students' thinking; the visual and vivid courseware rand help them to transforms English learning into capacity cultivation. And such in-class activities as group discussion, subject discussion, and debates can also offer more opportunities for communication among students and between teachers and students. So multimedia technology teaching has uniquely inspired students' positive thinking and communication skills in social practice.

Understanding the Need of Global Culture:

The multimedia courseware can offer the students abundant information; more plentiful than textbooks, and help them to get of displays vivid cultural background, rich content and true-to-life language materials, which are much natural and closer to life. Not only could learners improve their listening ability, but also learn the western culture. Grasping information through various channels can equip; the students with knowledge and bring about information-sharing among students and make them actively participate in class discussion and communication.

Effective Teaching:

Multimedia teachings enrich teaching content and make the best of class time and break the "teacher centered" teaching pattern and fundamentally improve class efficiency. Due to large classes it is difficult for the students to have speaking communication. The utilization of multi-media sound lab materializes the individualized and co-operative teaching. The traditional teaching model mainly emphasized on teachers' instruction, and the information provided is limited due to traditional classes. On the contrary, multimedia technology goes beyond time and space, creates more vivid, visual, authentic environment for English learning, stimulates students' initiatives and economizes class time meanwhile increases class information.

Problems existing in practical teaching using Multimedia Technology for English Teaching:

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Axially Symmetric Cosmological Models In $f(R,T)$ Gravity With Time Varying Deceleration Parameter

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Abstract: In the present paper an attempt has been made to study an axially symmetric space-time is considered in the presence of a perfect fluid source in the framework of $f(R,T)$ gravity. We consider two types of scale factors (i) $a(t)=\sinh(\alpha t)$ and (ii) $a(t)=te^{t}$ which yield time dependent DP. To get deterministic solution, expansion scalar θ is proportional to the shear scalar σ have been used. Some physical behavior for both models have been discussed by using physical parameters.

Keywords: $f(R, T)$ gravity, Axially symmetric space-time, Deceleration Parameter

1. INTRODUCTION

During last decade, there has been several modifications of general relativity to provide natural gravitational alternative for dark energy. It has been suggested that cosmic acceleration can be achieved by replacing the Einstein-Hilbert action of general relativity with a general function Ricci scalar, *f (R)*. Modification of general relativity are attracting more and more attention to explain late time acceleration and dark energy. There have been several modified theories like *f* (*R*) gravity, *f* (*G*) gravity f(T) gravity or *f* (*R*,*G*) gravity and so on investigated by several researchers. A generalization of *f* (*R*) modified theories of gravity was proposed in [1]. Among the various modifications, *f* (*R*) theory of gravity is considered as the most suitable due to the cosmologically important *f* (*R*) models. It has been suggested that cosmic acceleration can be achieved by replacing the Einstein–Hilbert action of general relativity with a general function Ricci scalar, *f* (*R*). Nojiri *et al* [2] have studied *f* (*R*), *f* (*G*) or *f* (*R*,*G*) gravity in various contexts. Many researchers [3–11] have investigated *f* (*R*) gravity in different contexts. Shamir [12] has proposed a physically viable *f* (*R*) gravity model, which shows the unification of early-time inflation and late-time acceleration. Paul et al. [13] obtained FRW models in f(R) gravity while Sharif and Shamir [14,15] have studied the solutions of Bianchi type I and V space-times in the frame work of f(R) gravity. Shamir [16] studied the exact vacuum solutions of Bianchi type I, III and Kantowski-Sachs space-times in the metric version of f(R) gravity. Adhav [17] has obtained LRS Bianchi type I cosmological model in f(R, T) gravity. Reddy et al. [18] have discussed Bianchi type III cosmological model in f(R, T) while Reddy et al. [19], Reddy and Shanthikumar [24] studied Bianchi type III dark energy model and some anisotropic cosmological models, respectively, in f(R, T) gravity. Chaubey and Shukla [20] have constructed a new class of Bianchi cosmological model in f(R, T) gravity. The exact solutions of the Einstein-Rosen cosmological model filled with perfect fluid have been derived in f(R, T) gravity by Rao and Neelima [21].

Axially symmetric cosmological models with string dust cloud source developed by Bhattacharaya and Karade [22]. Axially symmetric space-times representing material distribution were obtained by Marder [23].

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Axially symmetric space-times play an important role in the study of universe on a scale in which anisotropy and inhomogeneity are not ignored [24]. Kilinc [25] showed that axially symmetric cosmological models have made significant contributions in understanding some essential features of the universe such as the formation of galaxies during the early stages of the evolution. Jain et al. [26] studied axially symmetric space-time with wet dark fluid in bimetric theory. Energymomentum localization in Marder's axially symmetric space-time has been studied by Aygun et al. [27]. Recently Rao et al. [28] have obtained axially symmetric cosmological model with perfect fluid in general relativity and in f(R, T) gravity. Sahoo et al. [29] obtained the exact solution of the field equations in f(R, T) theory with the help of special law of variation for Hubble parameter. Two fluid axially symmetric cosmological models in f(R, T) theory obtained by Pawar et al. [30].

The constant DP is commonly used by cosmologist in literature with various aspects. In order to make more detailed description of the kinematics of cosmological expansion, it is useful to consider various forms of time dependence deceleration parameter. One of the most popular form is known as linearly varying deceleration parameter (LVDP). Linear parametrization of the DP represents quite naturally. The next logical step towards the behaviour of future model is either it expands forever or ends with a Big Rip in finite future. This can be parametrized with redshift parameter z, cosmic scale factor a and with cosmic time t. Transition of the universe from the decelerated phase to the present accelerating phase motivate us to consider variable DP. Several researchers (Pradhan *et al.* [31], Amirhashchi *et al.* [32], Akarsu and Dereli [33]) have discussed the evolution of the universe with variable DP. Also Mishra et al [34] have proposed a linearly varying deceleration parameter and using it they have investigated Bianchi Type-II dark energy model in f(R, T) gravity. It is used in Bianchi type-V cosmological model with of holographic dark energy to escape the Big Rip singularity [35]. Singh et al.[36] have been studied the homogeneous and anisotropic Bianchi type-I cosmological model in the presence of viscous uid source of matter, which starts with a big bang and ends in a Big Rip. The kinematical behaviour of LVDP along with null energy condition (NEC) has been explored in the framework of f(R; T) gravity for Bianchi type -I and V space-time[37]. Akarsu et al.[38]have described the fate of the universe through parametrization $q = q0+q1(1-t/t_0)$, which is linear in cosmic time t, along with two well-known additional parametrization of the DP $q = q_0+q1(1-a/a_0)$ and $q = q_0 + q_1z$, where z and a are the redshift parameter and scale factor respectively. Furthermore, they have studied the dynamics of the universe in comparison with the standard ^CDM model. Sahoo and Sivakumar [39] have obtained the model for perfect fluid source coupled with strange quark matter with linearly cosmic time parametrization of the deceleration parameter.

The present paper is organized as follows. In sect.1, a brief introduction is given. The field equations in metric version of $f(R, T)$ gravity is given in sect. 2. In section 3, explicit field equations in $f(R, T)$ gravity are obtained by using the particular form of the functions $f(T) = \lambda T$, which are used by Harko et al. [40], with the general class of axially symmetric metric in the presence of perfect fluid. Section 4 deals with cosmological solutions of the field equations using the linearly varying deceleration parameter by considering physically relevant assumptions and also discuss some

physical properties of the model. Conclusions are given in sect.5.

2. GRAVITATIONAL FIELD EQUATIONS OF $f(R,T)$ GRAVITY

The $f(R,T)$ theory of gravity is the modifications of General Relativity (GR). The field equations of $f(R,T)$ gravity are derived from the Hilbert-Einstein type variational principle. The action for the modified $f(R,T)$ gravity is

$$S=\frac{1}{16\pi}\int\left[f(R,T)+L_m\right]\sqrt{-g}\,d^4x, \tag{1}$$

where $f(R,T)$ is an arbitrary function of the Ricci scalar R, T is the stress energy tensor T_{ij} of the matter and L_m is the matter Lagrangian density, The energy momentum tensor T_{ij} is defined as

$$T_{ij}=-\frac{2}{\sqrt{-g}}\frac{\delta\left(\sqrt{-g}\right)L_m}{\delta g^{ij}}. \tag{2}$$

Here we assume that the dependence of matter Lagrangian is merely on the metric tensor g_{ij} rather than its derivatives.

In this case, we obtain

$$T_{ij}=g_{ij}L_m-\frac{\partial L_m}{\partial g^{ij}}. \tag{3}$$

The $f(R,T)$ gravity field equations are obtained by varying the action S with respect to metric tensor g_{ij}.

$$f(R,T)R_{ij}-\frac{1}{2}f(R,T)g_{ij}+\left(g_{ij}\otimes-\nabla_i\nabla_j\right)f_R(R,T)=8\pi T_{ij}-f_T(R,T)T_{ij}- \tag{4}$$

where $\theta_{ij}=-2T_{ij}+g_{ij}L_m-2g^{\alpha\beta}\frac{\partial L_m}{\partial g^{ij}\partial g^{\alpha\beta}}$. (5)

Here

$$f_R(R,T)=\frac{\partial f(R,T)}{\partial R},\quad f_T(R,T)=\frac{\partial f(R,T)}{\partial T},\ \otimes=\nabla^i\nabla_i$$

where ∇_i denotes covariant derivative.

Now contraction of equation (4) gives

$$f_R(R,T)R+3\otimes f_R(R,T)g_{ij}-2f(R,T)=8\pi T-f_T(R,T)(T+\theta), \tag{6}$$

Where $\theta=\theta_i^i$. Equation (6) gives a relation between Ricci scalar R and the trace T of energy momentum tensor. Using matter Lagrangian L_m the stress energy tensor of the matter is given by

$$T_{ij}=(\rho+p)u_iu_j-pg_{ij}, \tag{7}$$

where $u^i=(0,0,0,1)$ is the four velocity in commoving coordinates which satisfies the condition $u^iu_i=1$ and $u^i\nabla_ju_i=0$. ρ and p are energy density and pressure of the fluid, respectively, and the matter Lagrangian can be taken as $L_m=-p$ since there is no unique definition of the matter Lagrangian. Then with the use of (5) we obtain the variation of stress energy of perfect fluid expression

$$\theta_{ij} = -2T_{ij} - pg_{ij},$$

(8)

On the physical matter of the matter field, the field equations also depend through the tensor θ_{ij}. Hence in the case of $f(R, T)$ gravity depending on the nature of the matter source, we obtain several theoretical models corresponding to different matter contribution for $f(R, T)$ gravity are possible. However, Harko et al. [40] gave three cases of these models.

$$f(R, T) = \begin{cases} R + 2f(T) \\ f_1(R) + f_2(T) \\ f_1(R) + f_2(R) f_3(T) \end{cases}$$

(9)

In this paper, we are focused to the first class, i.e. $f(R, T) = R + 2f(T)$

where $f(T)$ is an arbitrary function of stress energy tensor of matter. We get the gravitational field equations of $f(R, T)$ gravity from equation (4) as

$$R_{ij} - \frac{1}{2}Rg_{ij} = 8\pi T_{ij} - 2f'(T)T_{ij} - 2f'(T)\theta_{ij} + 2f(T)g_{ij}$$

(10)

where the prime denotes differentiation with respect to the argument. If the matter source is a perfect fluid then the field equations (in view of equation (8)) becomes

$$R_{ij} - \frac{1}{2}Rg_{ij} = 8\pi T_{ij} + 2f'(T)T_{ij} + [2pf'(T) + f(T)]g_{ij}$$

(11)

3. METRIC AND FIELD EQUATIONS

We consider the axially symmetric metric (Bhattacharya and Karade [22]) as

$$ds^2 = dt^2 - A^2(t)\left[d\chi^2 + f^2(\chi)d\phi^2\right] - B^2(t)dz^2,$$

(12)

with the convention $x^1 = \chi,\ x^2 = \phi,\ x^3 = z \quad and \quad x^4 = t$, *and* A, B are functions of the proper time t alone while f is a function of the coordinate χ alone . In view of equation (7) for axially symmetric space-time (12) , the field equations (11) leads to

$$\frac{\ddot{A}}{A} + \frac{\dot{A}\dot{B}}{AB} + \frac{\ddot{B}}{B} = p(8\pi + 3\lambda) - \rho\lambda,$$

(13)

$$2\frac{\ddot{A}}{A} + \left(\frac{\dot{A}}{A}\right)^2 - \frac{f''}{A^2 f} = p(8\pi + 3\lambda) - \rho\lambda,$$

(14)

$$\left(\frac{\dot{A}}{A}\right)^2 + 2\frac{\dot{A}\dot{B}}{AB} - \frac{f''}{A^2 f} = -\rho(8\pi + 3\lambda) + p\lambda,$$

(15)

where an overhead dot and dash represents differentiation with respect to t and χ respectively.

The functional dependence of the metric together with equation (14) and (15) imply that

$$\frac{f''}{f} = m^2, \quad m^2 = cons\tan t.$$

(16)

If $m = 0$, then $f(\chi) = c_1\chi + c_2, \ \chi > 0$

(17)

where c_1 *and* c_2 are integrating constants. Without loss of generality, by taking $c_1 = 1$ *and* $c_2 = 0$ we get $f(\chi) = \chi$ resulting in the flat model of the universe (Hawking and Ellis [41]).

Now the field equations (13)-(15) reduces to

$$\frac{\ddot{A}}{A} + \frac{\dot{A}\dot{B}}{AB} + \frac{\ddot{B}}{B} = p(8\pi + 3\lambda) - \rho\lambda,$$

(18)

$$2\frac{\ddot{A}}{A} + \left(\frac{\dot{A}}{A}\right)^2 = p(8\pi + 3\lambda) - \rho\lambda,$$

(19)

$$\left(\frac{\dot{A}}{A}\right)^2 + 2\frac{\dot{A}\dot{B}}{AB} = -\rho(8\pi + 3\lambda) + p\lambda.$$

(20)

The spatial volume is given by

$$V = a^3 = A^2B$$

(21)

where a is the mean scale factor.

The mean Hubble parameter H for axially symmetric metric is given by

$$H = \frac{\dot{a}}{a} = \frac{1}{3}\left[2\frac{\dot{A}}{A} + \frac{\dot{B}}{B}\right]$$

(22)

The directional Hubble parameter in the directions of χ, ϕ *and* z are

$$H_\chi = H_\phi = \frac{\dot{A}}{A} \text{ and } H_z = \frac{\dot{B}}{B}$$

(23)

The deceleration parameter is

$$q = -\frac{a\ddot{a}}{\dot{a}^2}$$

(24)

4. SOLUTIONS OF THE MODEL

Equations (18)-(20) are three independent equations in four unknowns A, B, p, ρ . Hence to find a determinate solution, we assume expansion scalar θ is proportional to the shear scalar σ which yields

$$A = B^n$$

(25)

Subtracting (18) from (19) and taking second integral, we obtain the following relation

$$\frac{A}{B} = k_2 e^{k_1 \int \frac{1}{a^3} dt}$$

(26)

Thus equation (26) gives values of A, B as

$$A = k_2^{\frac{n}{(n-1)}} e^{\frac{k_1 n}{(n-1)}\int \frac{1}{a^3}dt} \quad n \neq 1$$

(27)

$$B = k_2^{\frac{1}{(n-1)}} e^{\frac{k_1}{(n-1)}\int \frac{1}{a^3}dt} \quad n \neq 1$$

(28)

Thus the metric functions are found explicitly in terms of average scale factor a.

4.1. Case I: $a(t) = \sinh(\alpha t)$

As suggested by Pradhan et al. [42], firstly we consider the variation of scale factor a with cosmic time t by the relation

$$a(t) = \sinh(\alpha t)$$

(29)

where α is an arbitrary constant.

Using equation (29) into (27) and (28), we have the following set of expressions for the scale factors

$$A = k_2^{\frac{n}{(n-1)}} e^{\frac{k_1 n}{(n-1)}\int [\sinh(\alpha t)]^{-3} dt} \qquad n \neq 1$$

(30)

$$B = k_2^{\frac{1}{(n-1)}} e^{\frac{k_1}{(n-1)}\int [\sinh(\alpha t)]^{-3} dt} \qquad n \neq 1$$

(31)

The physical quantities of observational interest in cosmology such as directional Hubble parameters (H_i), spatial volume (V), mean anisotropy parameter (Δ), shear scalar (σ^2) and expansion scalar (θ) are respectively given by

$$H_\chi = H_\phi = \frac{k_1 n}{(n-1)\sinh(\alpha t)}$$

(32)

$$H_z = \frac{k_1}{(n-1)\sinh(\alpha t)}$$

(33)

$$V = \sinh^3(\alpha t)$$

(34)

$$\Delta = \frac{2}{3}\frac{(3n^2 + 2n + 1)}{(2n+1)^2}$$

(35)

$$\sigma^2 = \frac{k_1^2(3n^2 + 2n + 1)}{(n-1)^2 \sinh^2(\alpha t)}$$

(36)

$$\theta = \frac{3k_1(2n+1)}{(n-1)\sinh(\alpha t)}$$

(37)

The deceleration parameter as

$$q = -\tanh^2(\alpha t)$$

(38)

Using equations (30) and (31) in (19) and (20), we obtain the values of pressure and energy density as

$$p = \frac{k_1 n}{(n-1)^2 \sinh^2(\alpha t)\left[(8\pi + 3\lambda)^2 - \lambda^2\right]}\left[(8\pi + 3\lambda)(3k_1 n - 2\alpha(n -$$

(39)

$$\rho = \frac{k_1 n}{(n-1)^2 \sinh^2(\alpha t)\left[(8\pi+3\lambda)^2-\lambda^2\right]}\left[\lambda(3k_1 n - 2\alpha(n-1)\cosh(\alpha t)) - (8\pi+3\lambda)k_1(2+n)\right]$$

(40)

4.2. Physical Behavior of the model

When $t=0$ the scalar expansion and shear scalar are infinity but at $t=\infty$ the scalar expansion and shear scalar are zero. The model of the universe start with big bang Spatial volume expands exponentially as t increases and becomes infinitely large as $t\to\infty$.The directional Hubble parameters H_χ, H_ϕ, H_z are infinite at $t=0$ and vanishing at $t\to\infty$.The shear scalar become zero as $t\to\infty$. We observe pressure and energy density remains always positive and it converges to zero as $t\to\infty$. From equations (30) and (31) we observe that the spatial scale factor become constant at the initial epoch $t=0$. Since $\lim_{t\to\infty}\frac{\sigma}{\theta}\neq 0$ the model does not approach isotropy for large value of t.

4.3. CASE II: $a(t)=te^t$

Following Amirhashchi et al.[43], we consider the following scale factor

$$a(t)=te^t$$

(41)

Using equations (41) in (27) and (28), we have the following set of expressions for the scale factors

$$A = k_2^{\frac{n}{(n-1)}} e^{\frac{k_1 n}{(n-1)}\int\left[te^t\right]^{-3}dt} \quad n\neq 1$$

(42)

$$B = k_2^{\frac{1}{(n-1)}} e^{\frac{k_1}{(n-1)}\int\left[te^t\right]^{-3}dt} \quad n\neq 1$$

(43)

The physical parameters as described in the case I are expressed as

$$H_\chi = H_\phi = \frac{k_1 n}{(n-1)t^3 e^{3t}}$$

(44)

$$H_z = \frac{k_1}{(n-1)t^3 e^{3t}}$$

(45)

$$V = t^3 e^{3t}$$

(46)

$$\Delta = \frac{2}{3}\frac{\left(3n^2+2n+1\right)}{(2n+1)^2}$$

(47)

$$\sigma^2 = \frac{k_1^2\left(3n^2+2n+1\right)}{(n-1)^2 t^6 e^{6t}}$$

(48)

$$\theta = \frac{3k_1(2n+1)}{(n-1)t^3 e^{3t}}$$

(49)

The deceleration parameter as

$$q = -\frac{t(t+2)}{(t+1)^2}$$

(50)

Using equations (42) and (43) in (19) and (20), we obtain the values of pressure and energy density as

$$p=\frac{k_1 n}{(n-1)^2 t^6 e^{6t}\left[(8\pi+3\lambda)^2-\lambda^2\right]}\left[(8\pi+3\lambda)\left(-6(n-1)(t+1)t^2e^{3t}+3k_1n\right)-\lambda k_1(2+n)\right] \quad (51)$$

$$\rho=\frac{k_1 n}{(n-1)^2 t^6 e^{6t}\left[(8\pi+3\lambda)^2-\lambda^2\right]}\left[\lambda\left(-6(n-1)(t+1)t^2e^{3t}+3k_1n\right)-(8\pi+3\lambda)k_1(2+n)\right] \quad (52)$$

4.4. *Physical Behavior of the model*

We observe that the spatial volume is zero at $t=0$ and expansion scalar is infinite, which shows that the universe starts evolving with zero volume at $t=0$ which is big bang scenario. We observe that the spatial volume increases exponentially with time. The physical quantities pressure (p), energy density (ρ), Hubble factor (H), shear scalar (σ^2) and expansion scalar (θ) diverge at $t=0$. As $t\to\infty$ volume becomes infinite whereas $p,\ \rho,\ H,\ \theta$ approaches to zero. We observe that the average scale factor $a(t)\to 0$ as $t\to 0$ and $a(t)\to\infty$ as $t\to\infty$ .This indicates that there exists inflation. Since $\lim_{t\to\infty}\frac{\sigma}{\theta}\neq 0$ the model does not approach isotropy throughout the evolution of the universe.

5. CONCLUSION

In this paper, we have considered a cosmological model in the presence of perfect fluid and variable deceleration parameter in *f* (*R*, *T*) theory of gravity. According the choice of *f* (*R*, *T*), we are focused to the first class, i.e. $f(R,T)=R+2f(T)$.

The exact solutions of the modified Einstein's field equations are obtained for the axially symmetric universe with perfect fluid. We assumed two types of scale factors (i) $a(t)=\sinh(\alpha t)$ and (ii) $a(t)=te^t$ which yield time dependent DP.

The observations of both the model are as follows:
The mean anisotropy parameter becomes constant for both models. It can be observed that our models are expanding and accelerating universe which starts at a big bang singularity. In both the cases energy density is positive valued and decreasing function of time. It is interesting to notice that q decreases very rapidly and then after it remains constant. It is observed that, our derived model has accelerated expansion at present epoch which is consistent with recent observation of type Ia supernova and CMB anisotropies.

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THE ROLE OF TECHNOLOGY IN THE AGRICULTURE DEVELOPMENT OF INDIA

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ABSTRACT

In the development of our country technology has been proving very resourceful for all round development of the society at large. In short technology has the potential to play an important role in economic growth and social development. , India has come up with various technological innovations in every sector. This paper reviews several aspects of role of technology in the evolution of Indian Economy.

Keywords: Agriculture, Technology, India

INTRODUCTION

Technology has been spreading all over the world by leaps and bounds. It has encroached every walk of life. India as a country has made progress in every sector after her independence. In the last seven decades, in the fields of industry, agriculture, education and banking, our country has made tremendous progress. India is a mixed economy and its base is agriculture. Our nation cannot progress unless we make development in the field agriculture. The complete raw materials are sought from agricultural resources. Thus, every industry runs with the support of agricultural products only.

It has changed the face of industry, banking, agriculture, education and means of transportation. The Indian economy has geared up its speed in present context. Indian industry has growth many manifold since 1980s. The industry has contributed considerably to the economic in terms of GDP employments and foreign exchange earnings. Because of spread of technology the competence of industry is increasing and almost all sectors of the economy like services and at banks, post offices, railways airports etc.

Information technology is a knowledge based industry, IT industry embraces production, manipulation, storage and dissemination of information. IT sector has a remarkable potential for accelerating economic growth of the nation. It has made our governance efficient. It enhances excess to information, excess to government services, protects consumers, makes skill development and training more effective, progresses delivery health services and promotes transparency. Thus the role of IT industry in enhancing the economic development of country has been acknowledged by the government.

Beside IT Biotechnology has brought radical changes in agriculture. Use of Biotechnological tools in agriculture could make food crops high yielding and more robust to biotic and a - biotic stresses. This could stabilized and increase food supplies which is important against the background of increasing food demand, climate change and land and water scarcity. Due to biotechnological tools the productivity of the food crops have increased immensely, such as soybean, corn, cotton etc. Bt cotton has certainly increased the profitability of the farmers and at the same time it reduced the use of chemical pesticides in this crop drastically. Studies suggest that the introduction of Bt technology has reduced food insecurity by 15-20% among Indian cotton growers. The country has also developed golden rice which is rich in B-carotene. This is a great solution for India as nearly Five Thousand children go-blind every year because of deficiency of B-carotene. Thus biotechnology has supported the Indian Economy.

Nanotechnology can be used in agriculture in many ways. It can help in promoting soil fertility and balanced crop nutrition, effective weed control, enhancing seed emergence using carbon nanotubes, delivery of agriculture chemicals, field sensing system to monitor the environmental stressed and crop conditions and improvement of plant trades against environmental stresses and diseases. Application within animal husbandary might include improving feeding efficiency and nutrition of agricultural animals, minimizing losses from animal diseases, and turning animal by products and waste and environmental concerns

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into value added products. In short, nanotechnology after considerable opportunities for the development of innovative products and application for agriculture, water treatment, food production, processing, preservation and packaging. Its use may bring benefits to farmers, food industry and consumers alike. Thus, nanotechnology has huge potential in revolutionizing the food packaging.

Protected cultivation or greenhouse cultivation is the most promising area where productions of horticultural crops has improved qualitatively world over in the last few decades. At present Spain, the Netherland and Israel are the leaders in cultivation of crops in polyhouses and greenhouses. The application of plasticulture can decrease the costs and therefore can lead to high productivity with a better quality of crops. In India the area under protected cultivation is around 25000 ha while the greenhouse vegetable cultivation area is about 2000 ha. India and the Netherlands having more or less same land under flower cultivation but in flower export, the contribution of Netherlands is 70% and India's contribution is just 1% because of advanced technology of polyhouses in the Netherlands. There technology based methods of cultivation have made a great revolution in the world market. Gradually, India is making a more in that direction of technology.

Technology has geared up the use of modern irrigation methods because of which the agricultural income has been increased immensely. Availability of enough water for crops in India is very critical. Raining in India is uncertain. Without water expected yield can not be achieved from agricultural sector. In India 78% water goes to the agriculture sector while the remaining goes to drinking, industry and other usage. But in modern times by using science and technology different irrigation system have been developed, such as dripping sprinkling and water guns, mechanisms have been devised. It has helped the country like India to save water on large scale. These modern techniques of irrigation will increase irrigation potential in the direction of the optimal utilization of water resources to optimum irrigation scheduling. Micro irrigation is advance techniques of irrigation and it will increase water used efficiency and crop productivity.

Indian agriculture market is flourishing compared to that of past because modern technology has developed fastest transfer tools. Now most of the action and work related to farming have become technology supported the sowing of the seed, crop protection, harvesting, post harvest management to marketing have become sophisticated. Central government of India has under taken a program of connecting every Grampanchyat of the country with internet facilities. These Grampanchyat should become technology transfer hubs to the farmers.

Internet and mobile phones are powerful tools to impart knowledge on new developments, improve methods of cultivation in the field of agriculture. These tools can help in understand weather data and agro-climate condition, information of prices of agricultural products to the farmer. Throughout the country in each district KVKs have been established to make spread of latest technology in agriculture.

Variety of new methods is brought in force to make farming easy going business. Pesticides, fertilizers, micronutrients and computer assisted regulation have become a big boon to the Indian agriculture system.

In a way the use of technology in agriculture have supported the nation at large enhancing the ill-health of Indian economy. Technology has added its huge contribution in the general national income of our country.

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स्त्रियांनो - सुर्योदय होत आहे

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प्रस्तावना :- 'दोन घडीचा डाव याला जीवन ऐसे नाव' हा डाव आपण रडीचा की चिडीचा खेळणार हे आपण ठरवायचे. वैदिक काळात स्त्री स्वातंत्र्य अबाधित होते. पण उत्तर वैदिक काळात स्त्रियांवर बंधने लादण्यात आली. रामायणात सितेला लक्ष्मण रेषा आखून दिली होती. पण महाभारतात प्रत्येक स्त्री पात्र व्यासाने स्वयंपूर्ण साकारलेले आहे. ती स्वयंभूपणे जगणारी आहे. मानवी समाजात स्त्रियांचा सहभाग पुरुषांच्या बरोबरीने असला तरी स्त्रियांना समान दर्जा मात्र मिळालेला नाही. पुरुष प्रधान व्यवस्थेत जगाचा उध्दार करणारी स्त्री ही रजस्वावाच्या वेळी वेगळी मानल्या जावू लागली. मातृत्व आणि लैंगिकता यांच्या सीमा रेषा ठरविल्या गेल्या आणि स्त्रियांना दुय्यम स्थानात बंदिस्त केले.

इ.स.पुर्व ६ व्या शतकात स्त्री दास्यत्वाची कहानी सुरु झाली. शुद्रकाचे मृच्छकटिकम्, मनुस्मृती याज्ञवाल्यकल्य स्मृतीवरुन तत्कालिन स्त्रियांचे शैक्षणिक, राजकीय, आर्थिक हक्क, अधिकार लोप पावलेले दिसतात. मध्यकाळात तिच्या व्यक्ती स्वातंत्र्याची कल्पनाच समाजाने अमान्य केली. भारतीय समाजाने स्त्रियांची स्थिती दयनीय केली. तिच्या सर्वांगीण उन्नतीच्या अधिकारांची पायमल्ली झाल्याने कौटुंबिक व्यवस्थेत तिचे स्थान दुय्यम दर्जाचे झाले. तथापि झाशीची राणी लक्ष्मीबाई, अहिल्याबाई होळकर ही काही अपवादात्मक उदाहरण आहेत.

पुढे १९ व्या शतकात मात्र ब्रिटीशाच्या शैक्षणिक धोरणामुळे आधुनिक शिक्षण प्रणालीचा प्रारंभ होवून स्त्रियांना आशेचा किरण दिसू लागला. नवशिक्षित तरुण पाश्चात्यांच्या आधुनिक विचारांनी प्रभावित होवून त्यांनी स्त्रियांच्या अनेक प्रश्नांना वाचा फोडण्याचे काम केले. थोर राजाराम मोहनरॉय, ज्योतिबा फुले, धोंडो केशव कर्वे, विठ्ठल रामजी शिंदे, राष्ट्रसंत तुकडोजी महाराज, महात्मा गांधी, डॉ. बाबासाहेब आंबेडकर यांनी पोषक वातावरण निर्माण केले. राष्ट्रसंत तुकडोजी महाराज म्हणतात, स्त्रीला हीन समजणे तिचा अनादर करणे हे जर समाजाला मान्य असेल तर भारत कदापि शक्तीशाली राष्ट्र बनणार नाही. वरील सर्व महापुरुषांनी स्त्रियांची सामाजिक बंधनातून मुक्तता करण्याकरीता शिक्षणास प्राधान्य देवून परंपरांना मुठमाती दिली. स्त्रीचा सामाजिक दर्जा नाकारुन समाजाची ५०% क्षमता वाया घालवणे हे समाज आणि राष्ट्राच्या उन्नतीकरिता अत्यंत घातक आहे. यावर उपाय म्हणून अनेक कायदे अस्तित्वात आलेत. महिलांच्या उन्नतीच्या दृष्टीने डॉ. बाबासाहेब आंबेडकरांनी हिंदू कोड बील आणले. हिंदू कोड बील हा एक महत्त्वपूर्ण टप्पा समजल्या जातो. या बिलामुळे स्त्रियांना घटस्फोटाचे अधिकार, घटस्फोटीत स्त्रीला पोटगीचा अधिकार, संपत्तीचा अधिकार, आंतरजातीय विवाहास मान्यता हे अधिकार मिळाले म्हणजे स्त्रियांनी आता अर्धी लढाई जिंकली होती. सतीबंदी कायदा १८२९, विधवा विवाह कायदा १८५६, बालविवाह प्रतिबंध कायदा १९२९, मुलींचा अनैतिक व्यापार विरोधी कायदा १९५६, दत्तक घेण्याचा कायदा १९५६, हुंडा प्रतिबंध कायदा १९६१, हिंदू विवाह कायदा १८७२,समान वेतन विरोधी कायदा १९७६, कौटुंबिक हिंसाचार प्रतिबंध कायदा २००५. हे सर्व कायदे पारीत करुन भारतीय लोकशाहीने स्त्रियांना केवळ कौटुंबिक स्तरावर नव्हे तर आर्थिक, सामाजिक बाबतीत ही संरक्षण दिले. आज स्त्रिया ज्या प्रकारे कर्तृत्व गाजवत आहेत हे त्या कायद्याचे फलित आहे.

स्वातंत्र्यापूर्वी अबला समजल्या जाणारी स्त्री ज्ञात साधना बनली होती. कौटुंबिक जबाबदाऱ्या सांभाळून स्त्री यशस्वीपणे यशाची शिखरे गाठत होती. या सर्व बदलामुळे समान काम, समान वेतन स्त्रियांना मिळावे याची जाणीव झाली. १९७५ मध्ये ही मागणी केली. १९८८ नंतर मार्क्सवादी कम्युनिष्ट पक्षाने स्त्री मुक्ती संस्थेने पुरुषाइतकेच स्त्रीला वेतन मिळावे म्हणून लढा दिला. स्त्री संघटनांनी समान वेतनावर भर दिला. कायम स्वरुपात असलेल्या स्त्री कामगारांना त्याचा फायदा मिळाला. पण कायमस्वरुपी काम नसलेल्या कष्टकरी स्त्रिया मात्र वंचित आहे. आज गरज आहे अशा स्त्रियांचा प्रश्न सोडविण्याची. याशिवाय अनेक कायदे स्त्रियांसाठी पारीत करण्यात आले.

काही निवडक कायदे खाली नमुद करण्यात आले आहे.

१. **स्त्रियांना अटक करु शकत नाही -** सुप्रिम कोर्टाच्या आदेशानुसार सुर्यास्तानंतर स्त्रियांना अटक करता येत नाही. अगदी महिला शिपाही सुध्दा स्त्रीला अटक करु शकत नाही. फारच गंभीर गुन्हा असल्यास न्यायालयास अटकेचे लेखी कारण दर्शवावे लागते.
२. **प्रायव्हीचीचा अधिकार -** रेप पिडीत महिला खाजगी जबाब देवू शकते. त्यावेळी मॅजिस्ट्रेट सोबत असतात पिडीत स्त्री कॉन्स्टेबल आणि पोलीस सर्वांसमोर जबाब देण्यासाठी दबाव आणू शकत नाही.
३. **कितीही काळानंतर नोंदवू शकता तक्रार -** बऱ्याचशा महिला समाजाच्य, कुटुंबाच्या व इतर तत्सम कारणामुळे पोलिसांकडे तक्रार करत नाहीत पण कितीही उशीर झाला तरी स्त्री तक्रार करु शकते. ही तक्रार नोंदवायला पोलीस तक्रार देवू शकत नाहीत मात्र महिला ईमेलच्या माध्यमातूनही तक्रार देवू शकते.

पटलावर सतत संघर्ष करुन उच्चपद प्राप्त केले. त्या भारताच्या प्रथम महिला राष्ट्रपती बनल्या तर सिंधूताई सपकाळ ह्या अडचणीवर मात करुन हजारोंची आई झाल्या. जिला स्वत:चे घर नव्हते तीने हजारोंना आश्रय दिला. रझिया सुलतान, नलिनीताई लाडके, यशोमती ठाकुर, राणी बंग, अशा अनेक स्त्रियांची नावे नमुद करता येतील. यांनी प्रश्न सोडविण्याचे काम केले म्हणून त्यांच्या नावाची नोंद आपणास प्रेरणादाई वाटते.

समाजाचा दुसरा वर्ग म्हणजे कष्टकरी समाज कष्टकरी स्त्रियांचे आयुष्य पाहता परिस्थितीवर मात करुन धडपडत राहण्याची प्रेरणा त्यांना कशातून मिळते. स्त्री स्वांतत्र्य, स्त्री मुक्ती समानता या प्रश्नावर विचार तर सोडाच पण हे शब्दही त्यांच्या कानावरुन गेलेले नसतात. पण परिस्थितीचे आव्हान स्वीकारुन दारुडा नवरा, आर्थिक विवंचना, आजारी सासू सासरे, पडकी घरे, गलिच्छ वस्ती, कायमस्वरुपी नसणारे काम, एक ना अनेक प्रश्न घेवून केवळ इच्छा शक्तीच्या बळावर परिस्थितीवर मात करुन उरले सुरले सामाजिक भानही त्या जोपासतात. अशा स्त्रियांशी संभाषण केल्यास आपल्या जीवनातील लहान सहान दु:ख कुरवाळीत बसणाऱ्या आम्हा मध्यमवर्गीय स्त्रियांमध्ये काही जिद्द करारीपणा आणि चौकटी पलिकडे काही करण्याची उर्मी निर्माण होईल का? मला माहित नाही पण हे सर्व परिसंवादास उपस्थित असणाऱ्यांना विचार करायला लावणारे आहे.

सारांश :-आज समाजात स्त्रियांना शिक्षण आहे पण त्यांचा स्त्रियांनी वापर करणे शिकले पाहिजे. सरकारने सर्व सुविधा दिल्या तरी त्याची माहिती स्त्रियांनी स्त्रियांपर्यंत पोहचविली पाहिजे. काही कायद्यामध्ये सुधारणा घडवून आणली पाहिजे. यासाठी स्त्रियांनी पुढाकार घेतला पाहिजे. तलाक विरोधी कायद्याला स्त्रियांच मोर्चा काढून विरोध करतात. स्त्रियांनी या मुस्लिम समाजातील स्त्रियांच्या पाठीशी उभे राहून त्यांना मदतीचा हात दिला पाहिजे. सर्वात महत्त्वाचे तिने कायदे वाचून समजून घेतले पाहिजे. समान वेतनाचा कायदा किती कष्टकरी स्त्रियांना माहित आहे तो समजावून सांगण्याचे काम सुशिक्षित स्त्रियांचे आहे. समान काम समान वेतन हे रुजविण्याचे काम आता शिक्षित स्त्रियांनी केले पाहिजे. आज मुलींना शिक्षणाबरोबर घरातील कामे शिकविण्याची गरज आहे. कुटुंब व्यवस्था टिकवून ठेवायची असेल तर मुलामुलींच्या कामाची वाटणी करु नका. विधवा स्त्रियांना कमी लेखू नका. तुमच्या समारंभात त्यांनाही वाटेकरी करा. स्त्रीने स्त्रियांची बाजू समाजाला पटवून सांगायला हवी. स्त्रीने स्त्रीचा द्वेष करु नये.

स्त्रियांमध्ये नैसर्गिकरित्या दोन हार्मोन्स असल्यामुळे त्या पुरुषांपेक्षा अनेक कामे एकाच वेळी करु शकतात. स्त्रीमध्ये व्यवस्थापन असते. पुर्णब्रम्ह हॉटेल हे एका मराठी स्त्रीने काढलयं. आय.टी. क्षेत्रात तिने १७ वर्षे नोकरी करुन ती सोडून तिने हॉटेल टाकल. जगातले सर्वात मोठे शाकाहारी रेस्टॉरंट एका स्त्रीने सुरु केले. तेथे ५० टक्के स्त्री कामगार आहेत. तिच्या अंगभूत गुणांचा उपयोग करुन आदर्श गाव प्रकल्प, वसुंधरा बचाव, प्लॉस्टिक निर्मुलन, पाण्याचे नियोजन अशी अनेक कामे स्त्री करु शकते. स्त्रियांच्या अंगभूत गुणांना महत्त्व देवून स्त्रियांनीच आता स्त्रियांना प्रोत्साहन देण्याची गरज आहे. पाककलेत निपुण असणाऱ्या स्त्रियांनी व्यवसाय करावेत, गृहउद्योग करावेत, कर्ज काढण्यासाठी इतर सुशिक्षित स्त्रियांनी त्यांना मदत करावी.

आपल्या घरी काम करणाऱ्या बाईलाही महत्त्व दया. तिच्या सुखादु:खात आर्थिक भार सोसाण्याकरीता तिला मदतीचा हात दया नाहीतरी, ती कामाला आली नाही, तर घर कशी होतात हे आपण सर्वच जाणतो, नाहीतर संत कबीर एका दोह्यात म्हणतात,

माटी कहे कुम्हार से, तू क्या रौंदे मोहे |
इक दिन ऐसा होयेंगा, मै रौदूंगी तोहे ||

शासनाने महिलांच्या उन्नतीकरिता तसेच त्यांना समाजात पुरुषांबरोबर स्थान प्राप्त करण्याकरिता विविध कायदे आणून त्यांच्या सामाजिक परिस्थितीची सुपोदप होत असल्याची त्यांना जाणीव करुन दिलेली आहे.

संदर्भ ग्रंथ

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४. **झीरो FIR चा अधिकार** - रेप पिडीत महिलेला झीरो FIR नोंदविण्याचा अधिकार आहे. अशा केसमध्ये महिला कोणत्याही पोलीस स्टेशनमध्ये तक्रार नोंदवू शकते.

५. **चौकशीसाठी बोलवू शकत नाही** - कोणत्याही महिलेला चौकशीसाठी पोलीस स्टेशला बोलावले जावू शकत नाही. महिलेची चौकशी तिच्या घरीच एखाद्या महिला पोलिसांच्या उपस्थित करु शकता.

६. **गोपनीयतेचा अधिकार** - रेप केसमध्ये महिलेची ओळख गोपनीय ठेवणे गरजेचे आहे. पोलीस व मिडिया कोणीही पिडीताचे नाव उजागर करु शकत नाही.

७. प्रेग्नंट गरोदर कर्मचाऱ्यांची कंपनी कामावरुन हकालपट्टी करु शकत नाही.

८. कोणत्याही वेळी कोणत्याही हॉटेलमध्ये तुम्हाला पिण्याच्या पाण्याची मागणी करता येईल. तसेच बाँथरुमचा वापरही करु शकता तेही मोफत.

९. कायद्यानुसार एखाद्या हॉटेलमध्ये एखाद्या अविवाहीत जोडप्यांना प्रवेश नाकारण्याचा अधिकार नाही.

१०. महिलांना एखाद्याच्या विरोधात थेट पोलीस आयुक्त किंवा आयुक्तालाकडे इमेल किंवा रजिस्टर्ड पोस्टाच्या माध्यमातून तक्रार नोंदवता येतो.

११. एखाद्याला अटक केल्यानंतर २४ तासात कोर्टात हजर करावे लागते. नसता पोलीस त्याला ताब्यात ठेवू शकत नाही.

१२. एखाद्या विवाहीत पुरुषाने अविवाहीत महिलेबरोबर संबंध ठेवल्यास तो गुन्हा ठरत नाही.

१३. मुली आणि मुलांना कायद्यानुसार समान हक्क असतो.

१४. लग्नाला किमान एक वर्ष झाल्याशिवाय एखाद्या दाम्पत्याला घटस्फोटासाठी अर्ज करता येत नाही.

१५. पोलीस अधिकाऱ्याने एखाद्याला अटक करतांना एखाद्या महिलेबर थेट व्यभिचाराचा आरोप लावता येत नाही.

१६. तुमची तक्रार नोंदवण्यास तक्रार देणाऱ्या किंवा टाळाटाळ करणाऱ्या पोलिसांला ६ महिने ते २ वर्ष या तुरुंगवासापर्यंत शिक्षा होऊ शकते.

भारत सरकारने स्त्रियांशी संबंधित बाईट प्रथा संपविण्यासाठी आणि स्त्रियांच्या उत्थानासाठी विविध कायदे केले. या सर्व कायद्यांनी स्त्रियांना संपूर्ण प्रकारचे संरक्षण प्राप्त झाले. स्त्रियांना संपूर्ण स्वातंत्र्य व हक्क मिळाले. सर्व क्षेत्रात पुढे जाण्याची संधी मिळाली. एकेकाळी अनेक बंधनात असलेल्या अबला म्हणून हिनवल्या गेलेल्या स्त्रीने आज प्रगतीची सर्व शिखरे पुरुषाच्या बरोबरीचे किंबहुना काही ठिकाणी त्याही पेक्षा जास्त प्रमाणात पादाक्रांत केलेली आहेत. भारत सरकारने केलेल्या कायद्यामुळे स्त्रियांना संरक्षण प्राप्त झाले. खऱ्या अर्थाने कायद्याने स्त्री मुक्त झाली. भारतीय राज्यघटनेने स्त्रियांना दिलेले अधिकार स्त्रियांच्या उन्नतीसाठी अथक परिश्रम करणाऱ्या समाजातील थोर स्त्री पुरुषांच्या प्रयत्नांना आलेले यश हे नाकारता येत नाही.

मुलींसाठी शासनाने पुरस्कार, सवलती, शिष्यवृत्या जाहीर केलेल्या आहेत. वसतीगृहे स्थापन करुन स्त्रियांना प्रोत्साहन दिले. आर्थिक दृष्टया मागास वर्गातील विद्यार्थ्यांना मिळणारी गुणवत्ता शिष्यवृत्ती, मागासवर्गीय मुलींसाठी कल्याणकारी योजना सार्वजनिक आरोग्यविषयक योजना, सावित्रीबाई फुले दत्तक पालक योजना अशा अनेक योजना सरकारने राबविल्या. या सर्व योजनांचा स्त्रियांनी फायदा करुन घेतला आहे.

आज कोणत्याही विद्यापीठाच्या विविध परीक्षेत मुली सर्वाधिक सुवर्ण पदके प्राप्त करुन उत्तीर्ण झालेल्या दिसतात. महाविद्यालयातील स्तरावरही मुली विविध उपक्रमात पुढे आहेत. शहरी भागाची टक्केवारी पाहता शिक्षणाचे प्रमाण अधिक आहे. यात मुस्लिम स्त्रियांचे शिक्षणाचे प्रमाण नगण्य आहे. गरज आहे त्यांचे मानसिक परिवर्तन करण्याची. यासाठी हमीद दलवाई यांनी महाराष्ट्रातील प्रतिगामी मुस्लिम समाजास आधुनिकतेच्या मुख्य प्रवाहात आणण्याचे काम जोमाने केले. मुस्लिम समाजाचे प्रबोधन घडवून आणून त्यांना सेक्युलर राष्ट्रवादी बनविणे, त्यांच्यात वैज्ञानिक दृष्टी निर्माण करणे. मुस्लिम स्त्रियांचे सशक्तीकरण करणे हे कार्य जोमाने सुरु केले. ही प्रेरणा त्यांनी महात्मा फुले कडून घेवून २२ मार्च १९७० साली मुस्लिम सत्यशोधक मंडळ स्थापन केले. अनेक चळवळी राबविल्या. याद्वारे समान नागरी कायदा चळवळ, मुस्लिम स्त्रियांना मिळणारा एकतर्फी तोंडी तलाक, तसेच प्रार्थना स्थळी स्त्रियांना प्रवेश मिळावा याकरीता देखील स्त्रियांनी यशस्वी आंदोलने केली.

मुस्लिम समाजात होणारे बहुविवाह, त्यामुळे घरातील स्त्रियांचे कमी होणारे महत्त्व. मुस्लिम स्त्रीचे कायद्याद्वारे संरक्षण व्हावे म्हणून भारतातील अनेक शहरामध्ये तलाक विरोधात स्त्रियांना एकत्र आणून त्यांना संघटीत करुन लढा देण्यास सशक्त बनविले. कलम १२५ अन्वये पोटगीचा अधिकार मिळवून दिला. कुटुंब नियोजनाचा कायदा मुस्लिम स्त्रियांनी स्विकारावा. १९८६ ला काही प्रमाणात मुस्लिम स्त्रियांना पोटगी मिळाली. २०१८ ला त्रितलाक बंद झाला. वरील संदर्भ पाहता आजही भारतात पुरुष प्रधान संस्कृती आहे हे अमान्य करुन चालणार नाही. याही परिस्थितीत सुध्दा स्त्रियांनी मोठ्या प्रमाणात आपल्या कार्याचा ठसा उमटविला हेही नाकारुन चालणार नाही.

स्त्रियांनी सामाजिक भान जोपासून केलेले कार्य :- गोदावरी परुळेकर यांनी (१९०७-१९९६) भारतीय समाजातील अतिशय उपेक्षित आदिवासी समाजात राहून त्यांचे प्रश्न समजून त्यांना न्याय हक्क मिळवून दिले. १९१०-१९९२ यांनी आदिवासी समाजाच्या उध्दारासाठी संपुर्ण आयुष्य खर्ची घातले. आदवासी समाजाच्या मुलामुलींना समाजाच्या मुख्य प्रवाहात आणण्यासाठी अनुताई वाघ जीवनभर संघर्ष करीत होत्या. कुसुमताई पटवर्धन यांनी महिलांच्या अधिकारासाठी सतत संघर्ष करीत राहिल्या. साधनाताई आमटे यांनी बाबा आमटे यांच्या खांदयाला खांदा लावून कुष्ठरोग्यांसाठी कार्य केले आहे. महामहिम राष्ट्रपती प्रतिभाताई पाटील यांनी राजकीय

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IS SOCIAL MEDIA CONTAGION TO EMOTIONAL STATES OF COLLEGIANS OFFERING VARIOUS STUDY STREAMS?

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ABSTRACT

Life of young collegians is highly influenced by social media. It has led to develop e-identity and e-personality. Now a day emotions of the youngsters are no more personal experience, but has become e-emotions. The present study aimed to study whether social media addiction is contagion to emotional states of the collegians. The sample comprised of 161 college students (Male-56, Female-105). Social Media Disorder Scale and Eight State Questionnaire were used. Mean scores obtained on both measures shows little variation. T value of between correlated means of emotional states exhibited non significant result. Correlation coefficient between media addiction and emotional states was negative and non-significant. Even Chi square test across study stream and gender exhibited non significant results. It is concluded that social media is not contagion to emotional states. Changes in emotional states are only temporary and can be attributed to the factor of chance.

Keywords: Social media disorder, emotional states, body dissatisfaction, emotional contagion.

INTRODUCTION

Recently, social media was in media due to its adverse effects on teenagers and the youngsters. The internet games like 'Blue whale challenge', 'Pink whale challenge', 'Pokoman go', taking selfies at risky places like on running railways or at the overflow dams indicates that in younger generation internet addiction is increasing day by day and they are becoming over conscious about their presence in social media. Even in interpersonal relationships, social media has caused tremendous change. One-to-one contact is replaced by virtual relationship and this has led to e-identity, e-personality and have divulged the emotional life of youngsters.

The speed of forwarding the message and posting selfie is so fast that it seems like a contagion. Even the emotional states can be transferred to other via emotional contagion, leading people to experience the same emotions without their awareness. In other words, due to social media emotional world of an individual is now no more private, but emotions have become e-emotions.

Emotional contagion is well established in laboratory experiments. In such experiments it is found that without knowing people transfer positive and negative emotions to others. Data from large real-world social network, collected over a 20 year period suggests that longer lasting moods (e.g. depression, happiness) can transferred through networks, but the results are controversial (Flower and Christakis, 2008).

OPERATIONAL DEFINITIONS

Social media disorder- Social media disorder means preoccupation with instagram, facebook, selfie taking behavior that enable the user to continuous chatting on computer and smart phone. In the present work, nine factors related to social media have been incorporated. They are preoccupation, tolerance, withdrawal, persistency, escapism, problems, deception, displacement and conflict.

Emotional states-Emotional states are a mixture of psychological and physiological reactions. In the present work eight emotional states are taken into consideration. They are anxiety, stress, depression, regression, fatigue, guilt, extraversion and arousal.

SOCIAL MEDIA ADDICTION AND EMOTIONAL STATES

Over the past decade, social media addiction has emerged two major arena of research. First, use of internet for gambling and pornography are common among youngsters (Kuss and Griffiths, 2012; Griffiths, 2012). Secondly, excessive use of social media has manifest a range of certain psychological problems such as depression, attention deficit, hyperactivity disorder, social

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isolation and low self esteem (Guangheng, et al. 2011).

Young collegians, both males and females, are more conscious about physical appearance. However, intense desire to be physically attractive leads to discrepancy between real and ideal body image which ultimately results in certain psychological problems including body dissatisfaction and disturbances in emotional states. Researchers have cited that mass media is a culprit behind the growing trend of body dissatisfaction among young women (Dittmar, 2009). Fredrickson and Roberts (1997) asserted that body image is important for both men and women; however, women are more prone to body dissatisfaction because they are more likely to be seen as physical and sexual objects whose social values can be inferred from bodily appearance. Young women who experience a large amount of body dissatisfaction might take and post selfies in an attempt to garner affirming messages that might boost their own self confidence.

Research on gender differences in use of social media and selfie behavior are equivocal. Fox and Rooney (2015) found that males are more prone to selfie posting than females. On the contrary, Manago, Graham, Greenfield and Salimkhan, (2008) have reported that females are more prone to use social media for posting selfies. This is mainly because frequent posting of selfies by women could be related to their need for physically attractive for self-presentation or an elevated need to belong in a group, which may be as less important to men. Dhir, et al. (2016a) have reported preponderance of women in use of social media and they are less likely to use privacy – preserving strategies compared to young male adults. Their selfie photos to make them look impressive before posting them on social media. It tends to portray women of below average thinness and retouches and airbrushes their subjects until they reach unrealistically perfect level of physical beauty (Hass, et al., 2012). Young women might develop body image issues if they compare themselves to social norms of beauty as displayed in these media representation (Bergstorm, et al., 2009). Peer pressure is also one of the important variables in selfie behavior. Tandoc, Ferrucci and Duffy (2015) have reported that individuals who are in peer groups are characterized by high degrees of social comparison and competition among members are more likely to take selfies and post photos on social networking sites to make themselves look more outstanding than their peers.

The foregoing review states that excessive use of social media may be particularly problematic to young people. Therefore, in the present work the factor of social media addiction, study stream and gender were incorporated. It aimed to find whether social media is contagion to emotional states of youngsters offering various study streams.

AIM AND OBJECTIVES OF THE STUDY

Main aim of this study is to find impact of social media on emotional states of youngsters from various study streams.

Objectives- Major objectives of the study are...

1- To explore the social media contagion on emotional states of collegians.
2- To find the strength of association between social media disorder and emotional states of youngsters.
3- To study differences in the use of social media among students offering different study courses.
4- To study gender differences in the use of social media among college youngsters.
5- To study differences in the emotional states of collegians offering different study courses.
6- To study gender differences in the emotional states of college youngsters.

Hypotheses:

Assuming other factors are kept constant it is hypothesized that

H1- Social media addiction is contagion to emotional states of collegians.
H2- There will be strong positive strength of association between social media disorder and emotional states.
H3- Students offering various study courses will not differ significantly in the use of social media.
H4- Gender will not be a significant factor in the use of social media.
H5- There will not be significant difference in the emotional states of collegians offering different study courses.
H-6 Gender will not be significant factor in the emotional states of college youngsters.

Sample: The sample comprised of 161 (Male- 56 and Female- 105) under graduate and post graduate students from science, computer, pharmacy and management stream.

Tools: The Social Media Disorder Scale by Ringa, et al. (2016) was used. The scale comprised 27 items and nine subscales including preoccupation, tolerance, withdrawal, persistency, escapism,

problems, deception, displacement and conflict. IPAT Eight States Emotional State Questionnaire was used to assess emotional states of the subjects. The test comprised of 96 items. It measures anxiety, stress, depression, regression, fatigue, guilt, extraversion and arousal. The validity and reliability reported by the authors of the tools is quite high.

STATISTICAL INTERPRETATION

In the present study three independent variables were incorporated, they are social media addiction, gender and study stream. A social media disorder scale and emotional states questionnaire were administered in group form. The average scores obtained by the subjects are given in following tables.

Table: 1 Faculty-wise distribution of Mean values on sub-tests of Social Media Disorder Scale.

Faculty/Sub-tests	Preoccu pation	Tole rance	With drawal	Persis tency	Esca pism	Prob lems	Decep Tion	Displace ment	Con flict
Science	9.85	9.55	8.39	9.07	9.16	7.85	7.83	7.67	7.32
BCA	10.28	9.66	9.33	9.46	9.3	9.25	8.92	8.61	8.35
Pharmacy	9.14	8.02	7.32	7.91	8.41	7.08	5.82	6.91	6.73
MBA	9.78	9.64	8.67	9.28	9.92	8.82	7.85	7.64	7.21

Table No. 2 Faculty-wise distributions of Mean values on sub-tests of Emotional States Questionnaire

Faculty/Sub-tests	Anxiety	Stress	Depre Ssion	Regre ssion	Fatigue	Guilt	Extra version	Arousal
Science	16.30	14.07	16.58	14.98	17.55	16.25	15.19	7.32
BCA	16.30	15.30	15.12	15.28	16.97	16.48	16.41	8.35
Pharmacy	17.05	15.79	14.97	13.58	18.00	17.02	16.17	6.73
MBA	16.35	14.46	15.32	13.57	18.39	15.96	15.50	7.21

Values depicted in table no. 1 and table no. 2 are average scores obtained by students offering various study courses. Careful observation of the values in the above tables shows that there is considerable variation in the responses of all groups. However, in the present work only total test/scale values are incorporated for interpretation.

Table: 3 Stream-wise Mean and Standard Deviation values obtained on the basis of total score on Social Media Disorder Scale and Emotional States Questionnaire.

		Social Media Disorder		Emotional States	
Faculty	N	Mean	SD	Mean	SD
Science	56	69.41	21.00	124.75	20.73
BCA	39	74.84	19.05	126.56	17.04
Pharmacy	34	60.64	22.46	125.26	22.06
MBA	32	71.64	19.60	121.71	14.75

Table: 4 Gender-wise Mean and Standard Deviation values obtained on the basis of total score on Social Media Disorder Scale and Emotional States Questionnaire.

		Social Media Disorder		Emotional States	
Gender	N	Mean	SD	Mean	SD
Male	56	73.90	19.02	122.17	17.04
Female	105	73.99	24.61	126.05	11.22

The values depicted in table no 3&4 shows that, stream-wise there is a greater variation in average performance on Social Media Disorder Scale. Whereas in emotional states there is not much variation except MBA students exhibiting lowest score. Gender-wise distribution shows that on Social Media Disorder Scale, male and female subjects exhibiting almost similar scores. In emotional states, females surpassing males, exhibiting higher average score but less variation.

Table: 5 Mean, Correlation Coefficient and t values obtained on the basis of total score on Emotional States Questionnaire and Social Media Disorder Scale.

	Social Media Disorder	Emotional states
Mean	76.20	123.28
SD	24.69	21.62
r	-0.05 (N=161)	
t *	1.67	

*Between correlated means of Emotional States Scores

Table: 6 Chi square values obtained across faculty and gender on Emotional States Questionnaire and Social Media Disorder Scale.

Faculty/Gender	Social Media Disorder	Emotional States	df
Faculty	1.60	0.1	3
Gender	0.001	0.06	1

The main objective of the present work was to find out the whether social media addiction is contagion to emotional states of the college youngsters. In order to reveal this effect Social Media Disorder Scale was administered between two sessions of Emotional States Questionnaire. t value (Table-5) between two correlated means of Emotional States Questionnaire yielded non significant result (p>.05, df= 160). It means that social media contagion is occurred by chance only, in other words changes in emotional states are temporary.

In order to fetch the strength of association between Social Media Disorder and Emotional Sates Pearson Product Moment Correlation was computed. The obtained value is -0.05, it is negative and non significant (p>.05, df=160). For further interpretation the data were treated by Chi Square test of significance. Faculty wise on Social Media Disorder Scale and on Emotional Sates Questionnaire the obtained values are 1.6 and 0.1 respectively and are non significant (P>.05 df=3). In case of gender differences they are 0.0001 and 0.06, respectively (Table-6), on both measures are non significant (p>0.06 and p>0.0001, df=1). It indicates that differences in obtained scores are attributed to the factor of chance only.

DISCUSSION

The younger generation is quite aware about their physical appearance, status and position in the group and quite conscious about their e-personality and internet profile. Many researchers have examined the role of social media and personality traits. The results of these studies suggest that social media activity is related to several obsessed personality traits including emotional problems. This is a big avenue to investigate whether these traits are developed out of the influence of social media or such traits enable an individual to use this media at great extent.

The present work entailed to test six different hypotheses. On the basis of the data as well as test of significance (t test and Chi Square) it is concluded that first two hypotheses were not strongly supported. It was hypothesized that social media addiction is contagion to emotional states of collegians. The results were not as per expectations. On the contrary, previous studies revealed that excessive use of internet and social networking platforms could weaken the connections between individuals and their families, friends and loved ones. And it makes an individual to feel lonelier, depressed and certain problems related to emotional states (Pantic, 2014; Yellowes and Marks, 2007). The second hypothesis was there will be strong positive strength of association between social media disorder and emotional states. The data did not support the hypothesis. It means that social media does not play significant role in emotional states. Therefore, whatever the differences in average score observed they are attributed to the factor of chance only and variations in emotional moods are temporary.

Remaining four hypotheses (H3, H4, H5 and H6) were related to stream-wise and gender-wise differences in the use of social media and differences in the emotional states of young collegians. All these hypotheses were strongly supported by the data. This is mainly because communication technology is changing vary rapidly. As far social media is concerned, this change is fast. It appears that there is a synchrony between media generation (i.e., 1-G, 2-G, 3-G, 4-G ....) and human generation. Even new generation is more techno-savvy than the previous one, college students are not exception to this. Secondly, the virtual platforms such as internet and social media allow the young collegians to be anonymous by disguising their identity, they can act as a person they are not and express themselves more comfortably (Kurtalan, 2008). However, Xu and Tan (2012) suggest that the transition from normal to problematic social networking use

occurs when social networking is viewed by the individual as an important mechanism to relieve stress, loneliness or depression. They contended that those who frequently engage in social networking are poor at socializing in real life. For these people, social media use provides continuous rewards (e.g., self-efficacy, satisfaction) and they end up engaging in the activity more and more, eventually, leading to many problems (e.g., ignoring real life relationships, work/educational conflicts etc.). These resulting problems may then exacerbate individuals' undesirable moods. This then leads such individuals to engage in the social networking behavior even more as a way of relieving unhappy mood states.

CONCLUSIONS

On the basis of findings and statisticalinterpretation it is concluded that...

1) Social media addiction is not contagion to emotional states.

2) Strength of association between social media disorder and emotional states is very poor and negative.

3) There was no significant difference in the use of social media among students offering different study courses.

4) Male and female students exhibited similar trend in the use of social media.

5) There were no significant differences in the emotional states of collegians offering different study courses.

6) There were no significant gender differences in the emotional states of college youngsters.

LIMITATIONS

The study has several limitations. Firstly, the scope is limited to the collegians offering various study courses enrolled in a single college affiliated to SGB Amravati University. Secondly, the investigation is based on responses given by the collegians. To study the contagion effect, laboratory study is required. Thirdly, inspite of the validity and reliability of the tools, the gravity of respondents is the major constraint in drawing conclusions. Finally, due to the space restrictions, interpretation and conclusions are drawn only on the basis of total test/scale score. Sub-test/scale scores are not incorporated

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Revealing Gender Isonomy with Respect to Capacity, Domestic Chores and Domestic Violence.

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Abstract : Gender isonomy is one of the most studied and discussed phenomena. The issue is multidimensional in nature and widely affected by socio-cultural norms. Present work aimed to search the extent of gender isonomy in the form competency, interest, domestic chores and domestic violence among collegians. Sixteen itemscale was used. Total sample was comprised of 110 students (58 female & 52 Male). Their age range was 18-20 years. Mean, SD and item wise percentage was computed. A Chi square test was used to test the significance of difference in the responses of boys and girls.

Results revealed that in capacity and interest domain there are strong belief. 73.52% boys and only 20.63% girls have accepted that 'boys are naturally better at maths and science than girls' whereas35.29% boys and 84.48% girls agreed that 'girls are naturally better at social studies and language than boys'. Data supported the hypothesis.

Second domain was related to domestic chores. In case of 'changing diapers, giving a bath, and feeding kids is the mother's responsibility', 44.11% boys and 56.89% girls answered affirmatively. However, the difference was non significant. The hypothesis was partially accepted.

Last domain was related to domestic violence. Interestingly in case of all six items the percentage to 'yes' response was at lower end. This shows that still there is a trend that domestic violence should not be discussed openly. The hypothesis was not accepted.

Key words: Capacity domain, domestic chores, domestic violence.

Introduction: In ancient times, Indian women were in the position of high esteem and were treated in the form of 'Mata' or 'Devi'. However, the practice of polygamy deteriorated the position of women and in the medieval period, certain practices came into force like purdha, dowry and sati system. With the passage of time the status of women has lowered. The situation became more pathetic in two decades. In 1980s sex selection phenomenon and in 1990s due to urbanization lot of families have moved to cities to look for work. People became much wealthier but at the same time there is pressure to produce sons as an heir. This has worsened the women's position in our society (Jha& Nagar, 2015).

Gender is a common term generally refers to the socially constructed roles, activities and attributes that a particular society considers appropriate for men and women (Shastri, 2014). Traditionally in every society, a female role is to look after house, children, family relatives and on the other hand men are made to earn a bread and hardship. Such type of societal outlook makes women weaker and deprived from basic things. The distinct role and behavior may give rise to gender discrimination which is a prejudicial treatment of an individual or group due to gender.

The process of gendering and gender discrimination starts right from the birth of a child. Birth of a male child is celebrated with fun just like a festival; whereas birth of a female child is considered as a burden, which they have to carry till her marriage. In a nation-wide study Anandlakshmy (1994)has noted, "the birth of a girl child tends to be greeted with devilishjoy, if not grief and that she continues to be treated within the family and outside as a second-class citizen" (p. 43). In Maharashtra, especially the in villages in Western Maharashtra, there are some girls named as 'Nakusa' (unwanted), 'Dagadi' and 'Dhondi', which means 'stone' (Times of India, 4th Sept, 2011).Such nomenclature shows how girl is treated as an unwanted child.

Gender discrimination is observed in various forms like competency, interest, domestic chores etc. In every society there are certain gender based beliefs and stereotypes. It is believed that girls are weak in mathematics and in some cognitive as well as physical abilities. Boys have higher competence beliefs than girls for Maths and sport and girls have higher competence beliefs for language, reading and social activities. These differences increase after puberty (Eccleset al 1993). Even domestic responsibilities and roles are also fixed as per gender.

Gender-based violence (GBV) is one of the burning issues discussed and studied throughout the world. In our constitution there are several legal provisions for men and women (eg. article 14, article 15(3), article 16, and article 39(d)). In 2005, for the protection of women from

different types of violence. Domestic Violence Act, 2005 passed by parliament. However, only making laws and enforcing them is not enough but there is a need of social awakening and change in the attitude of masses. According to United Nations Development Program Human Development Report-2013 (cf. Jha& Nagar, 2015), India ranks 132 out of 187 countries on gender inequality index, lowers than Pakistan. Report states that all countries in South Asia, with the exception of Afghanistan, were a better place for women than India. Considering these realities this study was aimed to search the extent of gender isonomy in the form competency, interest, domestic chores and domestic violence among collegians.

Aim: Main aim of the study was to search the extent of gender isonomy with respect to competency, interest, domestic chores and domestic violence among collegians.

Objectives: Major objectives of the study are...

- To study gender differences in capacity and interest domain of the collegians.
- To study the attitude of collegians towards domestic chores and daily life responsibilities.
- To study the attitude of the collegians towards domestic violence.

Hypotheses: Assuming other factors as constant, it is hypothesized that...

- There willbe a significant difference in the attitude of boys and girls towards capacity and interest belief.
- There willbe a significant difference among boys and girls regarding attitude towards domestic responsibilities.
- There will a significant gender difference in the attitude towards domestic violence.

Methodology:

Sample: Initially, the sample was comprised of 135 under graduate students from Social Science and Science streams. After scrutiny it was found fifteen respondents have not attempted the scale properly. Hence, effective sample was comprised of 110 students (58 female & 52 Male). Their age range was 18-20 years. The scale was administered in group form, containing 25-30 students in each.

Variables: Gender is treated as independent variable. Belief towards capacity, domestic chores and violence were considered as dependent variables.

Operational definitions: Capacity and interest domain: In every society there are certain gender specific stereotypes. Girls are assumed to be better in language and arts; whereas boys are good in mathematics and sports. In the present work the respondent's belief towards maths, science, sports and computer were treated as capacity and interest domain.

Domestic chores and daily life domain: It involves attitudes towards gender specific domestic responsibilities assigned to a mother and a father.

Violence domain: It involves certain beliefs towards domestic violence like violence against wife is a private matter and it should be tolerated by her to keep family together.

Tool used for data collection: Gender Equitable Men (GEM) Scale by Geeta Nanda (2011) was used. Items related to Domestic chores and daily life and violence were incorporated. Capacity and interest related items were added separately.

Statistical Treatment: First Mean, Standard Deviation and item wise percentage were computed. Then the data were treated by Chi Square Test of significance.

Delimitations: The study is based on Under Graduate students only. The tool used for data collection was English version. Only single independent factor, i.e. gender was incorporated.

Findings, Interpretation and Discussion: Throughout the world, the culture what so ever it may be, societyis dominated by the males. Activities or duties outside the home are performed by males while household activities are to be carried out by females. Males have better opportunities of receiving different types of experiential interactions through which they could develop their potentialities. Experiential field of the females is limited; their interactions with different kinds of environments are also restricted. Obviously, they could not get more opportunities to develop different kinds of cognitive abilities. Even though the scenario in India had changed radically, yet the functions and duties of males and females are gender specific. This has led to develop specific beliefs and stereotypes towards capacity, domestic responsibilities and domestic violence.

Table 1: Mean, SD and Chi Square values obtained on three domains

	Male				Female			
Domain	D1	D2	D3		Domain	D1	D2	D3
Mean	3.64	2.67	2.64		Mean	2.58	2.29	2.96
SD	0.93	1.04	1.3		SD	0.94	1.14	1.35
Chi Square Value	.02, df = 2, p>.05				Chi Square Value	.35df = 2, p>.05		

Chi Square Value.001df = 1, p<.05

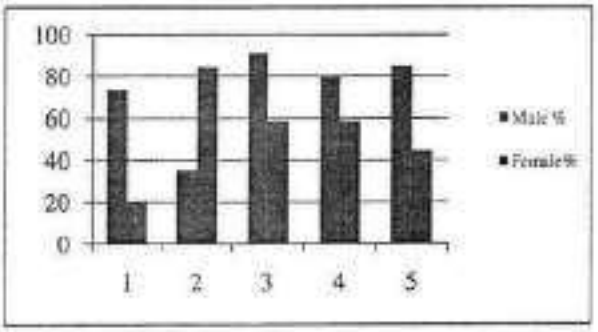
Figures depicted in table no. 1 are Mean, SD and Chi square values obtained by male and female students on three domains, namely capacity and interest (D1), domestic chores and daily life (D2) and domestic violence (D3). Careful observation of the above table shows that male respondents have obtained highest Mean score on capacity and interest domain, whereas in remaining areas male and female have obtained more or less similar

scores. It means that on the basis of sub scale scores views of the respondents are almost similar. For further treatment the data were treated by Chi square test of significance. Domain wise obtained values are .02 and .35 for boys and girls, respectively. These values are non significant (df = 2, p> .05). Even male female difference is also non significant(df = 1 .001, p> .05). It means that the responses of boys and girls are almost similar. And whatever the differences in opinion occurred, they are attributed to the factor of chance only.

For more interpretation the data were treated by domain-item wise percentage and Chi square test of significance.This is the major concern of this study. These values are depicted in table no. 2, 3, and 4.

Table 2: Item wise percentage and Chi square values obtained on Capacity and Interest Domain.

Item No.	1	2	3	4	5
Male %	73.52	35.29	91.17	79.41	85.29
Female%	20.68	84.48	58.62	58.62	44.82
Chi Square Values	29.63 **	20.19 **	7.07 **	3.13	12.58 **



In capacity and interest domain, item no. 1 stands for 'boys are naturally better at maths and science than girls'. It was found that 73.52% boys and only 20.63% girls have answered this statement affirmatively and the difference is significant (29.63**, df = 1, p<.01). This shows that there is a firm belief that maths and science are meant for boys.

Second statement was 'girls are naturally better at english, social studies and language than boys'. In this case 35.29% boys and 84.48% girls have answered affirmatively. The difference between these two groups is significant (20.19**, df = 1, p<.01).

Third statement was 'boys are naturally better at most sports'. Here 91.17% boys and 58.62% girls have answered 'yes'. The difference is significant (7.07**,df = 1, p<.01).

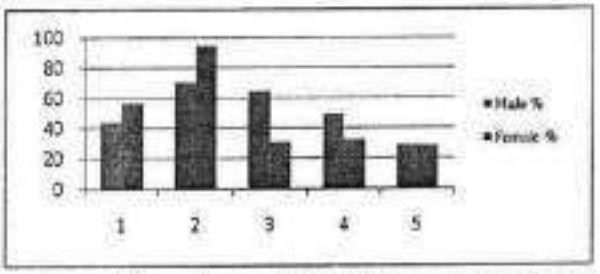
Fourth item was 'boys need sports activities for their psychological development more than girls do'. Here 79.41% boys and 58.62% girls have answered 'yes'. Though there is a difference in the opinion, but it is non significant (3.13,df = 1, p>.05).

Last statement in this domain was 'boys are naturally better at learning to use computers'. In this case 85.29% boys and 44.82% girls have replied positively. The difference is significant (12.58**, df = 1, p<.01).

The first hypothesis was related to capacity and interest domain. It was hypothesized that'there will be a significant difference in the attitude of boys and girls towards capacity and interest belief'.The hypothesis was strongly supported by the data. Referring to item no. 1, 2, 3 and 5 the difference is significant. Subject related beliefs are highly favorable to boys. Even with respect to item no. 4 the responses are more favorable to boys but the difference is non significant. This is mainly because in our society since childhood boys are prepared and educated to have a good profession which is believed to be possible by offering maths, science and computer. Whereas girls are trained for domestic responsibilities and low capacity jobs hence they are forced to offer social science and language. Secondly, masculinity meant for boys and therefore, they are inspired to have games and sports. This distinction is caused due to the parents, teachers and social attitude. Parents and teachers give boys more attention and instructions than girls (yet boys get lower grades than girls, Board and University examinations show the same trend). This results in lower self-esteem of girls (Santrock, J. W., 2007). All these findings and trends show that there are several gender specific differences in cognitive abilities and academic achievement. However, socio-cultural variables along with personality dispositions decide the extent and severity of such differences.

Table 3: Item wise percentage and Chi square values obtained on Domestic chores and daily life domain.

	1	2	3	4	5
Male %	44.11	70.58	64.7	50	29.41
Female %	56.89	94.82	31.03	32.75	29.31
Chi Square Values	0.65	3.55	11.85 **	3.6	0.00001



Second dependent variable in this study was belief related domestic chores and daily life domain. Item no. 1 was 'changing diapers, giving a bath, and feeding kids is

the mother's responsibility.' In this case 44.11% boys agreed that it is mother's responsibility whereas more number of girls (56.89) girls answered positively. Nevertheless, boys are also accepting that it is their responsibility, though % of response is rather low. The Chi Square value is non significant (.65,df = 1, p>.05). It means that though there is a difference in the opinion of boys and girls, but it is not very large, it is occurred by the factor of chance only. In other words regarding baby care boys and girls have accepted that baby care is a combine responsibility. It is a changing outlook of the youngster.

Next item was 'a woman's role is taking care of her home and family.' 70.58% boys and 94.82 % girls are agreed with this statement. Percentage of boys and girls is at higher end. This shows the traditional outlook of our society that a women's role is bound to household activities. Even girls are accepting this reality. However, obtained Chi square value is non significant (3.55,df = 1, p>.05) which indicates that the difference in opinion can be attributed to chance factor, otherwise regarding women's role the views of boys and girls are similar.

Third statement was 'the husband should decide to buy the major household items.' Here 64.70% boys and 31.03% have answered positively. Chi square value was found significant (11.85**, df = 1, p<.01). It means that regarding financial decisions still male are dominant and women has to accept it.

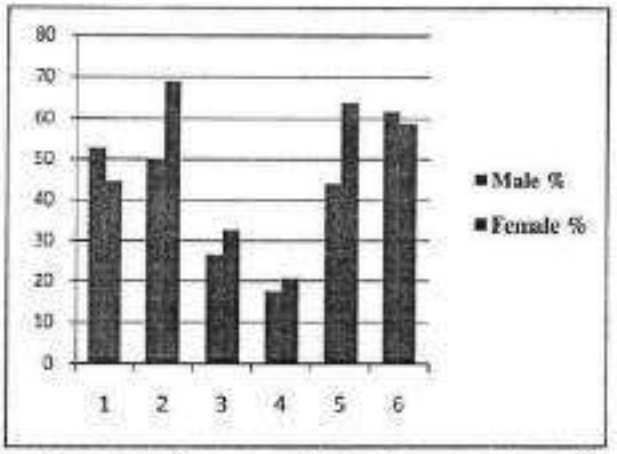
Fourth item in this domain was'a man should have the final word about decisions in his home.' 50% boys and 32.75% girls answered affirmatively. Higher percentage of boys shows male domination in decision making at home. However, Chi square value is nonsignificant (3.6, df = 1, p>.05). The difference has occurred due to chance otherwise, the opinions of boys and girls are similar.

Last item in this domain was 'a woman should obey her husband in all things.' Referring to this statement it was observed that gender wise percentage is almost similar (Boys= 29.41% and girls = 29.31%). This lower percentage shows changing attitude of the youngsters. The Chi square value is also non significant (.0000), df = 1, p>.05).

Second hypothesis in this study was related to domestic responsibilities. It was hypothesized that'there will be a significant difference among boys and girls regarding attitude towards domestic responsibilities'. This hypothesis was partially supported by the data. Only in terms of item no. 3 supportive evidences were observed; whereas in remaining items (1, 2, 4 and 5) the differences were non significant. This shows changing outlook of the youngsters. But careful observation indicates that still there is a difference in the attitudeof boys and girls. It is assumed that baby care is the mother's responsibility whereas financial and major domestic decisions are rest on male member of the family. This is mainly due to patriarchal nature of our society. In India, when women's role is discussed emphasis is given on reproduction, family planning and childbearing, while women's independent personality has been relatively neglected. And this is imprinted on her mind since childhood.

Table No. 4 Item wise percentage and Chi square values obtained on Domestic violence domain.

	1	2	3	4	5	6
Male %	52.94	50	26.47	17.64	44.11	61.76
Female %	44.82	68.96	32.75	20.68	63.79	58.62
Chi Square Values	0.67	3.02	0.66	0.24	3.58	0.08



Domain no. three was related to domestic violence. It was assessed with the help of six items. Item no. 1 was 'there are times when a woman deserves to be beaten.' With respect to this item,percentage of boys and girls is rather moderate (boys = 52.94%, girls = 44.82%). The Chi square value is non significant (0.67, df = 1, p>.05). Higher percentage of boys indicates that to beat a woman is natural a thing.

Item no. 2 was 'a woman should tolerate violence to keep her family together.' 50% and 68.96 % girls agreed affirmatively. The Chi square value is non significant (3.02, df = 1, p>.05). Higher percentage of girls shows that they are acceptingviolence as natural thing in domestic life.

Item no. 3 was 'it is alright for a man to beat his wife if she is unfaithful.' Here 26.47% boys and 32.75% girls answered 'yes'. The Chi square value is non significant (.66,df = 1, p>.05). This lower percentage shows that the issue of 'unfaithfulness' is not openly discussed.

Item no. 4 was 'a man can hit his wife if she won't have sex with him'. In accordance to this statement 17.64% boys and 20.68% girls answered positively. Chi square value is non significant (.24, df = 1, p>.05). This

lower percentage shows a mental set that private issues like 'sex' are not openly discussed.

Item no 5 was 'if someone insults a man, he should defend his reputation with force if he has to'. Here 44.11% boys and 63.79% girls answered positively. Chi square value is non significant (3.58, df = 1, p>.05). This higher percentage of girls shows typical Indian feminine psychology that in case of insulta woman takes an initiative to protect the reputation of her husband.

Last item was 'man using violence against his wife is a private matter that shouldn't be discussed outside'. For this statement 61.76% boys and 58.62% girls answered 'yes'. Obtained Chi square value is non significant (0.08, df = 1, p> .05).Higher percentage shows that boys and girls are accepting domestic violence but they do not want to discuss this issue openly, hence the difference is non significant.

Third hypothesis in this study was related to domestic violence. It was hypothesized that 'there will a significant gender difference in the attitude towards domestic violence'. The data did not support this hypothesis. In case of all six items obtained Chi square values were non significant. This shows that whatever the differences in the opinion towards domestic violence they are attributed to chance factor, otherwise the opinions of boys and girls are more or less similar. Another interesting thing observed in this domain was that percentage of boys and girls with respect to all six items were rather low as compared to first two domain. This shows that the issue of domestic violence still is not openly accepted. The reasons are deep rooted in socializaiion process because we treat boys as masculine and prepare him for outside world. On the contrary, girls are prepared for domestic responsibilities and taught to develop tolerance.Generally psychological consequeaces of gender based violence (GBV) on women and children living in povertyare openly discussed. However, in affluent families, due to social prestige, the incidents of GBV are repressed easily. The problems of women who face domestic violence from husband and in-laws have not been openly reported and discussed in society because the system considers these acts of violence as acceptable Due to religious, cultural and social bindings they are forced to remain in the vicious circle of religious and cultural birdings(**Shubha Kumar, et al. 2005**).

Conclusions: On the basis of statistical findings and test of significance it is concluded that...

1. In case of capacity and interest there are firm beliefs. Boys are considered as superior in maths, science, computer and sports, whereas social studies and language are considered as suitable subjects for girls.
2. In domestic chores still male-female roles are fixed, however, the difference was not significant. But regarding financial decisions still male are dominant and his words are final, there is no gender isonomy.
3. Percentage regarding all six items of domestic violence is at lower end which indicate that domestic problems and violence should not be discussed openly.

Limitations: There are several limitations imposed on the study. Firstly, the sample size was small, though statistically, it was large. Secondly, the respondents were from a single college only. Therefore, findings cannot be generalized. Thirdly, only single independent variable, i.e. gender was incorporated in the study. Finally, the tool used for data collection was in English version. Inspite of utmost care, there is some possibility of misinterpretation on the part of the respondents.

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Gender Equality and Women Empowerment of India in Current Scenario

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Abstract: Gender is seen closely related to the roles and behaviour assigned to women and men based on their sexual differences. As soon as a child is born, families and society begin the process of gendering. The birth of the son is celebrated, the birth of a daughter filled with pain; sons are showered with love, respect, better food and proper health care.

Female foeticide is heinous and a process opposed to Natural Laws. Every alive being has a right to survive. So how do us negeclect girls. They are equal in status in society. None has authority to distinguish between girl and boy child. In overall comparison, women are at par with men in all arenas. There are numerous examples which also show that they have excelled at work when compared to men.

Today's age is an age of globalization. With respect to age there is need to change us and our mentality about gender inequality. Women reflected the expression of her work in every field.

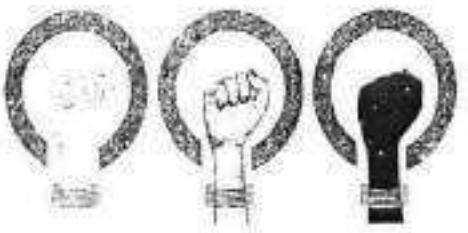
(Key Words-Culture, religion, progress, unity, efforts etc)

Introduction- Women are the backbone of society. Society never complete without women. Men and women are the two wheels of the life. There should be uniformity in both parties. But when we see the structure of Indian society, it always gives the secondary status to the women. As per the development of education, the changes have been taking place in the position of women.

India is predominately a patriarchal society has a child sex ratio of 914, according to the census of 2011,which is even lower than all over female sex ratio it decreased 1.40% during last decade. In 2001 child sex ratio was 927. The women were treated as the deity and the one, who gives birth to the men, now is struggling for survival.

Gender inequality can further be understood through the mechanisms of sexism and discrimination which is takes place in this manner as men and women are subject to prejudicial treatment on the basis of gender. Sexism occurs when men and women are framed within two dimensions of social cognition. Objective rules applied rigidly to women but leniently to men. Economical, social, psychological and cultural differences between men and women is the part of Indian society. Literacy for females stands at 65.46%, compared to 82.14% for males. Behind 1000 men there are 933 women. Means in comparison both factors are unequal. Job profile is shown the effect of gender bias. Women do not own property under their own names and usually do not have any inheritance rights to obtain a share of parental property. Carry forward of race is the name of sons only.

The bias against female in India is related to the facts that sons are called upon to provide the income. They are the ones who do most of the work in field. In this way sons are looked to as a type of insurance .This problem is also intimately tied to the institution of dowry, in which the family of a prospective bride must pay enormous sum of money to the family in which the women would live after marriage. After independence, the gender inequality in India had not been emphasized so much. The current scenario reports many cases at various parts of India. For eradication and sorting out the problems, there is need to do collective efforts and work at all the levels of society. Collective efforts, role of intellectual class and education can eradicate the gender inequality related issues in India.



Women Problems in current scenario-

Un-attraction of Female Education: Since ancient time we have been seen that generally women ignored from the education. 'Ladki to paraya dhan hoti hai' is common tendency observe among the Indians. Accordingly, much attention is paid to the education of women after

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independence. The female literacy level is also increasing steadily. It has increased from 18.7% in 1971 to 39.42% in 1991 and to 64% in 2001. In spite of this change in the trend towards literacy, some problem has cropped up.

Dowry a curse: At the time of marriage ceremony, the gift or amount given by the parents of girl is general trend in India. In later stage it became problem called dowry. Every year so many cases of dowry exposed in India. It is a very serious problem faced by Indian women and their parents.

Violence against women: Sexual exploitation, female foeticide, dowry, domestic violence etc are the common practices can see in Indian society. The rate of such problems is high in rural society. Main cause of it is that spoil mentality with old customs and traditions.

Sexual Harassment: Now days so many cases are exposing related to sexual harassment of women. Delhi gang rape and so many incidents' taking place in India. Child abuse, sexual exploitation, human trafficking, child labour etc are the various problems are present in Indian society.

Organizational problems: In working place, women face a lot of problems regarding various matters. May be some times sexual harassment and other conflicts can creates at working place. Excessive bossing, unequal shifts, unwanted demands by high authority etc are the factors responsible for women exploitation in organization.

Familiar and Social Problems: Family and society quickly takes the cognizance about women issues. The intensity and proportion of works is always more than men. In religious and cultural activities women generally ignore and put secondary place. Whatever the situation is there the women assume a responsible for that act. Also there is a tendency that women are the factories of child creation.

Marginalization and women in India



Marginalization is a individual level as well as group wise process. Marginalization of aboriginal communities is a product of colonization. In marginal groups, aboriginal communities lost their land, were forced into destitute areas, lost their sources of income, and were excluded from the labor market. This situation can see in India everywhere in society.

The full development of personality and fundamental freedoms and equal participation by women in political, social, economic and cultural life are concomitants for national development, social and family stability and growth culturally, socially and economically is important.

Suggestions-

1. Strict action and provision of punishment-Affected persons should be booked with full proof charge sheets and exemplary actions be executed on them. This strict action can be the lesion to others in society.
2. Provision of awards and incentives-The special schemes and plans should be executed and spread the awareness in society those family are having only daughters. Maharashtra government already started and that can be model for other states.
3. Government record maintaining -institutions operating USG machines should be made more accountable towards record keeping and reporting towards higher authority.Government, semi government and private hospital should be under observation.
4. Overall observation and cognizance regarding sex discrimination and gender bias various groups in society.
5. All births should be registered under the relevant Act.
6. Health staff to be made accountable for tracking all pregnancies and their outcomes.
7. Self motivated pregnant women should not be entertained for sex selective procedures, and any influence of family pressure and relatives.
8. The positive role of family education and planning with women empowerment
9. Change the structure and framework of society regarding gender inequality.
10. Emphasis on the role of NGOs, social thinkers, sociologists and social workers.

Recommendations-

1. Strict application of legal provisions.
2. Women empowerment and development.
3. Proper education for awareness and spread the message in society.
4. Dowry prohibition act should be implemented effectively.
5. Reaching the masses through religious/spiritual leaders
6. Role of media and entertainment.
7. Social awareness for changing public mind-set

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8. Strict implementation of PNDT and MTP Acts
9. Curbing quackery, sensitization of doctors, NGOS, govt. machinery, panchayat leaders.
10. Protect unborn girl child.
11. Educating/sensitizing male members of family.
12. Equal treatment, dignity and respect for girl child
13. Fight against social evils.
14. Women empowerment: to make it a reality.
15. Role of NGO's administration and Government.

Some of the plans for women implemented by Government of India-

1. Mahila cosh yojana-
2. Training and employment programme for women (TEPW)
3. Rashtriya Mahila Kosh (RMK)
4. Rajiv Gandhi Scheme for Empowerment of Adolescent Girls (RGSEAG)
5. Central Social Welfare Board (CSWB)
6. Indira Gandhi Matritva Sahyog Yojana (IGMSY)
7. Swayam Siddha yojana
8. Short Stay Home for Women and Girls (SSH)
9. Swadhar

Conclusion: Community awareness on the benefits of empowering women should be carried out in order that the empowerment may be supported by the community as whole. For the proper construction of society there is needed to give special attention on women empowerment in India. Also traditional attitude has to change regarding women. Awareness programme, education and positive role of every indivisible will help to development in women empowerment in India. Indian government is always fewer rebel and conscious about women development. Time to time different schemes and planning have been implemented for the success of women. Behind this problem, many root causes are responsible and affect on social system. Suitable social structure can be maintain with following suggestions and recommendations-

For adequate social change, development and social control, there is a need of time to eradicate this problem as early as possible and maintain the developmental tract in society.

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BASIC KNOWLEDGE AND ATTITUDE AMONG COLLEGE STUDENTS TOWARDS SNAKES IN AMRAVATI

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ABSTRACT



Snakes belongs to class reptilian, plays a vital and critical role in any ecosystem as a prey as well as a predator. Due to lack of knowledge and misguidance snakes can be categorized under threatened species. Students and youths are important part of any society. They play an important role in framing the society. Their perspective towards environmental education is very crucial for conservation and preservation of any flora and fauna especially the snakes. A cross-sectional study was conducted among the under graduate students of Vidya Bharati Mahavidyalaya College Amravati, Maharashtra during the period of January 2018 to know their knowledge of snakes and attitude toward snakes. In the present study majority of the participants had basic knowledge about venomous snake, snake bite and their conservation and they show a positive attitude towards snake

KEYWORDS : *Snakes, Conservation, Venomous, Attitude, Amravati.*

INTRODUCTION:

Snakes belongs to class reptilian, plays a vital and critical role in any ecosystem as a prey as well as a predator. Humans in various cultures have feared snakes, provoking an aversion and persecution that hinders conservation efforts for these reptiles (Alves *et al.*, 2014). Snakes may be keystone predators especially in agricultural and grassland ecosystems, because snakes are effective predators of rodents and they indeed likely help to regulate food webs in important ways that other predators cannot (Mills *et al.*, 1993, and Kotliar *et al.*, 1999). Snakes are also excellent ecological indicators due to their sensitivity to temperature and climate change (Beaupre and Douglas, 2009). Therefore, disappearance of snakes can have negative impacts on interactions in ecosystems and may affect predator–prey population dynamics in different ways. Snakes were the fifth most dislike fauna in animal kingdom due to fear (Kellert, 1980). The lack of knowledge is dangerous for both human and snakes because when people get frightened they tend to make irrational decisions that often results in snake death or increased risk of snake bite, this also became a human snakes conflict (Chrstoffel, 2007).

In India most of the people have lack of proper knowledge about snakes. They have learned about snakes more by traditional knowledge, through movies than factual knowledge from books and literatures.

Snakes provide a variety of ecosystem services to human but their populations are decreasing globally and locally. There can be both positive and negative attitude towards snakes from human. Due to lack of knowledge and misguidance snakes can be categorized under threatened species. We should ensure that future conservation planners and policymakers, who determine the future of snakes, express positive

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attitude towards snakes or demonstrate a capacity to view snakes objectively (Calderon Arrieta 2017). In order to ensure the need of conservation of snakes which directly or indirectly affects the health of an ecosystem, we need to develop an informed population to understand the need and importance of snakes in an ecosystem.

Students and youths are important part of any society. They play an important role in framing the society. Their perspective towards environmental education is very crucial for conservation and preservation of any flora and fauna especially the snakes. Through Environmental Education, students can be agents of change as well as future decision makers on sustainable use of biodiversity. Such education will make them become active and responsible environmental to value our biodiversity.

The present study was undertaken to assess the knowledge, current attitude and myths about snakes in undergraduate students of Vidyabharti Mahavidyalaya College Amravati (M.H).

MATERIAL AND METHODS

Prior the study, permission was taken from the Principal Vidyabharti Mahavidyalaya College. This cross-sectional study was conducted among the under graduate students of Vidya Bharati Mahavidyalaya College Amravati, Maharashtra during the period of January 2018. Simple random survey method was adopted. Questionnaire was used to interview the study participants and various in depth questions regarding knowledge, current attitude and myths about snakes were asked. Three pictures of venomous snakes were shown to study participants for identification based questions. Statistical analysis was done by using Microsoft Excel and the results were calculated in percentages.

RESULTS

Out of the total 200 study participants, 88 (44%) were males and 112 (56%) were females. To assess the knowledge regarding species identification and venomosity of snakes, four images of locally prevalent venomous and non-venomous snakes were shown to the respondents. Among the 3 venomous snake 175 (87.5%) of the study participants correctly identified Indian spectacled Cobra, 37 (18.5%) identified common Krait correctly, 30 (15%) study participants identified Russell viper correctly and 22 (11%) study participants were not able to identify any one of three venomous snake.

From the venomous snakes 167(83.5%) study participants correctly identified Indian Spectacled Cobra as venomous and 17 (8.5%) identified viper correctly as venomous and 5 (2.5%) identified krait correctly as venomous.

When asked about measures taken upon encountering a snake near human settlement, maximum number of respondents 147 (73.5%) opined calling a forest official or a snake friend, followed by leaving the snake as it is 39 (19.5%) and kill 16 (8%).

When asked about the immediate measures taken by the study participants if a person is bitten by a snake, 136 (68%) of the study participants stated that they would prefer to take the victim to the nearest health facility while 64 (32%) of the study participants stated that they would prefer first aid measure. 156 (78%) of the study participants knew that medical treatment is available for snakebite while 130 (68.5%) participants knew about antivenom. Nearly 191 (95.5%) of the total study participant opted myth instead of fact for the question that snake's drinks milk and 196 (98%) opted myth for the question that snakes seek revenge when somebody harms them.

178 (89%) study participants know about that snakes are protected under wild life protection act 1972 but none of the students know about that under which schedule of wild life protection act they are protected. 147 (73.5%) of student participants opined that if they found someone trafficking snake they will inform the forest official and 53(26.5%) will ignore it.

100% of the study participants believed that snakes are very important for our ecosystem and removal of snake from any area can have direct or indirect negative impact on the health of that ecosystem. When asked about the knowledge they acquired about snakes, 78(39%) study participants opted knowledge

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from books and lectures, 87 (43.5%) opted from movies and 35 (17.5%) opted traditional knowledge and folklore knowledge.

DISCUSSION

In the present study 175 (87.5%) of the total study participants could identify the Spectacled Cobra correctly and 167 (83.5%) correctly identified it to be venomous which was significantly more as compared to other snakes. This could be due to the fact that Spectacled Cobra has a prominent hood which makes them easily identifiable and also they are mentioned and portrayed in many Indian religious literatures and also in many Indian movies and daily soaps. Similar results have been found in the studies done by Duminda *et al.*, (2014) in Sri Lanka. According to study done by Pandey (2015) in Nepal, 95% study participants were aware that Common spectacled Cobra is venomous. Alves *et al.*, (2014) assumed that the cultural beliefs associated with snakes might be related with the fear of snakes that they found in their primary-education student sample size.

One of the major positive findings in our study was that 156 (78%) of the participants knew about medical treatment being available for snake bite which was quite similar to the study done by Pandey *et al.*, (2016).

It was noted that 136 (68%) study participants opted that they will rush to the nearest hospital if someone is bitten by Snake followed by first aid measures 64 (32%). Also, it was wonderful to know that in the present study all participants would prefer going to hospital than considering a traditional healer as a treatment option after snake bite, this finding was similar to the study done by Pandey *et al.*, (2016). While in other similar studies 86% of snakebite victims in Bangladesh, 75% in Pakistan, and 61% in Maharashtra, India still visit traditional healers (Inamdar *et al.*, 2007 and Chandio *et al.*, 2000).

CONCLUSION

In the present study majority of the participants had basic knowledge about venomous snake, snake bite, their conservation and myths related to snake. Majority of the students were in the favor that snakes should be protected and conserved, which shows a positive attitude. Most correctly identified venomous Snakes were Spectacled Cobra followed by Russell's viper and common krait respectively. All the participants knew that there is medical treatment available for snakebite, although majority of the participants were not aware about antivenom. Also most of the participants considered the concept of snake's drinks milk and take revenge if they are harmed as a myth as they were aware of the fact that snakes are strictly carnivores. Most of the participants believed that Snakes are important part of the ecosystem and also know the importance of snake to the ecology and ecosystem and also they are protected under Indian wild life protection Act 1972 but they were not aware about the schedule of wild life protection Act 1972 under which they are protected.

Students play an important role in the society therefore their proper knowledge is important for the conservation of any wildlife. Therefore awareness camps, seminars and workshop on basic knowledge about snake identification, snakebite prevention, conservation strategies of snakes and clearing misconceptions should be held in schools, colleges, universities several other institutions. Proper first aid measures for snakebites should be demonstrated through various outreach activities, workshop and increased awareness about snake and snakebite identification among students and general population should also be done for conservation of the snake fauna.

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ANURAN INVENTORY OF VIDARBHA REGION, MAHARASHTRA

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ABSTRACT

The use of some drugs during pregnancy may causes abnormalities to the embryo. Sometime the drug also effect to the new born if the drug transferred through lactation. The present experiment used the Clarias batrachus as model to check the effect of norfloxacin on hatching rate of eggs. The 10, 20, 50, 100 µg/ml concentrations of drug were used. No significant mortality or malformations were observed in fish embryos. Hatching was stared from 36 hr. In control group, 90% hatching rate was observed. Lowest hatching rate was observed in highest concentration (100µg/ml). Present investigation suggests the possibility that high dosage can harm the unborn baby or new born babies, if the mothers use norfloxacin.

Key words: Anuran fauna, diversity, Maharashtra, Vidarbha.

INTRODUCTION

The diversity of flora and fauna on the earth and its genesis has long been a source of questionable curiosity (Joshi *et al.*, 2015). The study of biodiversity includes both the inherent and anthropocentric principles allied with it. The importance of these incredible biological factors is renowned in relation of the ecosystem services (Baumgartner 2007). Biodiversity is the foundation for maintaining the ecosystem and the operative facets of the species that offers many goods and services to for human well being. Examinations of species diversity of a region facilitate the evaluation of potential serviceable role of the species. In any ecosystems, observing the species diversity can be used as a contrivance to minimize the mismanagement and contamination in urbanized, industrial, rural, and managed areas by human (Wilson 1997). Extending this view, the species diversity review in any ecosystems is essential to understand the effect of anthropocentric development on the integrity and sustenance of ecosystem.

The inventories of species diversity are immense resource that provides recent and previous information on their topographic distribution. The elementary species occurrence data have various applications. Species inventories that contain such elementary and collective species-occurrence data, plays a fundamental role in providing information on the status of species transpire in different spatial scales. These inventories have been used for taxonomic and biogeographic studies as well for conservation planning, reserve selection, climate change studies, agriculture, forestry and fishery, and species translocation studies (Chapman 2005a). The meticulousness of the taxonomic and spatial information is valuable reflection for determination of data quality and validation of the species occurrence data. Hence the significance of the data excellence in the inventory of Indian fauna hardly needs emphasis (Chapman 2005b).

The anuran diversity has been focused in many studies explaining their dominance in the terrestrial and aquatic ecosystems and also the provision of ecosystem services (Joshi *et al.*, 2014). In this perspective, the present communication is part of an effort to verify the validity of anuran species based on a review of the earlier checklists published over the past two decades. Finally, a comprehensive anuran inventory of Vidarbha region of Maharashtra has been provided along with source literature.

MATERIALS AND METHODS

Study area: Vidarbha is one of the most diversified Regions in Maharashtra State of India, with respect to biodiversity. Its healthy climate, mountainous terrain, rugged configuration and sudden fall in elevation are phenomenal. It is located between 20.9374° north and 77.7796° east. It has a total area of 97,321 square

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kilometers. The climatic condition of this district is characterized by a hot summer, well-distributed rainfall during the south-west monsoon season and generally dry weather during rest of the year. The cold season is from December to February. The average annual rainfall in the district is 795.7 mm. During summer the mean daily maximum temperature in summer was 44.2° C to minimum as 26.7° C while it decreased toward winter with the mean daily maximum temperature was 27.8° C and minimum 14.9° C.

Primary inventory: The present inventory of fauna has been compiled primarily from articles and technical reports published in scientific journals. However reports in newsletters, unpublished reports, personal field observations and personal communications with other herpetologists and field workers have also been taken into account. Information on species distribution and taxonomy has been compiled from literature published until July 2017.

Taxonomic Treatise: The list provided, is at the species level and the taxonomy follows, Daniel (2002) and Ahmed *et al.*, (2009).

Validity of species listed: Based on the distributional records available, the validity of the species listed in the earlier checklists of India, particularly Maharashtra and neighborhood published in the past two decades has been reviewed.

RESULTS AND DISCUSSION

The present comprehensive inventory is based on a review of the earlier checklists of the anuran fauna published over a past decade. The review cleared the presence of following twelve species belongings to Five families (Table 1).

Table 1: Anuran inventory of Vidarbha region, Maharashtra, India

Sr.	Family	Species	Common name
1.	Bufonidae	*Duttaphrynus melanostictus* (Schneider,1799)	Asian common toad
2.		*Duttaphrynus stomaticus* (Lutken, 1864)	Indian marbled toad
3.	Dicroglossidae	*Euphlyctis cyanophlyctis* (Schneider, 1799)	Indian skipper frog
4.		*Euphlyctis hexadctylus* (Lesson, 1834)	Indian green frog
5.		*Fejervarya limnocharis* (Gravenhost, 1829)	Asian grass frog
6.		*Hoplobatrachus tigerinus* (Daudin,1803)	Indian bullfrog
7.		*Hoplobatrachus crassus* (Jerdon,1853)	Jerdon's bullfrog
8.		*Sphaerotheca breviceps* (Schneider, 1799)	Indian burrowing frog
9.	Microhylidae	*Microhyla ornata* (Dumeril and Bibron, 1841)	Asian ornate frog
10.		*Kaloula taprobanica* (Parker 1934)	Asian painted frog
11.	Ranidae	*Hylarana malabarica* (Tshudi, 1838)	Fungoid frog
12.	Rhacophoridae	*Polypedatus maculatus* (Gray, 1830)	Indian tree frog

Vidarbha is most diversified region with lush green deciduous forests through large protected areas which are home to variety of flora and fauna. It has approximately 37,251 km^2 forest cover. Vidarbha also has many popular wildlife sanctuaries and parks *viz.* Melghat in Amaravti, Amba-barwa and Nalganga in Buldhana, Tadoba-Andhari in Chandrapur, Nagzira and Navegaon Bandh in Gondia, etc. The region is represented with rich faunal diversity. The utility of species as indicators of environmental conditions is a basis for preparation of present inventory.

The present inventory of anuran fauna of Vidarbha region is based on available locality records by providing relevant source literature on specimens that would be ensuring its quality. Because, the accurate and precise quality data on species occurrences are imperative for the assessment of conservation status and drawing management considerations hence used for further research purposes such as predictions on species distributions, habitat suitability, and threat assessments etc.

Many researchers from Vidarbha region had given their valuable contribution in development of anuran studies. The monumental works on anuran fauna of Vidarbha region mainly includes the Dhande and Khandare (2013), Pandharikar *et al.* (2015), Sawarkar and Kasambe (2009), Wagh *et al.* (2017) to name a few.

According to Joshi *et al.* (2017), the fauna is always threatened by anthropogenic and environmental factors. The diverse habitats of the

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Vidarbha Region are rapidly changing due to new irrigation projects and industrialization. Forest areas are being de-notified for implementing development projects such as mining, industry, communication and tourism. This has resulted in alternating climate as well shrinkage, fragmentation, degradation and destruction of natural habitats. Road accidental killing on highways across wildlife refuges are an intrusion and affect the wildlife and its habitats adversely. Misconceptions and fear about these species especially about snakes are also threatening this important creature of the ecosystem.

In parity with the anuran species observed in Vidarbha region, Maharashtra, India, it may be assumed that the species carry out diverse functional roles for the sustenance of the ecosystems. The availability of the green space and the heterogeneity of the habitats in terms of the available vegetation and allied factors that render stability to the population and species assemblages in the landscapes are possibly important contributors to the observed variations in the saurian species observed in the present study. The present diversity study is confined to limited area and selected habitats. There are, in future, chance of more species being reported because of few pockets and habitats in the studied area required more extensive exploration.

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नैराकरण / उपाय / सल्ला :-

- तणाव, चिंता, नैराश्य यातून सुटका होण्यासाठी योगा आणि प्राणायाम यांचा उपयोग नियमित करावा.
- नैराश्य दूर करण्यासाठी परिस्थितीशी जुळवून घेणे व समस्येचे भावनीक समायोजन करण्यास शिकणे.
- जीवनशैली साधी व सरळ ठेवणे.
- बालमनावर कुटुंब व शाळेमधून सकारात्मक स्वसंकल्पनेची बीजे रुजविणे.
- स्वत:ची क्षमस्थाने आणि उणीवा ओळखून त्याचा स्वीकार करणे.
- नकारात्मक विचार, गैरसमजुती, व्यसनाधीनता यापासून दूर राहणे. रागावर नियंत्रण ठेवावे.
- विनोदबुध्दी, छंद जोपासणे, मैत्रीपूर्ण नातेसंबध ठेवणे, सारेसा जीवनसाथी शोधणे, आपले काम प्रामाणिकपणे करणे व आनंदी राहणे.
- स्वआदरभाव राखून स्वत:चा व इतरांचा मानसन्मान करणे.
- अपमान सहन करायला शिकले पाहीजे.
- सकारात्मक प्रेरणा देणाऱ्या महामानवांच्या जीवनावरील पुस्तकाचे वाचन करावे. जसे छत्रपती शिवाजी महाराज, महात्मा ज्योतीराव फुले, सावित्रीबाई फुले, डॉ. बाबासाहेब आंबेडकर, डॉ. ए.पी.जे. अब्दुल कलाम, बाबा आमटे इ.
- स्वत:चा आत्मविश्वास वाढवावा, मी माझे मानसिक आरोग्य उत्तम ठेऊन आनंदाने आयुष्य जगू शकतो असे स्वत:ला सुचवित राहावे.
- सकारात्मक विचार देणाऱ्या चित्रपट , टी.व्ही. मालिका पाहाव्या.

ताणतणाव, चिंता व नैराश्य यावर मात करुन सुखी व आनंदी जीवन जगण्यासाठी प्रत्येकांनी प्रयत्न करावा व सकारात्मक विचारधारेचा अंगीकार करावा.

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विदर्भातील सार्वत्रिक लोकसभा निवडणूक २०१४ : एक दृष्टिक्षेप

नितीन वसंतराव खोब्रागडे
विद्याभारती महाविद्यालय, कॅम्प, अमरावती

(17)

भारतीय लोकशाही ही एक सर्वोत्तम व्यवस्था असून आदर्शांच्या स्वरुपात सर्वमान्य झाली आहे. लोकशाहीत चालू वर्तमानकाळाचा आवाज असल्यामुळे जनतेकडुन नैतिक समर्थन प्राप्त झाले आहे. लोकशाही व्यवस्थेमध्ये निवडणूका ह्या राजकीय इच्छा आकांक्षेची अद्वितीय माध्यम असल्यामुळे आधुनिक युगात विशिष्ट भुप्रदेश निश्चित करुन प्रतिनिधीद्वारे लोकशाही निवडणूकीच्या माध्यमातून कियान्वित केली जाते.

जनतेच्या भावना लक्षात घेवून राजकीय व्यवहाराची समीकरणे मांडली जातात. ज्यामध्ये लोकशाही यशस्वितेकरीता जनतेकडुन निवडून दिलेला प्रतिनिधी हा लोकांच्या माठी योजना, आशा, आकांक्षा पूर्ण करण्यासाठी राजकीय लोकशाहीचं अस्तित्व टिकविण्यासाठी स्विकृत मार्गाने लोकशाहीचा अवलंब करीत असतो. त्याअनुषंगाने आपण विदर्भातील निवडणूक 2014 चा विचार करुन भारतीय राजकीय लोकशाही मुल्यव्यवस्थेत भारतीय इतिहासाचे पाळेमुळे रुजली आहेत का? असतील तर त्याचा विदर्भावर काय परिणाम होतो, ते जाणून घेण्याकरीता आदर्श लोकशाहीचा वापर करुन विदर्भातील निवडणूक यशस्वी झाली आहे का? त्याचे उत्तर शोधण्याचा प्रयत्न केला जात आहे.

विदर्भातील सोळावी लोकसभा निवडणूकीची पार्श्वभूमी लक्षात घेतांना विदर्भाचे एकुण क्षेत्रफळ 97,321 चौ.कि.मी. असून त्याची लोकसंख्या 23003,179 इतकी आहे. भारतातील राज्यांमध्ये एक प्रमुख राज्य असलेल्या महाराष्ट्र राज्यामध्ये एकुण 35 जिल्हे व सहा प्रशासकीय विभाग आहेत. त्यापैकी नागपूर महसूल विभाग व अमरावती महसूल विभागाचा प्रामुख्याने विदर्भ प्रांतामध्ये समावेश होतो. विदर्भामध्ये असलेला अमरावती महसूल विभाग हा 'पश्चिम विदर्भ' नावाने परिचीत आहे, तर नागपूर महसूल विभाग हा पूर्व विदर्भ या नावाने नावरुपास आहे. अमरावती महसूल विभागामध्ये अनुक्रमे अमरावती, अकोला, यवतमाळ, बुलढाणा व वाशिम या जिल्ह्यांचा समावेश होतो. तर नागपूर विभागामध्ये प्रामुख्याने नागपूर, वर्धा, भंडारा, गोंदिया, गडचिरोली व चंद्रपूर या जिल्ह्यांचा समावेश होतो. एका अभ्यासिकेनुसार या दक्षिण पठारातील एका भूभागावर राजश्री यादवाचा पुत्र विदर्भ याने विदर्भ नगरीची स्थापना केली, या नगरीला राजधानी बनवून विदर्भाने समोवतालच्या भूभागावर राज्य केले, अशाप्रकारे हा भूभाग 'विदर्भ' या

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नाव्याने ओळखला जातो. विदर्भातील लोकसभा क्षेत्र 10 आहेत, तर विधानसभा क्षेत्र हे 67 आहे.

विदर्भातील जिल्हानिहाय लोकसंख्येचे विवरण पुढील तक्त्याद्वारे दर्शविता येईल.

अ.क्र	जिल्हा	स्त्री	पुरुष	एकुण
1	अमरावती	1462845	1404981	2867626
2	अकोला	966226	852391	1818617
3	वाशिम	621228	575486	1196714
4	यवतमाळ	1525593	1341864	2775457
5	बुलढाणा	1342152	1245887	2588039
6	नागपूर	2388558	2264613	4653171
7	चंद्रपूर	1120316	1073946	2194262
8	भंडारा	603471	594431	1198810
9	गोंदिया	662524	659607	1322331
10	गडचिरोली	542813	28982	1071795
11	वर्धा	665925	630232	1296157

सोळावी लोकसभा निवडणूकीमध्ये मतदारांनी 66.38 टक्के एवढे विक्रमी मतदान केले आहे. प्रचार-प्रसार माध्यमे आणि मतदारांचा नव्या उमेदवारांसबंधीचा दृष्टिकोण यांना अंतर्गत सोळावी लोकसभा निवडणूक दिसून आला आहे. त्यात प्रामुख्याने राष्ट्रीय कॉंग्रेसपक्ष आणि दुसरीकडे भारतीय जनता पार्टीने तयार करुन नविन चेहरा दिलेली मोदी लाट यांच्यातील संघर्ष प्रकर्षाने दिसतो. मोदींचा प्रभाव अधिक आणि कॉंग्रेसचे पूर्वाश्रमीचे आरोप प्रत्यारोप त्यामुळे भारतीय राष्ट्रीय कॉंग्रेस पक्षाला मतदारांनी बाजूला सारुन भाजपा व राष्ट्रीय स्वयंसेवक संघ यांना मतदारांनी सत्ताकेंद्री स्थापन केले. भविष्यात कधीही न होणारा विजय हा नरेंद्र मोदींच्या बाजूने मतदारांनी कौल दिला आहे. त्यामुळे सोळावी लोकसभा निवडणूक जात, धर्म, पंथ, पक्ष बाजुला सोडून नवोदिताना संधी देणारी ठरली.

सोळावी लोकसभा निवडणूकीमध्ये राजकीय वर्तुळामध्ये नव्याने विचार करावयाची संधी मिळाली आहे. दीर्घकाळ सत्ता असलेली राष्ट्रीय कॉंग्रेस व त्याचे सहयोगी पक्ष मिळून बनलेली संयुक्त पुरोगामी आघाडी (युपीए) यांच्या विरोधात भाजपच्या नेतृत्वाखालील राष्ट्रीय लोकशाही आघाडी (एन.डी.ए.) ला नवमतदारांनी संधी देवून त्यांना सत्तेवर विराजमान केले आहे. नरेंद्र मोदी यांचे नेतृत्व भाजपाला पर्यायाने एन.डी.ए.ला संधी देण्यास कारणीभूत ठरले.

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विदर्भातील सोळावी लोकसभा निवडणूक 2014 यांचे सैध्दांतिक विश्लेषण केले असता विदर्भातील लोकसभा मतदारसंघ व त्या दहा लोकसभा मतदारसंघातील व्यवहारवादी विश्लेषण केले असता संबंधित लोकसभा निवडणूकीत परंपरागत मुल्यव्यवस्था नाकारुन नव्या सरकारची नवी व्यवस्था हा मतदारांचा दृष्टिकोण व्यवहारवादी जरी दिसत नसला तरी एकसंध सत्ता एकाच्या हाती जास्त काल दिली तर तो पक्ष हुकूमशाहीला आव्हान करीत असते आणि ते आव्हान मतदारांनी नाकारले आहे. त्यामुळे राष्ट्रीय कॉंग्रेस पक्ष मागे पडून, नवा पक्ष, नव्या जाणीवा घेवून मतदारांना काम देवू शकतो हे येणारा काळच त्याची ग्वाही देईल असे वाटते.

संशोधन क्षेत्रामध्ये लोकशाहीच्या अंगाने विचार करताना अनेक अडथळे येतात अनेक क्षेत्रात खोट्या अफवा, व्यक्तीचे हितसबंध, जातीय हितसंबंध, धार्मिक व सामाजिक, राजकीय पक्ष आणि त्या पक्षप्रमुखाची मगतेदारी ही निवडणूक प्रक्रियेत सक्रिय होतांना दिसते, त्यामुळे कधी जातीच्या, धर्माच्या नावावर निवडणूक लढविण्याचा व प्रतिनिधी देण्याचा मानस राष्ट्रीय पक्ष करीत असतात ते सत्तेच्या दृष्टीकोणातून योग्यही आहे. बोदकवात सत्ता संघर्ष हाच लोकशाहीचा मुलाधार असल्यामुळे जनतेचा कौल लोकप्रतिनिधीला शेवटपर्यंत समजत नाही, कारण ही लोकशाही गुप्त मतदान पध्दतीची आहे.

विदर्भातील सोळावी लोकसभा निवडणूक 2014 यांचे व्यवहारवादी विश्लेषण केले असता प्रामुख्याने भौगोलिक परिस्थितीचा विचार करुन धार्मिक, सामाजिक, आर्थिक व राजकीय परिस्थिती विचारात घेवून मागील निवडणूकीचा इतिहास आणि त्याचे परिणाम आणि 2014 च्या लोकसभा निवडणूकीतील परिणाम यांचा तुलनात्मक अभ्यास केला असता विदर्भ हा राष्ट्रीय कॉंग्रेस पक्षाचा बालेकिल्ला असला तरी लोकसभा निवडणुकीत तो ढासळलेला दिसत आहे. भारतीय जनता पक्षाने प्रयत्नाची पराकाष्टा करुन विदर्भातील एकुण दहा लोकसभा मतदार संघापैकी भाजप सहा लोकसभा मतदारसंघात विजय प्राप्त केला आहे. तसेच शिवसेना व घटक पक्षाने चार लोकसभा मतदार क्षेत्र भाजपाच्या प्रभावशाली नेतृत्वाखाली प्राप्त केले आहे, आणि राष्ट्रीय कॉंग्रेस पक्षाचा दारुण पराभव करुन भारतीय जनता पक्ष प्रणीत एन.डी.ए. ला बहुमत मिळवून विजय संपादन करुन दिला आहे.

विदर्भातील सोळावी लोकसभा निवडणूक 2014 चे विश्लेषण अभ्यासिले असता लोकशाही प्रवृत्तीच्या मानवी संस्कृतीमध्ये प्रगल्भ व विकसित लोकशाही मुल्यांचा लोकमानसाने यथायोग्य वापर केलेला आहे. लोकतांत्रिक प्रणालीमध्ये सहभागी होवून जे दुर्गुण राज्यकर्त्यांमध्ये, पुढाऱ्यांमध्ये जे दिसत होते, ते बाजूलण्याचा खरा प्रयत्न मतदारांनी केला आहे. त्यात प्रामुख्याने भ्रष्टाचार, महागाई, बेरोजगारी, कुपोषण,

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आरोग्य आदि तिकाणी सरकारने निष्क्रियता दाखविल्यामुळे जागृत झालेला मतदार 66. 38 टक्के मतदार करुन नव्या मतदारांचा उत्साह दिसून आला आहे.

सोळावी लोकसभा निवडणूक 2014 मध्ये विजयी झालेले उमेदवार त्यांचे मतदारक्षेत्र, पक्ष मिळालेली मते व टक्केवारी खालीलप्रमाणे आहे.

अ. क्र.	मतदार क्षेत्र	उमेदवाराचे नाव	पक्ष	मिळालेली मते	टक्केवारी
1	अमरावती	आनंदराव अडसूळ	शिवसेना	467212	46.72
2	अकोला	संजय धोत्रे	भाजपा	456472	
3	बुलढाणा	प्रतापराव जाधव	शिवसेना	509145	52.01
4	यवतमाळ–वाशिम	भावना गवळी	शिवसेना	477905	46.27
5	नागपूर	नितिन गडकरी	भाजपा	577766	54.17
6	रामटेक	कृपाल बालाजी तुमाने	शिवसेना	519892	44.48
7	गडचिरोली–चिमूर	अशोक नेते	भाजपा	433982	52.18
8	वर्धा	रामदास तडस	भाजपा	537518	53.04
9	भंडारा–गोंदिया	नानाभाऊ पटोले	भाजपा	606129	50.62
10	चंद्रपूर	हंसराज अहिर	भाजपा	508049	45.77

वरील सर्व उमेदवार हे भाजपा तसेच भाजपाप्रणित राष्ट्रीय लोकशाही आघाडीचे विजयी उमेदवार आहेत.

प्रस्तुत शोधनिबंधामध्ये भारतीय लोकशाहीतील निवडणूक प्रक्रिया आणि मतदार व्यवहार यांचा संयुक्तपणे अभ्यास करुन काही निष्कर्ष हाती लागले आहेत. राष्ट्रीय काँग्रेस पक्ष प्रणीत (यु.पी.ए.) व भारतीय जनता पक्ष प्रणीत (एन.डी.ए.) यांमध्ये मुख्य लढत दिसून आली. रा.कॉ. पक्ष (यू.पी.ए.) या पक्षाने वर्षानुवर्ष सत्ता उपभोगूनसुध्दा लोकसभेत दारुण पराभव स्विकारावा लागला असून, साधे विरोधी पक्षनेतेपद सुध्दा टिकविता आले नाही. नरेंद्र मोदींचे विकासतंत्र, गुजरात मॉडेल, आणि प्रभावी भाषाशैली मतदारांना प्रभावित करण्यात कारणीभूत ठरली. हिंदुत्ववादी संघटना व रा.स्व.सं. च्या परिणामुळे भाजपाला स्पष्ट बहुमत मिळविण्यात मदत झाली. गांधी परिवाराचा मतदारांवरील प्रभाव कमी झाल्याचे दिसून आले. काँग्रेस पक्षाचा भ्रष्टाचार राष्ट्रीय नेतृत्वाचा अभाव प्रामुख्याने दिसून आला. प्रादेशिक पक्षांना झुगारुन मतदारांनी राष्ट्रीय पक्षाला दिलेली पसंती, नवमतदारांनी निवडणूकीमध्ये दाखविलेला उत्साह व त्यामुळे वाढलेली मतदारांची टक्केवारी भाजपला विजयश्री खेचून आणण्यास यशस्वी ठरली.

सोळावी लोकसभा निवडणूक ही लोकप्रतिनिधींचे गुणदोष याचे अध्ययन करणारी असली तरी तिचे अंतरंग तपासले असता 1991 पासून एकहाती सत्ता असलेला पक्षाला युतीचे संमिश्र सरकार आणि बहुमताचे सरकार यात मतदारांनी संयुक्त पुरोगामी आघाडीला बाजुला ठेवून भाजपाचे मोठ्या प्रमाणात उमेदवार निवडून दिले. आजपर्यंत ज्या पक्षाला अपेक्षित यश मिळाले नाही, त्यांच्या हातात एक हाती सत्ता देवून सोळावी लोकसभा निवडणूक खऱ्या अर्थाने सार्वत्रिक ठरली. तसेच नवनियुक्त प्रथमच लोकसभेत पोहचलेली व्यक्ती पंतप्रधानपदी विराजमान झाली. हे यश मोदींच्या राजकीय चातुर्यामुळे मिळाले हे नाकारता येत नाही.

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Gender Inequality in Political System - A Global Problem

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Absract: Gender inequality is a problem not only across India but also all over the world, there is a power gap between men and women. Women have less access to parliamentary and executive power. They are less educated, have fewer good jobs and are less wealthy than men. Gender inequality can be found in the patriarchal structure of the cultural background of every ethnicity, nation or people. Also all religious communities, whether Jewish, Muslim, Hindu, traditional or Christian, give more power to men than to women. We think that gender inequality is not as much of a problem in our generation as it was in our parents' and grandparents' generations. This article aims to analyze gender inequality in the political system.

Key words : Gender inequality, political system, women enpowerment

Introduction: Gender inequality leading to deprivation of power among women continues to be a political reality in India today. Women are perpetually excluded from decision-making at every step of the ladder, starting from the household to the top layer of policy making. Although the Constitution of India attempts to remove gender inequalities by interdicting discrimination based on sex and class, and enshrining fundamental rights for all citizens, women still have only *de jure* rather than *de facto* access to these rights.

There is no denying the fact that greater participation of women in the political process would be a pre-condition for their economic and social emancipation. However, even though a significantly large number of women vote in the country, yet only a few of them assume the reins of power..

Measuring Gender Inequality: To measure inequality the United Nations Development Programme (UNDP) developed two indicators: the Gender-related Development Index (GDI) and the Gender Empowerment Measure.The GDI measures (the same as the Human Development Index, HDI) life expectancy, knowledge and the quality of life. The indicators are (1) the life expectancy at birth; (2) the adult literacy rate and the combined gross enrolment ratio for primary, secondary and tertiary schools; and (3) the Gross Domestic Product (GDP) per capita in purchasing power parity (PPP).

Electoral Systems: Elections, generally to choose amongst political parties or candidates for a house of representatives, can be held in different systems. There are two main systems of representation: proportional and majoritarian representation. From a gender perspective th proportional Generally women don't participate as muc as men due to the aforementioned reasons. If the participate they use more non-conventional ways. The are more engaged in social movements and non governmental organizations than in governments parliaments or political parties. Generally the parliamen should be a mirror of the society. All groups should b represented equally.

Data Analysis and Discussion : One instrument for th empowerment of women in the government is a quot system, since aside from the aforementioned cultural economic and social and historical reasons, femal participation also depends on the electoral system. On reason for the huge gender inequality is the lack o empowerment of women which is also reflected i women's representation in parliament. Women' representation in India parliament was only 4.9%, whic is almost the lowest among its neighbors the onl exceptions being Sri Lanka and Bhutan where th representation was only 4.9%. In contrast women' representation was 13% in Myanmar, 20% each i Bangladesh and Pakistan, 23.6% in China and 29.5% i Nepal.

To remedy the low participation of women electors India in 1994 established quotas (reservations) vide th 73rd and 74th constitutional amendments to reserve 3 per cent of the seats in local governments for women. Th Women's Reservation Bill (108th amendment) has als been introduced in the national Parliament to reserve 3 per cent of the LokSabha seats for women, but the bill i yet to be passed. It is believed that though increasing th number of women in national government may no guarantee an impact on governance, a critical mass o women in power can bring about transformation i leadership

The core idea of quotas is to increase the politica participation of women or religious or ethnic or othe minorities. Quotas are an instrument against under-representation and especially they are helpful to realise critical minority instead of only a few token women i political life.

Conclusion : Equal participation of women and men i politics is an important condition for effective democracy and good governance. Apart from strengthening an enhancing the democratic system, the participation o more women in political decision-making has man positive effects on society that can help improve the live

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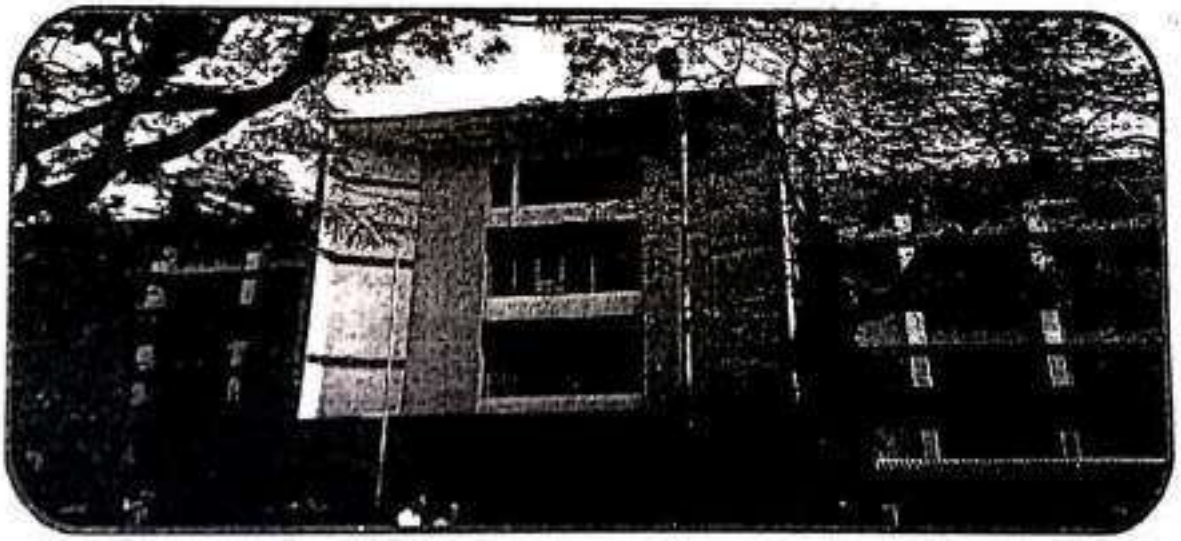
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1 RESEARCH ARTICLE

QSAR Analysis for Antioxidant Activity of Dipicolinic Acid Derivatives

Vesna Rastija[*a], Maja Molnar[b], Tena Silađi[b], and Vijay Hariram Masand[c]

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Abstract: ***Aim and Objective*****:** The aim of this study was to derive robust and reliable QSAR models for clarification and prediction of antioxidant activity of 43 heterocyclic and Schiff bases dipicolinic acid derivatives. According to the best obtained QSAR model, structures of new compounds with possible great activities should be proposed.

Methods**:** Molecular descriptors were calculated by DRAGON and ADMEWORKS from optimized molecular structure and two algorithms were used for creating the training and test sets in both set of descriptors. Regression analysis and validation of models were performed using QSARINS.

Results**:** The model with best internal validation result was obtained by DRAGON descriptors (*MATS4m, EEig03d, BELm4, Mor10p*), split by ranking method (R^2 = 0.805; R^2_{ext} = 0.833; F = 30.914). The model with best external validation result was obtained by ADMEWORKS descriptors (*NDB, MATS5p, MDEN33, TPSA*), split by random method (R^2 = 0.692; R^2_{ext} = 0.848; F = 16.818).

Conclusion**:** Important structural requirements for great antioxidant activity are: low number of double bonds in molecules; absence of tertial nitrogen atoms; higher number of hydrogen bond donors; enhanced molecular polarity; and symmetrical moiety. Two new compounds with potentially great antioxidant activities were proposed.

Keywords: QSAR, antioxidant activity, dipicolinic acid, polar surface area, hydrogen bond donors, derivatives.

1. INTRODUCTION

Dipicolinic acid (DPA) (2,6-pyridinedicarboxylic acid) is naturally inherent in the spores of *Bacillus* [1] and *Clostridium genusus* [2] that exists in the core in the form of chelates with calcium ions [3]. DPA contributes to the spore resistance to UV radiation [4], wet heat [5], and protecting spore DNA from damage [6]. DPA forms stable chelates with metal ion, and these complex compounds show a variety of biological activities, such as antimicrobial, antifungal [7-9], anticancer [10] and antioxidant activities [11].

It was discovered that a series of substituted mono- and bis-dipicolinic derivatives possessed antimicrobial and antioxidant activities [12-15]. In our previous work, we have reported synthesis of Schiff bases [16] and heterocyclic compounds [17] derived from DPA. Many of the obtained compounds exhibited significant antifungal and antioxidant activities. The above-mentioned studies identified significant chemical features for the most active compounds. In a series of synthesized mono- and bis-dipicolinic acid heterocyclic derivatives – thiosemicarbazides, triazoles, oxadiazoles and thiazolidinones, and thiosemicarbazides showed predominant antioxidant activity. Influence of different substituents is obvious, since in almost all compounds phenyl substitution results in a better 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity compared to the alkyl substitution [17]. In a series of Schiff bases derived from dipicolinic acid, compounds derived from di-hydrazide showed higher antioxidant activity than the ones derived from mono-hydrazide [16].

The structure-activity relationship (SAR) of the antibacterial and antiproliferative potential of some 1-pyridinecarbonyl-4-substituted thiosemicarbazide derivatives showed that substitution at the position 2 of the pyridine ring enhances biological activity.

In the present study, the main goal was to build robust and reliable QSAR models for the description and prediction of antioxidant activity of heterocyclic and Schiff bases dipicolinic acid derivatives. The relevance of the best QSAR model should also be to provide a chemical and structural explanation of antioxidant activities of the most active compounds. Also, the aim of this study was to compare the statistical performance of different algorithms for splitting data into training and test set, as well as models obtained by two sets of descriptors calculated by different computer programs.

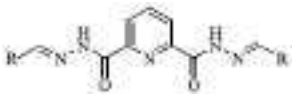
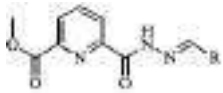
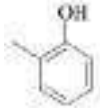
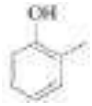
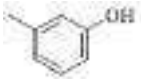
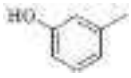
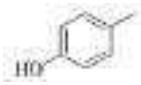
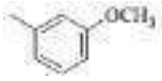
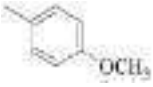
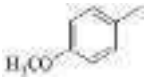
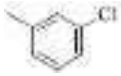
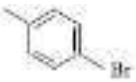
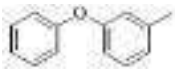
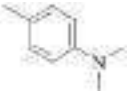
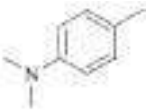
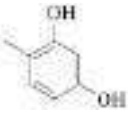
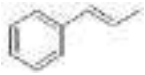
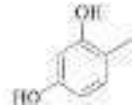
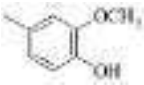
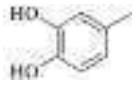
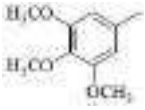
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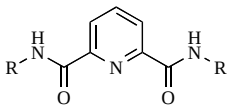
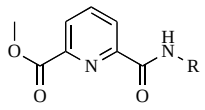
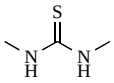
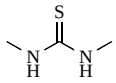
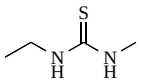
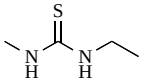
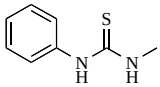
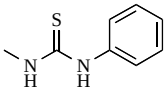
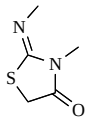
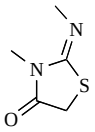
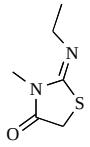
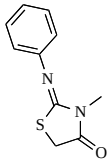
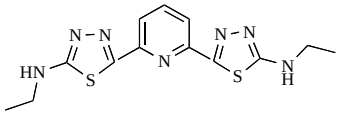
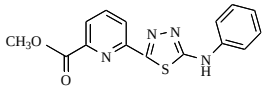
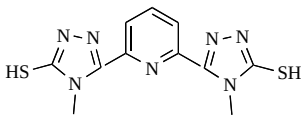
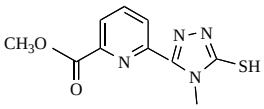
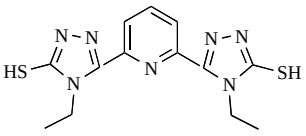
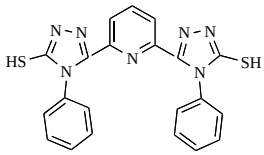




Table 1. Structures along with experimentally determined antioxidant activities (expressed as log % DPPH) of 2,6-pyridinedicarboxylic acid derivatives [16, 17].

					
Cpd.	**R**	**log %DPPH**	**Cpd.**	**R**	**log %DPPH**
1		-0.31	2		0.894
3		0.782	4		0.582
5		0.701	6		0.845
7		0.834	8		0.786
9		0.671	10		0.68
11		0.748	12		0.705
13		0.768	14		0.656
15		0.608	16		-0.495
17		-0.854	18		0.955
19		0.874	21		0.856
20		-0.42	23		1.692
22		0.874	25		1.429
24		1.732			
26		1.621			
27		0.736			

(Table 1) Contd….

					
Cpd.	**R**	**log %DPPH**	**Cpd.**	**R**	**log %DPPH**
31		1.061	**28**		1.583
32		1.566	**29**		1.68
33		1.688	**30**		1.936
41		0.301	**40**		0.114
42		0.996			
43		0.362			
36		1.134	**34**		1.1
37		1.487	**35**		1.401
38		1.504	**39**		1.49

2. MATERIALS AND METHODS

2.1. Data Set

The synthesis and antioxidant evaluation of 43 DPA derivatives have been described in our previous studies [16, 17]. Antioxidant activities, expressed as % scavenging activity on DPPH (using ascorbic acid as standard), were converted in the form of the logarithm (log %DPPH). Higher value of log %DPPH means more powerful antioxidant activity. Structural details of all studied molecules along with experimental log %DPPH are shown in Table **1**.

2.2. Descriptor Calculation and Selection

The three-dimensional (3D) structures of 43 DPA derivatives were optimized using the molecular mechanics force field (MM+) [18] applying the Avogadro 1.2.0. (University of Pittsburgh, Pittsburgh, PA, USA). Subsequently, all structures were submitted to the geometry optimization using semiempirical AM1 method [19]. The molecular structures were optimized using Polak-Ribiere algorithm until the root mean square gradient (RMS) was 0.001 kcal/(Åmol).

The Polar Surface Area (PSA) surface was generated from an optimized structure by VEGA ZZ (Department of Pharmaceutical Sciences of the University of Milan, Milan, Italy) [20]. The Polar Surface Area (PSA) was calculated considering polar and apolar atom surfaces, as dotted shape, with probe radius 1.4 and density 60.

Two set of descriptors were calculated by two different softwares 1. DRAGON descriptors – were calculated using Parameter Client (Virtual Computational Chemistry Laboratory, an electronic remote version of the Dragon program [21]. Seventeen groups of two-dimensional (2D) and three-dimensional (3D) Dragon's descriptors were used to generate QSAR models: constitutional, topological, walk and path counts, connectivity, information, 2D auto-correlations, edge adjacency, BCUT (Burden eigenvalues), topological charge, eigenvalue-based, geometrical, RDF (Radial Distribution Function), 3D-MoRSE (3D-molecular representation of structures based on electron diffraction), WHIM (WeigHted Covariance Matrices), GETAWAY (Geometry, Topology, and Atom-Weights AssemblY) descriptors, functional group counts, and molecular properties [22]. In order to reduce huge number of calculated descriptors (about 1260), firstly, zero values descriptors were excluded from initial pool. Further exclusion was performed using QSARINS-Chem 2.2.1 [23]: constant and semi-constant descriptors, i.e. those having chemical compounds with a constant value for more than 80 %, and too inter-correlated descriptors (> 85%) were rejected.

2. ADMEWORKS descriptors – calculated by ADMEWORKS ModelBuilder, tool for building mathematical models (Version 7.9.1.0(build.187.4934.2102) Enterprise Edition Copyright (C) 2011 Fujitsu Kyushu Systems Limited). Numerous groups of 2D and 3D molecular descriptors have been calculated, such as: charged partial-surface-area (CPSA) descriptor, atom-specific CPSA descriptor (DATOM), carbon type (CTYPE), molecular distance edge descriptor (DEDGE), fragment descriptors generation routine (DMFRAG), hydrogen bond specific descriptors for pure (HBPURE) and mixed (HBMIX) compounds, measure of the conformational flexibility, Hückel molecular orbital calculation (HMO), MOPAC descriptor, molecular strain energy calculation (STRAIN), etc. [24]. Elimination of irrelevant descriptors was performed using Feature Selection command of ADMEWORKS ModelBuilder that includes following tests: a) missing values test - which excludes descriptors with missing values; b) zero test - which excludes descriptors with less than the specified percentage of non-zero values; c) automated correlations test - deletes all parameters that have single or multiple correlations to other parameters, with the R^2 value larger than the specified threshold (0.7).

2.3. Training and Test Set Compounds Selection

Two algorithms were used for creating the training and test sets in both set of descriptors:

1. Data sets were randomly divided into training (80 %, N_{train} = 35) and prediction (20 %, N_{test} = 8) set using QSARINS.

2. Data sets were split by ranking method: Compounds were ranked by the activities from the most active to the least active compound. Then, the activities were divided into the bins by grouping the values into the six class intervals. Finally, one or two compounds were selected randomly from each class for the test set (N_{train} = 35, N_{test} = 8) [25].

2.4. Regression Analysis and Validation of Models

The best QSAR models were obtained by using a Genetic Algorithm (GA) using QSARINS. In order to avoid the overfitting the smallest number of descriptors that can adequately model the activity of the compounds in the study should be used. According the Topliss-Costello rule [26], the number of variables should be higher or equal to 5. In this study, considering we worked with the small data set (35 compounds in the training set), the number of descriptors (k) in the multiple regression equation was limited to four. Additional descriptors, will be resulted in overfittied and not predictive models. The models have been assessed by: fitting criteria; internal cross-validation using leave-one out (LOO) method and Y-scrambling; and external validation. Fitting criteria included: the coefficient of determination (R^2), adjusted R^2 (R^2_{adj}), cross-validate R^2 using leave-one-out method (Q^2_{LOO}), global correlation among descriptors (Kxx), difference between global correlation between molecular descriptors and y the response variable, and global correlation among descriptors (ΔK), standard deviation of regression (s), and Fisher ratio (F) [27-29]. Collinearity among the descriptors has also validated by variance inflation factor (VIF). VIF is the reciprocal of tolerance: $1/(1-R^2_i)$ where R^2_i is the squared multiple correlation of the ith independent variable regressed on the other independent variables in the analysis [30].

Internal and external validations also included the following parameters: the coefficient of determination of test set (R^2_{ex}), root-mean-square error of the training set ($RMSE_{tr}$); root-mean-square error of the training set determined through cross validated LOO method ($RMSE_{cv}$), root-mean-square error of the external validation set ($RMSE_{ex}$), concordance correlation coefficient of the training set (CCC_{tr}), test set using LOO cross validation (CCC_{cv}), and of the external validation set (CCC_{ex}) [27], mean absolute error of the training set (MAE_{tr}), mean absolute error of the internal validation set (MAE_{cv}) and mean absolute error of the external validation set (MAE_{ex}) [27], predictive residual sum of squares determined through cross-validated LOO method ($PRESS_{cv}$) in the training set and in the external prediction set ($PRESS_{ex}$). The analysed external validation parameters also include. Robustness of QSAR models was tested by Y-randomisation test.

Investigation of the applicability domain of a prediction model was performed by leverage plot (plotting residuals vs. leverage of training compounds). The warning leverage h^* is defined as $3p'/n$, where n is the number of training compounds and p' is the number of model adjustable parameters [31]. Tools of regression diagnostic as residual plots and Williams plots were used to check the quality of the best models and define their applicability domain using QSARINS.

3. RESULTS AND DISCUSSION

Four models were obtained by two different sets of descriptors (calculated by Dragon and ADMEWORKS software) and two different methods (random and ranking) for creating training and prediction set.

Models obtained by DRAGON descriptors:

The random splitting model

log %DPPH = -1.073 – 0.492 *IVDE* – 0.492 *Mor08u* – 11.755 *Dp* + 1.736 *R5u* (1)

Compounds in the test set: **15**, **20**, **23**, **31**, **33**, **36, 37**, **42**

The ranking splitting model

log %DPPH = 2.954 – 1.427 *MATS4m* + 1.093 *EEig03d* – 4.2 *BELm4* + 0.974 *Mor10p* (2)

Compounds in the test set: **1**, **2**, **7**, **16, 29**, **33**, **34**, **35**

Models obtained by ADMEWORKS descriptors:

The random splitting model

log %DPPH = 0.545 – 0.4 *NDB* – 2.2 *MATS5p* – 0.182 *MDEN33* + 0.014 *TPSA* (3)

Compounds in the test set: **1**, **4**, **6**, **7**, **11**, **13**, **28, 29**

The ranking splitting model

log %DPPH = 3.361 – 0.281 *NDB* – 0.432 *GATS8v* – 1.235 *MATS5p* + 0.129 *NUMHBD* (4)

Compounds in the test set: **1**, **2**, **7**, **16, 29**, **33**, **34**, **35**

The statistical results for the obtained models are presented in Table **2**.

Description of descriptors included is given in Table **3**. In order to exclude collinearity of descriptors included in same model, correlation matrix was generated (Tables **4-7**). Descriptors included in models (1-4) are not mutually correlated (correlation coefficient, $R \leq 0.7$). *VIF* values of individual descriptors from each model were also presented in Tables **4-7**. Linear dependence within the correlation descriptors sets has been rejected since the all *VIF* < 5 [32]. Low collinearity is also verified by the low values of *Kxx* (Table **2**). The molecular descriptor values have been tabulated in Supplementary File 1 (SF 1). Experimental and calculated log %DPPH by model (1-4) are shown in Supplementary File 2 (SF 2).

Satisfaction of fitting criteria implies the following: the closer R^2 values are to unity, the more similar calculated values are to the experimental ones, that is, $R^2 \geq 0.60$. The minimum acceptable statistical parameters for internal and external predictivity include the following conditions: $R^2_{ext} \geq 0.60$; $CCC \geq 0.85$; *RMSE* and *MAE* close to zero; and $RMSE_{tr} < RMSE_{cv}$. Robust QSAR models should have R^2_yscr and Q^2_yscr < 0.2, as R^2_yscr > Q^2_yscr [33]. Also, larger *F* statistic and lower standard deviation means that the model is more significant. Analysis of Table **2** indicates that all four models satisfy threshold for most of the internal validation parameters. However, models (1) and (2), created by Dragon descriptors, have better fitting performances (higher R^2, R^2_{adj}, *F*, and CCC_{tr}, and lower *s*, $RMSE_{tr}$, MAE_{tr} than models (3) and (4), obtained by ADMEWORKS descriptors. Also, models (1) and (2) showed a better performance in the

Table 2. The statistical results for the QSAR models for antioxidant activity.

	Model (1)	**Model (2)**	**Model (3)**	**Model (4)**
N_{tr}	35	35	35	35
N_{ex}	8	8	8	8
Fittinig criteria				
R^2	0.821	0.805	0.692	0.646
R^2_{adj}	0.797	0.779	0.650	0.599
s	0.281	0.278	0.381	0.374
F	34.455	30.914	16.818	13.689
p	$< 10^{-5}$	$< 10^{-5}$	$< 10^{-5}$	$< 10^{-5}$
Kxx	0.357	0.325	0.251	0.192
ΔK	0.034	0.004	0.031	0.074
$RMSE_{tr}$	0.260	0.257	0.353	0.257
MAE_{tr}	0.212	0.19	0.290	0.257
CCC_{tr}	0.902	0.892	0.818	0.785
Internal validation criteria				
Q^2_{LOO}	0.753	0.725	0.576	0.522
$RMSE_{cv}$	0.306	0.305	0.414	0.403
MAE_{cv}	0.250	0.226	0.340	0.300
$PRESS_{cv}$	3.268	0.849	5.989	5.670
CCC_{cv}	0.866	0.849	0.750	0.715
R^2_Yscr	0.118	0.118	0.119	0.116
Q^2_Yscr	-0.224	-0.232	-0.208	-0.215
External validation criteria				
$RMSE_{ext}$	0.674	0.550	0.231	0.520
MAE_{ext}	0.611	0.365	0.197	0.381
$PRESS_{ext}$	3.637	2.424	0.426	2.160
R^2_{ext}	0.717	0.833	0.848	0.639
Q^2_{F1}	-0.009	0.55	0.842	0.562
Q^2_{F2}	-0.078	0.507	0.84	0.56
Q^2_{F3}	-0.203	0.106	0.868	0.203
CCC_{ext}	0.678	0.657	0.908	0.666
$\overline{r_m^2}$	0.261	0.083	0.765	0.26
Δr_m^2	0.366	0.651	0.12	0.4
Applicability domain				
N compounds outlier	2 (**16**,**17**)	3 (**1**,**16**,**27**)	0	2 (**16**,**17**)
N compounds out of app.dom.	3 (**39**, **42**, **20**)	1 (**17**)	0	0

internal validation (higher Q^2_{LOO}, CCC_{cv}, and lower $RMSE_{cv}$, MAE_{cv}, and $PRESS_{cv}$. The results of Y-scrambling demonstrated that all models were not obtained by chance correlation (Q^2_yscr < 0.2, and R^2_yscr< 0.2; R^2_yscr > Q^2_yscr). In spite of a good fitting performance and good internal validation, the real predictive power of model (1) and (2) is failed according to the external validation parameters and outliers and compounds outside of applicability domain. Moreover, negative values of Q^2_{F1}, Q^2_{F2} and Q^2_{F3} of model 1, as well as very low values (< 0.7) of model (2) and (4), including values of $\overline{r_m^2}$ < 0.6 indicate these models are useless for external predictivity.

Model (3) was generated by ADMEWORKS descriptors and random splitting methods. In spite of its powerless fitting and internal performances, model possess real predictivity for the chemicals in the validation set according to high values of parameters for external validations (R^2_{ext} = 0.848; CCC_{ext} = 0.908) and small difference between $RMSE_{tr}$ and $RMSE_{ex}$, and between MAE_{tr} and MAE_{ex}.). Also, Williams plot for same model reveals no outliers, and no compounds outside of applicability domain (Fig. **1**). A scatter plot of experimentally obtained antioxidant activity by model (3) is shown in Fig. (**2**). Model (4) has weakest parameters of external validation, as well as one outlier (**16**), and one compound out of the applicability domain (**17**).

Despite of difference in predictive potential of the proposed models, included molecular descriptors may relieve in elucidation of important physicochemical and structural requirements for the antioxidant activity of heterocyclic and Schiff bases dipicolinic acid derivatives. Negative sign of variable that represents a number of double bonds (*NDB*) in equations (3) and (4), means that this type of covalent bond is unfavourable for the antioxidant power (except double bonds in phenyl or heterocyclic ring). Thus, the most active compound **30** (log %DPPH = 1.936) has 3 double bonds, while the compounds with low antioxidant activity have 6 double bonds (**41,** log %DPPH = 0.301; **17**, log %DPPH = -0.854). Negative sign of descriptor *MDEN33* in model (3) indicates that higher distance between tertial nitrogen atoms negatively influences on the antioxidant activity. Compounds without tertial nitrogen atoms have a higher antioxidant potential, such as thiosemicarbazides (**28**-**33**). Since DPPH test is based on the capability of stable free radical 2,2-diphenyl-1-picrylhydrazyl to react with H-donors [34], positive coefficient of hydrogen bond donors (*NUMHBD*) in model (4) is expected. That implies that higher number hydrogens attached to the oxygen, nitrogen or sulphur atoms, positively influences on antioxidant activity, such as secondary nitrogen atoms in thiosemicarbazides (**28**-**33**). This supports our recent findings that enhanced value of hydrophilic factor, which is related with number of –OH, –NH_2, and >NH groups in molecule, is favourable for antioxidant activity of coumarinyl Schiff bases [35]. Also, it corresponds with previously statement about negative influence of enhanced number of tertial nitrogen atoms on antioxidant activity. However, five compounds (**22**, **24**, **31**-**33**) have more than five hydrogen bond donors, and according the Lipinski's rule of five [36], as potential drug, they could have poor absorption or permeation. Topological polar surface area (*TPSA*) in model (3), is descriptor that also characterized drug absorption, including intestinal absorption, bioavailability and blood–brain barrier penetration. Polar surface area (*PSA*) is sum of surface of polar atoms (oxygen, nitrogen, sulphur, etc.) [37]. Although model (3) implies that molecules with enhanced values of *TPSA* have higher antioxidant activity, these molecules could poorly penetrate through the cell membranes [15, 38]. According the data presented in Supplementary File 1, value of *TPSA* for the most active compound (**30**) is larger (124.44) than for the least active (**17**) (114.27). *TPSA* is a useful descriptor in QSAR models, which a sign its coefficient can indicate whether a more polar ligand is favoured or disfavoured for enhanced activity. However, it is based only on the contribution of tabulated polar fragments, not from the 3D conformations of these chemical groups. Also, *TPSA* does not include the influence of positional changes of functional groups [38]. In order to additionally clarify sense of PSA for antioxidant activity of Schiff bases dipicolinic acid derivatives, we were calculated and compared PSA of the most active (**30**) and the least active compound (**17**). Apolar atom surface takes into account C and H atoms bonded to C atoms. Polar atoms are O, S, N, P and H, not bonded to C. Because of higher number of polar atoms in molecule (**30**), their PSA (203.4 $Å^2$) is much higher than molecule (**17**) (165.6 $Å^2$). Moreover, apolar surface area of the most active compound (**30**) is significantly lower (590.3 $Å^2$) than at least active compound (**17**) (983.2 $Å^2$). Fig. (**3**) shows a mapped PSA of the most active molecule (**30**) and the least active molecule (**17**), for comparison. Apolar and polar surfaces are presented as gradient of two color codes: black (apolar surface) and grey (polar surface).

3D-MoRSE descriptors, *Mor08u* and *Mor10p*, are involved in models (1) and (2). These descriptors were generated from electron diffraction studies and reflect the three-dimensional arrangement of atoms in a molecule [39]. Descriptor *Mor08u* denotes unweighted descriptors with scattering parameter s = 7 $Å^{-1}$. Since it is unweighted, the descriptor has no discriminative ability and treats each atom equally. It has the possibility to distinguish the difference between the bond lengths of any kinds of atoms at least 0.12 Å. Consider that their final values are derived mostly from long distances atoms, it has great power to distinguish mono- from bis-substituted dipicolinic derivatives (Table **S1**). Negative coefficient of *Mor08u* in Eq. (1) implies that lower values of that descriptor are favourable for the exhibition of antioxidant activity. Descriptor *Mor10p* reflects the contribution of 3D distribution of atomic polarizability (p) at a scattering parameter s = 9 $Å^{-1}$. According to model (2), it is expected that increased values of *Mor10p* indicates higher antioxidant activity. As can be noticed from Table **S1**, this descriptor is extremely sensitive to the position of the sulphur atoms (atom with higher polarizability, p = 19.6) in molecules.

MATS5p, *MATS4m* and *GATS8v* belong to the 2D autocorrelation molecular descriptors that describe how a considered property is distributed along a topological molecular structure. *MATS5p* corresponds to the Moran autocorrelation –lag 5 / weighted by atomic polarizability, while *MATS4m* is the Moran autocorrelation descriptor –lag 5 / weighted by atomic masses.

Table 3. Summary table for descriptors included in models 1-4.

Symbol	Descriptor name	Groups of descriptors
IVDE	Mean information content on the vertex degree equality	Information
Mor08u	3D-MoRSE signal 08 / unweighted	3D-MoRSE
Mor10p	3D-MoRSE signal 10 / weighted by polarizability	3D-MoRSE
Dp	D total accessibility index / weighted by polarizability	WHIM
R5u	R autocorrelation of lag 5 / unweighted	GETAWAY
MATS4m	Moran autocorrelation of lag 4 weighted by mass	Autocorrelations
MATS5p	Moran autocorrelation of lag 4 weighted by atomic polarizabilities	Autocorrelations
GATS8v	Geary autocorrelation of lag 8 weighted by van der Waals volume	Autocorrelations
EEig03d	Eigenvalue 03 from edge adj. matrix weighted by dipole moments	Edge adjacency
BELm4	Lowest eigenvalue 4 of Burden matrix / weighted by atomic masses	BCUT
NDB	Number of double bonds	DMFRAG
MDEN33	Molecular distance edge between all tert tert N	EDGE
TPSA	Topological polar surface area	Mol. properties
NUMHBD	Number of hydrogen bond donors	H acceptor/donor

Table 4. Correlation matrix for the descriptors included in model 1 and variance inflation factor (VIF) for individual descriptor.

	VIF	***IVDE***	***Mor08u***	***Dp***	***R5u***
IVDE	1.45	1.00			
Mor08u	1.69	0.38	1.00		
Dp	1.23	0.00	0.01	1.00	
R5u	1.45	0.18	0.33	0.37	1.00

Table 5. Correlation matrix for the descriptors included in model 2 and variance inflation factor (VIF) for individual descriptor.

	VIF	***MATS4m***	***EEig03d***	***BELm4***	***Mor10p***
MATS4m	1.49	1.00			
EEig03d	1.49	0.43	1.00		
BELm4	1.11	-0.28	0.09	1.00	
Mor10p	1.37	-0.41	-0.34	0.17	1.00

Table 6. Correlation matrix for the descriptors included in model 3 and variance inflation factor (VIF) for individual descriptor.

	VIF	**NDB**	**MATS5p**	**MDEN33**	**TPSA**
NDB	1.96	1.00			
MATS5p	1.15	-0.20	1.00		
MDEN33	1.96	-0.49	-0.01	1.00	
TPSA	1.49	0.21	-0.01	0.34	1.00

Table 7. Correlation matrix for the descriptors included in model 4 and variance inflation factor (VIF) for individual descriptor.

	VIF	NDB	GATS8v	MATS5p	NUMHBD
NDB	1.49	1.00			
GATS8v	1.35	-0.13	1.00		
MATS5p	1.39	-0.20	0.01	1.00	
NUMHBD	1.85	0.43	-0.38	-0.02	1.00

GATS8v is Geary autocorrelation of lag 8 weighted by van der Waals volume [22]. These descriptors reflect contribution of pairs of atoms different polarizability/mass/ van der Waals volume at the defined topological distance or spatial lag. Therefore, *MATS5p*, *MATS4m* and *GATS8v* indicate dependence of one atom on value of polarizability /mass/ van der Waals volume of other atoms at the topological distance 5, 4, and 8, respectively. Their negative regression coefficients in models (3) and (4) suggest in unfavorable effect of increased autocorrelation contents of five-, four-, eight-member structural graphs weighted by atomic polarizability, mass, and van der Waals volume for the activity.

WHIM is geometrical descriptor calculated on the projections of the atoms along principal axes [24]. Descriptor *Dp* is total accessibility index weighted by atomic polarizability, which values are strongly influenced by kind and position of substituents on phenyl ring. Negative coefficient of *Dp* in model (1) implies that 3D distribution of substituents with the increased atomic polarizability (Cl, Br atoms) could negatively influenced to the antioxidant power. It explains weak antioxidant activity of compounds with Br (**16**) and Cl atoms (**14**, **15**). Descriptor *IVDE* is mean information content on the vertex degree equality [24]. Since it is a measure of the lack of structural homogeneity or the diversity of a molecule [40], its negative coefficient in model (1) suggests that molecules with symmetrical moiety are potentially more active.

Descriptor *BELm4* in model (2) belongs to the BCUT descriptors. BCUT descriptors are the eigenvalues of a modified connectivity matrix, the Burden matrix, which capture useful measurement of molecular diversity [41]. Highest value of *BELm4* have most inactive compounds, **17** and **20** (*BELm4* = 1.894 and 1.607, respectively, Table **S1**), which correspond with a negative coefficient of that variable in model (2). Descriptor *EEig03d* in model (2) is related to the molecular polarity, which mainly described the electronic effect of molecule and the hydrophobic properties. Same as *TPSA* in model (3), positive regression coefficient of *EEig03d* in model (2) suggests that enhanced molecular polarity positively influence on antioxidant activity of compounds.

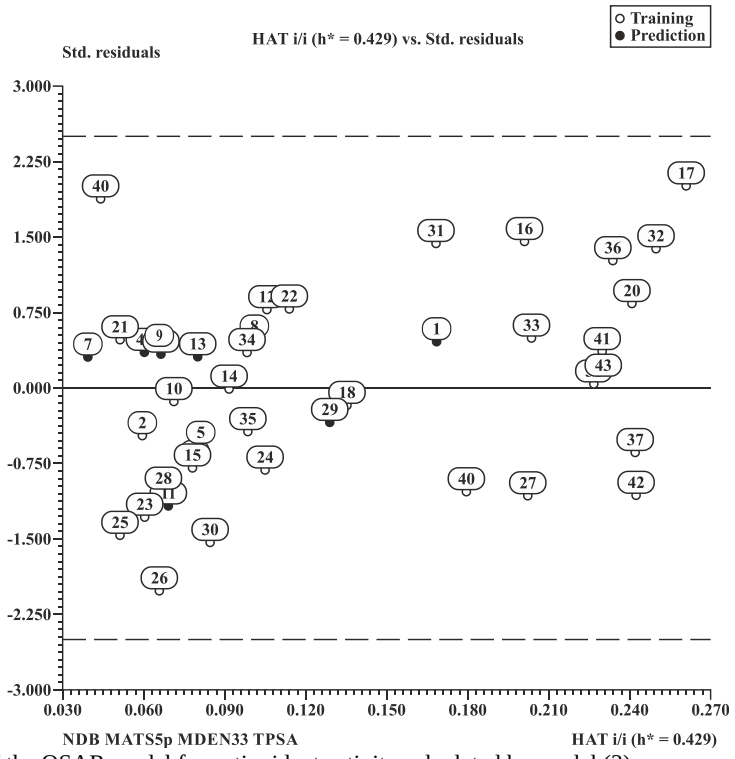


Fig. (1). Applicability domain of the QSAR model for antioxidant activity calculated by model (3).

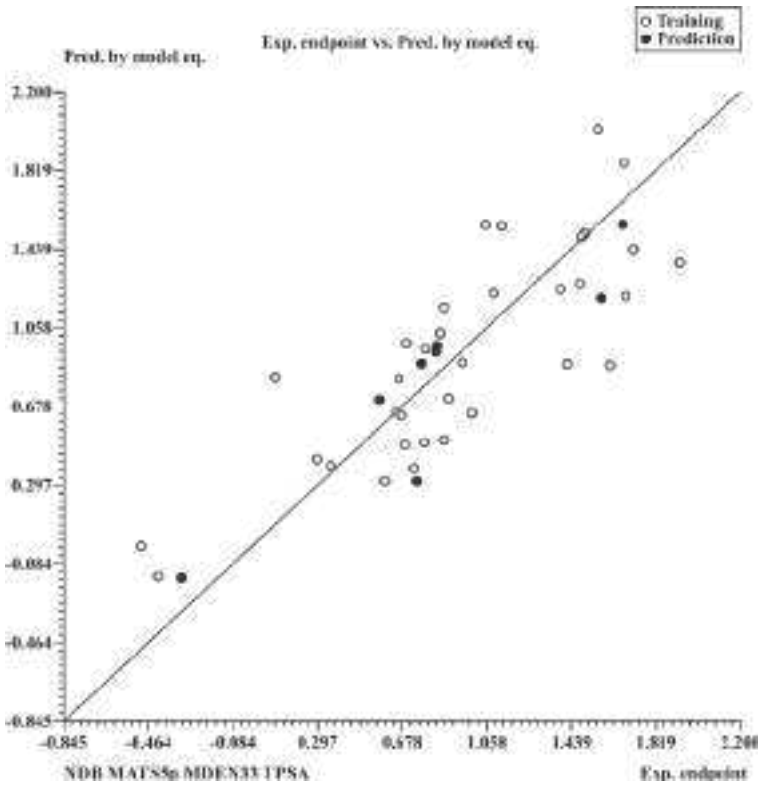


Fig. (2). Observed versus predicted log %DPPH for the 43 dipicolinic acid derivatives calculated by model (3).

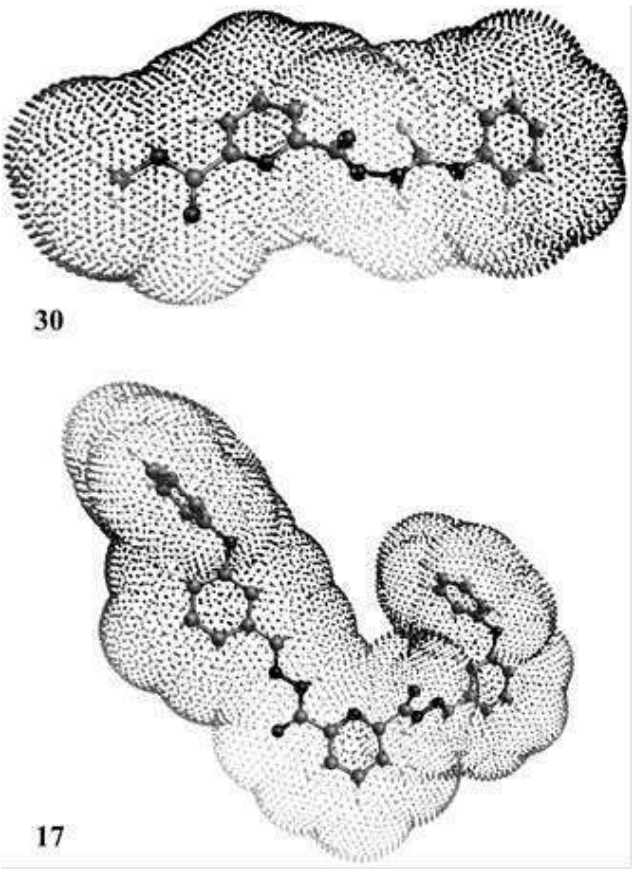


Fig. (3). Dotted polar surface area (PSA) for the compound with highest (30), and compound (17) with lowest antioxidant activity. PSA is presented as gradient of two colors: black (apolar surface) and grey (polar surface).

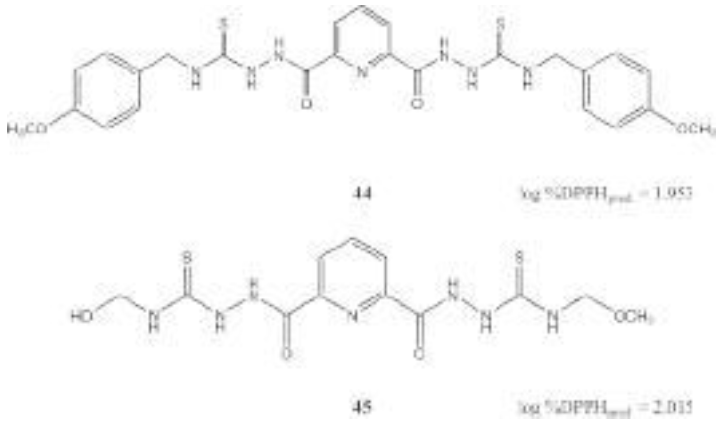


Fig. (4). Structures of the proposed molecules as promising antioxidant agents. Antioxidant activities have been predicted according the model (3).

Based on the conclusions given in the QSAR analysis, structures of two new compounds (**44**, **45**) with possible great activity are proposed (Fig. **4**). Antioxidant activities of the proposed compounds have been predicted by means of the model (3) (log %DPPH = 1.953 and 2.015, for **44** and **45**, respectively). Calculated descriptors are shown in Supplementary File 1. Applicability domain of the proposed new potentially active derivatives has been verified. Leverage (HAT) values of both compounds are inside the applicability domain of a model (0.267 for **44,** 0.321 for **45**; $h^* = 0.429$). The Williams plot of the regression is presented in Supplementary File 3 (SF 3).

CONCLUSION

The results of the QSAR analysis suggest that derivatives of dipicolinic acid with the following structural feature may exhibit great antioxidant activity: low number of double bonds in molecules; absence of tertial nitrogen atoms; higher number of hydrogen bond donors; enhanced molecular polarity; substituents without halogen atoms; and symmetrical moiety. Model with the best external validation result was obtained by ADMEWORKS descriptors, and the test set was generated by random method. Obtained models could help in suggesting design of novel molecules with improved activity profile. According to developed model, structures of two new compounds with possible great activities were proposed. Thus, the model provides a practical tool for the prediction of antioxidant activity of new and untested antioxidant.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY MATERIAL

Supplementary materials are available on the publisher's web site along with the published article:

SF 1. Values of the most relevant descriptors in QSAR models (1)-(4).

SF 2. Values of the experimental and calculated log %DPPH by QSAR models (1)-(4).

SF 3. Applicability domain of the proposed new potentially active derivatives (44, 45) calculated by model (3).

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Digitalization of Ecotourism and Allied Services in Melghat Tiger Reserve of Vidarbha

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ABSTRACT

Ecotourism is an alternative form of tourism whose sole purpose is holiday activities and the core elements of this type of tourism is natural-based. The basic intention of this type of tourism is to raise awareness amongst travelers about the natural place they visit for and at the same time minimize any corrosive impact of human activity along with the upliftment of the localites of the particular area. In the digital era of technology, travel agendas rarely rely on trusted word-of-mouth recommendations and physical guidebooks; breakthroughs in digitalisation have given customers independence and choice in a really big way. Let's not forget that travel is essentially about connecting – places, people, experiences and memories. One thing that technology does well, is connect things.Before going on a trip, most people research the place they're about to visit. Once they arrive at the destination, the search for the best places to visit continues. Thankfully, the power of Wi-Fi allows travelers to use their devices anywhere from the hotel room to coffee shops and touristic attractions. As a result, planning any trip becomes as easy as visiting a review website and choosing the next destination point. A Descriptive approach was adapted to conduct the study on digitalization of ecotourism and other related services in the Melghat Tiger Region, the researcher could that digital services has in a way created varied sources of revenue generation and employment opportunities for the local people called as 'korku'. It is due to the vision of making India digital Melghat is crowned with Harisal- India's first digital village.

Keywords: Digitalisation, Ecotourism, Employment, Services, Tiger Reserves.

What is Ecotourism?

Ecotourism (also called sustainable tourism) can be defined by a variety of travel practices, but it all comes down to a general set of ideas. As an eco-tourist, you decide to travel in a way that shows respect to nature and does not contribute to its degradation.

Additionally, ecotourism is a part of environmental conservation, and understanding what the needs of the people are who are local to the area so that you can help to improve their quality of life. It also involves learning more about the history of other cities and preserving the historical landmarks.

As per The International Ecotourism Society,

"*Ecotourism is now defined as "responsible travel to natural areas that conserves the environment, sustains the well-being of the local people, and involves interpretation and education. Education is meant to be inclusive of both staff and guests.*"

Ecotourism is a responsible tourism which conserves the environment and sustains the well being of local people. It...

- Builds environmental awareness
- Provides direct financial benefits for conservation
- Provides financial benefits and empowerment for local people
- Respects local culture
- Supports human rights and democratic movementssuch as:

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- conservation of biological diversity and cultural diversity through ecosystem protection
- promotion of sustainable use of biodiversity, by providing jobs to local populations
- sharing of all socio-economic benefits with local communities and indigenous peoples by having their informed consent and participation in the management of ecotourism enterprises
- tourism to unspoiled natural resources, with minimal impact on the environment being a primary concern.
- minimization of tourism's own environmental impact
- affordability and lack of waste in the form of luxury
- local culture, flora, and fauna being the main attractions
- local people, who benefit from this form of tourism economically, and often more than mass tourism

Objectives of Ecotourism:

Eco tourism or sustainable tourism is designed to make travelers aware of the environment and carry out all tourism operations in an eco-friendly manner. We have listed down a few aims and objectives of ecological tourism. Have a look:

- Maintaining the Sanctity of the Environment
- Utilizing All Types of Resources Efficiently
- Preserving the Biological Diversity
- Ensuring the Economic Progress
- Increasing the Scope of Employment
- Strengthening the Cultural Bonding

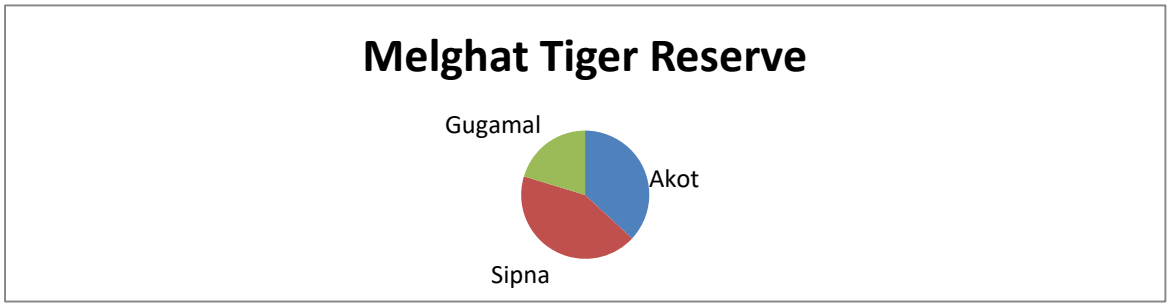
Melghat Tiger Reserve:

Melghat means ‘meeting of the ghats’ which is just what the area is, a large tract of unending hills and ravines scarred by jaggesd cliffs and steep climbs. The exquisite hill forests, thick undergrowth and moss-covered trees underscore its virgin confines.

Melghat was declared a tiger reserve and was among the first nine tiger reserves notified in 1973-74 under the Project Tiger. It is located inAmravati District of Maharashtra State in India. The Tapti River and the Gawilgadh ridge of the Satpura Range form the boundaries of the reserve. In 1985 Melghat Wildlife Sanctuary was created. The Tapi river flows through the northern end of the Melghat Tiger Reserve, through a forest which lies within the catchment area of the river system. Many different kinds of wildlife, both flora and fauna, are found here.

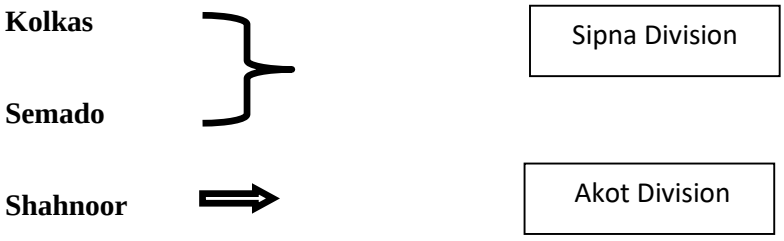
Melghat Tiger Reserve Division:

The Melghat Tiger Reserve is divided under three sub-divisions namely,



There are various rest houses at-

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Korku tribes of Melghat:

Korku have derived their name from the combination of the word 'Koru' meaning Man and 'Ku' which make it plural meaning tribal men.

Forming an important part of its identity, India remains home to a large number of aboriginals, untouched by the modern lifestyle of the city these people continue to live in the remotest of location with dense forest, raging rivers and varied wildlife. Living so close to nature, these people are filled with love, compassion and warmth.

Digitalization in Ecotourism:

There's no denying that technology plays a pivotal role within the travel and tourism sector.

Along with the exponential growth of extension and using the Internet and the World Wide Web, both at home and at work, have increased also the opportunities for travel providers to distribute information and to process bookings for potential buyers. The development processes within the information technology, communications and Internet, have revolutionized the entire tourism industry, creating new business models, changing the structure of distribution channels of the tourism and reprojecting all products of this industry and last but not least, influencing the touristic packages suppliers , destinations and stakeholders. (Organism or group of people with major interests in the conduct and results of the company). Some hotels have implemented a fully automated check-in process, stepping back from personal contact and relying on an electronic process to meet the customer's needs. As long as the small tourism operators can be reached on the Internet, the trend will grow up in their direction, because the Internet is similar to a "playground" in which with a well done web site, the small businesses can advertise as professional as their larger competitors. In this context, we assist to a more and more emphasized development of the electronic commerce, hence of the electronic tourism (or e-tourism).

Our day-to-day lives are made easier through the use of the internet and technology – whether it be on our mobile devices, at home or in the work place using a desktop or laptop. Significant developments in technology have now made this achievable on a global scale.

It's seen by many that technology – namely social media – has created a global village, connecting everybody to everyone, everywhere. Some argue that this has made us less sociable, inhibiting face to face and physical interaction. However, the concept that globalisation and technology allows us to overcome the limitations of physical distance through our finger tips, presents countless opportunities for the travel and tourism industry to flourish.

People always have and always will continue to travel around the world to experience new things… and advances in technology are there to influence and inspire this: not prohibit.

Websites, booking platforms, apps and using social media all provide the opportunity to engage and connect with customers on a variety of levels to allow an enhanced travel experience. Now that this information for customers is easily accessible (through various mediums), it inevitably means that it's important for companies to get smarter and adapt to remain competitive.

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The digitalization impact has spread its wings to the nearby villages and its people too. Harisal, about 270km from Nagpur, is going to be India's "first smart village". The state and central governments have big plans for the hamlet, located in a hilly area deep inside the Melghat Tiger Reserve and inhabited by 2,000 people, mostly Korku Adivasis. They plan to provide each of the 406 households with solar electricity and Internet connections.



So far, Harisal has been known mainly for its malnutrition deaths. Now the words "digital" and "smart" are on everybody's lips - right from unlettered villagers to the few who have been to school. The government wants to introduce the Internet and computers to the villagers, mostly farmers, to put the village on the digital map. On the agenda are cashless markets, WiFi zones, mobile connectivity, health cards and telemedicine facilities.

In summary, developments in technology have led to big changes in the way that customers use it to enhance their full travel experience. Consequently, travel companies must adapt to continue providing their customers with the best customer experience possible along with the upliftment of the localites in the region.

Research Methodology:

Research in common parlance refers to a search for knowledge. Once can also define research as a scientific and systematic search for pertinent information on a specific topic.

The process used to collect information and data for the purpose of coming to a conclusion giving suggestion and taking decision for which the methodology included books, publication research, interviews with official at the Forest Office of Melghat Tiger Reserve and Maharashtra Tourism Development Corporation Amravati.

Statement of Problem:

The traditional method of providing information and services are limiting the growth of tourism industry. Digitalization of these services will save the time and cost of the tourist which will result into the higher satisfaction level and increase in their number.

Hence the researcher under took the study “Digitalization of ecotourism and allied services in Melghat Tiger Reserve of Vidarbha”.

Objectives of the Study:

1. To study the various segment of forest tourism.
2. To analyze the Traditional and Digital Methods of tourism.
3. To analyze the impact of digitalization on the related services and tourist.
4. To study the impact of digitalization on the growth of tourism in Melghat Tiger Reserve.
5. Ti study the impact of digitalization on providing employment opportunities to localites.

Tiger Reserve- An Introduction:

India is home to 70% of tigers in the World. There are around 50 tiger reserves in India which are governed by Project Tiger administrated by the National Tiger Conservation Authority (NTCA).

Initially 9 Tiger Reserves were created for Project Tiger in 1973-74

1. Manas Wildlife Sanctuary (Assam)
2. Palmau Tiger Reserve (Bihar)
3. Similipal National Park (Orissa)

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4. Corbett National Park (Uttar Pradesh now UttaraKhand)
5. Kanha National Park (Madhya Pradesh)
6. Melghat Tiger Reserve (Maharashtra)
7. Bandipur National Park (Karnataka)
8. Ranthambore (Rajasthan)
9. Sunderban Wildlife Sanctuary (West Bengal)

List of Tiger Reserves in Maharashtra

Tiger Reserve	Year declared	Core Area(km^2)	Buffer Area(km^2)	Total Area (km^2)
Melghat	1974	1,500	1,268	2,769
Tadoba	1993	626	1,102	1,728
Pench	1977	257	484	741
Sahyadri	2007	600	565	1,166
Nawegaon-Nagzira	2013	654	1241	1895
Bor	2014	138	678	816
Total		**3775**	**5338**	**9113**

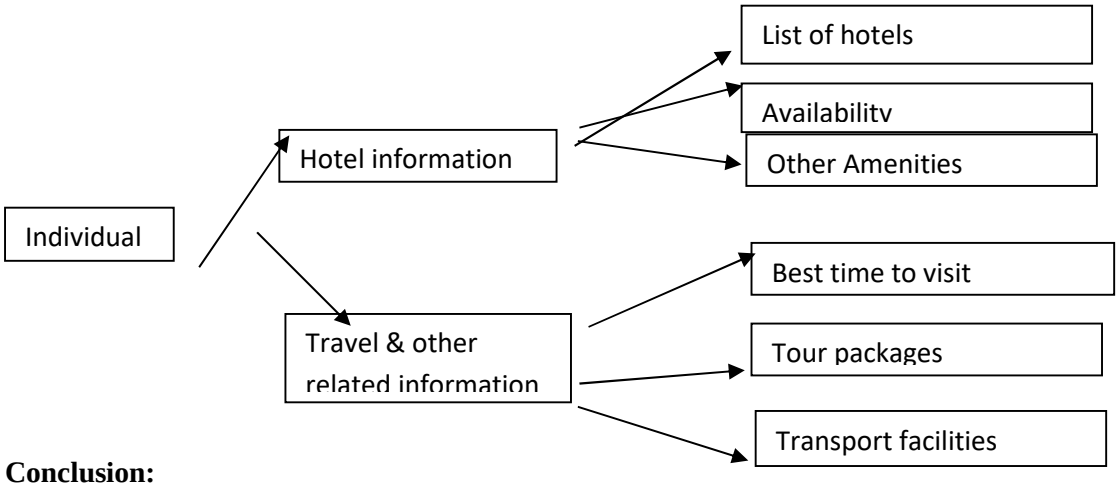
(Source: https://en.wikipedia.org/wiki/Tiger_reserves_of_Maharashtra)

Findings:

It is found that the traditional method of tourism included various middlemen and lot of tedious structure of the booking and reservation process. Whereas, the world of technology have enhanced the reservation system by Douglas Foster- Do-it-yourself reservation system, wherein all the information and booking are available at just one click.

The digital initiative has, among other things, focused on providing Internet facilities to schools. Students and teachers will be given online training. Computer labs are being set up, along with a digital library with the help of Sant Gadge Baba Amravati University.

It is also found that the digital method have given a boost to the tourism sector in the region as compared to the traditional methods of tourism with help of Do-it-yourself model.



Conclusion:

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From the above findings and survey done during the research process it can be concluded that-

- There are various avenues available in the region of Melghat Tiger Reserve, such as jungle safari, adventure sports at Shahnoor rest house.
- The digital methods of tourism have given a boost to the ecotourism in the last 3 years as a result a new gate for jungle safari has been opened from Chikhaldara from February 2017.
- The digital growth in the the region is been such that the local people are been given training and computer literacy so that they can sell their handmade bamboo items online globally.
- Melghat is one of the oldest tiger reserves in India and is now acknowledged world wide due to digitalization.
- There is almost a hike of 8-10% annually in the number of visitors in the region.
- It can also be concluded that the digitalization of ecotourism and their allied services have generated moderate employment opportunities for the localites- such as tour guides, catering, handicrafts, various sports activities tutors etc.

Suggestions:

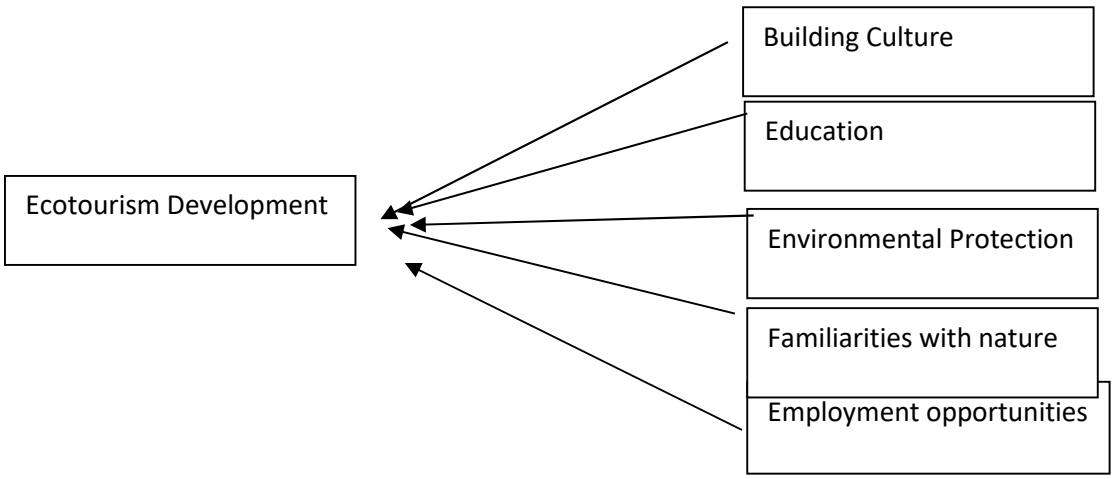
There is huge scope of growth in the tourism industry in the region of Melghat.

Adequate supply of electricity

More number of mobile and wifi towers.

Residential facilities in Korku huts for proper understanding of the local culture and environment.

The ecotourism can develop when the other related factors are in proper coordination with it.



Proper synchronization of the above factors will channelize the ecotourism in an effective manner for a better tomorrow for the people in the region of Melghat and the generation to ccome in the digital era.

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SYNTHESIS OF SOME CHLOROSUBSTITUTED THIAZOLES, IMIDAZOLO-THIAZOLES-AS EFFICIENT ANTIBACTERIAL AGENTS

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ABSTRACT
In the past 2,3 decades, the literature survey is enriched with progressive finding about the synthesis and pharmacological evaluation of fused heterocycles containing imidazole and thiazole moeities. Due to their vital role in biological activities, it was thought interesting to synthesize some chlorosubstitutedthiazoles and their imidazole containing derivatives. The newly synthesized compounds when screened for antibacterial activities against some plant pathogens showed good to excellent activity.

KEYWORDS: thioureas, thiazoles, imidazolo-thiazoles, antibacterial agent.

INTRODUCTION

Literature survey reveals that many heterocyclic[1] compounds containing fused ring system have a broad spectrum of biological[2-3] as well as physiological activities. It is also revealed that thiazole moieties have attracted considerable attention of medicinal chemists as they are endowed with a wide range of diverse biological activities[4] such as anti-inflammatory[5], analgesic, antifungal[6], antimicrobial[7], anti-oxidant activity.[8] Imidazole is also one of the most fascinating classes of compounds possessing variety of biological activities[9-14] such as anti-HIV, anti-histamine, antibacterial, tranquillizer *etc*. Morever imidazole[15] motif is found in number of chemo-therapeutic agents such as etomidate, zolpidem, nafimidone, cimetidine, clodine, pilocarpine and metronidazole. Encouraged by the earlier reports, we have designed and synthesized some new chlorosubstituted thiazoles and their imidazolo-thiazole blends. These titled compounds were screened for their antibacterial[16-19] assay against some *ornamental plant pathogens* viz. *Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa and Salmonella typhi* by using Agar disc diffusion method.

EXPERIMENTAL

Physical characterization data of all the compounds are given in Table-1.

TABLE-1: Characterization data of newly synthesized compounds

Compound	Molecular Formula	Melting Point (^oC)	Yield (%)	R_f
1a	$C_8H_6Cl_2O_2$	221(B.P)	75	0.81
2a	$C_8H_6Cl_2O_2$	53	74	0.84
3a	$C_{15}H_8Cl_4O_2$	130	78	0.74
4a	$C_{15}H_6Cl_4O_2$	122	75	0.86
5a	$C_{15}H_8Cl_4O_3$	141	59	0.77
6a	$C_{15}H_7BrCl_4O_3$	100	60	0.79
7a	$C_{16}H_8Cl_4N_2O_2S$	150	59	0.88
7b	$C_{22}H_{12}Cl_4N_2O_2S$	141	56	0.86
8a	$C_{24}H_{12}Cl_4N_2O_4S$	111	65	0.80
9a	$C_{25}H_{11}Cl_6N_3O_3S_2$	103	70	0.75

The synthetic routes which furnished the target compounds are shown below along with their IR and NMR data.





Scheme-I

Preparation of 2,4-dichlorophenyl acetate (1a): 2,4-Dichlorophenol (0.01M) was mixed with acetic anhydride (0.01M) and anhydrous sodium acetate (5g). The mixture was refluxed for about an hour. It was then cooled and poured into cold water. Acetate layer thus separated was washed with water for several times. Finally it was purified by distillation and the distillate of compound (1a) was collected at about 221^{o}C; yield: 75%, b.p: 221^{o}C.

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)ethanone (2a): The compound (1a) (50ml) was mixed with anhydrous aluminum trichloride (120 g) and heated at 120^{o}C for 45 minutes on sand bath. The reaction mixture was decomposed by ice cold water containing a little HCl to get the crude product. It was then purified by recrystalization using ethanol to get a greenish white solid as compound(2a); yield:74%; m.p.:53^{o}C.

IR(KBr ν_{max})=3423cm^{-1}(-OH str),1664cm^{-1}(C=Ostr), 1300cm^{-1}(C-Ostr), 766cm^{-1}(C-Clstr).

NMR: δ12.69(s,1H,Ar-H) , δ7.25 to 7.63 (m,2H,Ar-H) , δ2.60,(s,3H,-CH_3).

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)prop-2-en-1-one (3a): The compound (2a)(0.01M) dissolved in ethanol and 2,3-dichloro benzaldehyde (0.01M) was added to it, the mixture was heated to boiling, aqueous sodium hydroxide solution 40% (10ml) was added to it dropwise with constant stirring. The mixture was mechanically stirred for 30 minutes at room temperature and kept overnight. Then the mixture was acidified with HCl (10%). The solid product thus obtained was filtered, washed with sodium bicarbonate (10%) followed by washing with water to get the crude product. It was crystallized from ethanol-acetic acid mixture to get the compound (3a); yield:78%; m.p.:130^{0}C.

IR(KBr ν_{max})=3445cm^{-1}(O-Hstr),1649(C=Ostr),3068cm^{-1}(ArC-Hstr),1608cm^{-1} (C=Cstr), 780cm^{-1}(C-Clstr).

NMR: δ13.16(s,1H,Ar-OH),δ8.39(d,1H,-CH), δ8.35(d,1H,-CH), δ7.26-7.78(m,5H,Ar-H).

Preparation of 6,8-dichloro-2-(2,3-dichlorophenyl)-4*H*-chromen-4-one(4a): The compound (3a)(0.01) suspended in 10 ml DMSO refluxed with crystals of iodine for 45 minutes. After cooling the reaction mixture was diluted with water. The solid thus obtained was filtered, washed with 20% sodium thiosulphate solution and finally crystallised from ethyl alcohol to get the compound (4a);yield:75%, m.p.:122^{o}C.

IR(KBr ν_{max})=1664cm (C=Ostr), 1176cm^{-1} (C-Osrt), 780cm^{-1} (C-Clstr).

NMR: δ7.8-8.1(m,5H,Ar-H), δ6.7(s,1H,=CH).

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)propane-1,3-dione (5a): The compound (4a) (0.01M) dissolved in ethanol (25ml) treated with HCl solution (25ml) (20%). The reaction mixture was then refluxed for 45 minutes, cooled and diluted with cold water. The product thus separated was filtered and washed with water and finally recrystallised from ethanol to get the compound (5a); yield:59%, m. p.:141^{o}C.

IR(KBr ν_{max})=3364cm^{-1}(O-Hstr),1690cm^{-1} (C=Ostr),1310cm^{-1}(C-Osrt),798cm^{-1}(C-Clstr).

NMR: δ10.45(s,1H,Ar-OH), δ7.2-7.9(m,5H,Ar-H), δ3,9(s,2H,CH_2).

Preparation of 2-bromo-1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)propane-1,3-dione (6a): The compound (5a) (0.01M) dissolved in acetic acid (10 ml), treated with bromine in acetic acid reagent (0.01M) (0.5ml). The mixture was allowed to stand for 1 h. at room temperature. The reaction mixture was decomposed with ice cold water to get the compound 6a; yield:60%, m.p.:100^{o}C.

IR(KBr ν_{max})= 3367cm^{-1}(O-Hstr),1692cm^{-1} (C=Ostr),1162cm^{-1}(C-Osrt),782cm^{-1}(C-Clstr), 630cm^{-1} (C-Br str).

NMR: δ12.9(s,1H,Ar-OH), δ7.2-7.9(m,5H,Ar-H), δ3.3(s,1H,C-H).

Preparation of 2-amino-4-(2,3-dichlorobenzoyl)-5-(2-hydroxy-3,5-dichlorophenyl)-1,3-thiazole (7a) and **2-aminophenyl-4-(2,3-dichlorobenzoyl)-5-(2-hydroxy-3,5-dichlorophenyl)-1,3-thiazole (7b):** The compound (6a) (0.01M) refluxed separately with thiourea (0.01M) and phenyl thiourea(0.01M) in presence of aqueous KOH solution (25ml, 0.02M) in ethanol (25ml) to obtain the compounds (7a); yield 59%; m.p. 150^{o}C and (7b); yield 56%; m.p. 141^{o}C respectively.

IR(KBr ν_{max})= 3510cm^{-1} (O-Hstr), 3340cm^{-1} (sharp,NH_2str), 1660cm^{-1} (C=Nstr), 1600cm^{-1} (C=Ostr),1310cm^{-1} (C-Ostr),780cm^{-1}(C-Clstr).

NMR: δ10.20(s,1H,Ar-OH), δ7.2-7.9(m,5H, Ar-H), δ4.0(s,2H,-NH_2).

Preparation of 2-({5-(3,5-dichloro-2-hydroxyphenyl)-4-[(2,3-dichlorophenyl)carbonyl]-1,3-thiazol-2-yl}amino)-1-(2,3-dichlorophenyl) ethanone (8a)

The compound (7a) (0.01M) was refluxed with 2-bromo-1-(3,5-dichloro-2-hydroxyphenyl) ethanone (0.01M) in absolute alcohol for 1 h. On cooling, the mixture was decomposed in ice cold water. The product thus separated was filtered and crystallized from alcohol to get the compound (8a); yield:65%; m.p.:111^{o}C.

IR(KBr ν_{max})=3460cm^{-1} (O-Hstr), 3367cm^{-1} (sharp,NH_2str), 1622cm^{-1} (C=Ostr), 1583cm^{-1} (C=Nstr),1310cm^{-1} (C-Ostr),796cm^{-1}(C-Clstr).

NMR: δ12.72(s,2H,Ar-OH), δ7.25-7.65(m,7H, Ar-H), δ2.65(s,2H,-CH_2), δ1.8(s,2H,-NH_2).

Preparation of 2-[2-mercapto-4-(2-hydroxy-3,5-dichlorophenyl) imidazolo]-4-(2,3-dichlorobenzoyl)-5-(2-hydroxy-2,3-dichlorophenyl)-1,3-thiazol (9a)

The compound (8a) (0.01M) was refluxed with KSCN in glacial acetic acid (20 ml) for about 4 h. On cooling, the reaction mixture was poured into ice cold water. The product thus separated was filtered and recrystallised from ethanol to get the compound (9a); yield:70%; m.pt.:103^{o}C.

IR(KBr ν_{max})=3341cm^{-1} (O-Hstr), 3068cm^{-1} (sharp,NH_2str), 2548cm^{-1} (S-Hstr), 1662cm^{-1} (C=Ostr),1641cm^{-1} (C=Nstr),796cm^{-1}(C-Clstr).

NMR: Δ12.61-13.0(S,2H,AR-OH), Δ7.25-7.92(M,8H, AR-H), Δ2.5(S,1H,-SH).

ANTIBACTERIAL ACTIVITY

The test compounds were screened for their antibacterial assay against *ornamental plant pathogens* viz. *Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa and Salmonella typhi* by using Agar disc diffusion method. The zones of inhibition formed were measured in mm and are shown in table-2.

Table No.2: Impact of newly synthesized chlorosubstituted heterocycles against plant pathogens.

Sample Code	*Pseudomonas aeruginosa* MTCC-424 (Gram Negative)				*Salmonella typhi* ATCC-25812 (Gram Negative)				*Staphylococcus aureus* ATCC-33591 (Gram Positive)				*Staphylococcus epidermidis* MTCC-3086 (Gram Positive)			
	AB	SP	ABSP	CL	AB	SP	ABSP	CL	AB	SP	ABSP	CL	AB	SP	ABSP	CL
7a	23	16	25	00	27	22	31	00	15	17	17	00	26	16	27	00
7b	23	16	25	00	26	21	32	00	14	18	16	00	26	17	27	00
8a	23	17	24	00	26	19	33	00	14	21	17	00	28	16	28	00
9a	23	16	24	00	27	18	31	00	13	21	17	00	27	16	27	00

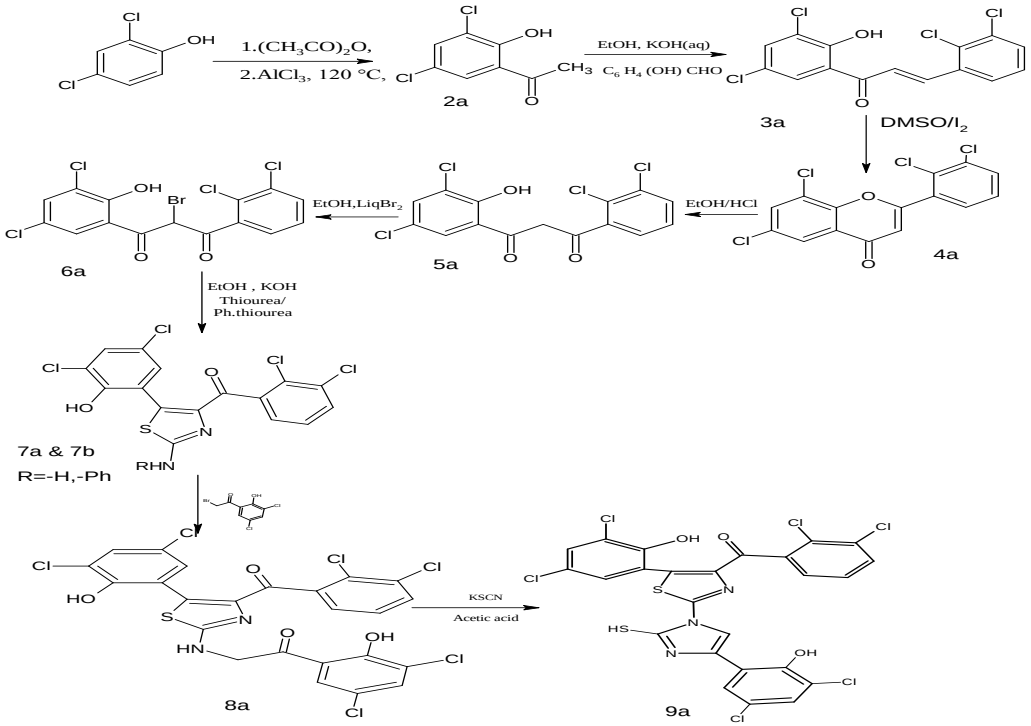
Diameter of inhibition zone (mm)

AB- Antibiotic Disc (Chloramphenicol-10), SP- Sample, ABSP- Antibiotic+Sample, CL- Control (DMSO).

RESULTS AND DISCUSSION

The newly synthesized compounds (7a,7b,8a and 9a) showed good to excellent activity against test pathogens. A further detailed study in the light of Plant pathology is advised.

Scheme-1



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Quantitative structure–activity relationships (QSARs) and pharmacophore modeling for human African trypanosomiasis (HAT) activity of pyridyl benzamides and 3-(oxazolo[4,5-b]pyridin-2-yl)anilides

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DOI 10.1007/s00044-016-1664-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Quantitative structure–activity relationships (QSARs) and pharmacophore modeling for human African trypanosomiasis (HAT) activity of pyridyl benzamides and 3-(oxazolo[4,5-b]pyridin-2-yl)anilides

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Abstract In the present work, quantitative structure–activity relationship and pharmacophore modeling analysis were performed for human African trypanosomiasis healing activity of pyridyl benzamides (dataset-1) and 3-(oxazolo [4,5-b]pyridin-2-yl)anilides (dataset-2). For quantitative structure–activity relationship analysis, a pool of descriptors (mono-dimensional to three-dimensional) was generated, followed by descriptor reduction using objective and subjective feature selection. Multiple splitting was employed for the generation of multiple quantitative structure–activity relationship models to get maximum information about the descriptors that have correlation with the HAT activity of pyridyl benzamides and 3-(oxazolo[4,5-b]pyridin-2-yl)anilides. The genetic algorithm-multilinear regression quantitative structure–activity relationship models have excellent statistical robustness with good external predictive ability. The pharmacophore model and quantitative structure–activity relationship analyses furnished complementary and consensus results to each other.

Keywords QSAR · Pharmacophore model · Human African trypanosomiasis (HAT) · Pyridyl benzamides · 3-(Oxazolo[4,5-b]pyridin-2-yl)anilides

Introduction

Human African trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease usually transmitted by the bite of an infected tsetse fly (*Glossina* genus) and caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* (Ferrins et al., 2014; Sykes et al., 2012). This neglected disease has high occurrence in Africa continent, except North Africa. However, the genome of the parasite has been sequenced and many proteins have been recognized as prospective targets for drug development. Analysis of the genome revealed that *T. brucei* has over 800 genes that make proteins the parasite 'mixes and matches' to evade immune system detection, consequently, developing a vaccine for this disease is very difficult (Barrett et al., 2011; Lutje et al., 2013; Simarro et al., 2012). Moreover, the type of treatment depends on the stage of the disease. The drugs used in the first stage of the disease have lower toxicity and easy to administer. The earlier the disease is identified, the better the probabilities of a cure. But, in majority of cases, the disease is identified in second stage (Barrett et al., 2011; Carvalho et al., 2014; Ferrins et al., 2014; Lutje et al., 2013; Simarro et al., 2012; Sykes et al., 2012). A drug that can cross the blood–brain barrier to reach the parasite is crucial for treatment success in the second stage. Such drugs are mostly toxic and problematical to administer (Barrett et al., 2011; Lutje et al., 2013; Simarro et al., 2012). In Fig. 1, the marketed drugs

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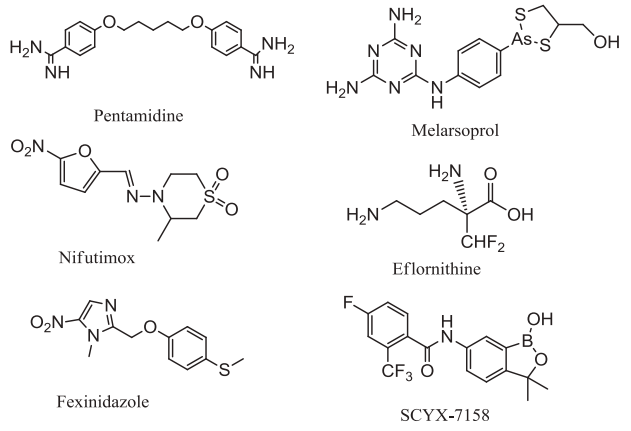


Fig. 1 Marketed and clinical stage drugs for HAT

and drugs in clinical stages have been depicted (Barrett et al., 2011; Carvalho et al., 2014; Ferrins et al., 2014; Gilbert, 2014; Lutje et al., 2013; Nagle et al., 2014; Simarro et al., 2012; Sykes et al., 2012).

To overcome these difficulties, Sykes et al. (2012) employed high-throughput screening (HTS) against *T. brucei* using a library of 87,296 compounds, and discovered a good number of classes with encouraging activity. Unfortunately, some inhibitor series like pyridyl benzamide and its derivatives were excluded in the initial HTS work because they did not satisfied the predefined selection criteria. Later studies (Ferrins et al., 2014) revealed that derivatives of pyridyl benzamide possess HAT activity in nM range with the possibility to treat the disease in second stage. Despite the efforts executed till this date, the search for specific biological target or targets of this series of compounds still persists (Ferrins et al., 2014). In such a situation, computer-aided drug design is considered an attractive tool for lead optimization.

In the past decades, computer-based techniques have emerged as attractive alternatives to conventional 'trial and error' methodology of drug design/discovery to map the mysterious ways of bio-chemistry of drug action, optimization and toxicity reduction (Bukhari et al., 2014, 2015; Ebalunode et al., 2011; Rastija and Masand, 2014; Yoon et al., 2013). Computer-aided drug designing (CADD) is a faster, cheaper and highly result oriented thriving modern technique involving amalgamation of different fields with major emphasis on understanding how different biological molecules interact, to probe the mechanisms of disease and to determine the effective structural features linked with activity/toxicity (Alafeefy et al., 2012; Bandgar et al., 2012; Chavan et al., 2013; Mahajan et al., 2012; Masand et al., 2013; Patil et al., 2012; Pourbasheer et al., 2015). Quantitative structure–activity relationship (QSAR), molecular docking, pharmacophore modeling, etc. are popular CADD methods, which when used in chorus results in highly successful analysis giving maximal of information required for lead (and drug) optimization. These methods provide information about the structural features that govern the specific activity/toxicity of drug candidate and better insight in mechanism of drug action (Barakat et al., 2014; Bukhari et al., 2014, 2015; Huang and Fan, 2011; Masand et al., 2014c, 2015; Rastija and Masand, 2014; Rastija et al., 2013; Yang et al., 2014; Yoon et al., 2013).

Molecular docking is especially more promising when enough information is available about the target receptor (protein or bio-polymer) with which the drug interacts (Mahajan et al., 2012). The receptor with which pyridyl benzamides and 3-(oxazolo[4,5-b]pyridin-2-yl)anilides interact is unknown (Ferrins et al., 2014), hence, QSAR and pharmacophore modeling were performed to determine the structural features that have good correlation with the HAT activity of pyridyl benzamides and 3-(oxazolo[4,5-b]pyridin-2-yl)anilides.

Experimental methodology

Experimental datasets

In the present work, HAT activities of two different datasets comprising different heterocyclic scaffolds were subjected to QSAR and pharmacophore modeling. The reported IC_{50} (μM) values for HAT activity were converted to pIC_{50} ($-\log_{10}IC_{50}$) before QSAR analysis.

Dataset-1

The dataset-1 consists of 32 pyridyl benzamides screened against *T. brucei* with a variety of substituents at diverse positions (Ferrins et al., 2014). The IC_{50}, pIC_{50} along with the substituents are tabulated in Table 1.

Dataset-2

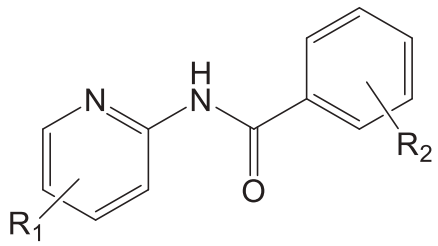
The datset-2 selected for the present study comprises 31 derivatives of 3-(oxazolo[4,5-b]pyridin-2-yl)anilide previously reported to have HAT activity (Ferrins et al., 2013). The molecules possess different types of substituents present at different positions. The IC_{50}, pIC_{50} along with the substituents are tabulated in Table 2.

Modeling and molecular descriptors calculation

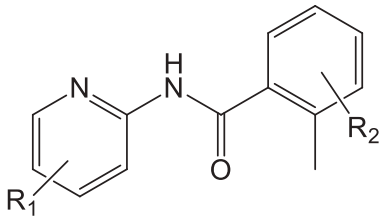
In the present work, for QSAR analysis the procedure reported in the literature has been followed (Mahajan et al., 2012; Masand et al., 2013, 2015; Rastija and Masand, 2014; Rastija et al., 2013). The structures were drawn using ChemSketch 12 freeware followed by energy minimization

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Table 1 IC_{50}, pIC_{50} along with the substituents for dataset-1



1-23



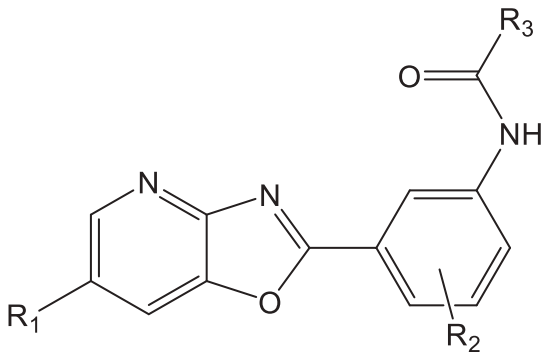
24-32

S. no.	R_1	R_2	Exp. IC_{50}	Exp. pIC_{50}
1	H	2-Me	3.03	5.5190
2	4-CN	2-Me	2.3	5.6380
3	4-Me	2-Me	2.1	5.6780
4	4-Cl	2-Me	2.1	5.6780
5	4-Br	2-Me	1.8	5.7450
6	4-F	2-Me	0.51	6.2920
7	4-C≡CPh	2-Me	1.7	5.7700
8	4-C≡CCH_2-*i*Pr	2-Me	1.1	5.9590
9	4-Ph	2-Me	2	5.6990
10	5-OMe	2-Me	3.8	5.4200
11	6-CH=$CH(CH_2)_2CH_3$	2-Me	6	5.2220
12	6-NH_2	2-Me	4.6	5.3370
13	H	H	9.07	5.0420
14	H	2-Et	2.74	5.5620
15	H	2-Me, 3-F	0.89	6.0510
16	H	3-F	7.33	5.1350
17	H	2-Me, 3-Cl	0.63	6.2010
18	H	2-Me, 3-Br	5.7	5.2440
19	H	2,3-diMe	3.5	5.4560
20	H	2-Me, 4-F	1.9	5.7210
21	H	2-Me, 4-Cl	1.1	5.9590
22	H	2-Me, 4-Br	1.1	5.9590
23	H	2,4-diMe	0.98	6.0090
24	H	3-F, 4-F	0.41	6.3870
25	4-Me	3-F	0.83	6.0810
26	4-Me	3-F, 4-F	0.9	6.0460
27	4-Cl	3-F	0.47	6.3280
28	4-Cl	3-F, 4-F	0.53	6.2760
29	4-F	3-F	0.1	7.0000
30	4-F	3-F, 4-F	0.19	6.7210
31	5-OMe	3-F	2.3	5.6380
32	5-OMe	4-F	2.6	5.5850

using MMFF94 force field in TINKER. The optimized structures were used as input for calculation of myriad number of descriptors using PaDEL 2.21 as a descriptor calculator. The descriptor pool of more than 16,000 descriptors consists of mono-dimensional (1D) to three-dimensional (3D), electro-topological, finger-prints and other descriptors. As all the calculated descriptors do not contain valuable information, hence, objective feature selection was employed to reduce the number of descriptors. As a rule, constant, near constant (>85 %) and highly correlated ($|R| > 85$ %) descriptors were eliminated before subjective feature selection (SFS) using QSARINS-Chem 2.2.1. This resulted in a reduced cluster of 264 and 181 descriptors for dataset-1 and 2, respectively, with a wide set

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Table 2 IC_{50}, pIC_{50} along with the substituents for dataset-2



S. no.	R_1	R_2	R_3	IC_{50}	pIC_{50}
1	H	4-Cl	2-Furanyl	0.22	6.658
2	H	4-Cl	3-Me-2-furanyl	0.65	6.187
3	H	4-Cl	5-Isoxazolyl	3.2	5.495
4	H	4-Cl	5-Oxazolyl	1.5	5.824
5	H	4-Cl	3-Furanyl	0.3	6.523
6	H	4-Cl		1.8	5.745
10	H	4-Cl	Phenyl	1.5	5.824
13	H	4-Cl	2-Pyridinyl	5.7	5.244
14	H	4-Cl	4-Pyridinyl	3.4	5.469
17	H	H	2-Furanyl	0.34	6.469
18	H	H	3-Me-2-furanyl	0.17	6.77
19	H	H	5-Oxazolyl	2.9	5.538
20	H	H	3-Furanyl	0.6	6.222
21	H	H	4-Thiazolyl	1.3	5.886
26	H	4-OMe	2-Furanyl	1.1	5.959
27	H	4-Me	2-Furanyl	6.2	5.208
28	H	4-F	2-Furanyl	6.3	5.201
32	H	6-Me	2-Furanyl	0.94	6.027
33	H	6-Me	3-Me-2-furanyl	0.57	6.244
35	H	6-Me	3-Furanyl	0.31	6.509
36	H	6-Me	4-Thiazolyl	2.6	5.585
37	H	6-F	2-Furanyl	0.29	6.538
38	H	6-F	3-Me-2-furanyl	0.1	7
39	H	6-F	5-Oxazolyl	2	5.699
40	H	6-F	3-Furanyl	0.12	6.921
41	H	6-F	4-Thiazolyl	0.76	6.119
42	Ph	H	2-Furanyl	0.12	6.921
43	4-OMe-Ph	H	2-Furanyl	0.63	6.201
44	4-Cl-Ph	H	2-Furanyl	0.55	6.26
45	H	H	2-Furanyl	0.78	6.108
46	H	H	3-Furanyl	1	6

of theoretical molecular descriptors that takes into account different structural features, viz. constitutional (0D), 1D, bi-dimensional (2D), and 3D, capturing and magnifying distinct aspects of chemical structures.

Model development

QSAR models are developed (1) to determine the structural features that are correlated with the desired activity, and (2) to predict for a compound before its actual synthesis and/or biological screening (Masand et al., 2014a, b 2015). The predictive ability of a QSAR model can be defined as the ability of a model to correctly predict the biological activity of compounds that were not used for model development.

To get maximal information, models were developed using divided and undivided whole datasets. The datasets were randomly divided into training (80 %) and prediction (20 %) set before descriptor selection. Multiple splitting was performed to develop multiple QSAR models. A molecule in the training set of a splitting may or may not be in the training set of another splitting. The Genetic Algorithm (GA) module of QSARINS-Chem 2.1.1 (Gramatica et al., 2013, 2014) was used for selection of optimum number and set of descriptors. For the sake of simplicity and to avoid the problem of over-fitting, the heuristic search of descriptors was limited to three (for dataset-1) and four (for dataset-2) descriptors using the defaults settings in QSARINS-Chem 2.1.1. Q^2_{loo} was used as a fitness function to avoid the problem of naive Q^2. The strategy used in QSAR model development has been summarized in Fig. 2.

Model validation

Appropriate model validation is an important aspect of QSAR model development. The statistical qualities and validity of the genetic algorithm-multilinear regression (GA-MLR) equations were established by means of: (a) internal validation or cross-validation (CV) by leave-one-out (LOO) and leave-many-out (LMO) procedure; (b) using the prediction set; (c) data randomization, i.e., Y-scrambling; and (d) examining if the following conditions are satisfied (Masand et al., 2015): $R^2_{tr} \geq 0.6$, $Q^2_{loo} \geq 0.5$, $Q^2_{LMO} \geq 0.6$, $R^2 > Q^2$, $R^2_{ex} \geq 0.6$, $RMSE_{tr} < RMSE_{cv}$, $\Delta K \geq 0.05$, $CCC \geq 0.80$, $Q^2\text{-}F^n \geq 0.60$, $r^2_m \geq 0.6$, $(1-r^2/r_o^2) < 0.1$, $0.9 \leq k \leq 1.1$ or $(1-r^2/r'^2_o) < 0.1$, $0.9 \leq k' \leq 1.1$, $|r_o^2 - r'^2_o| < 0.3$ with RMSE and MAE close to zero. The threshold values of these parameters ensure robustness and external predictive ability of a GA-MLR model. Thus, all the models having low internal and external predictive ability were subsequently rejected.

Pharmacophore model development

For pharmacophore modeling, all the molecules in the dataset were aligned using the lowest energy conformer of the most active compounds in the datasets. PyMOL 1.7 and

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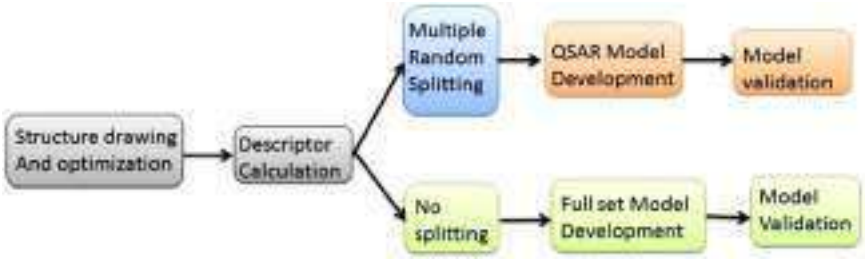


Fig. 2 Strategy used in QSAR model development

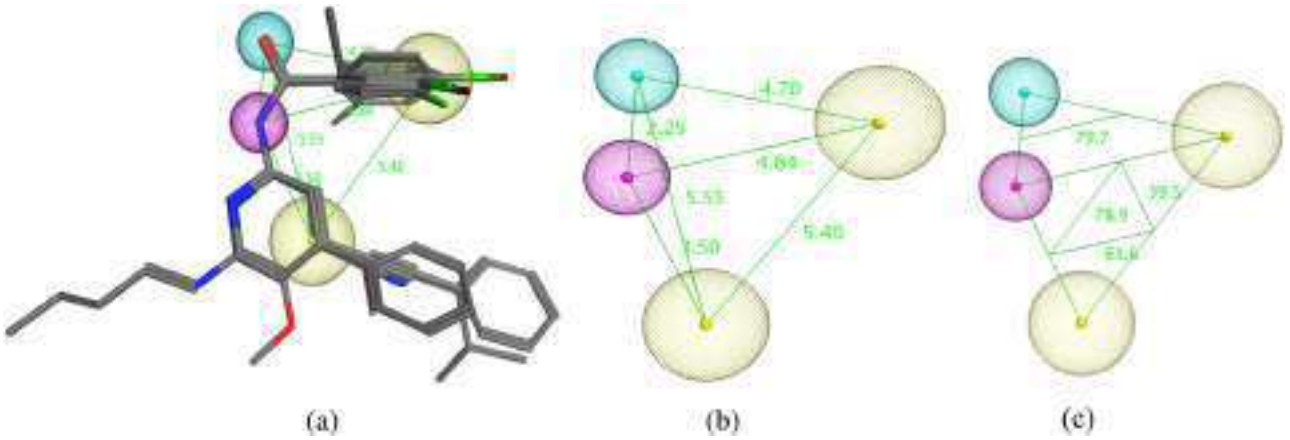


Fig. 3 Consensus pharmacophore model for dataset 1 (*cyan*: H-acceptor, *magenta*: H-donor, *yellow*: hydrophobic). **a** Pharmacophore model with aligned ligands; **b** pharmacophore model with distances (Å) between different features; **c** pharmacophore model with angles between different features

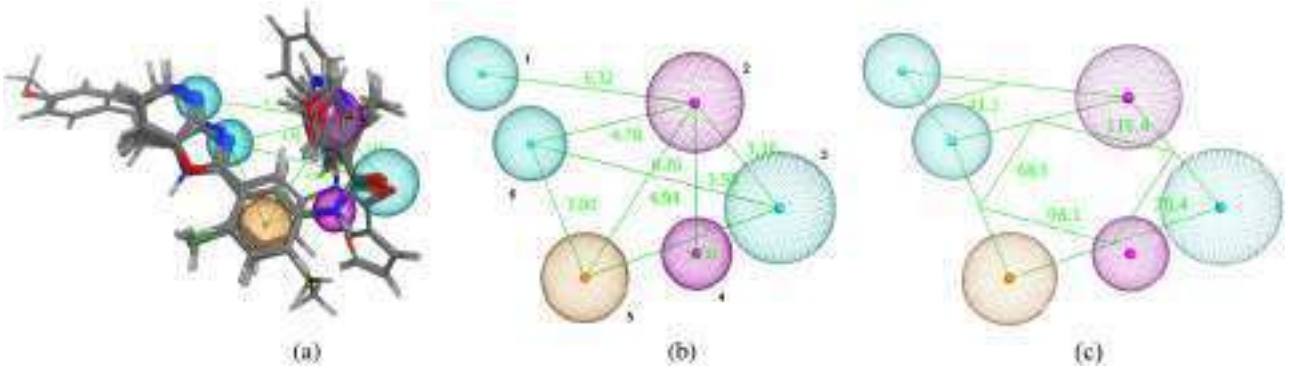


Fig. 4 Consensus pharmacophore model for dataset 2 (*cyan*: H-acceptor, *magenta*: H-donor, *yellow*: hydrophobic). a Pharmacophore model with aligned ligands; **b** pharmacophore model with distances (Å) between different features; **c** pharmacophore model with angles between different features

LIQUID 1.0 were used for the generation of consensus pharmacophore model using default settings.

Results and discussion

Consensus pharmacophore model for dataset-1

The consensus pharmacophore model reveals that the pharmacophoric pattern (see Fig. 3) for dataset-1 consists of two hydrophobic regions at a distance of 5.40 Å from each other, one H-bond acceptor at distance of 4.70 and 5.55 Å from the two hydrophobic regions, and a H-bond donor region at a distance of 4.84 and 3.50 Å from the two hydrophobic regions.

Consensus pharmacophore model for dataset-2

The consensus pharmacophore model for dataset-2 consists of six pharmacophoric features (see Fig. 4). The H-bond

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Table 3 Statistical parameters for various GA-MLR QSAR models for dataset-1

S. no	Statistical parameter	Model-1.1	Model-1.2	Model-1.3	Model-1.4
1	N_{tr}	32	26	26	26
2	N_{ex}	--	6	6	6
3	Number of descriptors	3	3	3	3
4	R^2_{tr}	0.8284	0.8155	0.8142	0.8139
5	$R^2_{adj.}$	0.8100	0.7903	0.7889	0.7886
6	LOF	0.0509	0.0628	0.0466	0.0467
7	Kxx	0.2148	0.1665	0.2122	0.2358
8	ΔK	0.1547	0.1717	0.1569	0.2031
9	$RMSE_{tr}$	0.1833	0.1928	0.1785	0.1786
10	MAE_{tr}	0.1572	0.1597	0.1161	0.1115
11	CCC_{tr}	0.9061	0.8983	0.8976	0.8974
12	S	0.1960	0.2096	0.1941	0.1942
13	F	45.0488	32.4047	32.1362	32.0824
14	R^2_{cv} (Q^2_{loo})	0.7719	0.7342	0.7707	0.7672
15	$RMSE_{cv}$	0.2114	0.2314	0.1983	0.1998
16	MAE_{cv}	0.1806	0.1923	0.1319	0.1303
17	CCC_{cv}	0.8746	0.8556	0.8741	0.8754
18	Q^2_{LMO}	0.7343	0.7425	0.7456	0.7240
19	R^2_{Yscr}	0.1072	0.1092	0.1236	0.1100
20	$RMSE_{ex}$	–	0.1504	0.2283	0.2235
21	MAE_{ex}	–	0.1266	0.1929	0.1931
22	R^2_{ex}	–	0.8298	0.8271	0.8271
23	Q^2_{F1}	–	0.8770	0.8289	0.8359
24	Q^2_{F2}	–	0.8092	0.8186	0.8260
25	Q^2_{F3}	–	0.8878	0.6962	0.7086
26	CCC_{ex}	–	0.8871	0.9074	0.9021

donor feature **2** is at a distance of 4.94, 6.32, and 4.78 Å from hydrophobic **5**, H-bond acceptor **1** and **6** features, respectively. The H-bond acceptor region **3** is at a distance of 3.16, 6.76, and 5.00 Å from H-bond donor region **2**, H-bond acceptor region **6**, and hydrophobic region **5**, respectively.

QSAR analysis

The datasets used in the present study are small but the molecules are either positional or functional isomers, thereby, cover significant chemical space. For small datasets, we have previously demonstrated (Masand et al., 2015) that at least one QSAR model must be built using undivided whole dataset to capture maximum relevant descriptors, which in turn not only provides useful information for future modification but is useful for comparison and assessment of QSAR models constructed using divided datasets, also. Therefore, models were derived using divided and undivided datasets.

While performing the QSAR analysis, generally stepwise regression, GA, etc. algorithms are employed for SFS. This results in a good number of MLR models with nearly comparable statistical characters embracing different descriptors. Mostly, in such a situation, only one MLR model is selected on the basis of its statistical performance. The drawbacks, however, of this 'first among equals' approach (Masand et al., 2014a, b) are (1) accurate and rational association of descriptors with correct structural features is challenging for a QSAR model involving complex/esoteric descriptors only, (2) a single QSAR model may be influenced by (i) the method of splitting, composition of training and prediction sets, procedure used for descriptor pruning and selection, and (ii) some molecules in the training/prediction dataset. An easy and possible solution to overcome the different drawbacks of 'first among equals' approach is to build multiple models using multiple splitting (Masand et al., 2014a, 2015). This also helps in capturing less privileged yet useful structural features that govern the activity. Hence, in the present study, multiple models were built for both the sets.

Dataset-1: For dataset-1, the various GA-MLR QSAR models are as follow:

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Table 4 Experimental and predicted pIC_{50} values along with the status of the molecules in different models

S. no.	Exp. pIC_{50}	Status model-1.1	Pred. pIC_{50} model-1.1	Status model-1.2	Pred. pIC_{50} model-1.2	Status model-1.3	Pred. pIC_{50} model-1.3	Status model-1.4	Pred. pIC_{50} model-1.4
1	5.5190	Training	5.4457	Training	5.4674	Prediction	5.4166	Prediction	5.4850
2	5.6380	Training	5.5113	Training	5.5605	Training	5.5774	Training	5.6531
3	5.6780	Training	5.6936	Training	5.4025	Training	5.3535	Training	5.4856
4	5.6780	Training	5.7937	Training	5.7839	Training	5.7267	Training	5.7525
5	5.7450	Training	5.6184	Prediction	5.6472	Training	5.6961	Training	5.7507
6	6.2920	Training	6.0440	Training	6.1053	Training	6.2829	Training	6.1439
7	5.7700	Training	5.5688	Training	5.9221	Training	5.8677	Training	5.8572
8	5.9590	Training	5.8578	Training	5.6516	Prediction	5.5349	Prediction	5.5589
9	5.6990	Training	5.5577	Training	5.7362	Training	5.7246	Training	5.6937
10	5.4200	Training	5.5854	Training	5.6094	Training	5.5644	Training	5.5986
11	5.2220	Training	5.3502	Prediction	5.4240	Training	5.3370	Training	5.3955
12	5.3370	Training	5.2989	Training	5.4585	Prediction	5.3818	Prediction	5.5919
13	5.0420	Training	5.1085	Training	5.1915	Training	5.0538	Training	5.0516
14	5.5620	Training	5.4327	Training	5.6515	Training	5.6200	Training	5.4868
15	6.0510	Training	6.0293	Prediction	6.0860	Training	6.0680	Training	6.0254
16	5.1350	Training	5.1857	Prediction	5.3721	Training	5.3065	Training	5.1638
17	6.2010	Training	5.9086	Training	5.9231	Training	5.6231	Training	5.6841
18	5.2440	Training	5.6305	Training	5.6857	Training	5.6521	Training	5.7911
19	5.4560	Training	5.6239	Training	5.6531	Training	5.6474	Training	5.5023
20	5.7210	Training	5.8896	Training	5.7213	Prediction	5.9763	Prediction	5.8707
21	5.9590	Training	6.0595	Prediction	5.9813	Training	5.9427	Training	5.9459
22	5.9590	Training	5.7816	Training	5.7378	Training	5.9660	Training	5.9743
23	6.0090	Training	5.7663	Training	5.7348	Training	5.7544	Training	5.9328
24	6.3870	Training	6.1195	Training	6.0564	Training	6.2657	Training	6.1155
25	6.0810	Training	6.3177	Training	6.0790	Training	5.9855	Training	6.0830
26	6.0460	Training	6.3863	Training	6.0855	Prediction	6.2253	Prediction	6.1972
27	6.3280	Training	6.2824	Training	6.4306	Training	6.3806	Training	6.2962
28	6.2760	Training	6.3741	Training	6.3844	Training	6.3129	Training	6.3017
29	7.0000	Training	6.7187	Training	6.9288	Prediction	6.8487	Prediction	6.8315
30	6.7210	Training	6.7775	Training	6.8455	Training	6.7595	Training	6.8521
31	5.6380	Training	5.9028	Training	5.8545	Training	5.7107	Training	5.7471
32	5.5850	Training	5.7374	Prediction	5.4196	Training	5.5969	Training	5.4917

Model-1.1 (undivided dataset): $pIC_{50} = 4.8523(\pm 0.3676) - 0.9802(\pm 0.4082) * GATS8c + 0.1240(\pm 0.0734) * RDF40p + 0.0552(\pm 0.0099) * RDF55s$

Model-1.2: $pIC_{50} = 6.4521(\pm 1.2282) - 3.1455(\pm 2.3630) * E1s + 0.0545(\pm 0.0492) * RDF40m + 0.0489(\pm 0.0111) * RDF55s$

Model-1.3: $pIC_{50} = 5.2245(\pm 0.9946) - 3.4904(\pm 1.8452) * E1s + 0.2540(\pm 0.1731) * AD2D423 + 0.9151(\pm 0.2562) * cbrtRDF55s$

Model-1.4: $pIC_{50} = 7.4582(\pm 0.9582) - 0.8339(\pm 0.5028) * GATS6m + 0.0425(\pm 0.0128) * RDF55s - 3.2008(\pm 1.8707) * E1s$

The various parameters calculated for models 1.1–1.4 have been tabulated in Table 3. From Table 3, it is clear that the developed models satisfy threshold values for most of the internal and external validation parameters. For dataset-1, GA analysis for undivided whole dataset resulted in many QSAR models, but, only one model (model-1) was found to satisfy the threshold values for various statistical parameters. A simple comparison of different statistical parameters for different models (see Table 3) reveals that the models 1.1–1.4 are statistically robust with good external predictive ability. For the model 1.2, $Q^2_{F1} > R^2$, this leads to the contrasting inference that the model

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Table 5 Statistical parameters for various GA-MLR QSAR models for dataset-2

S. no.	Statistical parameter	Model-2.1	Model-2.2	Model-2.3	Model-2.4
1	N_{tr}	31	31	25	25
2	N_{ex}	--	--	6	6
3	Number of descriptors	4	4	4	4
4	R^2_{tr}	0.8176	0.7834	0.8292	0.8650
5	$R^2_{adj.}$	0.7895	0.7500	0.7951	0.8380
6	LOF	0.0840	0.0997	0.0948	0.0750
7	Kxx	0.2711	0.2185	0.2343	0.2425
8	ΔK	0.0590	0.1123	0.0738	0.0593
9	$RMSE_{tr}$	0.2150	0.2343	0.2094	0.1862
10	MAE_{tr}	0.1753	0.1968	0.1741	0.1663
11	CCC_{tr}	0.8996	0.8785	0.9067	0.9276
12	*s*	0.2348	0.2558	0.2341	0.2082
13	*F*	29.1302	23.5052	24.2815	32.0406
14	R^2_{cv} (Q^2_{loo})	0.7480	0.6889	0.7348	0.7864
15	$RMSE_{cv}$	0.2527	0.2808	0.2610	0.2343
16	MAE_{cv}	0.2076	0.2357	0.2175	0.2094
17	CCC_{cv}	0.8604	0.8267	0.8539	0.8841
18	Q^2_{LMO}	0.7441	0.7246	0.7420	0.8083
19	R^2_{Yscr}	0.1426	0.1495	0.1479	0.1690
20	$RMSE_{ex}$	–	–	0.2378	0.2456
21	MAE_{ex}	–	–	0.1828	0.1874
22	R^2_{ex}	–	–	0.7574	0.7417
23	Q^2_{F1}	–	–	0.7670	0.7515
24	Q^2_{F2}	–	–	0.7478	0.7310
25	Q^2_{F3}	–	–	0.7798	0.7651
26	CCC_{ex}	–	–	0.8477	0.8302

is able to predict better for the prediction set than the training set.

In all the models, RDF55s (radial distribution function-055/weighted by relative I-state, a 3D-descriptor) is commonly present with a positive coefficient. Therefore, RDF55s has a positive correlation with the activity. Another descriptor with positive relation with the activity is AD2D423 (presence of oxygen-halogen at a topological distance of 6). E1s (1st component accessibility directional WHIM index/weighted by relative I-state, a 3D-descriptor) is present in the models 2–4 with a negative coefficient, indicating its negative relation with the activity.

Model-1.1

The high value of R^2_{tr}, CCC_{tr}, R^2_{cv}, CCC_{cv} and *F* with close value of R^2_{adj} indicates that the model is statistically robust with adequate number of descriptors, i.e., it is free from over-fitting. This is further confirmed by the low value of LOF, $RMSE_{tr}$, *s*, $RMSE_{cv}$, and R^2_{Yscr}. The correlation, residual, and applicability domain plots further confirm the statistical quality of the model. In addition, the model is based on descriptors having very low inter-correlation (see the supplementary material).

Models 1.2–1.4

For models 1.2–1.4, R^2_{tr}, CCC_{tr}, R^2_{cv}, CCC_{cv}, R^2_{adj} and *F* satisfy the recommended threshold value, which indicates that the models are statistically robust with acceptable number of descriptors. The CV parameters R^2_{cv}, $RMSE_{cv}$, MAE_{cv}, CCC_{cv}, and Q^2_{LMO} vindicate the statistical robustness of the models. The external predictive ability of the models is confirmed by the high values of R^2_{ex}, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, and CCC_{ex}.

In Table 4, the experimental and predicted pIC_{50} values along with the status of the molecules in different models have been tabulated.

Dataset-2: For dataset-2, the statistical parameters for various GA-MLR QSAR models are tabulated in Table 5.

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Table 6 Experimental and predicted pIC_{50} values along with the status of the molecules in different models

S. no.	Exp. pIC_{50}	Status model-1	Pred. pIC_{50} model-1	Status model-2	Pred. pIC_{50} model-2	Status model-3	Pred. pIC_{50} model-3	Status model-4	Pred. pIC_{50} model-4
1	6.6580	Training	6.5467	Training	6.4296	Training	6.5480	Training	6.4840
2	6.1870	Training	6.2442	Training	6.1332	Training	6.2457	Training	6.3019
3	5.4950	Training	5.6939	Training	5.4748	Training	5.7024	Training	5.7097
4	5.8240	Training	5.6856	Training	5.7094	Training	5.6941	Training	5.7602
5	6.5230	Training	6.5996	Training	6.4762	Training	6.6009	Training	6.5297
6	5.7450	Training	5.7470	Training	5.6548	Training	5.7577	Training	5.8656
7	5.8240	Training	5.5625	Training	5.5603	Training	5.5795	Training	5.5277
8	5.2440	Training	5.3701	Training	5.3789	Prediction	5.3871	Prediction	5.4355
9	5.4690	Training	5.8982	Training	5.8452	Training	5.9079	Training	5.7716
10	6.4690	Training	6.3096	Training	6.1833	Training	6.3113	Training	6.3235
11	6.7700	Training	6.3267	Training	6.2714	Prediction	6.3271	Prediction	6.2664
12	5.5380	Training	5.4968	Training	5.5203	Training	5.5056	Training	5.4149
13	6.2220	Training	6.4666	Training	6.3659	Prediction	6.4676	Prediction	6.3956
14	5.8860	Training	5.7585	Training	5.7135	Training	5.7683	Training	5.6735
15	5.9590	Training	5.6389	Training	5.7195	Training	5.6374	Training	5.7643
16	5.2080	Training	5.3692	Training	5.4802	Training	5.3752	Training	5.2679
17	5.2010	Training	5.3822	Training	5.7036	Training	5.3890	Training	5.4388
18	6.0270	Training	6.3231	Training	6.2825	Training	6.3310	Training	6.2565
19	6.2440	Training	6.0928	Training	6.0622	Training	6.1008	Training	6.0480
20	6.5090	Training	6.5092	Training	6.4943	Prediction	6.5165	Prediction	6.4971
21	5.5850	Training	5.4202	Training	5.4028	Training	5.4376	Training	5.4607
22	6.5380	Training	6.6790	Training	6.7607	Training	6.6888	Training	6.7277
23	7.0000	Training	6.6736	Training	6.7892	Training	6.6827	Training	6.6325
24	5.6990	Training	5.6207	Training	5.8055	Training	5.6388	Training	5.7560
25	6.9210	Training	6.9418	Training	7.0711	Training	6.9505	Training	7.0062
26	6.1190	Training	6.1746	Training	6.3624	Training	6.1920	Training	6.2441
27	6.9210	Training	6.5269	Training	6.5242	Training	6.5261	Training	6.7398
28	6.2010	Training	6.3307	Training	6.3314	Training	6.3300	Training	6.3100
29	6.2600	Training	6.2680	Training	6.2274	Prediction	6.2681	Prediction	6.4581
30	6.1080	Training	6.3574	Training	6.3239	Prediction	6.3573	Prediction	6.1536
31	6.0000	Training	6.3396	Training	6.2961	Training	6.3397	Training	6.2262

Model-2.1 (undivided dataset): $pIC_{50} = 3.6176(\pm1.1170) + 4.7639(\pm1.2164) * MATS7s - 0.3082(\pm 0.1906) * FP144 + 0.9061(\pm0.2021) * KRFPC3159 - 1.2136(\pm0.9844) * AM1_LUMO$

Model-2.2 (undivided dataset): $pIC_{50} = 3.4617(\pm1.2086) + 3.9877(\pm1.2580) * MATS7s - 0.2446(\pm0.2206) * ExtFP474 + 0.8142(\pm0.2232) * KRFPC3159 - 1.4583(\pm1.0627) * AM1_LUMO$

Model-2.3: $pIC_{50} = 3.6318(\pm1.2369) + 4.7733(\pm1.2560) * MATS7s - 0.3012(\pm0.2150) * FP144 + 0.8978(\pm0.2222) * KRFPC3159 - 1.2077(\pm1.0827) * AM1_LUMO$

Model-2.4: $pIC_{50} = 3.6897(\pm0.8080) + 4.7111(\pm1.1005) * MATS7s - 0.2938(\pm0.1905) * FP144 + 0.9284(\pm0.1977) * KRFPC3159 + 0.0221(\pm0.0133) * PEOE_VSA_POL$

From Table 5, it is clear that all the models satisfy the threshold value for many parameters that are used to judge the external predictive ability of a QSAR model. MATS7s (Moran autocorrelation–lag 7/weighted by I-state, a 3D-descriptor) and KRFPC3159 (a finger print descriptor which stands for presence of furan ring) are present in all the models with positive coefficient. This indicates that furan ring has good correlation with the activity and it must be retained in future developments. A plausible explanation of molecular descriptor MATS7s could be that the compounds should have atoms at a topological distance of 7 with different I-state as a tendency. This means that one atom *i* should have I-state higher than the average I-state of the molecule and the other atom *j* should display the opposite.

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From models 2.1–2.3, it appears that AM1_LUMO (least unoccupied molecular orbital calculated by AM1 method) has negative correlation with the activity. AM1_LUMO signifies the overall eletrophilicity of a molecule. To enhance the activity, the value of MATS7s and KRFPC3159 must be as high as possible, whereas reverse is true for AM1_LUMO. PEOE_VSA_POL is a descriptor that corresponds to van de Waal's polar surface area. The positive coefficient for PEOE_VSA_POL indicates its positive correlation with the activity.

In Table 6, the experimental and predicted pIC_{50} values along with the status of the molecules in different models have been presented.

Conclusions

In conclusion, robust QSAR models with good external predictive ability have been developed. The developed models, since, satisfy the threshold values for many statistical parameters that are essential to ascertain the quality and utility of a QSAR model, the developed models could be useful for future optimization of the activity profile of the molecules used in dataset 1 and 2. The pharmacophore models revealed the characteristic features that are essential for activity. Both pharmacophore and QSAR models provide consensus and complementary prospective ideas about the structural features that must be considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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Computational Strategies to Explore Antimalarial Thiazine Alkaloid Lead Compounds Based on an Australian Marine Sponge *Plakortis Lita*

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ABSTRACT

In this work, an attempt was made to propose new leads based on the natural scaffold Thiaplakortone-A active against malaria. The 2D QSAR studies suggested that three descriptors correlate with the anti-malarial activity with an R^2 value of 0.814. Robustness, reliability and predictive power of the model were tested by internal validation, external validation, Y-scrambling and Applicability domain analysis. HQSAR studies were carried out as an additional tool to find the sub-structural fingerprints. The CoMFA and CoMSIA models gave Q^2 values of 0.813 and 0.647, and R^2_{ncv} values of 0.994 and 0.984, respectively. Using the 2D-QSAR equation, the activity values of the seven modified compounds were calculated and it was found that three molecules showed good anti-malarial activity. Molecular docking of the 42 Thiaplakortone-A derivatives with *P. falciparum* calcium-dependent protein kinase 1 (*Pf*CDPK1) was carried out to find out protein-ligand interactions. Data mining of the bioassay dataset AID: 504850 using the classifier based on Random Forest (RF) of Weka suggested that all of the eight molecules selected and three out of the seven virtual molecules were anti-malarial active. Both the virtual molecules and drug molecules were docked with CYP3A4, indicating that the virtual molecules could metabolize easily. Toxicity studies using Osiris shows that three molecules showed no toxic characters.

Keywords: Malaria, 2D-QSAR, HQSAR, 3D-QSAR, Molecular docking

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Introduction

Malaria is a devastating global health threat. Approximately half of the world population is at the risk of being infected by the disease (White et al., 2014). Malaria is caused by five *Plasmodium* species: *P. falciparum, P. ovale, P. vivax, P. malarie* and *P. knowlesi*, of which *P. falciparum*, sources cerebral malaria and is the primary cause of mortality. Because of the emergence of multi drug-resistant pathogens, there is an urgent necessity for the development of new drugs. Many of the newly synthesized medicines do possess many side effects. Many multinational drug companies keep unethical business and profit-oriented mindset which leaves, insufficient input in promoting research. Thus research and development, leading to the discovery of medicines for diseases which affect the third world countries, are meager. The increase and spread of artemisinin-resistant parasites is alarming, since no drugs are available to replace the ACTs as the frontline anti-malarial treatment. This necessitates the importance of modification of the existing drugs or of designing new drugs.

Calcium-dependent protein kinases are lacking in human beings, but their presence is reported in plants and Alveolates (Harper and Harmon, 2005). *Pf*CDPK1 is a calcium-dependent calmodulin-independent protein kinase which is expressed in the asexual blood stages of the parasite responsible for disease pathology (Zhao et al., 1993). It is concerned in parasite motility and host cell invasion, where it is able to phosphorylate components of the molecular motor that drives parasite invasion of red blood cells (Green et al., 2008; Holder et al., 2012). The prevention of this invasion process could break the parasite lifecycle, causing the parasites to die. Pf CDPK1 therefore represents a novel target for the potential treatment of malaria. Earlier workers have reported inhibitors of *Pf*CDPK1 and inhibitors of the CDPK1 enzymes from the

related Apicomplexan protozoa, Toxoplasma gondii and Cryptosporidium parvum (Kato et al. 2008; Lemercier et al. 2009).

The effectiveness of natural products has stimulated scientists to search for new paths in drug design (Newman et al., 2012)**.** Due to the ease of accessibility, pharmaceutical synthesis has drawn greatest consideration towards herbal medicines. One fourth of the drugs prescribed worldwide at present comes from plants and 60% of anti-infectious drugs already on the market or under clinical investigations are of natural origin (Sala et al., 2011). This highlights the importance of developing natural products based drugs for diseases like malaria (López et al., 2009).

Many scientists have put in their efforts to conduct studies to understand the anti-malarial activities of plant based products. Researchers have reported the *in vivo* and *in vitro* studies of the *Aspidosperma* (Apocynaceae) plant against malarial parasite and concluded that the plant species is likely to be useful in the further development of an anti-malarial drug (Aguiar et al., 2015). Mojarrab et al., studied the anti-malarial activity of the three Iranian *Artemisia* species, *A. ciniformis*, *A. biennis* and *A. turanica* by invitro β-hematin formation assay. They observed that the dichloromethane (DCM) extract of *A. ciniformis* and ethyl acetate (EtOAc) extracts of *A. biennis* and *A. turanica* showed significant anti-malarial activities (Mojarrab et al., 2015). But it can be seen that many of the phytochemicals as such are not so active against the malarial parasites. Possibility of another derivative with more biological activity is not probed. This could result in the loss of vital information regarding the formulation of any active derivatives out of the chosen phytochemicals. Therefore it is wise to develop derivatives out of the phytochemicals and examine their activities.

Thiaplakortones A-D displayed significant growth inhibition against chloroquine-sensitive (3D7) and chloroquine-resistant (Dd2) *P. falciparum* (IC_{50} values <651 nM) and showed only moderate cytotoxicity against HEK293 cells (IC_{50} values >3.9 μM). Thiaplakortone-A, is the most active natural product found in the Australian marine sponge *Plakortis lita* and shows IC_{50} values of 51.0 and 6.6 nM against chloroquine-sensitive (3D7) and multidrug resistant (Dd2) *P. falciparum* parasite lines, respectively (Davis et al., 2013). These studies suggest that none of the modification resulted in getting derivatives with activity higher than that of Thiaplakortone-A.

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Synthesis and structural characterization of new compounds and the subsequent understanding of their biological activity are rather cumbersome procedures which demand time, expense and hard work. This is where computational drug design comes for our help and understanding. Quantitative Structure-Activity Relationship (QSAR) study can be used to demonstrate how the structural features of molecules relate to the biological activity using chemometric methods. Thus we can replace the expensive biological tests or experiments, since QSAR studies can be used to predict the responses to the new compounds. The QSAR technique mathematically correlates the biological activity of the molecules with their various structural features called molecular descriptors. Accordingly, the QSAR technique has been widely reformed by different groups of researchers for identifying novel chemical entities. We have earlier reported the QSAR and molecular docking studies for a series of 7-substituted-4-aminoquinoline derivatives to study their anti-malarial activity (Shibi et al., 2015). Sainy and Sharma have reported the anti-malarial activity studies of thiolactone derivatives using QSAR and molecular docking studies (Sainy and Sharma, 2015). Masand et al., 2015 reported the application of QSAR studies to find out the anti-proliferative activity of substituted Phenyl 4-(2-Oxoimidazolidin-1-yl) benzenesulfonates. In an attempt for finding out new potent anti-malarial agents, we have performed 2D- and 3D-QSAR studies on Thiaplakortone-A derivatives for quantifying the necessary structural and physicochemical requirements for designing some leads as potent anti-malarial drugs.

The present study is focused on understanding the theoretical aspects of the structural features of the natural scaffold Thiaplakortone-A and the derivatives for designing new drug molecules. For the purpose, more than 15000 molecular descriptors which represent the structural characterization of Thiaplakortone-A and its derivatives are generated to understand a logical correlation between structure and activity. We also constructed highly predictive and acceptable HQSAR model (Moda et al., 2007). The comparative molecular field analysis (CoMFA) was carried out to find the correlation of steric and electrostatic properties with that of their biological activity (Cramer et al., 1988). The role of steric, electrostatic, hydrophobic and H-bond donor in properly curating the molecules is of utmost importance. Hence we carried out comparative molecular similarity indices analysis (CoMSIA) studies (Klebe et al., 1994).

Molecular docking also plays an important role in drug design and elucidation of protein-ligand complex structures (Amtul et al., 2007). It can be used prior to experimental screening and

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can be considered as a dominant tool to reduce the effort and cost needed for the development of new drug molecules. The interactions of drug molecules with the receptor protein were effectively understood by a molecular docking analysis. Several studies have revealed the pivotal role played by the drug candidates in interacting with the protein *P. falciparum* calcium-dependent protein kinase 1 (*Pf*CDPK1), which prompted us to select the same proteins for our study (Bansal et al., 2013; Holder et al., 2012). A series of 42 analogues of Thiaplakortone-A were selected for the present study.(Schwartz et al., 2015). All the 42 compounds were docked with both the two protein targets which aided the filtering of eight molecules. Based on the structural information gathered from the above studies seven new virtual molecules were created. Using the 2D-QSAR model developed, the biological activity of the new virtual molecules were computed and were found to be very much promising. Before further analysis another screening was carried out by artificial intelligence method based on Random Forest (RF) algorithm of Weka. Based on the RF model virtual screening of all the 42 Thiaplakortone-A derivatives and seven virtual molecules was conducted and it was found that 18 molecules from the Thiaplakortone-A bunch and four of the new virtual molecules possess anti-malarial properties. It is also interesting to note that those molecules screened by Weka and possessing high docking score are also validated by Osiris software which exemplifies their lead like properties. Several studies found out that the metabolic action with respect to Cytochrome P450 gives a proper indication regarding the toxicity of the selected molecules.

Materials and Methods

Datasets

The 3D-structures of the 42 Thiaplakortone-A derivatives were drawn in Molecular Operating Environment (MOE) software (MOE Version 2007.09, Chemical Computing Group, Inc.). Each compound was energy minimized and optimized by using Merck Molecular Force Field (Halgren, 1996). Structures of the selected Thiaplakortone-A derivatives and their respective inhibitory activities are given in **Table 1.**

2D-QSAR

2D-QSAR studies require the calculation and selection of suitable descriptors. The energy-minimized geometry of each molecule was used for the calculation of the various descriptors. The MOE and PaDEL-Descriptor programs were used for the calculation of 15533

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different descriptors. Descriptor selection is carried out by the software PHAKISO. “General” and “CORCHOP” are the main descriptor filtration algorithms in PHAKISO. “General” method is used to remove descriptors which have the same values and with missing values. And “CORCHOP” method was used to remove the repeated, inter-correlated and correlated descriptors. After the selection, the pool of descriptors was reduced to 214. These descriptors were selected as independent variables and IC_{50} as the dependent variable. The IC_{50} (nM) values were converted into pIC_{50} (-log IC_{50}), which can be used as dependent variable for subsequent 2D-QSAR analysis. The dataset was split into 85% training set and 15% test set for model development and subsequent validation. The software QSARINS was employed to search the optimum number and set of descriptors using multiple linear regression (MLR) models. (Gramatica et al., 2013)

2D-QSAR model validation

The quality of the built model is evaluated by internal validation, using squared cross validated corrrelation coefficient (Q^2).

$$Q^2 = 1 - \frac{\sum_{i=1}^{n}(Y_{pred} - Y_{exp})^2}{\sum_{i=1}^{n}(Y_{pred} - Y_{mean})^2} \quad (1)$$

where Y_{pred}, Y_{exp} and Y_{mean} are the predicted, experimental and mean values of the pIC_{50}, respectively.

The predictive ability of the developed QSAR model is estimated using correlation coefficient (R), standard deviation (s), Fischer’s test (F), level of confidence (p), predicted residual sums of squares standard deviation (S_{PRESS}) and standard deviation error in prediction (S_{DEP}).

The model is further validated by external validation, Y-randomization and applicability domain calculation. The external validation of the built model is tested with the following parameters: r^2_{ext} (external determination coefficient), Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, Concordance Correlation Coefficient (CCC), CCC_{ext}, r^2_m, and Δr^2_m. Δr^2_m estimated the closeness between the values of the predicted and the corresponding observed activity values. Y-randomization experiment is performed to detect the chance correlations between the dependent variable and the descriptors. (Rücker et al., 2007)

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Other parameters such as R_0^2, $R_0'^2$, k, and k' are also calculated. R_0^2 (Predicted vs. observed activities) and $R_0'^2$(observed versus predicted activities) are the coefficients of correlation obtained by the regression lines through the origin, with the intercept set to zero. Generally for a model with good predictive ability, R_0^2 or $R_0'^2$ must be equal to or lower than R^2. For the slope value k (predicted versus observed activities) or k' (observed versus predicted activities), suitable range is $0.85 \leq k \leq 1.15$ or $0.85 \leq k' \leq 1.15$. (Golbraikh & Tropsha, 2002; Zhang et al., 2006)

Applicability domain (AD) calculation is applied to investigate the possible presence of outliers in the whole data set. The AD of the developed QSAR models is evaluated using the standardization approach. (Roy et al., 2015)

HQSAR

The structures of Thiaplakortone-A derivatives were converted into fragments initially utilizing the default fragment size of 4-7 atoms per fragment. All fragments were assigned in characterized molecular hologram lengths (53, 59, 61, 71, 83, 97, 151, 199, 257, 307, 353, 401 bins) and fragment distinction examination was performed in terms of atoms, bonds, connectivity, hydrogen and donor/acceptor atoms. During the HQSAR runs, different combinations of these parameters were considered. After the partial least-squares (PLS) analysis, several QSAR models were generated for each distinguishing fragment. The internal validation was performed by leave-one-out (LOO) cross-validation. An external validation was performed with the test set of 7 compounds, which was not considered in the HQSAR model development.

3D-QSAR

All the selected Thiaplakortone-A derivatives and their inhibition zone were used to construct CoMFA and CoMSIA models using the program SYBYL (Tripos International, Missouri, USA). For both CoMFA and CoMSIA analysis, the standard Tripos force field was employed. The total set of 42 molecules was divided into two subsets: the training set and the test set comprising 35 and 7 compounds, respectively, in such a way that both sets cover the entire range of biological activity (Table 1). The training set was used to generate the models and the test set was used to validate the quality of the models. The partial atomic charges of the compounds were calculated by the Gasteiger-Hückel method and energy minimizations were performed using the Tripos force field (Gasteiger and Marsili, 1980) with 1000 iterations, a

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distance-dependent dielectric and the Powell conjugate gradient algorithm convergence criterion of 0.01 kcal mol^{-1} Å (Clark et al., 1989).

3D-QSAR model construction

The steric (S) and electrostatic (E) CoMFA potential fields were computed at every lattice intersection of a regularly spaced grid of 2.0Å. The grid pattern was generated automatically by the SYBYL/CoMFA routine. The steric (Lennard-Jones potentials) and electrostatic (Coulombic potentials) fields were ascertained utilizing the standard Tripos force fields in 3D grid with a spacing of 2.0 Å and extended at least 4.0 Å beyond the van der Waals around aligned compounds in all directions. A distance-dependent dielectric constant of 1.00 was used. A sp^3 hybridized carbon atom with +1 charge served as probe atom to calculate steric and electrostatic fields. The steric and electrostatic contributions were reduced to +30.0 kcal/mol and electrostatic contributions were ignored at the lattice intersections with maximal steric interactions. The minimum sigma (column filtering) was set to 2.0 kcal/mol to increase the efficiency of the predictive models and to decrease the noise so that the columns possessing less energy variance in contrast to this value were excluded from analysis. To derive appropriate results, the "StDev*coeff" (the standard deviation and the coefficient) values as different weighing factors in addition to the grid spacing were performed.

For CoMSIA examination, five similarity indices comprising of steric (S), electrostatic (E), hydrophobic (H), hydrogen bond donor (D) and hydrogen bond acceptor (A) fields were computed for each lattice with a grid of 2Å. The CoMSIA descriptors were acquired utilizing the settings of sp^3 carbon atom as a probe atom with a +1 charge, +1 hydrophobicity, +1 hydrogen bond donor and +1 hydrogen bond acceptor at each lattice. A default value of 0.3 was used as the attenuation factor.

3D-QSAR Statistical Results

Partial least squares (PLS) methodology for cross-validation with leave-one-out (LOO) method is used in 3D-QSAR to produce a series of coefficients (Bush and Nachbar, 1993; Wold et al., 2001). The most active molecule tpk1 was selected as the template for alignment. Different statistical parameters such as the cross-validated correlation coefficient (Q^2), non-cross-validated correlation coefficient (R^2_{ncv}), the predicted correlation coefficient (R^2_{pred}), standard error of

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estimate (SEE), the optimum number of components (ONC) and F values were taken into consideration to validate the model.

The LOO cross-validation was performed to identify the cross-validated correlation coefficient (Q^2) values. Then the ONC perceived in the LOO cross-validation process was utilized in the final non-cross-validated PLS run with a column filter value of 2.0 kcal/mol. In CoMSIA, five descriptors available are considered. In all cases it has been established that the five different descriptor fields are not totally independent of each other and that such dependency among individual field usually decrease the statistical significance of the models (Bringmann and Rummey, 2003). We have generated 14 different models in order to build the optimal 3D-QSAR models with the highest Q^2 values and other statistical results for each class.

To evaluate the predictive power of 3D-QSAR models, the biological activities of the external test set were predicted. The R^2_{pred}, is calculated using the equation

$$R^2_{pred} = 1 - \frac{\sum(Y_{predicted} - Y_{observed})^2}{\sum(Y_{observed} - Y_{mean})^2} \qquad (2)$$

where $Y_{predicted}$, $Y_{observed}$ and Y_{mean} are predicted, actual and mean values of the activity, respectively. $\sum(Y_{predicted} - Y_{observed})^2$ is the predictive sum of squares (PRESS).

To further validate the predictive ability of the constructed models, the following equation was used (Rännar et al., 1994):

$$R^2_{m\,(overall)} = R^2 \times \left(1 - \sqrt{R^2 - R_0^2}\right) \qquad (3)$$

Molecular docking

Molecular docking studies were performed using MOE (Chemical Computing GroupInc, Montreal, Quebec, Canada), in order to investigate the interaction mechanism and probable binding mode of Thiaplakortone-A derivatives at the active site of Plasmodium falciparum calcium-dependent protein kinase 1 (*Pf*CDPK1). The 3D crystal structures of *Pf*CDPK1 (PDB ID: 3I79 & 3HZT) were retrieved from the protein data bank (Berman et al., 2007). This structure was protonated and energy minimized in MMFF94x force field to a gradient of 0.0001 kcal/mol/Å (Halgren, T.A. 1996). The “Site Finder” module in MOE was used to identify and place dummy atoms into the active site pocket. The default settings for all of the parameters including Ligand Placement (Triangle Matcher) and Rescoring (London dG) were used. The top scoring ligand pose from each docking run was used for calculation of binding energy.

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The physicochemical properties of the selected protein molecules 3I79 and 3HZT were determined using Expasy ProtParam tool (Gasteiger et al., 2003). ProtParam in Expasy Proteomics Server computes various physicochemical properties that can be deduced from a protein sequence. The properties such as theoretical isoelectric point (pI), molecular weight, total number of positive and negative residues in the query, its value extinction coefficient, instability index (II), aliphatic index (AI) and grand average hydropathy (GRAVY) were computed.

Data mining

Data mining was carried out using Weka software, using RF algorithm. The RF algorithm creates multiple decision trees using bootstrap samples from the original training data set. Then the set of trees is used for classification. The RF algorithm is an ensemble classifier. It gives high accuracy and time efficiency for predictive data modeling. Classifier performance is evaluated via k-fold cross-validation. 10-fold cross-validation (CV) was used here as it gives higher bias in the expected prediction error but lower variance. The result from the test set is presented by a confusion matrix which consists of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN). It gives an idea to understand the results of the classification method. TP (TN) represents the total number of correctly classified instances and FN (FP) refers to the total number of respectively misclassified instances.

Prediction of metabolic behavior of the virtual molecules

SMARTCyp is used for predicting the reactivity at C, S, N, and P positions in a given ligand. (Rydberg et al., 2010) The results are obtained in the form of a structure and a table for each molecule. The 3 top ranking atoms are highlighted in the structure and table. From this the site with the highest probability of metabolism can be understood. If a given substrate had more than one known site of metabolism (SOM), only the highest predicted SOMs were considered.

Results and Discussion

2D-QSAR

In the present study, the natural scaffold Thiaplakortone-A based derivatives were taken to understand a logical correlation between structure and activity. Using the MLR analysis method the following 2D-QSAR model was obtained.

$\mathbf{pIC_{50}}$ = - 0.0072 (± 0.0033) **SMR_VSA1** - 0.0713 (± 0.0324) **MNDO_LUMO** - 6.4747 (± 3.4349) **maxHssNH** + 6.1505 (± 0.0429) .(4)

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$R^2 = 0.814$; $R^2\text{-}_{Adj.} = 0.790$; s = 0.1258; F = 33.825; $Q^2 = 0.757$; $p < 0.0001$

where $R^2\text{-}_{Adj}$ refers to the adjusted coefficient of determination, s is standard deviation, F indicates F-ratio test, Q^2 indicates cross validated correlation coefficient.

The three physicochemical descriptors (SMR_VSA1, MNDO_LUMO and maxHssNH) were involved in this QSAR equation. All the descriptors were found to contribute negatively to the biological activity of the compounds which indicates that decrease in their values would result in an increase in activity. The negative coefficient of the three descriptors indicates that the values should be kept as low as possible to have acceptable activity. The model has good capacity to explain the observed values of biological activity because it possesses high cross validated correlation coefficient ($Q^2 = 0.757$) and is further confirmed by the low standard deviation (s = 0.1258). The model explains 81.4% of the variance in the antimalarial activity.

The predictive ability of the model is very high, which is reflected by the external validation parameter values $RMSE_{ext} = 0.0981$, $Q^2_{F1} = 0.9311$, $Q^2_{F2} = 0.9244$, $Q^2_{F3} = 0.8684$ and $CCC_{ext} = 0.9524$, $r^2_{m\ aver} = 0.7117$, $\Delta r^2_m = 0.0954$. Other statistical parameters, i.e., R_0^2 and $R_0'^2$ were 0.758 and 0.700, respectively, whereas k and k' were 1.00 and 0.99, respectively. All the parameters were within acceptable range, and a small residual difference between the observed and predicted activities proved that the developed model is good.

SMR_VSA1 is the sum of v_i such that R_i is in (0.11,0.26). It belongs to the category generally called as the Subdivided Surface Areas which are descriptors based on an approximate accessible van der Waals surface area (in $Å^2$) calculated for each atom, v_i along with some other atomic property, p_i. If n_i is the number of occurrences of atomic number i in the molecule, then $p_i = n_i / n$ where n is the sum of the n_i. The v_i values are calculated using a connection table approximation. Each descriptor in a series is defined to be the sum of the v_i over all atoms i such that p_i is in a specified range (a,b). R_i denotes the contribution to Molar Refractivity for atom i as calculated in the SMR descriptor.

MNDO_LUMO is a potential energy based descriptor. It denotes the energy (eV) of the Lowest Unoccupied Molecular Orbital calculated using the MNDO Hamiltonian (Stewart, 1993). maxHssNH is a 2D descriptors which means Maximum atom-type H E-State of -NH-. Table 2 gives the values for observed, predicted antimalarial activities and residual values.

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In the present work, only three descriptors have been incorporated in the final 2D-QSAR model, as adding more descriptors in the model resulted in negligible improvements only in the value of R^2. Hence, the heuristic search was limited to three descriptors to avoid over-fitting and to keep the model as simple as possible. Thus the model predicts the anti-malarial activities of the set molecules with greater predictability using the selected parameters.

Y-randomization test

Y-randomization experiment is performed to detect the chance correlations between the dependent variable and the descriptors. (Rücker et al., 2007) In the Y-randomization test, the dependent variable is scrambled and new QSAR models are developed using the same set of independent variables as present in the un-randomized model. The models obtained should be of poor quality. The statistics of the randomized models (Q^2 and R^2) should be poor, otherwise, each resulting model may be based on pure numerical effects. For an acceptable QSAR model, the average correlation coefficient (R_r) of randomized models should be less than the correlation coefficient (R) of non-randomized model. The extent of difference in the values of the mean squared correlation coefficients of the randomized (R_r^2) and that of the non-randomized (R^2) models is reflected in the value of $^cR_p^2$ parameter. (Todeschini, 2010) The value of $^cR_p^2$should be more than 0.5 for passing Y-randomization test.

$$^cR_p^2 = R \times \sqrt{R^2 \times R_r^2} \quad (5)$$

The biological activity, which is the dependent variable, is randomized keeping the others descriptors as such. In the present study, fifty randomized models were constructed and the model parameters obtained are presented in table 3. Since the $^cR_p^2$ value obtained is 0.792, the Y-randomization test was passed for our model.

Applicability domain (AD) analysis

In addition to Y randomization, AD of the developed QSAR model was analyzed by employing basic theory of standardization approach. It helps to define the model limitations with respect to its structural domain and response space. Applicability domain is the area of the physicochemical, structural, or biological space where the model is expected to be exploitable and the predictions are assumed to be trustable. The training set compounds define the boundaries of the chemical space where predictions could be considered as the result of data

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interpolation. The algorithm and methodology proposed by Roy et al was used to define outliers (in the case of the training set) and to identify the compounds residing outside the AD to cross-examine and substantiate the QSAR model (Roy et al., 2015). No-X outliers were identified either in the training or in the test set which eliminates the chances of uncertainty in the predictions. This also proves that compounds in the training set are similar and their modelled 3D descriptors and modelled response reside within the AD.

HQSAR

It is not clear which substitution position and what kind of substituents could provide the most significant contribution to the *Pf*CDPK1 inhibitory activity. So HQSAR study was conducted to obtain more inclusive information. HQSAR is a 2D-QSAR method which creates structure activity relationship based on the fragments (Salum and Andricopulo, 2009). The extended form of the fingerprint used by it is known as a molecular hologram which contains all the possible molecular fragments within a molecule. The advantage of HQSAR technique is that it does not require the alignment of dataset on common template. HQSAR requires only 2D structure which employs specialized fingerprints as predicted variable of pharmacological activity, which is considered as dependent variable. Even though this method is 2D in nature, it utilizes 3D information such as chirality and molecular hybridization.

The best HQSAR model for *Pf*CDPK1 inhibitors was found to be the model with atoms, bonds, connectivity and hydrogen atoms (A/B/C/H) as the fragment distinction parameters. The results of the HQSAR analysis are reported in Table 4. The model shows good predictive capacity (R^2_{cv} = 0.682), high data fitting (R^2_{ncv} = 0.958) and low cross-validated standard error (SEP = 0.198).

Considering only the HQSAR contribution maps of the most active compound tpk1, (Fig. 1a), the generated model is able to identify fragments which increase the biological activity which are colored in yellow and green). However, in the case of least active compound tpk22, (Fig. 1b), the model identifies the fragments that decrease the activity which are coloured in red and orange in the model. The fragments colored in white (neutral contribution) highlights fragments without correlation with the biological activity variation.

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The fragment CH_2 adjacent to the pyrrole ring exerts maximum contribution. Besides this, the hydrogen atom attached to the nitrogen of the pyrrole ring has also been marked green. The fragments contributing moderately to the activity profile of the molecules constitute N atom of the pyrrole ring bearing the R1 substituent. Thus, compounds bearing all of the essential molecular fragments exhibit potent anti-malarial activity, while those lacking the essential fragments lie down in the lower activity range.

Even though the above model explains how various alkyl groups affect the activity of a compound, the fragment collision is the limitation of HQSAR technique. Also the predictive quality of an HQSAR model is dependent on the setting of the atoms, bonds, connections, hydrogens and chirality parameters. So, 3D-QSAR studies have been carried out to find out how the presence of certain groups affects the anti-malarial activity of the compounds.

3D-QSAR

CoMFA statistical analysis

CoMFA and CoMSIA were generally used for understanding the QSAR at the 3D level. In 3D-QSAR methods the active conformer and superposition rule for a set of molecules were employed to clarify how the molecular structures of the compounds and bio-activity are related whereby the potency of the molecules could be predicted. The CoMFA methodology assumes that a suitable sampling of the steric and electrostatic fields around a set of aligned molecules provides all the information needed for understanding their biological properties. The statistical parameters of standard CoMFA models constructed for Thiaplakortone-A derivatives with steric and electrostatic fields are given in Table 6. PLS analysis of the training set showed a high Q^2 value of 0.813 with seven ONC. The non-cross-validated PLS analysis with the ONC results in an R^2_{ncv} of 0. 994, F = 216 and a SEE of 0.027.

Considering both steric and electrostatic field contributions, the former accounts for 59%, while the latter contributes 41%, indicating that the steric factor contributes slightly more to the binding affinities of the ligands to the target. The SEP (0.149) suggest a high degree of confidence in the analysis.

To further evaluate the reliability and predictability of the built model, the external test set of 7 compounds was used. The statistic parameters, R^2_{pred} = 0.892 and $R^2_{m\ (overall)}$ = 0.788,

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suggested a good predictive ability of our CoMFA model. Table 7 lists the experimental, predicted activities and the residual values of the dataset.

CoMFA contour map analysis

The CoMFA contour map of steric field is revealed in Fig. 2a. The green contour recommends where increased steric bulk is connected with enhanced *Pf*CDPK1 inhibitory activity, whereas the yellow contour indicates the regions where sterically bulky groups would decrease the *Pf*CDPK1 inhibitory activity.

Near the R2 region, there is one big green contour which demonstrates the favorable impact of bulky groups in increasing the inhibitory activity of compounds. This is illustrated by comparing the activities of molecules 11 and 6 where the presence of bulky groups like i-Butyl, (> Ethyl) as R2 substituent would bring about higher pIC_{50} values (6.270 > 6.153), respectively.

This is additionally seen between compounds 12 and 8 where compound 12 possessed Cyclopentylmethyl group and displayed higher inhibitory activity (pIC_{50} = 6.219) and bulky characteristics than compound 8 which contained c-Propyl group as the R2 substituent (pIC_{50} = 5.943). By means of the bulky substituents (−Chloromethoxyphenyl > −Fluorophenyl) as R2 substituent would prompt pIC_{50} values in the compounds: 23 (pIC_{50} = 6.034) and 17 (pIC_{50} = 5.889).

This outcome can also be observed between compounds 36 and 27 where the higher activities can be related to the presence of − N(H)-adamantyl and − Furanyl substituents., The increase in the bulky behavior of the substituent (−Furanyl < − N(H)-adamantyl), increases the inhibitory activities also. (5.967 < 6.200).

The contour map of the electrostatic field of CoMFA model is shown in Fig. 2b. Increasing positive charge is favored in blue regions (contribution level of 80%) and increasing negative charge is favored in red regions (contribution level of 20%). The electrostatic contours map shows red contour at the R2 substituent. The presence of red contours illustrates the favorable effect of negative charge in some series of compounds. The electrostatic contour plot has a blue contour near R1 group and red contours around R2 group. The red contour above the R2 group can be explained by comparing compounds 14 and 13 where replacing of phenyl with

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2-Fluorophenyl increases the negative charge behavior of this substituent. Consequently, the pIC_{50} values also increase (6.235 < 6.352). Further, the influence of the substituents can be understood by comparing compounds 19 (having −2, 6-Difluorophenyl group with pIC_{50} = 5.962) and 17 (having −4-Fluorophenyl group with pIC_{50} = 5.889) where the use of the negative charge group as R2 would lead to the increase of the inhibitory activities. The red contours observed near R2 substituent can be described considering compounds 23 and 16.; When the negative charge features increase (3-Chloro-4-methoxyphenyl > −3-Bromophenyl), the inhibitory activities (6.034 > 5.847) decrease. The blue contour above the R1 group can be explained by comparing compounds 41 and 42 where Benzyl is replaced with 4-Chlorobenzyl resulting in the negative charge behavior of this substituent, which was confirmed by the increased inhibitory activity (6.356 > 6.197).

CoMSIA statistical analysis

CoMSIA uses Gaussian approximation for calculating similarity indices at various grid points. But in CoMFA analysis the lattice points located inside the molecules are not taken into account in the statistical correlation analysis. Partial least square analysis with the CoMSIA descriptors resulted in satisfactory Q^2 and R^2_{ncv} values. Table 5 shows the summary of the statistical analysis of CoMSIA. In the CoMSIA, the LOO cross-validated value Q^2 with combined steric (S), electrostatic (E), hydrophobic (H) and hydrogen bond donor (D) fields was 0.647 with six ONC for training set. The non-cross-validated PLS analysis with the ONC results in an R^2_{ncv} of 0. 984, F = 292.970 and a SEE of 0.042. The percentage of the variance explained by S, E, H and D descriptors are 0.151, 0.313, 0.188 and 0.349, respectively.

The predicted pIC_{50} values with the CoMSIA model is found to be in good agreement with the experimental data within a statistically tolerable error range, with R^2_{pred} value of 0.718.

CoMSIA contour map analysis

The electrostatic contour map of the CoMSIA model is shown in the Fig. 3a, where increasing positive charge is favored in blue regions (contribution level of 80%) and increasing negative charge is favored in red regions (contribution level of 20%). The large blue contour around R2 group is explained by comparing compounds 11 and 32 where replacing i-Butyl with Ot-Bu increases the positive charge behavior of this substituent and accordingly, the pIC_{50} values

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are increased (compound 11; pIC_{50} = 6.270 < compound 32; pIC_{50} = 6.123). Comparison of compounds 36 and 34 suggests that the negative charge groups (−N(H)-adamantyl> −N(Me) OMe) impart higher biological activities (6.200 > 6.130), to compound 36. As shown by the pIC_{50} values, the presence of groups such as −Difluorophenyl (compound 19 with pIC_{50} = 5.963) in contrast to –Phenyl (compound 13 with pIC_{50} = 6.235) resulted in the decrease of activity.

Fig. 3b describes the CoMFA steric contour map. In the CoMSIA steric contour map, green colour represents areas were more bulk groups are favorable, while the unfavorable steric areas are indicated by yellow contours. A large green contour is present near the R2 group which demonstrates that the presence of bulk group will increase the activity of the molecules. This is explained by considering the molecules 23 and 16 where replacing 3-Chloro-4-methoxyphenyl with 3-Bromophenyl increases the steric behavior of the substituent and consequently, the pIC_{50} value is increased (compound 23; pIC_{50} = 6.034 < compound 16; pIC_{50} = 5.847). The presence of Cyclopentylmethyl ring in the compound 12 exhibits (pIC_{50} = 6.219) higher inhibitory activity compared to the compound 8 (pIC_{50} = 5.943), having a c-Propyl group in the R2 position.

The magenta region of the CoMSIA hydrophobic contour plot in Fig. 3c, reveals that the hydrophobic substituents in this region could enhance the inhibitory activity while the orange contour represents the enhancement of the inhibitory activity by the hydrophilic substituents in this region.

In the CoMSIA hydrogen bond donor contour maps, as observed in Fig. 3d, the cyan contour indicates that hydrogen bond donor substituents in this region will improve the activity while the purple contour indicates that hydrogen bond donor substituents in this region will lead to decrease in activity.

The steric and electrostatic field contributions to the CoMFA model were 59% and 41%, respectively. The field graphics obtained from CoMSIA analysis elucidated the relationships between differences in the fields and variations in the dependent variable. The contributions of steric, electrostatic, hydrophobic, H-bond donor and acceptor fields to CoMSIA were 15.1, 31.3, 18.8 and 34.9%, respectively.

Comparison of the QSAR models

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A consensus details regarding the prediction of activities from all the models is assessed by finding the correlation between the predicted and experimental pIC_{50} values for 2D QSAR, HQSAR, CoMFA and CoMSIA models and are presented in Fig.4. The trend lines with respect to 2D QSAR and CoMFA are very close with R^2 values of 0.843 and 0.757, respectively. The CoMSIA model shows an R^2 value of 0.851.The plot also identifies the existence of outliers of the HQSAR model. The HQSAR plot shows an R^2 value of 0.657. All the methods have provided consensus and complementary results.

Protein validation and Molecular docking

P. falciparum calcium-dependent protein kinase 1 (*Pf*CDPK1) is responsible for phosphorylation of components of the molecular motor that drive parasite invasion of red blood cells. If this invasion process can be prevented the parasite life cycle will be broken, leading to the destruction of the parasites. This could potentially prevent the infection. Therefore *Pf*CDPK1 represents a novel target for the potential treatment of malaria and offers promise for achieving selectivity over the kinases of the human host (Ahmed et al., 2012). The primary features of the proteins 3I79 and 3HZT were studied using Expasy proteomics server (Wilkins et al., 1999). By using ProtParam tool, the physicochemical characters were analyzed. The molecular weight of 3I79 obtained is 55289.55 Da and the theoretical pI is 5.70. The II of the protein is calculated by considering all the residues in the protein. This index has been used to predict whether a protein is stable (II<40; proteins that have an *in vivo* half-life of >16 h) or unstable (II >40; proteins that have an *in vivo* half-life of <5 h. (Guruprasad et al., 1990). The instability index is found to be 28.87 which classifies the protein as stable. The negative value of GRAVY (-0.423) illustrates that the protein molecule is hydrophilic. Similarly, the molecular weight of 3HZT obtained is 54603.45 Da, theoretical pI is 5.55. The instability index is found to be 31.96 which classifies the protein as stable. The AI of proteins can serve as a measure of thermostability of proteins (Ikai., 1980). The AI of the proteins 3I79 and 3HZT are 85.19 and 87.84, respectively, which shows that both the proteins are thermally stable. The negative value of GRAVY (-0.419) illustrates that the protein molecule is hydrophilic. 3I79 has the extinction coefficient 49070 $M^{-1}cm^{-1}$ in 280 nm solution assuming all pairs of Cys residues form cystines, while 3HZT shows 51840 $M^{-1}cm^{-1}$. The half-life estimated for both the proteins was 30 hours (unit measured based on mammalian reticulocyte *in vitro* studies).

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The quality of the proteins 3I79 and 3HZT (Fig 5) were evaluated using Ramachandran plot obtained from MOE 2007.09 (Lovell et al., 2003). The output of the result shows that the protein 3I79 has three outlier amino acids Asn 370, Ala 413 and Asp 415. The number of residues in the core region is 94.01%. The number of residues in the allowed region is 5.54% and the number of residues in the outlier region is only 0.66%. 3HZT has no outlier amino acids. The number of residues in the core region is 93.64%. The number of residues in the allowed region is 6.36%. Ramachandran's plot predicts that the final structure is highly reliable for molecular docking.

The molecular docking of 42 ligands with the proteins 3I79 and 3HZT were carried out using MOE 2007.09. The protein was made rigid and ligand was left free to rotate (flexible docking). This was necessary to ensure that the docking process was in accordance with lock and key mechanism. The 'Site Finder' tool of the program is used to find the active sites of the proteins. The results of the molecular docking are summarized in Table 8 and Fig. 6 and 7.

Molecular docking interaction studies of the selected ligands with 3I79

The molecular docking results of the eight active compounds with the protein **3I79** were shown in the Table 8. The binding interactions of the ligands and the proteins were studied using LigPlot. The 2D and molecular docking pose of the 8 active compounds with the protein **3I79** are shown in the Fig. 6.

Molecular docking of compound tpk1 (Fig. 6) with molecular docking score -13.6612 kcal/mole showed four side chain hydrogen bonding interactions between the residue Lys 59 and the groups $-NH_2$, carbonyl and sulfonyl group.

Compound tpk17 shows three side chain hydrogen bonding interactions (Fig. 6). The carbonyl group shows a side chain hydrogen bonding interaction with the polar residue Lys 59 (2.63 Å, 28%). One of the oxygen atoms of the sulfonyl group show two side chain hydrogen bonding interactions with the polar residues Lys 176 and Ser 61 (2.91 Å, 28%, 2.99 Å, 22%). It shows a molecular docking score of -13.2110 kcal/mole.

The binding mode observed (Fig. 6) for the compound tpk20 shows that the residue Lys 176 forms side chain hydrogen bonding interactions with the oxygen atoms of both the carbonyl

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and sulfonyl groups (2.44 Å, 56%, 2.57 Å, 58%). The proximity contour shows that the molecule is very closely hemmed in by the active site. A side chain hydrogen bonding interaction is observed between the –NH group and the residue Ser 83. The molecular docking score is found to be -13.2729 kcal/mole.

Compound tpk28 shows interactions like side chain hydrogen bonding interaction and backbone hydrogen bonding interaction (Fig. 6). The oxygen atom of the sulfonyl group shows a back bone hydrogen bonding interaction with the amino acid Ser 205 (2.6 Å, 86%). The carbonyl group forms a side chain hydrogen bonding interaction with the residue Ser 83 (3.0 Å, 12%). This compound shows a molecular docking score of -13.9943 kcal/mole.

Compound tpk34 shows a molecular docking score of -14.0290 kcal/mole. The -NH functional group of the ring shows a side chain hydrogen bonding interaction with the residue Asn 210 (1.98 Å, 17%). The proximity contour shows that the molecule as a whole is very closely hemmed in by the active site.

Molecular docking of compound tpk36 with molecular docking score -13.6347 kcal/mole showed a side chain hydrogen bonding interaction between the Oxygen atom of the S=O group and the residue Lys 209 (2.83Å, 18%). The carbonyl group shows a side chain hydrogen bonding interaction with the residue Lys 59 (2.51Å, 35%). The carbonyl group at the other end shows a backbone hydrogen bonding interaction with the residue Phe 62 (2.50Å, 22%).

The binding mode observed for the compound tpk41 shows that the carbonyl group of the forms a side chain hydrogen bonding interactions with residue Lys 59 (2.29 Å, 46%). The molecular docking score is found to be -15.0210 kcal/mole.

Compound tpk42 shows interactions with the active site of the protein molecule. The carbonyl group shows a side chain hydrogen bonding interaction with the amino acid Lys 59 (2.54 Å, 51%). The oxygen atom of the sulfonyl group present at the opposite side of the molecule shows a side chain hydrogen bonding interaction with the amino acid Lys 391 (2.64 Å, 84%). The benzene ring shows an arene-cation interaction with the residue Arg 442. This compound shows a molecular docking score of -11.2184 kcal/mole.

Molecular docking interaction studies of the selected ligands with 3HZT

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The molecular docking results of the 8 active compounds with the protein 3HZT are shown in the Fig. 7. Compound tpk1 showed two direct interactions with the residues of the binding cavity of the protein (Fig. 7). The binding site residues involved in these prominent interactions are Gln 367 and Asn 204. Gln 367 showed a side chain hydrogen bonding interaction with the carbonyl group at 2.55 Å. Asn 204 shows a side chain interaction with the carbonyl group 2.40 Å (21%). Asp 220 and Lys 201 were also incorporated in the linkage due to the presence of water molecules. The molecular docking score of the compound is -10.5007 kcal/mole.

In Compound tpk17, only one prominent interaction is observed and the binding site residue is Glu 160 (Fig. 7). Glu 160 showed a side chain hydrogen bonding interaction at 1.74 Å with the -NH group. The compound shows a docking score of -10.9846 kcal/mole.

Compound tpk20 showed indirect hydrogen bonding interaction with oxygen of morpholine ring with the amino acid residues Gly 159 and Tyr 156 (Fig. 7). The molecular docking score is -11.9554 kcal/mole.

Compound tpk28 showed three prominent interactions with the residues Asn 204 and Tyr 156 (Fig. 7) with a molecular docking score of -10.2702 kcal/mole. Asn 204 forms a side chain hydrogen bonding interaction with the carbonyl group at 2.78 Å. The amino acid residue Tyr 156 forms a back bone hydrogen bonding interaction with the carbonyl group of the pyrrolidinone ring at 3.06 Å. Asp 220 and Lys 201 were also involved in the interactions because of bridging water molecule.

In Compound tpk34, only one prominent interaction was observed (-11.0446 kcal/mole). Glu 160 showed a side chain hydrogen bonding interaction with the N atom of the pyrrolidine ring (1.30Å, 41%). It shows an indirect hydrogen bonding interaction with the oxygen atom of the methoxy group.

Compound tpk36 shows two prominent interactions with the residues Glu 160 and Ser 84 (-10.7451 kcal/mole). Ser 84 shows a backbone hydrogen bonding interaction with the -NH group of the pyrrole ring at 2.01 Å. The residue, Glu 160 shows a sidechain hydrogen bonding interaction with the -NH group of the compound at 1.38 Å.

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Compound tpk41 shows a polar side chain hydrogen bonding through amino acid residue Glu 160 with the –NH group of the compound at 1.87 Å. It shows a side chain hydrogen bonding interaction with the residue Asn 204 with the oxygen atom of the sulfonyl group (1.87 Å, 18%). The molecular docking sacore of the compound is -10.8624 kcal/mole.

The Compound tpk42 shows a prominent side chain hydrogen bonding interaction through the amino acid residue Ser 84 with the carbonyl group (2.76 Å, 18%). The residue Ser 84 is also interacted with the compound through the water molecule (-11.6409 kcal/mole).

Results of the molecular docking of 42 Thiaplakortone-A derivatives with 3I79 and 3HZT revealed that eight compounds namely, tpk1, tpk17, tpk20, tpk28, tpk34, tpk36, tpk41 and tpk42 exhibited good docking scores.

Design of new virtual molecules

In order to design new virtual molecules we have used information obtained from 2D-QSAR, HQSAR, CoMFA and CoMSIA models. The primary objectives of building a 2D-QSAR model are to find out the structural features correlated with activity and to predict the activity of a molecule. We have used the equation obtained from 2D-QSAR, to find out the activity of the modified compounds. The results of HQSAR model demonstrates that the fragment -CH_2- adjacent to the pyrrole ring positively contribute to the biological activity. So we have retained the methylene group in the modified molecules. Moreover, the HQSAR contribution plot shows that, the hydrogen atom attached to the nitrogen of the pyrrole ring also shows favourable contribution. Considering this fact, we have retained H atom in the four virtual molecules.

CoMFA and CoMSIA models derived for Thiaplakortone-A derivatives throw light on how to design novel molecules with improved anti-malarial activity. A remarkable elucidation of the CoMFA and CoMSIA contour maps gave us valuable information for amending the structure of the main scaffold. In CoMFA and CoMSIA electrostatic contour maps, the existence of a red contour near R2 position indicates that electronegative groups are favorable for increasing the anti-malarial activity. The CoMSIA hydrogen bond donor contour map also indicates that at the R2 position of the Thiaplakortone-A scaffold, a hydrogen bond donor group is favorable for anti-malarial activity. Based on these, we introduced electronegative and hydrogen bond donor

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groups at the R2 position and created 7 virtual molecules tpk(1a), tpk(1b), tpk(1c), tpk(1d), tpk(1e), tpk(1f) and tpk(1g). The suggested molecules are thus the result of harmonious use of CoMFA and CoMSIA with 2D-QSAR and HQSAR models.

The descriptors of the modified virtual molecules were calculated using PaDEL-Descriptor and MOE softwares. The descriptors used to find out the activity of the modified molecules using the equation obtained from 2D-QSAR are listed in the table 9. From the calculated activities, it is clear that out of the seven modified virtual molecules, tpk(1a), tpk(1b), tpk(1c), tpk(1d), tpk(1e), tpk(1f) and tpk(1g), three molecules tpk(1c), tpk(1d) and tpk(1e) showed good anti-malarial activity values of 6.159, 6.542 and 6.391, respectively.

Data Mining Using WEKA

Machine Learning (ML) method was employed in order to confirm whether molecules were active against malarial parasites or not. Using WEKA tools, binary classifiers for the molecules were created, based on their bio activity. For the purpose, the bioassay dataset AID: 504850 which contained compounds having the potential to inhibit apicoplast formation in the malarial parasite *Plasmodium* is taken. The assay was based on a Luciferase reporter assay and the compounds that cause inhibition of apicoplast formation was assayed by a delayed death response. Growth inhibition is detected by a decrease in luciferase activity. The dataset AID: 504850 contained a total of 2304 tested compounds. Compounds in AID: 504850 were characterized based on a compound ranking system called 'PubChem Activity Score'. Compounds having an activity score between 40 and 100 were considered as active (1172), all compounds with a score of 0 were considered as inactive (344) and the ones having a score between 1 and 39 were labeled as inconclusive (788).

PowerMV software was used to generate 179 molecular descriptors for each dataset, which includes 147 pharmacophore fingerprints, 24 weighted burden number and 8 property descriptors. The dataset was split into 20% test set and 80% training-cum-validation set. The selected compounds after the molecular docking studies were tested using the classifier based on RF. Earlier workers have observed that RF provides the best classifier (Sajeev et al., 2013; Seal et al., 2012; Periwal et al., 2011). The algorithm tries to find as good a distinction as possible between active compounds and others, on the basis of a set of molecular descriptors. It identifies

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features shared by different subsets of active compounds and accordingly filters out compounds within the target data set in which these combinations are lacking. It is the most accurate classifiers available. For evaluation of the RF classifier, we employed the 10-fold cross validation. With RF model, the selected 8 molecules were screened using AID dataset 504850 and the confusion matrix shows that all the selected 8 compounds; tpk1, tpk17, tpk20, tpk28, tpk34, tpk36, tpk41 and tpk42, were found to be active. The specificity and sensitivity of the built model was 62.7% and 76.8 %, respectively. The accuracy of the generated model was determined by the overall effectiveness of a classifier. The accuracy (Q) of the model was found to be 76.82 %, which depicts that the results are accurate. ROC area was 69.4%.

Data mining study was then performed to find out whether the modified molecules were active or not. The virtual screening carried out using the RF model based on the AID: 504850 shows that out of the seven modified molecules the compounds tpk(1e), tpk(1f) and tpk(1g) are anti-malarial active and can be considered to be the lead molecules (Fig. 8).

Prediction of toxicity risks and drug score assessment

The molecules screened will be safe for use only if they are not toxic to humans. The present study therefore further relied upon theoretical *in silico* methods to assess the toxicity of the molecules. Depending on the chemical structure of the molecules their pharmaceutical actions may vary. The pharmacokinetics of the molecules within the body and its action and performance rely upon absorption, distribution, metabolism and excretion.

The cytochromes P450, which contain heme, metabolize a wide range of therapeutic agents (Bezirtzoglou, 2012). The isoforms of CYP enzymes are CYP1A2, CYP2C9 and CYP2C19, CYP2D6 and CYP3A4. (Williams et al., 2004) Out of these CYP3A4 is the most abundant human hepatic P450 isoform which is responsible for the metabolism of about 50% of known drugs (Guengerich, 1999). The metabolite prediction of CYP3A4 substrates by MetaSite shows an accuracy of 78%. (Zhou et al., 2006). A better understanding of molecular interactions between CYP3A4 and drugs are useful perceptions for the development of new medications. The size and shape of the active site cavity of the CYP3A4 structures are remarkable. (Scott and Halpert, 2005)

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In order to find out whether the modified molecules will be metabolized or not, molecular docking of the commercially available drug molecules and the modified molecules were performed into the active site of the enzyme CYP3A4. (Kjellander et al., 2007; Oda et al., 2004). If these molecules are not metabolized by the enzyme they will accumulate and ultimately will be converted to toxic compounds. The shape and size of the active site present in the CYP3A4 shows that, it can metabolize several bulky substrates (Rendic, 2002).

The human microsomal cytochrome P450 3A4 protein structures, 1WOE and 1WOF, downloaded from Protein Data Bank were subjected to 3D protonation and energy minimization utilizing the MOE program. Using the processed CYP3A4 crystal structures, the 'Site Finder' tool of the program is used to find out its active site. The modified molecules were subjected to molecular docking. The energy data showed a rough correlation between the docking score values of the compounds and their interactions. The saved pose for the ligand-enzyme complex of each modified molecule was subjected to detailed 3D analysis for its interactions at the enzyme active site.

In order to correctly predict the CYP3A4 derived SOM, SMARTCyp was used. The prediction of the seven virtual molecules by SMARTCyp to identify the best three SOMs, are presented in the Fig. 9. The SOMs with first three ranks are represented with rings. The methylene group (-CH_2-) adjacent to amino group of compounds tpk(1a), tpk(1b), tpk(1c) and tpk(1e) are ranked as the best SOM. This is followed by amino group in rank two position. For the compound tpk (1e), the double bond adjacent to the -SO_2 group is regarded as the SOM. In compound tpk (1f), the methyl group and methylene group attached to the oxygen atom, are considered as SOM with highest ranks as shown in Fig. 9. In compound tpk (1g), the -CH- group connected to the hydroxyl group is identified as the SOM. The modified compounds bind tightly to CYP3A4, and they showed good docking scores than the drug molecules, consistent with the observation that they probably interacts with CYP3A4 through the active site. The present study therefore gives the metabolic nature of the lead like molecules. To summarize, we have shown that the modified compounds if taken by patients with malaria interact well with CYP3A4. These molecules also obeyed Lipinski's Rule of Five.

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Osiris Property Explorer was used to predict the toxicity and drug likeness of the compounds. The database of this online program contains *in vitro* and *in vivo* validated compounds and the predictions were based on the functional group similarity for the query molecule. The results were visualized using the color codes. Green color shows low toxic tendency, yellow shows the midcore and red color shows high tendency of toxicity. It is used to calculate toxicity risk parameters such as mutagenicity, tumorigenicity, irritation, and reproductive toxicity of all the modified compounds, and it was found that compounds tpk(1b) and tpk(1c) showed midcore and high tendency of irritation, respectively. Compound tpk(1d) indicated risk of mutagenicity and tumorigenicity. In order to assess the compound's overall potential to qualify for a drug, overall drug score (DS) was calculated, which combines drug-likeness, hydrophobicity (LogP), aqueous solubility (LogS), MW, and toxicity risk parameters. All the calculated values were given in Table 10.

The DS for tpk(1e) [(2-{1,1,5,9-tetraoxo-4H,5H,9H-1λ^6-[1,4]thiazino[2,3-f]indol-8-yl}ethyl)urea], tpk(1f) [2-methoxy-N-(2-{1,1,5,9-tetraoxo-4H,5H,9H-1λ^6-[1,4]thiazino[2,3-f]indol-8-yl}ethyl)acetamide] and tpk(1g) [2-hydroxy-N-(2-{1,1,5,9-tetraoxo-4H,5H,9H-1λ^6-[1,4]thiazino[2,3-f]indol-8-yl}ethyl)propanamide] show comparatively high values suggesting that they can be developed as potential anti-malarial drug. All these compounds have no effect on mutagenicity, tumorigenicity, irritation, and reproductive toxicity. Other drug-like properties are under the acceptable limits.

Conclusion

The analysis of 42 Thiaplakortone-A derivatives by 2D-QSAR, HQSAR, 3D-QSAR, molecular docking and Data mining studies provides a new path for the design of new series of anti-malarial drugs. In this study, 2D-QSAR models are generated by MLR method, and the robustness of the model is validated by internal, external, Y-randomization and Applicability domain analysis. The CoMFA and CoMSIA analysis have provided distinguishing key structural features affecting the anti-malarial activity of these inhibitors. We identified and confirmed the residues that play key role in the hydrogen bond donors, hydrophobic, steric and electrostatic interactions. All the 42 Thiaplakortone-A derivatives were subjected to molecular docking and the compounds with good docking score were selected and subjected to data mining. Data

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mining shows that 4 of the selected compounds with good docking score are anti-malarial active. Based on 3D-QSAR, seven virtual compounds were designed. These molecules were subjected to data mining and drug-likeness studies. The result shows that all the molecules obey Lipinski's RO5 and machine learning study reveals that out of the seven modified molecules three molecules are anti-malarial. Thus the generated models through modified approach provide a functional guideline to design and predict the activity of virtual compounds with enhanced inhibitory activities and thus help rational design of novel anti-malarial drugs.

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Figure captions

Fig. 1. Individual atomic contributions for the activity of the most potent compound tpk 1 (a) and the least potent compound tpk 22 (b). The colours at the red end of the spectrum reflect unfavourable contributions in the order of red>red-orange>orange colour, while colours at the green end indicate favourable (positive) contributions in the order of green>green-blue>yellow. Atoms with intermediate contributions are coloured in white.

Fig. 2 CoMFA field contour maps for active compound tpk 1. Electrostatic fields (a): Blue fields indicate electropositive groups favored, red fields indicate electronegative groups favored. Steric fields (b): Green fields indicate steric bulk favored, yellow fields indicate steric bulk disfavored

Fig. 3. CoMSIA field contour maps for active compound tpk 1. Electrostatic fields (a): Blue fields indicate electropositive groups favored, red fields indicate electronegative groups favored. Steric fields (b): Green fields indicate steric bulk favored, yellow fields indicate steric bulk disfavored. Hydrophobic fields (c): Magenta and orange represent favored and disfavored regions respectively for hydrophobic interaction. H-bond donor fields (d): cyan and purple represent regions for favored and disfavored for H bond donor groups respectively.

Fig. 4. Predicted anti-malarial activities with experimental values of 2D-QSAR, HQSAR, CoMFA and CoMSIA.

Fig. 5. Ramachandran Plot of the proteins.

Fig. 6. 2D interaction and molecular docking pose of the active compounds tpk1, tpk17, tpk20 and tpk28 in the binding pocket of the protein 3I79

Fig. 7: 2D interaction and molecular docking pose of the active compounds tpk1, tpk17, tpk20 and tpk28 in the binding pocket of the protein 3HZT

Fig. 8: Representation of SOMs by SMARTCyp.

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Table captions

Table 1. Representative skeletons and molecular structures of Thiaplakortone-A derivatives and their activity values

Table 2: Numerical values of the Observed Activity, Predicted Activity and Residual values of 2D-QSAR

Table 3: Statistical parameters after Y-randomization test

Table 4: Summary of the HQSAR statistical indices for various fragment distinction (FD) parameters using the default fragment size (4-7 atoms) for the Thiaplakortone-A derivatives (N=42).

Table.5: Statistical parameters of CoMSIA models

Table 6. Statistical results of CoMFA and the best CoMSIA models

Table 7: Experimental and predicted activities (pIC_{50}) with residual values

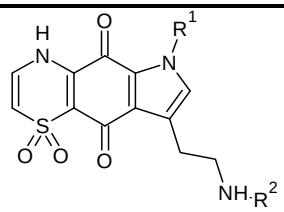
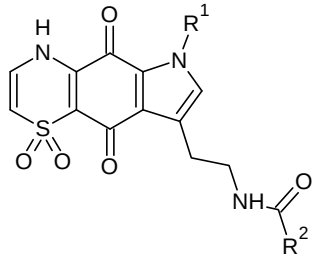
Table 8: Data of protein-ligand docking.

Table 9: Descriptors used to find out the anti-malarial activity value

Table 10: Predicted molecular parameters of the modified compounds

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Table 1. Representative skeletons and molecular structures of Thiaplakortone-A derivatives and their activity values

Compounds	R1	R2	IC_{50}	pIC_{50}
				
tpk1	H	H	104	6.983
tpk2	CH3	H	128	6.892
tpk3	CH3	CH3	137	6.863
				
tpk4	H	CH_3	160	6.795
tpk5	H	Methyl	472	6.326
tpk6	H	Ethyl	703	6.153
tpk7	H	n-Propyl	439	6.357
tpk8	H	c-Propyl	1139	5.943
tpk9	H	i-Propyl	537	6.270
tpk10	H	n-Butyl	644	6.191
tpk11	H	i-Butyl	537	6.270
tpk12	H	Cyclopentylmethyl	604	6.219
tpk13	H	Phenyl	582	6.235
tpk14	H	2-Fluorophenyl	445	6.351
tpk15	H	3-Fluorophenyl	1260	5.899
tpk16	H	3-Bromophenyl	1423	5.846
tpk17	H	4-Fluorophenyl	1290	5.889
tpk18	H	2,5-Difluorophenyl	1300	5.886
tpk19	H	2,6-Difluorophenyl	1090	5.962
tpk20	H	5-Fluoro-2-morpholinophenyl	1210	5.917
tpk21	H	2-(2-Fluorophenyl)acetyl	1300	5.886
tpk22	H	2-Fluoro-5-(trifluoromethyl)phenyl	1957	5.708
tpk23	H	3-Chloro-4-methoxyphenyl	925	6.033
tpk24	H	2-Hydroxy-4-methoxyphenyl	1412	5.850

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tpk25	H	3-(4-Methoxyphenyl)propyl	1633	5.787
tpk26	H	Isoquinolin-1-yl	824	6.084
tpk27	H	Furan-3-yl	1079	5.967
tpk28	H	(S)-5-Oxopyrrolidin-2-yl	1120	5.950
tpk29	H	1H-Indol-2-yl	886	6.052
tpk30	H	N(H)n-Bu	709	6.149
tpk31	H	N(H)t-Bu	685	6.164
tpk32	H	Ot-Bu	753	6.123
tpk33	H	N(H)-3,4-dimethoxybenzyl	1110	5.954
tpk34	H	N(Me)OMe	741	6.130
tpk35	H	$N(H)CH_2CO_2Et$	663	6.178
tpk36	H	N(H)-adamant-2-yl	631	6.200
tpk37	Methyl	CH_3	684	6.164
tpk38	Isopropyl	CH_3	937	6.028
tpk39	Cyclopentyl	CH_3	933	6.030
tpk40	(3-Methyloxetan-3-yl)methyl	CH_3	822	6.085
tpk41	Benzyl	CH_3	441	6.355
tpk42	4-Chlorobenzyl	CH_3	635	6.197

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Table 2: Numerical values of the Observed Activity, Predicted Activity and Residual

Compounds	Observed pIC_{50}	Predicted pIC_{50}	Residual	HAT i/i (h*=0.3571)	St Dev Res
tpk1*	6.9830	6.8039	-0.1791	0.3164	-1.7214
tpk2	6.8928	6.7100	-0.1828	0.2405	-1.6669
tpk3	6.8633	6.7997	-0.0636	0.3176	-0.6121
tpk4	6.7959	6.8615	0.0656	0.3398	0.6418
tpk5	6.3261	6.3036	-0.0225	0.2575	-0.2073
tpk6	6.1530	6.1714	0.0184	0.1030	0.1544
tpk7*	6.3575	6.3263	-0.0312	0.0741	-0.2576
tpk8	5.9435	5.9029	-0.0406	0.5683	-0.4906
tpk9	6.2700	6.1755	-0.0945	0.0733	-0.7801
tpk10	6.1911	6.2200	0.0288	0.0531	0.2355
tpk11	6.2700	6.2084	-0.0616	0.0568	-0.5044
tpk12	6.2190	6.1347	-0.0843	0.0865	-0.7006
tpk13	6.2351	6.2299	-0.0052	0.0520	-0.0426
tpk14	6.3516	5.9874	-0.3643	0.0924	-3.0387
tpk15*	5.8996	5.9689	0.0693	0.0899	0.5773
tpk16	5.8468	6.0483	0.2015	0.1028	1.6909
tpk17	5.8894	6.0140	0.1245	0.1000	1.0433
tpk18	5.8861	6.0510	0.1650	0.1336	1.4085
tpk19	5.9626	5.8392	-0.1234	0.1541	-1.0661
tpk20	5.9172	5.9937	0.0765	0.0934	0.6384
tpk21	5.8861	5.7658	-0.1202	0.1123	-1.0143
tpk22	5.7084	5.7471	0.0387	0.5009	0.4350
tpk23	6.0339	6.0199	-0.0140	0.0878	-0.1163
tpk24	5.8502	5.7790	-0.0711	0.2030	-0.6333
tpk25	5.7870	5.8311	0.0441	0.1003	0.3698
tpk26*	6.0841	6.0535	-0.0305	0.1002	-0.2557
tpk27	5.9670	6.1030	0.1360	0.0994	1.1388
tpk28	5.9508	6.0576	0.1068	0.1026	0.8963
tpk29	6.0526	6.0464	-0.0062	0.1030	-0.0518
tpk30	6.1494	6.0879	-0.0615	0.0977	-0.5145
tpk31	6.1643	6.1753	0.0110	0.1054	0.0927
tpk32*	6.1232	6.1423	0.0191	0.0890	0.1591
tpk33	5.9547	6.0826	0.1279	0.0787	1.0589
tpk34	6.1302	6.1884	0.0582	0.0435	0.4728
tpk35	6.1785	6.2311	0.0526	0.0522	0.4295
tpk36	6.2000	6.1232	-0.0768	0.0837	-0.6378
tpk37	6.1649	6.2184	0.0535	0.0585	0.4382
tpk38*	6.0283	6.1647	0.1365	0.0634	1.1205
tpk39	6.0301	6.2500	0.2199	0.0629	1.8054
tpk40	6.0851	6.1873	0.1022	0.1213	0.8663
tpk41	6.3556	6.1549	-0.2006	0.0976	-1.6784
tpk42	6.1972	6.1591	-0.0382	0.0645	-0.3135

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*-Test set compounds

Table 3: Statistical parameters after Y-randomization test

Random Models Parameters	
R_r :	0.315
R_r^2 :	0.109
Q_r^2 :	-0.159
$^cR_p^2$:	0.792

R_r - average correlation coefficient
R_r^2-mean squared correlation coefficients of the randomized
Q_r^2- average cross-validated correlation coefficient

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Table 4: Summary of the HQSAR statistical indices for various fragment distinction (FD) parameters using the default fragment size (4-7 atoms) for the Thiaplakortone-A derivatives (N=42).

Fragment	**R^2_{cv}**	**SEP**	**R^2_{ncv}**	**HL**	**N**
A/B/C	0.681	0.191	0.917	307	6
A/B/C/H	**0.682**	**0.198**	**0.958**	**151**	**8**
A/B/C/H/Ch	0.649	0.200	0.928	401	6
A/C/H/Ch/DA	0.468	0.238	0.803	401	4
A/B/C/H/Ch/DA	0.547	0.227	0.906	307	6
A/B/Ch/DA	0.398	0.262	0.897	61	6
A/B/C/Ch/DA	0.569	0.218	0.868	307	5
A/C/Ch/DA	0.407	0.247	0.655	71	3
A/B/H/Ch/DA	0.437	0.253	0.853	83	6

SEP: standard error of prediction, R^2_{cv}: cross-validated correlation coefficient, R^2_{ncv}: non cross-validated correlation coefficient, HL: hologram length, N: optimal number of components, Fragment distinction; A: atom, B: bond, C: connection, H: hydrogen, Ch: chirality, DA: donor and acceptor. The best model is in bold.

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Table.5: Statistical parameters of CoMSIA models

Model	Descriptors	$R^2_{LOO}(Q^2)$/ONC	R^2_{ncv}/ SEE_{ncv}	F value	$R^2_{m\ (overall)}$	R^2_{pred}
1	S and E	0.658/7	0.979/0.050	175.779	0.760	0.672
2	D and A	0.501/5	0.854/0.126	33.826	0.648	0.393
3	S, E and H	0.595/7	0.987/0.039	299.385	0.768	0.792
4	S, E and A	0.687/7	0.983/0.045	221.859	0.789	0.405
5	S, E and D	0.721/6	0.972/0.057	160.663	0.768	0.470
6	D, A and H	0.534/4	0.895/0.106	63.705	0.621	0.892
7	D, A and E	0.566/6	0.963/0.065	122.082	0.728	0.573
8	S, D and H	0.593/4	0.926/0.089	94.388	0.685	0.722
9	S, E, D and A	0.682/6	0.977/0.051	201.207	0.773	0.400
10	**S, E, D and H**	**0.647/6**	**0.984/0.042**	**292.970**	**0.770**	**0.718**
11	S, E, A and H	0.637/7	0.987/0.040	283.145	0.784	0.598
12	D, A, H and S	0.612/6	0.968/0.061	139.470	0.764	0.524
13	D, A, H and E	0.549/6	0.966/0.062	134.057	0.727	0.779
14	S, E, D, A and H	0.565/6	0.927/0.085	74.046	0.860	0.606

$R^2_{LOO}(Q^2)$- cross-validated correlation coefficient
ONC- Optimum Number of Components
R^2_{ncv}- Non cross-validated correlation coefficient
SEE_{ncv}- Standard Error of Estimate
R^2_{pred}-Predicted correlation coefficient
S-Steric, E-Electrostatic, D-Hydrogen bond donor, A- Hydrogen bond acceptor and H-Hydrophobic.
The best model is in bold.

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Table 6. Statistical results of CoMFA and the best CoMSIA models

	CoMFA	**CoMSIA (Model 10)**
Q^2/ONC	0.813/7	0.647/6
R^2_{ncv}	0.994	0.984
SEP	0.149	0.201
SEE	0.027	0.042
R^2_{pred}	0.891	0.718
F value	216	292.970
Field contribution		
steric	59	15.1
electrostatic	41	31.3
hydrophobic	-	18.8
H-bond donor	-	34.9

Q^2-cross-validated correlation coefficient.

ONC-Optimum number of components

R^2_{ncv} -non cross-validated correlation coefficient.

SEP- Standard error of prediction.

SEE-Standard errors of estimate.

R^2_{pred}- Predicted correlation coefficient for the test set

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Table 7: Experimental and predicted activities (pIC_{50}) with residual values

Compound id	**Actual** pIC_{50}	**HQSAR** predicted	residual	**CoMFA** Predicted	Residual	**CoMSIA** Predicted	Residual
tpk1	6.983	6.609	0.373	6.861	0.122	6.914	0.069
tpk2	6.892	6.764	0.128	6.841	0.051	6.916	-0.023
tpk3	6.863	6.855	0.007	6.767	0.096	6.822	0.041
tpk4	6.795	6.763	0.032	6.879	-0.083	6.880	-0.084
tpk5	6.326	6.393	-0.067	6.262	0.064	6.319	0.007
tpk6*	6.153	6.288	-0.135	6.220	-0.067	6.215	-0.062
tpk7	6.357	6.235	0.121	6.258	0.099	6.358	-0.000
tpk8	5.943	6.177	-0.233	6.008	-0.064	5.963	-0.019
tpk9	6.270	6.207	0.062	6.278	-0.008	6.300	-0.030
tpk10	6.191	6.258	-0.067	6.002	0.189	6.132	0.059
tpk11	6.270	6.175	0.094	6.339	-0.069	6.274	-0.004
tpk12	6.219	6.169	0.049	6.169	0.050	6.192	0.027
tpk13*	6.235	6.028	0.207	6.189	0.046	6.192	0.043
tpk14*	6.351	5.973	0.378	5.789	0.562	5.853	0.498
tpk15*	5.899	5.954	-0.054	5.900	-0.000	5.943	-0.043
tpk16	5.846	6.000	-0.153	5.854	-0.007	5.847	-0.000
tpk17	5.889	5.901	-0.011	5.945	-0.055	5.905	-0.015
tpk18	5.886	5.848	0.037	5.928	-0.041	5.894	-0.007
tpk19*	5.962	5.918	0.044	6.105	-0.142	6.007	-0.044
tpk20	5.917	5.592	0.325	6.055	-0.137	5.904	0.013
tpk21*	5.886	6.077	-0.190	5.960	-0.073	6.097	-0.210
tpk22	5.708	5.667	0.040	5.652	0.056	5.696	0.012
tpk23	6.033	5.783	0.249	5.863	0.170	6.000	0.033
tpk24	5.850	5.911	-0.061	6.054	-0.203	5.868	-0.017
tpk25	5.787	5.951	-0.164	5.645	0.142	5.822	-0.035
tpk26	6.084	5.897	0.186	6.149	-0.064	6.039	0.045
tpk27	5.967	6.230	-0.263	6.094	-0.127	6.065	-0.098
tpk28*	5.950	5.770	0.180	6.376	-0.425	6.373	-0.422
tpk29	6.052	5.882	0.170	5.966	0.086	6.047	0.005
tpk30	6.149	6.248	-0.099	6.237	-0.087	6.159	-0.009
tpk31	6.164	6.006	0.157	6.147	0.017	6.126	0.038
tpk32	6.123	6.284	-0.161	6.090	0.033	6.130	-0.006
tpk33	5.954	6.043	-0.089	6.061	-0.106	5.981	-0.026
tpk34	6.130	6.334	-0.203	6.085	0.045	6.076	0.054
tpk35	6.178	6.194	-0.015	6.186	-0.007	6.197	-0.018
tpk36	6.200	6.062	0.137	6.206	-0.006	6.231	-0.031
tpk37	6.164	6.606	-0.441	6.188	-0.023	6.211	-0.046
tpk38	6.028	6.130	-0.102	6.182	-0.153	6.062	-0.033
tpk39	6.030	5.891	0.139	6.104	-0.073	6.020	0.010
tpk40	6.085	6.176	-0.091	6.177	-0.091	6.036	0.049

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tpk41	6.355	6.151	0.204	6.168	0.187	6.365	-0.009
tpk42	6.197	6.260	-0.063	6.196	0.001	6.143	0.054

*-Test set compounds

Table 8: Data of protein-ligand docking.

Compounds	**3I79 (kcal/mole)**	**3HZT (kcal/mole)**
tpk1	-13.6612	-10.5007
tpk17	-13.2110	-10.9846
tpk20	-13.2729	-11.9554
tpk28	-13.9943	-10.2702
tpk34	-14.0290	-11.0446
tpk36	-13.6347	-10.7451
tpk41	-15.0210	-10.8624
tpk42	-11.2184	-11.6409

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Table 9: Descriptors used to find out the anti-malarial activity value

Modified molecules	**SMR_VSA1**	**MNDO_LUMO**	**maxHssNH**	**pIC_{50}**
tpk(1a)	11.9848	-0.3257	0.0188	5.872
tpk(1b)	26.9449	-0.1881	0.0392	5.498
tpk(1c)	13.1239	-0.0132	-0.0141	6.154
tpk(1d)	-17.9354	0.2459	-0.0231	6.543
tpk(1e)	-19.8345	0.0739	-0.0043	6.394
tpk(1f)	-19.8345	0.1285	-0.0079	6.425
tpk(1g)	5.5507	0.0787	-0.0084	6.168

SMR_VSA1- Molecular refractivity based descriptor
MNDO_LUMO- potential energy based descriptor
maxHssNH- Maximum atom-type H E-State of -NH-

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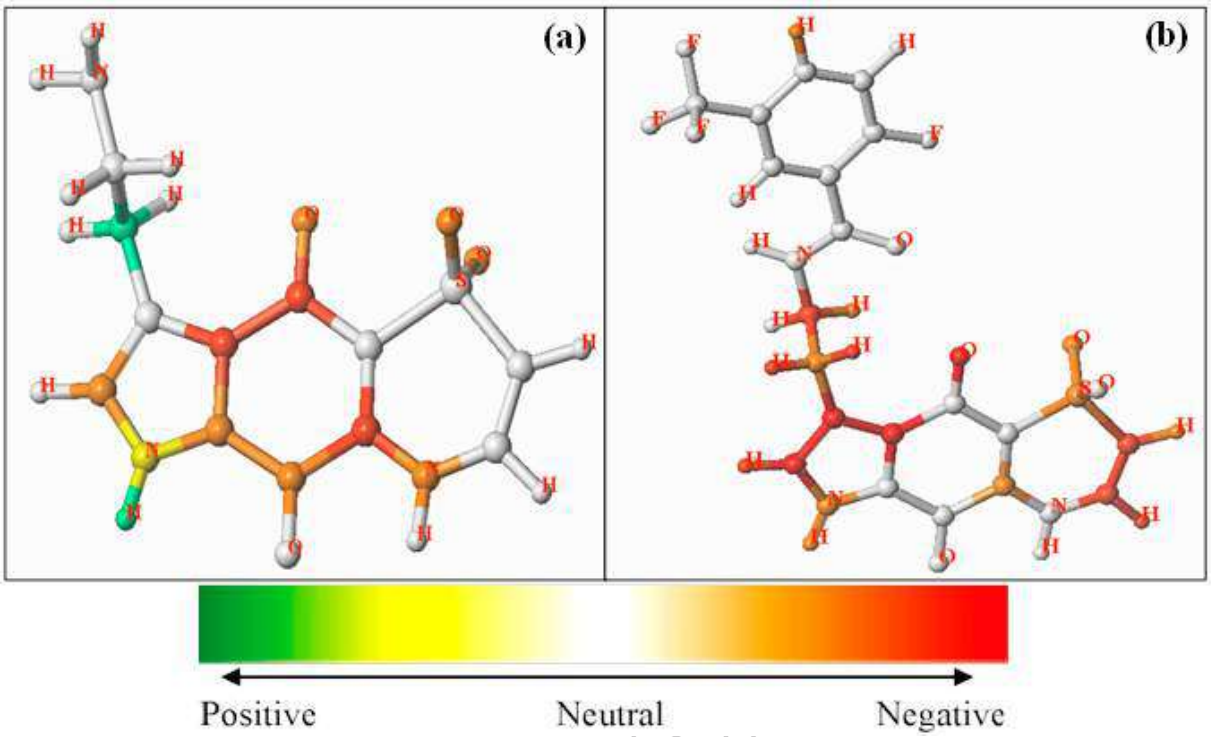
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Table 10: Predicted molecular parameters of the modified compounds

Compounds	ClogP	Solubility	Mol wt	Drug likeness	DS
tpk(1a)	0.19	-3.30	343	-0.37	0.604
tpk(1b)	0.82	-3.78	361	-3.12	0.337
tpk(1c)	-1.89	-2.28	332	-0.66	0.366
tpk(1d)	-1.74	-2.06	349	3.73	0.572
tpk(1e)	-1.74	-2.93	336	4.00	0.877
tpk(1f)	-1.62	-2.29	365	4.01	0.880
tpk(1g)	-1.68	-2.54	365	1.16	0.776

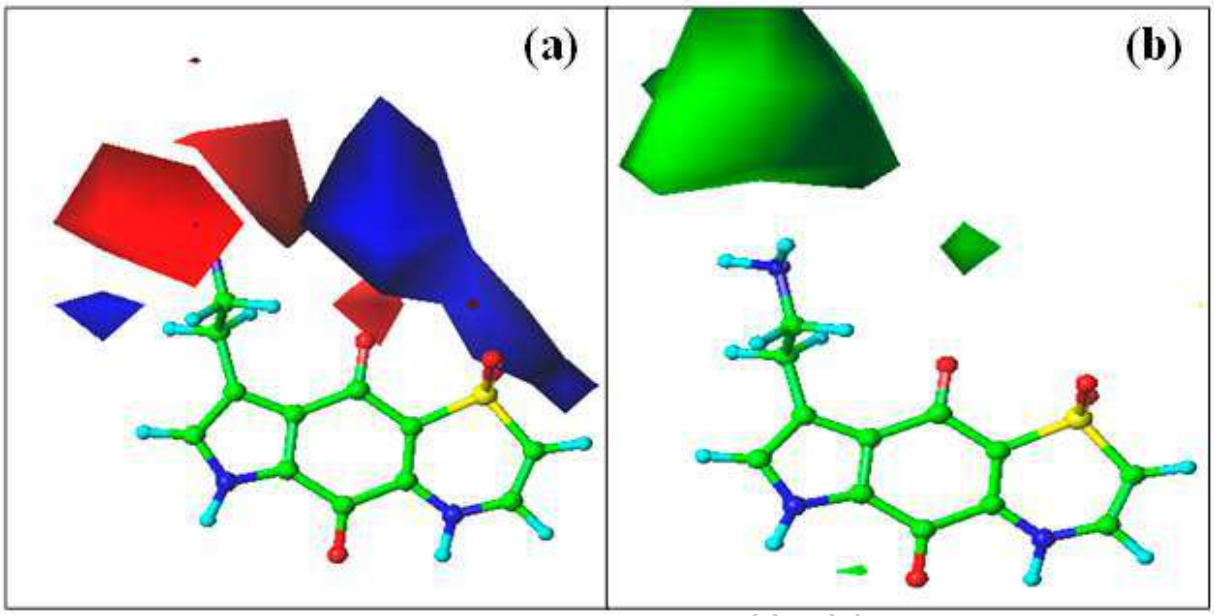
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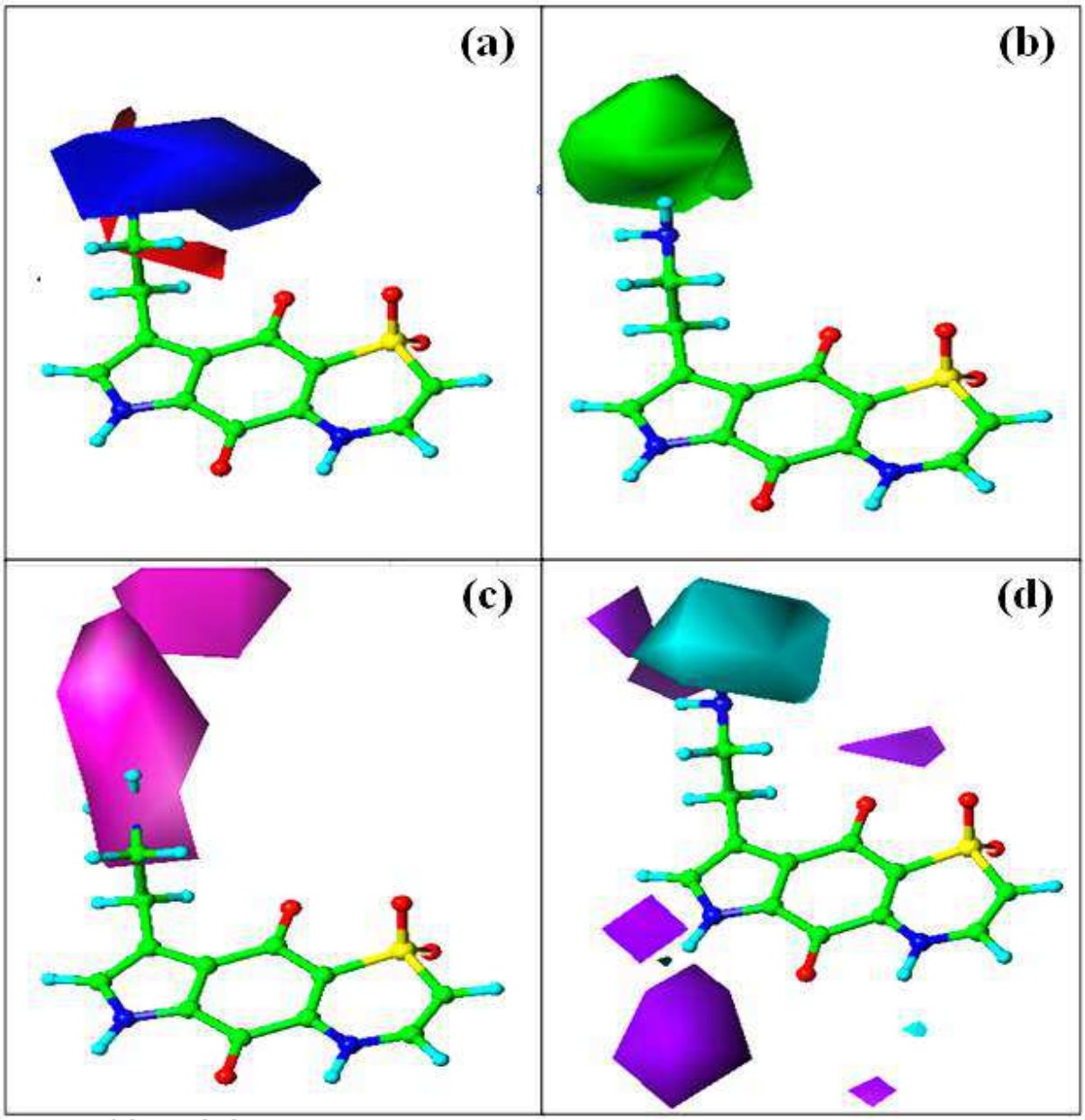
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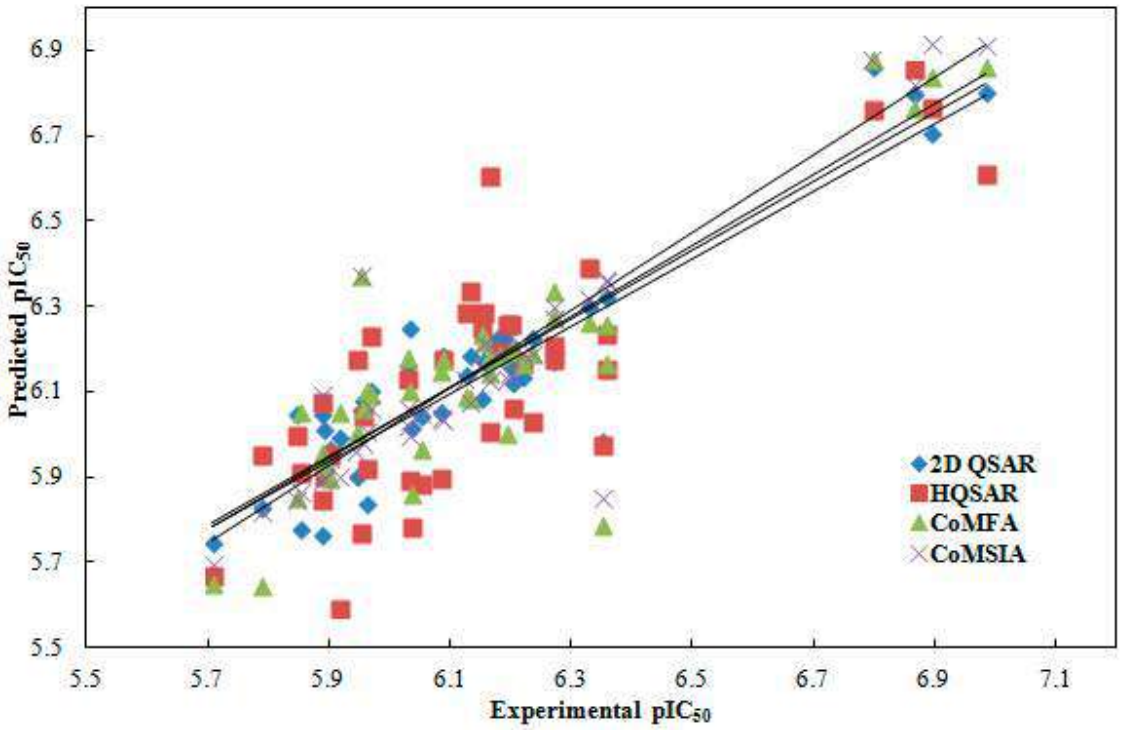
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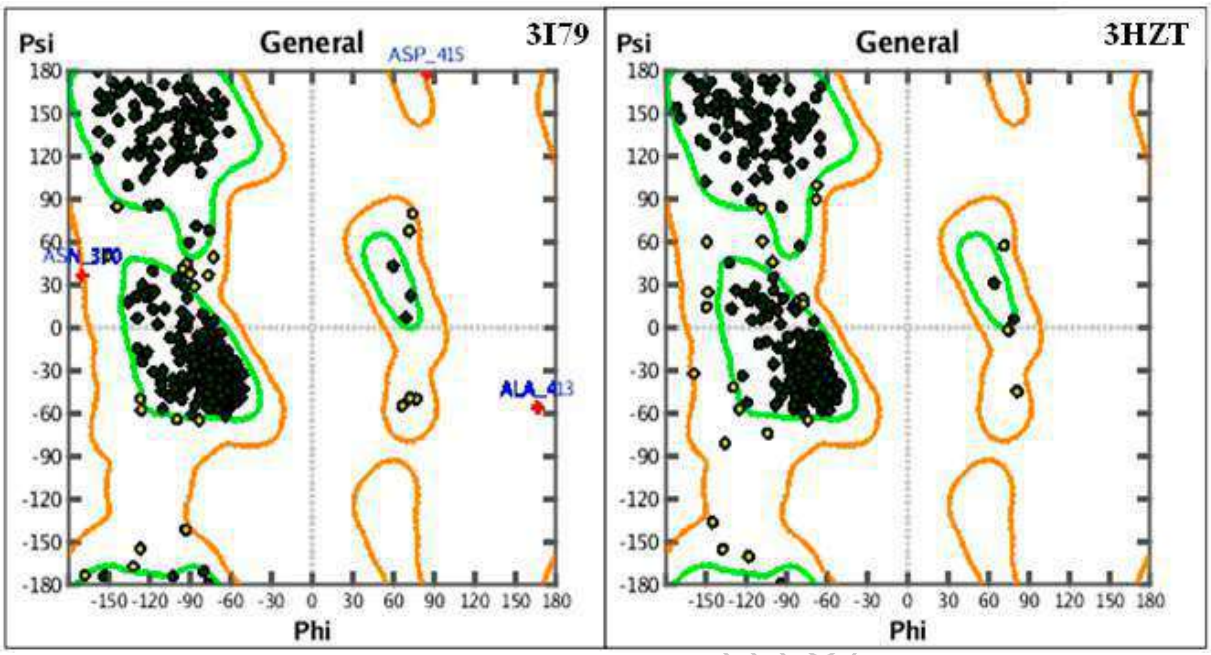


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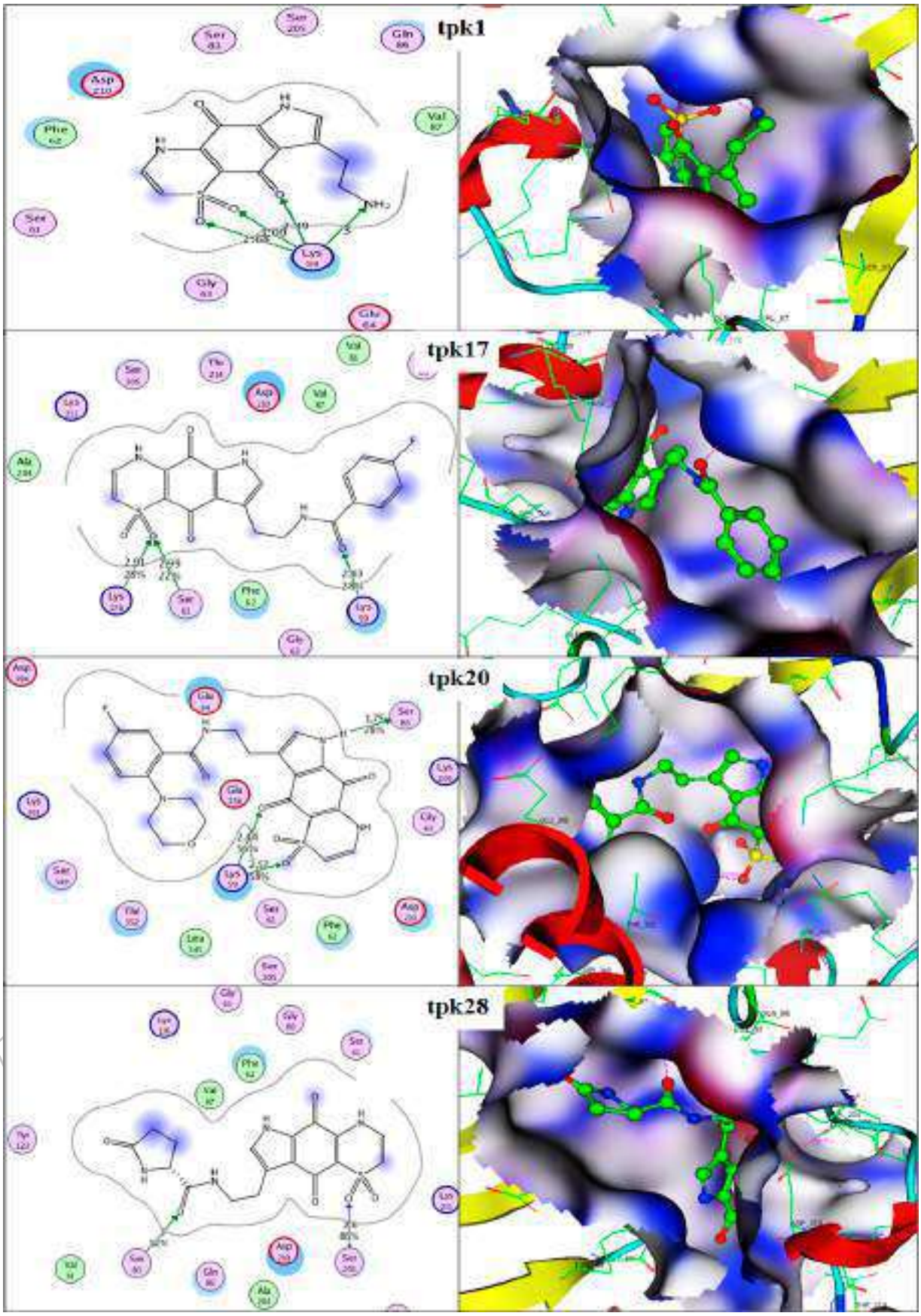
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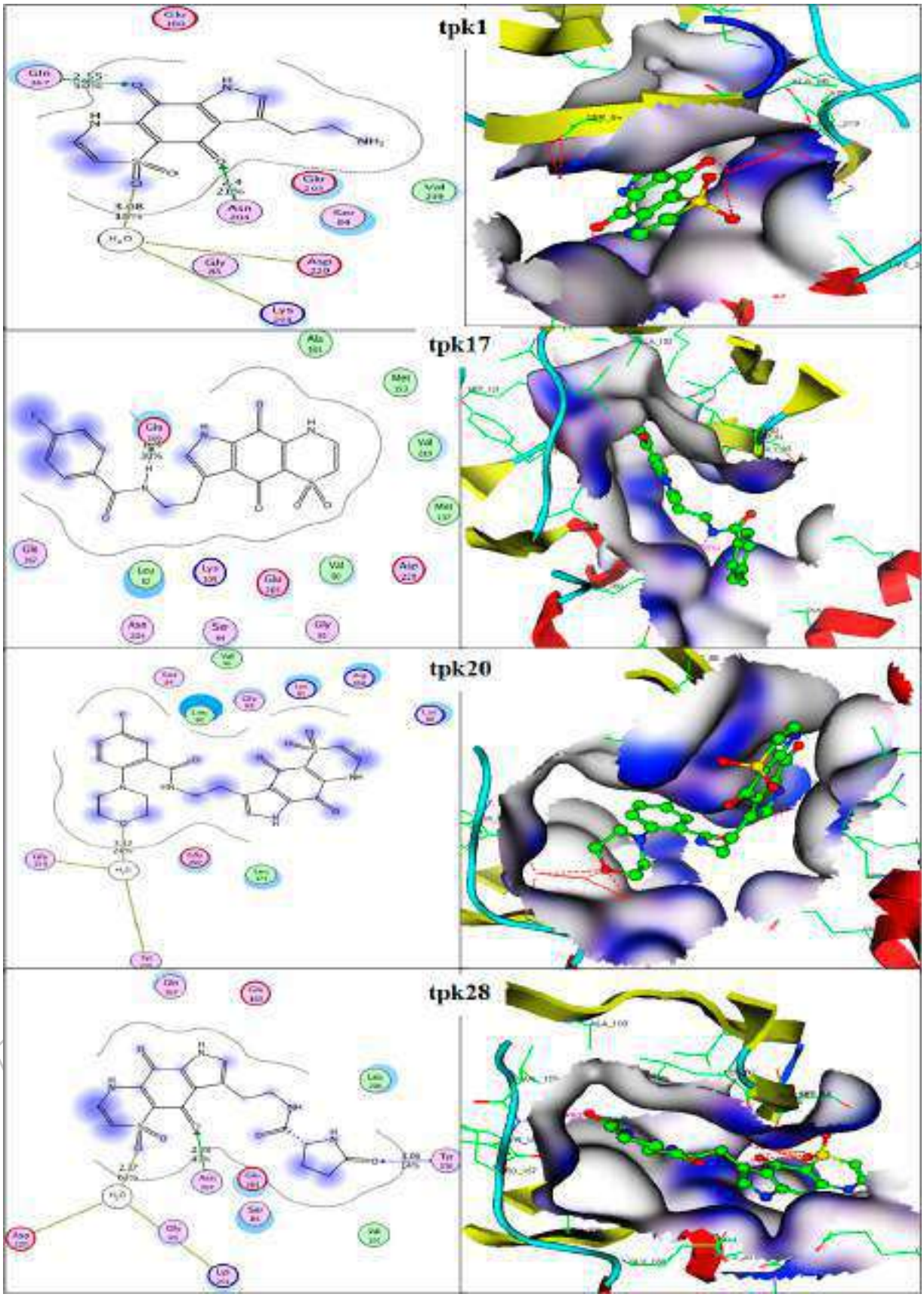
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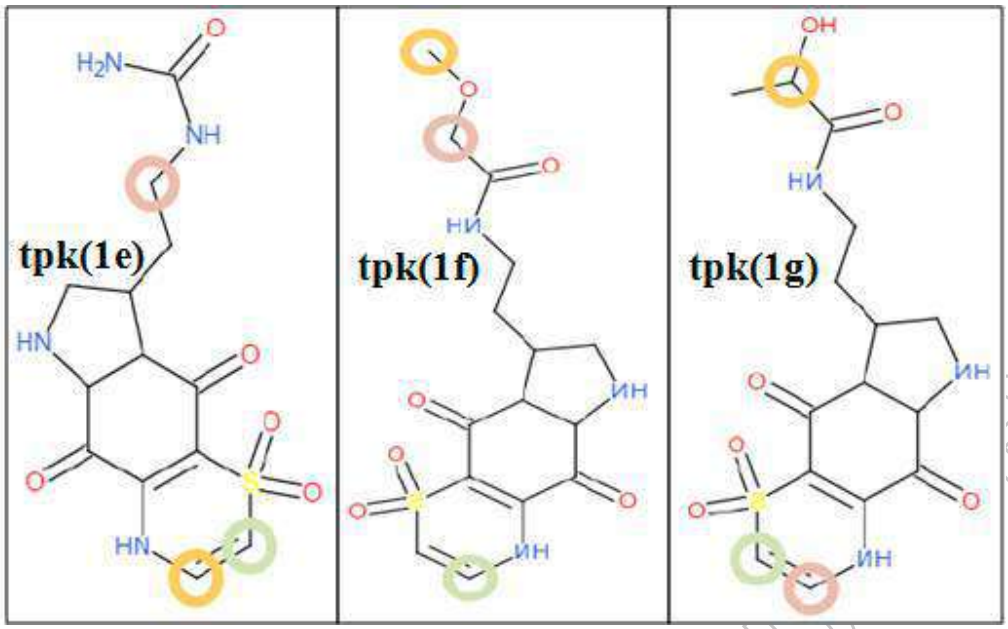
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QSAR modeling for anti-human African trypanosomiasis activity of substituted 2-Phenylimidazopyridines

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ABSTRACT

In the present work, sixty substituted 2-Phenylimidazopyridines previously reported with potent anti-human African trypanosomiasis (HAT) activity were selected to build genetic algorithm (GA) based QSAR models to determine the structural features that have significant correlation with the activity. Multiple QSAR models were built using easily interpretable descriptors that are directly associated with the presence or the absence of a structural scaffold, or a specific atom. All the QSAR models have been thoroughly validated according to the OECD principles. All the QSAR models are statistically very robust (R^2 = 0.80–0.87) with high external predictive ability (CCC_{ex} = 0.81–0.92). The QSAR analysis reveals that the HAT activity has good correlation with the presence of five membered rings in the molecule.
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1. Introduction

Sleeping sickness or human African trypanosomiasis (HAT), transmitted by tsetse flies (genus *Glossina*), has a major occurrence in rural populations in sub-Saharan Africa. HAT, considered as a neglected tropical disease, was nearly eradicated in the mid-1960s. The resurgence in the late 1990s, due to poor sanitation and suitable habitats for its vector in the Democratic Republic of the Congo (DRC), Angola, Central African Republic, southern Sudan, and Uganda, received considerable attention of the researchers to develop better diagnosis and treatment for the disease [1–3]. Recent reports indicate that in humans the disease is thought to be mainly caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, however the non-human-pathogenic trypanosome species *Trypanosoma brucei brucei*, *Trypanosoma congolense*, and *Trypanosoma evansi* are also responsible in some instances [1]. The disease has two stages; in stage 1 (hemolymphatic) the peripheral infection with non-specific clinical symptoms occur; and in stage 2 the parasite crosses the blood brain barrier (BBB) and intrudes the central nervous system (CNS) [1–3].

Suramin and pentamidine are the recommended drugs for stage 1 infection, whereas for stage 2, the therapeutic options are melarsoprol, eflornithine and the currently used combination therapy NECT (nifurtimox and eflornithine combination therapy). Unfortunately, vaccine cannot be developed due to a high degree of antigenic variation. In addition, the treatment is parasite- and stage-specific, depending on the ability of the compound to cross the BBB. For BBB clearance the drug must be sufficiently lipophilic, which results in poor water solubility, hence, such drugs are mostly toxic and problematical to administer. Consequently, the available drugs for stage 2 of the disease exhibit high toxicity, involve the complexity of administration procedures and progressive loss of efficacy in some geographical regions. Recent efforts identified Fexinidazole, furamidine, DB289 (parafuramidine), CPD-0802 (an aza analogue of parafuramidine) and SCYX-7158 (a boron based compound) as attractive lead/targets in the drug pipeline for

Abbreviations: HAT, Human African Trypanosomiasis; GA, Genetic algorithm; MLR, Multiple linear Regression; QSAR, Quantitative structure-activity analysis; WHO, World health organization; ADMET, Absorption, Distribution, Metabolism, Excretion and Toxicity; OLS, Ordinary Least Square; QSARINS-Chem, QSAR Insubria-Chemistry; OECD, Organization for Economic Co-operation and Development.

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developing better therapeutics for HAT (see Fig. 1). Despite the previous efforts executed high toxicity, poor oral bioavailability and blood–brain barrier penetration are the major obstacles ahead for these clinical candidates. Thence, the search for a drug candidate with adequate activity, ADME and toxicity profile still persists [1–4].

Recently, Tatipaka et al. [5] identified substituted oxazolopyridine **1** (see Fig. 2) as an attractive lead due to good whole-cell activity on *T. brucei*, no cytotoxicity on mammalian cell lines, acceptable exposure in the central nervous system, and satisfactory aqueous solubility. But, its poor metabolic stability in liver microsomes appeared as a severe liability. Later, to design a better analogue of **1** with the desired profile, they synthesized and screened a series of substituted 2-Phenylimidazopyridines. Since, the mechanism of action and the specific target with which these analogues interact is unknown [5]; in such a situation, a good strategy for lead optimization is to employ computer aided drug design (CADD) using the available information. Hence, in the present work, ligand based drug design technique, viz. QSAR (2D- and 3D-) has been executed to determine the structural features having a significant correlation with the HAT activity profile of substituted 2-Phenylimidazopyridines.

In the past decades, CADD has appeared as a thriving option to conventional 'trial and error' methodology of drug design/discovery to unknot the mysteries of structural patterns that govern the activity, pharmacokinetics, pharmacodynamics and toxicity profiles of a drug candidate. CADD is relatively fast, economical and significantly result oriented successful *in-silico* technique [6–10]. It encompasses a combination of different ideas, algorithms, tools and techniques of various scientific fields like computer, mathematics, statistics, etc. Its major emphasis is on simulation of interactions of different molecules, to determine the reasons behind the specific interactions of different molecules and identification of effective structural features associated with activity/toxicity. QSAR, molecular docking, pharmacophore modeling, etc. are established CADD methods, which when used in harmony provide significant and unrivalled information essential for lead/drug optimization [4,11–15]. These methods have been widely used for identification of the structural patterns that govern the specific activity/toxicity of drug candidates and provide better insight into the mechanism of drug action.

The main objective of the present work is to develop statistically robust and easily interpretable, in terms of structural fragments or specific atom, QSAR models with high external predictive ability.

2. Experimental methodology

2.1. Experimental datasets

In the present work, HAT inhibition activities of sixty substituted 2-Phenylimidazopyridines comprising different heterocyclic scaffolds and diverse substituents at various positions covering a meaningful portion of the chemical space were subjected to QSAR modeling [5]. The reported EC_{50} (μM) values for HAT activity were converted to pEC_{50} ($-\log_{10}EC_{50}$) before QSAR analysis. The EC_{50}, pEC_{50} and the substituents on 2-Phenylimidazopyridine moiety have been listed in Table 1.

2.2. Modeling and molecular descriptors calculation

In the present work, a QSAR analysis following the standard procedure recommended by OECD and different researchers was exercised [16–26]. The chemical structures were drawn using ChemSketch 12 freeware followed by energy minimization using MMFF94 force field in TINKER [4,12,15]. The optimized structures were used as input for the calculation of a good number of 1-3D, electro-topological, fingerprints and other descriptors. Two descriptor calculating softwares were used: PaDEL 2.21 and e-Dragon. Since, all the calculated descriptors (>18,000) do not contain significant information; objective feature selection was employed to reduce the descriptor pool. Nearly constant (>95%), constant, and highly correlated (|R| > 95%) descriptors were eliminated before subjective feature selection (SFS) using QSARINS-Chem 2.2.1 [16,17,20]. This resulted in a reduced cluster of 345 descriptors only. The very next step involved the elimination of highly esoteric descriptors, the descriptors for which an exact explanation is not available or it is difficult to interpret it in terms of structural features [26]. This led to a set of only 253 easily interpretable descriptors. The reduced set still consists a wide range of theoretical molecular descriptors that takes into account different structural features, viz. constitutional (0D-), mono-dimensional (1D-), bi-dimensional (2D-) and three-dimensional (3D-), capturing and magnifying the diverse aspects of the chemical structures.

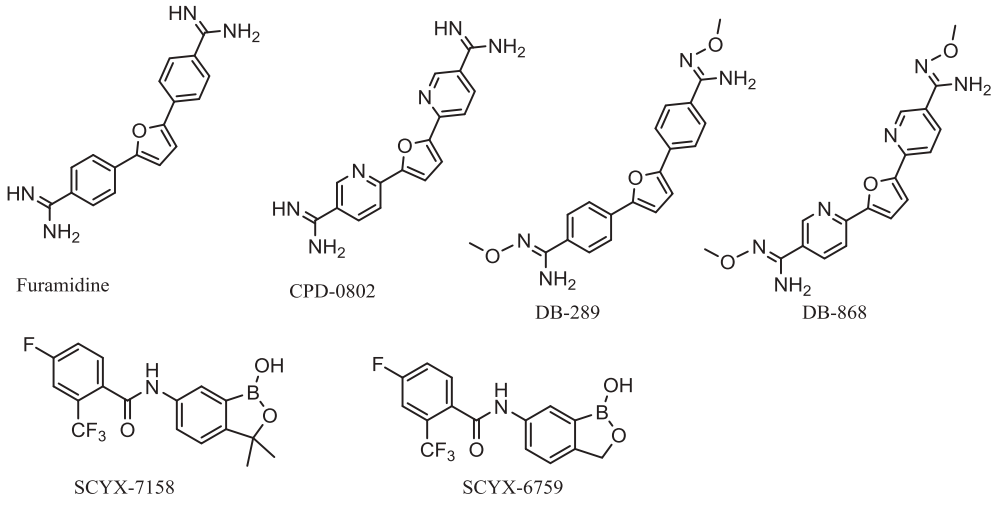
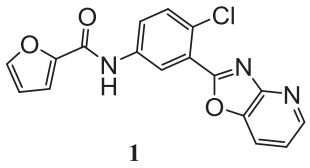


Fig. 1. Chemical structures of clinical drug candidates against HAT.



1

Ease of synthesis,
No stereogenic carbons,
Low MW and Lipinski rule-of-five compliance,
T. brucei in vitro EC_{50} = 220 nM,
Acceptable aqueous solubility,
Not cytotoxic to mammalian cells (L6, CRL-8155 and HepG2 cells),
Poor metabolic stability in liver microsomes

Fig. 2. Chemical structure and profile of substituted oxazolopyridine **1**.

2.3. QSAR model development

2.3.1. QSAR model

The very first principles and applications of QSAR analysis are to gain maximal information of activity related structural features and to predict the desired activity of a molecule before its actual synthesis and bio-screening. Hence, in order to achieve these goals easily interpretable descriptors were considered during model generation and multiple QSAR models were developed using divided and undivided datasets [19,27,28]. The dataset was divided into a training (80%) and a prediction (or test) (20%) sets in random fashion before descriptor selection. Multiple splitting were employed to develop multiple QSAR models [12,15], in this way a molecule in the training set of a splitting may or may not be in the training set of another splitting. Therefore, the multiple QSAR modeling approach ensured that maximum number and information is gained for molecular descriptors that govern the biological profile of the molecules. GA (Genetic Algorithm) module of QSARINS-Chem 2.2.1 was utilized for the selection of optimum number and set of descriptors. For the sake of simplicity and to avoid the problem of over-fitting, the heuristic search of descriptors was limited to four descriptors using the default settings in QSARINS-Chem 2.2.1. Q^2_{loo} was used as a fitness function to avoid the problem of naïve Q^2. The strategy used in QSAR model development has been summarized in Fig. 3 [12,15,24].

For development of QSAR models 6–10, HeuristicLab 3 was employed using different operand using the default settings.

2.4. Model validation

All QSAR models need to be appropriately validated to ascertain its predictive ability and utility. The statistical qualities and validity of the QSAR models were established by means of: (a) internal validation or cross-validation (CV) by leave-one-out (LOO) and leave-many-out (LMO) procedure; (b) using the prediction set; (c) data randomization i.e. Y-scrambling and (d) examining if the following conditions are satisfied [12,15]: $R^2_{tr} \geq 0.6$, $Q^2_{loo} \geq 0.5$, $Q^2_{LMO} \geq 0.6$, $R^2 > Q^2$, $R^2_{ex} \geq 0.6$, $RMSE_{tr} < RMSE_{cv}$, $\Delta K \geq 0.05$, $CCC \geq 0.80$, $Q^2 - F^n \geq 0.60$, $r^2_m \geq 0.6$, $(1 - r^2/r^2_0) < 0.1$, $0.9 \leq k \leq 1.1$ or $(1 - r^2/r'^2_0) < 0.1$, $0.9 \leq k' \leq 1.1$, $|r^2_0 - r'^2_0| < 0.3$ with *RMSE* and *MAE* close to zero. The threshold values of these parameters confirm the robustness and good external predictive ability of a GA-MLR model. Thus, all the models having low internal and external predictive ability were subsequently rejected.

3. Results and discussion

3.1. QSAR models

The GA analysis resulted in the generation of a good number of MLR models with nearly similar statistical performance but encompassing different descriptors. In such a situation, the usual practice followed by a QSAR modeller is to select only one MLR model on the basis of its statistical performance. However, this 'first among equals' approach is with following drawbacks [12,15] (1) a QSAR model consisting of only esoteric descriptors, suitable and realistic description in terms of structural features is highly problematic and challenging, (2) The single QSAR model may not be based on (i) appropriate composition of training and test sets, (ii) sufficient chemical and biologic space i.e. appropriate applicability domain, (3) the single QSAR model might have high predictive on a particular prediction set, but poor predictivity on another prediction set. To overcome these drawbacks of 'first among equals' approach, building and reporting multiple models or consensus modeling are two easy, practicable and efficient solutions. Recently, it has been established that developing multiple QSAR models based on divided and undivided dataset enhance the efficacy of QSAR in determining the dominant and concealed structural features that have significant correlation with the activity [12,15]. Therefore, in the present study, multiple QSAR models have been built following the OECD principles for acceptable QSAR models. This approach led to generation of ten QSAR models possessing excellent statistical performance. The GA-MLR QSAR models along with different statistical parameters, tabulated in Table 2, are as following:

3.2. Model-1 (Undivided dataset)

$$pEC_{50} = 6.486\ (\pm 0.378) - 0.214\ (\pm 0.067)\ *\ \text{C-024} + 0.756\ (\pm 0.273)\ *\ \text{nR05} - 1.087\ (\pm 0.318)\ *\text{F09[N–F]} + 0.897\ ((\pm 0.169)\ *\text{F10[C–F]}.$$

3.3. Model-2 (Undivided dataset)

$$pEC_{50} = 4.218\ (\pm 0.514) + 0.449\ (\pm 0.141)\ *\text{F02[N–N]} + 0.842\ (\pm 0.265)\ *\ \text{nR05} - 0.570\ (\pm 0.305)\ *\text{F09[N–F]} + 0.453\ (\pm 0.147)\ *\text{F10[C–F]}.$$

3.4. Model-3 (Divided dataset)

$$pEC_{50} = 5.148\ (\pm 0.537) + 0.518\ (\pm 0.399)\ *\text{B10[C–F]} + 0.624\ (\pm 0.292)\ *\ \text{nR05} - 0.558\ (\pm 0.476)\ *\text{B09[N–F]} + 1.178\ (\pm 0.404)\ *\text{B07[N–F]}.$$

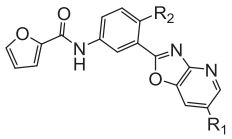
3.5. Model-4 (Divided dataset)

$$pEC_{50} = 5.729\ (\pm 0.258) - 1.328\ (\pm 0.724)\ *\ \text{nArNR2} + 1.450\ (\pm 0.337)\ *\ \text{nPyrrolidines} - 0.507\ (\pm 0.254)\ *\text{F10[N–F]} + 0.308\ (\pm 0.100)\ *\text{F09[C–F]}.$$

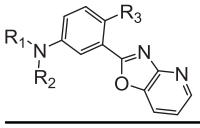
3.6. Model-5 (Divided dataset)

$$pEC_{50} = 5.789\ (\pm 0.258) - 1.375\ (\pm 0.743)\ *\ \text{nArNR2} + 1.322\ (\pm 0.331)\ *\ \text{nPyrrolidines} - 0.015\ (\pm 0.008)\ *\text{G(N..F)} + 0.381\ (\pm 0.121)\ *\text{F09[C–F]}.$$

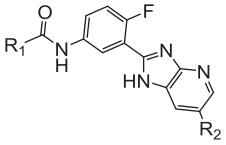
Table 1
Different substituted 2-Phenylimidazopyridines along with reported IC_{50} and pIC_{50}.



S.No.	R_1	R_2	EC_{50} (μm)	pEC_{50}(M)
1.	H	Cl	0.22	6.658
2.	H	F	0.12	6.921
3.	H	Me	0.43	6.367
4.	H	CN	0.4	6.398
5.	Br	F	0.23	6.638
6.	CN	F	0.38	6.42
7.	phenyl	F	0.04	7.398
8.	4-fluorophenyl	F	0.05	7.301
9.	3-chlorophenyl	F	0.05	7.301
10.	4-MeO-phenyl	F	0.17	6.77
11.	4-phenylphenyl	F	0.42	6.377

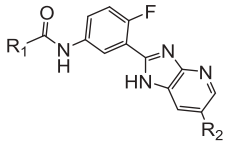


	R_1	R_2	R_3	EC_{50} (μM)	pEC_{50}(M)
12.	5-methylfuran-2-carbonyl	H	F	0.2	6.699
13.	3-methylfuran-2-carbonyl	H	F	0.1	7
14.	3-furanoyl	H	F	0.15	6.824
15.	benzoyl	H	Cl	7.1	5.149
16.	oxazole-5-carbonyl-	H	F	1.9	5.721
17.	2-thiophenoyl	H	Cl	1.5	5.824
18.	3-pyridinecarbonyl-	H	F	7	5.155
19.	pyrazine-2-carbonyl-	H	F	0.9	6.046
20.	N-methylpyrrole-2-carbonyl-	H	F	1.1	5.959
21.	methylsulfonyl	H	Cl	6.1	5.215
22.	2-furancarbothioyl-	H	F	0.41	6.387
23.	2-furanoyl	2-acetyl	F	0.5	6.301
24.	2-furanoyl	2-furanoyl	F	0.12	6.921
25.	benzyl	benzyl	F	1.1	5.959
26.	methylcarbamoyl	H	F	3.8	5.42
27.	isopropylcarbamoyl-	H	Cl	1	6
28.	phenylcarbamoyl-	H	Cl	12	4.921
29.	dimethylcarbamoyl-	H	Cl	0.4	6.398
30.	1-pyrrolidinoyl-	H	Cl	0.09	7.046
31.	1-piperidinoyl-	H	Cl	1.9	5.721



	R_1	R_2	EC_{50} (μM)	pEC_{50}(M)
32.	2-furanyl	H	0.2	6.699
33.	2-furanyl	Cl	0.07	7.155
34.	2-furanyl	F	0.2	6.699
35.	2-furanyl	5-Cl	10	5
36.	2-furanyl	7-Cl	0.12	6.921
37.	N-pyrrolidinyl	Cl	0.05	7.301
38.	N-pyrrolidinyl	phenyl	0.002	8.699
39.	N-pyrrolidinyl	3-methoxyphenyl	0.01	8
40.	N-pyrrolidinyl	2-methoxyphenyl	0.005	8.301
41.	N-pyrrolidinyl	3-Cl-phenyl	0.002	8.699
42.	N-pyrrolidinyl	2-chlorophenyl	0.005	8.301
43.	N-pyrrolidinyl	3-acetylphenyl	0.003	8.523
44.	N-pyrrolidinyl	3-Me-phenyl	0.002	8.699
45.	N-pyrrolidinyl	3-trifluoromethoxyphenyl	0.03	7.523
46.	N-pyrrolidinyl	3-methyl-4-fluorophenyl	0.02	7.699
47.	N-pyrrolidinyl	3-NH_2-phenyl	0.01	8
48.	N-pyrrolidinyl	3-furanyl	0.004	8.398
49.	N-pyrrolidinyl	3-thiophenyl	0.002	8.699
50.	N-pyrrolidinyl	2-thiophenyl	0.004	8.398
51.	N-pyrrolidinyl	3-pyridyl	0.005	8.301

Table 1 (*continued*)



	R_1	R_2	EC_{50} (μM)	pEC_{50}(M)
52.	N-pyrrolidinyl	5-(2-chloropyridyl)	0.01	8
53.	N-pyrrolidinyl	4-(2-chloropyridyl)	0.004	8.398
54.	N-pyrrolidinyl	5-(3-methylpyridyl)	0.01	8
55.	N-pyrrolidinyl	5-(2-methoxypyridyl)	0.005	8.301
56.	N-pyrrolidinyl	5-(3-pyrrolidino)	0.02	7.699
57.	N-pyrrolidinyl	5-(3-chloropyrimidinyl)	0.005	8.301
58.	N-pyrrolidinyl	5-pyrimidinyl	0.03	7.523
59.	N-pyrrolidinyl	5-(2-methoxypyrimidinyl)	0.06	7.222
60.	N-pyrrolidinyl	5-(2-chloropyrimidinyl)	0.04	7.398

3.7. Model-6 (Undivided dataset)

$pEC_{50} = 8.455\ (\pm0.292) - 0.013\ (\pm0.006)$ *G(N..F) $- 1.410\ (\pm0.392)$ * invsqr-nR05 $- 1.440\ (\pm0.273)$ *B03[N–O] $+ 0.318\ (\pm0.134)$ *F10[C–F].

3.8. Model-7 (Undivided dataset)

$pEC_{50} = 9.122\ (\pm0.407) - 0.013\ (\pm0.006)$ *G(N..F) $- 1.217\ (\pm0.341)$ * invsqr-nR05 $- 0.846\ (\pm0.159)$ * expB03[N–O] $+ 0.317\ (\pm0.135)$ *F10[C–F].

3.9. Model-8 (Divided dataset)

$pEC_{50} = 8.162\ (\pm1.455) - 0.022\ (\pm0.021)$ * Ss $- 2.053\ (\pm0.442)$ * invcube-nR05 $+ 0.948\ (\pm0.263)$ * C-041 $+ 0.901\ (\pm0.325)$ *B10[C–F].

3.10. Model-9 (Divided dataset)

$pEC_{50} = 8.540\ (\pm0.458) - 0.015\ (\pm0.011)$ *G(N..F) $- 1.603\ (\pm0.450)$ * invsqr-nR05 $- 1.416\ (\pm0.355)$ *B03[N–O] $+ 0.340\ (\pm0.160)$ *F10[C–F].

3.11. Model-10 (Divided dataset)

$pEC_{50} = 7.675\ (\pm0.331) + 0.388\ (\pm0.308)$ * Cl-089 $- 1.485\ (\pm0.412)$ * invcube-nR05 $- 1.118\ (\pm0.316)$ *B03[N–O] $+ 0.672\ (\pm0.308)$ *B10[C–F].

The statistical symbols have their usual meaning [12,16,17,20,23] and are available in the supplementary material, also. From statistical analysis (Table 2), it is clear that all the developed QSAR models are statistically robust and possess good external predictive ability, especially, the models 6–10. The models 6–10 outperform their counterparts apropos of fitting, internal validation and external predictivity criteria. As expected, establishing the models 6–10 helped in the identification of less dominant descriptors like Ss (sum of Kier-Hall electrotopological indices), G(N..F) (sum of geometrical distances between N and F), C-041 (an atom-centered fragment representing X–C(=X)–X), and Cl-089 (an atom-centered fragment representing Cl attached to sp^2 hybridized C) with correlation with the activity, which were not discovered while building the models 1–5. For all the developed models, the value of $R^2_{adj.}$ is quite close to R^2_{tr} suggesting that the number of descriptors in the models are not too high, thereby, indicating that the models are free from over-fitting [26]. This is further supported by the low value of LOF (Lack of fit) for all the models. The low Kxx

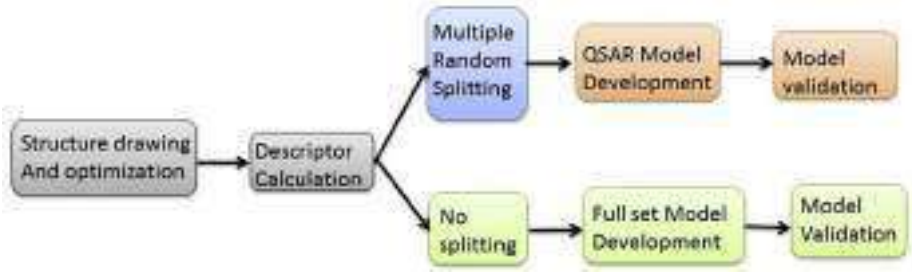


Fig. 3. Strategy used for developing the QSAR models.

Table 2
Statistical performance of different QSAR models.

S.No.	Statistical Parameter	Model-1	Model-2	Model-3	Model-4	Model-5	Model-6	Model-7	Model-8	Model-9	Model-10
1.	N_{tr}	60	60	48	48	48	60	60	48	48	48
2.	N_{ex}	–	–	12	12	12	–	–	12	12	12
3.	Number of Descriptors	4	4	4	4	4	4	4	4	4	4
Fitting Criteria											
4.	R^2_{tr}	0.807	0.806	0.822	0.823	0.812	0.863	0.862	0.839	0.876	0.874
5.	$R^2_{adj.}$	0.793	0.792	0.806	0.806	0.794	0.853	0.852	0.824	0.865	0.863
6.	R^2_{tr} - $R^2_{adj.}$	0.014	0.014	0.016	0.017	0.018	0.010	0.010	0.015	0.012	0.012
7.	LOF	0.288	0.289	0.292	0.301	0.312	0.205	0.206	0.246	0.214	0.217
8.	Kxx	0.255	0.300	0.398	0.365	0.406	0.441	0.440	0.306	0.478	0.374
9.	ΔK	0.119	0.139	0.119	0.064	0.058	0.064	0.063	0.131	0.080	0.104
10.	$RMSE_{tr}$	0.465	0.466	0.450	0.457	0.466	0.392	0.394	0.413	0.385	0.389
11.	MAE_{tr}	0.354	0.358	0.349	0.362	0.383	0.312	0.313	0.320	0.307	0.314
12.	RSS_{tr}	12.981	13.028	9.733	10.034	10.414	9.232	9.302	8.190	7.119	7.248
13.	CCC_{tr}	0.893	0.893	0.903	0.903	0.896	0.926	0.926	0.913	0.934	0.933
14.	s	0.486	0.487	0.476	0.483	0.492	0.410	0.411	0.436	0.407	0.411
15.	F	57.446	57.191	49.749	49.841	46.345	86.363	85.610	56.177	76.220	74.679
Internal Validation Criteria											
16.	R^2_{cv} (Q^2loo)	0.776	0.770	0.784	0.777	0.753	0.840	0.839	0.800	0.847	0.844
17.	R^2-R^2_{cv}	0.031	0.036	0.038	0.046	0.059	0.022	0.023	0.039	0.029	0.030
18.	$RMSE_{cv}$	0.501	0.508	0.496	0.513	0.533	0.423	0.425	0.461	0.428	0.432
19.	MAE_{cv}	0.382	0.394	0.389	0.411	0.442	0.340	0.341	0.358	0.344	0.351
20.	$PRESS_{cv}$	15.041	15.472	11.824	12.629	13.650	10.740	10.837	10.190	8.809	8.974
21.	CCC_{cv}	0.877	0.874	0.882	0.881	0.867	0.914	0.914	0.892	0.919	0.917
22.	Q^2_{LMO}	–	–	0.774	0.792	0.771	0.830	0.827	0.787	0.842	0.841
23.	R^2_{Yscr}	–	–	0.081	0.086	0.087	0.069	0.069	0.086	0.087	0.082
24.	Q^2_{Yscr}	–	–	−0.151	−0.178	−0.231	−0.137	−0.137	−0.144	−0.144	−0.144
External Validation Criteria											
25.	θ*	–	–	−10.983	3.116	2.325	–	–	−2.183	−2.328	1.261
26.	$RMSE_{ex}$	–	–	0.570	0.479	0.417	–	–	0.512	0.441	0.483
27.	MAE_{ex}	–	–	0.421	0.351	0.310	–	–	0.442	0.350	0.402
28.	$PRESS_{ext}$	–	–	3.894	2.756	2.085	–	–	3.148	2.330	2.801
29.	R^2_{ex}	–	–	0.673	0.838	0.924	–	–	0.819	0.779	0.787
30.	Q^2-F^1	–	–	0.690	0.748	0.830	–	–	0.807	0.759	0.711
31.	Q^2-F^2	–	–	0.673	0.713	0.800	–	–	0.804	0.752	0.702
32.	Q^2-F^3	–	–	0.716	0.805	0.849	–	–	0.753	0.838	0.806
33.	CCC_{ex}	–	–	0.805	0.886	0.916	–	–	0.905	0.882	0.875
34.	r^2m aver.	–	–	0.541	0.654	0.776	–	–	0.741	0.687	0.657
35.	r^2m delta	–	–	0.257	0.180	0.094	–	–	0.040	0.069	0.197
36.	R^2-ExPy	–	–	0.785	0.780	0.756	–	–	0.801	0.848	0.845
37.	R'^2_o	–	–	0.740	0.747	0.712	–	–	0.765	0.829	0.823
38.	k'	–	–	0.996	0.997	0.993	–	–	0.996	0.998	0.997
39.	1-(R^2/R'^2_o)	–	–	0.057	0.042	0.059	–	–	0.044	0.022	0.025
40.	r'^2m	–	–	0.413	0.639	0.597	–	–	0.650	0.731	0.722
41.	R^2_o	–	–	0.784	0.777	0.753	–	–	0.800	0.847	0.844
42.	k	–	–	0.999	0.998	1.002	–	–	0.999	0.999	0.999
43.	1-(R^2-ExPy/R^2_o)	–	–	0.001	0.004	0.004	–	–	0.001	0.001	0.001
44.	r^2m	–	–	0.767	0.737	0.716	–	–	0.780	0.829	0.829

R^2 – correlation coefficient, Q^2 – leave-one-out 'cross validated R^2', R^2_{adj} - adjusted R^2, SEE – standard error of estimates, RMSE - root mean squared error, MAE - mean absolute error, CCC - concordance correlation coefficient, for the training (tr), and test (ex) sets; LOF - lack of fit, F – Fischer's value; R^2_{LMO} and Q^2_{LMO} – leave many-out correlation coefficient and cross-validation coefficients; R^2_{Ycr} and Q^2_{Ycr} – Y–- scramble correlation and cross-validation coefficients.

(representing inter-correlation among descriptors) value in all the models indicates that low correlation among the descriptors used in a model [16,17,20]. The condition $RMSE_{tr} < RMSE_{cv}$ is satisfied by all the developed models. The values of cross validation parameters Q^2, Q^2_{LMO} and CCC_{CV} for the developed models are high, thereby, indicating the statistical robustness of the models. The low value of R^2_{Yscr} and Q^2_{Yscr} for all the models indicates that the models have not been developed by chance. For the models 3–5 and 8–10, the

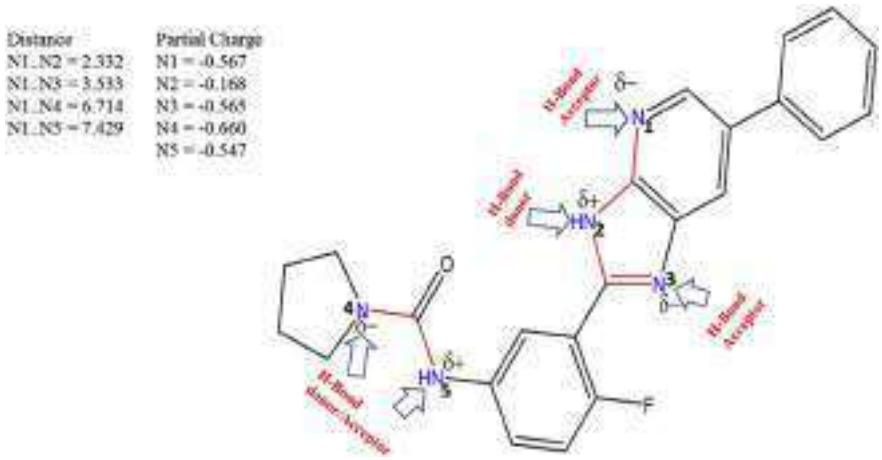


Fig. 4. Exemplification of F02[N–N] descriptor and H-bond donor/acceptor pattern associated with F02[N–N] using molecule **38** as a representative.

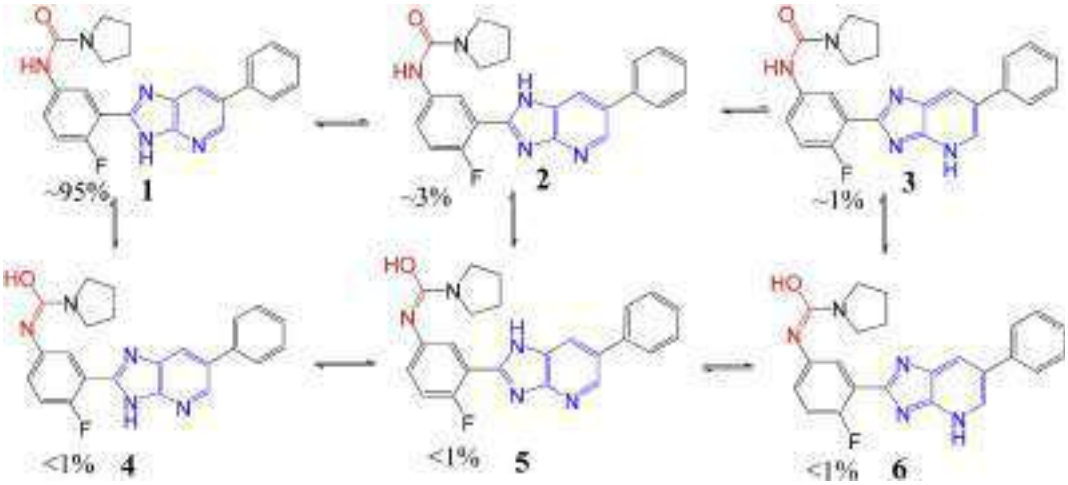


Fig. 5. Different possible tautomeric forms of **38**.

high value of various statistical parameters like R^2_{ex}, Q^2-F^1, Q^2-F^2, Q^2-F^3, CCC_{ex}, etc. indicate the models possess high external predictivity. This is further supported by the low value of $RMSE_{ex}$, MAE_{ex}, and $PRESS_{ext}$. In short, the developed models satisfy the recommended interrelations and threshold values for various statistical parameters suggested by different researchers. Interestingly, for model 5 a very rare observation is identified, the value of Q^2-F^1 (= 0.830) is greater than R^2 (= 0.812), thus, the model is able to predict new data better than fitting available ones, indicating that the molecules for which this model fits better are present in the prediction set [15,29,30]. This is again supported by the higher value of R^2_{ex} than R^2.

A commonly encountered problem associated with QSAR analysis is the interpretation or correlation of descriptors with specific structural fragment or atom. Therefore, in the present work, easily interpretable descriptors that are directly associated with the presence or the absence of a structural scaffold, or a specific atom were considered. This could be highly beneficial to synthetic chemists for future synthetic strategies.

In models 1–3, the 2D-constitutional type of descriptor 'nR05', representing the presence of a five membered ring, is present with a positive coefficient. The descriptors 'invsqr-nR05' and 'invcube-nR05' represent the inverse of square or cube of 'nR05', respectively, and have negative coefficients in models 6–10. Therefore, it appears that the presence of five membered rings in the molecules increases the activity. This observation is vindicated by comparing the activity of **1** with **15**, and **2** with **18**, as representatives. Therefore, in future modifications five membered ring must be retained to increase the activity. The 2D-descriptors, F09[N–F] and B09 [N–F], which correspond to the frequency and presence/absence of N and F at a topological distance of 9, respectively, have a negative correlation with the activity. Interestingly, in models 1–3, the positive correlation of F10[C–F] and B10[C–F], which correspond to frequency and presence/absence of C and F at a topological distance of 10, respectively, with HAT activity indicates that the presence of F favors the activity. This is again supported by the positive correlation of B07[N–F], which represents the presence/absence of N and F at topological distance of 7, in model 3.

The descriptor C-024, an atom centered descriptor corresponds to R–CH–R fragment, has a negative coefficient in model-1, hence, its value must be kept as low as possible. The descriptor 'nPyrrolidines' indicates the presence of number of pyrrolidine rings in the molecule, its presence is beneficial for activity, as evident from its positive coefficient in model 4 and 5. The descriptor 'nArNR2' which stands for the presence of number of tertiary amines (aromatic) in the molecule has a negative association with the activity, hence such groups must be avoided in future modifications. F02 [N–N] is a finger print descriptor that represents the frequency of

the presence of two nitrogen atoms at a topological distance of 2, its positive coefficient in the model 2 points out its positive influence on the activity. This descriptor has been depicted by red bonds in Fig. 4 using the molecule **38** as a representative. This descriptor is associated with an interesting pharmacophoric pattern of H-bond donor and acceptor nitrogen atoms present in a specific arrangement, in which a H-bond donor (like N2) is at a topological distance of 2 from at least one H-bond acceptor N (like N1 or N3).

The importance of this structural pattern is further supported by the fact that the presence of 5-chloropyridin-2-yl, as in *N*-(3-((5-chloropyridin-2-yl)carbamoyl)-4-fluorophenyl)furan-2-carboxamide, has negative influence on the activity. The compound *N*-(3-((5-chloropyridin-2-yl)carbamoyl)-4-fluorophenyl)furan-2-carboxamide ($EC_{50} = 7\ \mu M$) was not incorporated during the QSAR and pharmacophore model building, as the aim of the present work was to analyze the bicyclic derivatives only.

This interesting pattern of H-bond donor/acceptor nitrogen atoms also helps in attaining various tautomeric forms, thereby, providing additional flexibility to the molecules to acquire bioactive tautomeric form(s) while interacting with the target receptor. It has been established that a less stable tautomeric form of a molecule could be the true bioactive tautomeric form [12]. Thus, tautomeric transformations could be a possible reason behind higher activity of the molecules bearing imidazopyridine ring. Such a useful flexibility is diminished when an oxazolopyridine ring is present instead of an imidazopyridine ring. The various tautomeric forms along with their calculated distribution (using the software MarvinSketch 5.0) for the molecule **38**, as a representative, have been depicted in Fig. 5.

The descriptor B03[N–O], which represents the presence/absence of N and O at a topological distance of 3, or its exponential expB03[N–O] have negative coefficients in the model 6,7, 9, and 10. Therefore, the presence/absence of N and O at a topological distance of 3 has negative influence on the activity. Hence, such a combination of N and O must be avoided for better activity profile. This is supported by the observation that in the present series the molecules bearing oxazolopyridine ring, in general, are less active than those having an imidazopyridine ring.

4. Conclusions

The QSAR analysis revealed important information and observations about the structural features that steer the HAT activity of substituted 2-Phenylimidazopyridines. The developed models are statistically robust with high external predictive ability. The development of multiple QSAR models helped in identifying less dominant, but very useful descriptors, which have significant correlation with the activity. The QSAR models pointed out that the presence of five membered rings, especially the pyrrolidine ring, is beneficial for the HAT activity of the present series molecules.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2016.11.012.

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Synthesis, Antiphospholipase A_2, Antiprotease, Antibacterial Evaluation and Molecular Docking Analysis of Certain Novel Hydrazones

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Abstract: Some novel hydrazone derivatives **6a–o** were synthesized from the key intermediate 4-Chloro-*N*-(2-hydrazinocarbonyl-phenyl)-benzamide **5** and characterized using IR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis. The inhibitory potential against two secretory phospholipase A_2 (sPLA$_2$), three protease enzymes and eleven bacterial strains were evaluated. The results revealed that all compounds showed preferential inhibition towards *h*GIIA isoform of sPLA$_2$ rather than DrG-IB with compounds **6l** and **6e** being the most active. The tested compounds exhibited excellent antiprotease activity against proteinase K and protease from *Bacillus* sp. with compound **6l** being the most active against both enzymes. Furthermore, the maximum zones of inhibition against bacterial growth were exhibited by compounds; **6a**, **6m**, and **6o** against *P. aeruginosa*; **6a**, **6b**, **6d**, **6f**, **6l**, **6m**, **6n**, and **6o** against *Serratia*; **6k** against *S. mutans*; and compounds **6a**, **6d**, **6e**, **6m**, and **6n** against *E. feacalis*. The docking simulations of hydrazones **6a–o** with GIIA sPLA$_2$, proteinase K and hydrazones **6a–e** with glutamine-fructose-6-phosphate transaminase were performed to obtain information regarding the mechanism of action.

Keywords: benzo[*d*][1,3]oxazin-4-one; aroylhydrazides; *N*-acylhydrazones; hydrazones; benzylidene hydrazides; phospholipases; proteases; antimicrobial evaluation; molecular docking

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1. Introduction

Hydrazones bearing azomethine moiety can be formed by condensation of hydrazides of aroyl hydrazides with aldehydes [1–4]. These compounds are most widely used as building blocks for the synthesis of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles [5], different mono-, di- and

trisubstituted hydrazines [6,7], azetidin-2-ones, thiazolidin-4-ones and methyl thiazolidines [8,9], and formazan derivatives [10,11]. Hydrazones are well known to exhibit a wide spectrum of biological activities [12] and have been utilized as useful candidates for development of antimalarial [13], antitumor [14], antiviral [15,16], antimicrobial [17], antioxidant [18], analgesic, anti-inflammatory and anti-ulcerogenic agents [19,20].

Secreted phospholipases A_2 (sPLA$_2$s) are enzymes found in mammals and animal venoms that catalyze hydrolysis of glycerophospholipids at the *sn*-2 ester position to release a free fatty acid and a lysophospholipid [21]. Mammalian phospholipases have been categorized into ten groups IB, IIA, IIC, IID, IIE, IIF, III, V, X and XIIA [22,23]. It has been reported that sPLA$_2$s play a key role in a good number of bio-chemical processes, thus, on one the hand, group IB sPLA$_2$ has been proposed to be involved in various physiological and pathophysiological processes such as cellular proliferation, cell migration, hormone release [24] and apoptosis in neuronal cells [25]. In addition, higher levels of this enzyme were detected in the serum of patient with chronic renal failure [26] and acute lung injury [27] compared to healthy controls.

On the other hand, the GIIA sPLA$_2$ has been correlated to inflammatory diseases, which is due to elevated levels of this enzyme were detected in the fluids of patients suffering from various inflammatory diseases such as rheumatoid arthritis [28], acute lung injury-acute respiratory distress syndrome (ALI-ARDS) [29] and pancreatitis-associated adrenal injury in acute necrotizing pancreatitis [30], as well as in various cancers [31]. Therefore, seeking potent and selective inhibitors to this sPLA$_2$ may be considered an effective approach to develop novel anti-inflammatory and antitumor agents.

Proteases or proteinases enzymes are proteolytic enzymes that break down proteins into peptides and amino acids. They are classified into different classes depending on their source and functions [32] such as proteinase K, protease from *Bacillus* and protease-esperase. Biologically, proteases are involved in controlling many biological pathways in the life cycle of human, plants, animals, insects and pathogens such as fungi, bacteria and viruses. Many studies reported their involvement in the pathogenic processes of human diseases such as bleeding disorders [33], inflammation [34], cancer [35], hypertension [36] and AIDS [37]. Therefore, proteases inhibitors' can be considered as targets in drug design for developing therapeutics and prevention of diseases [38].

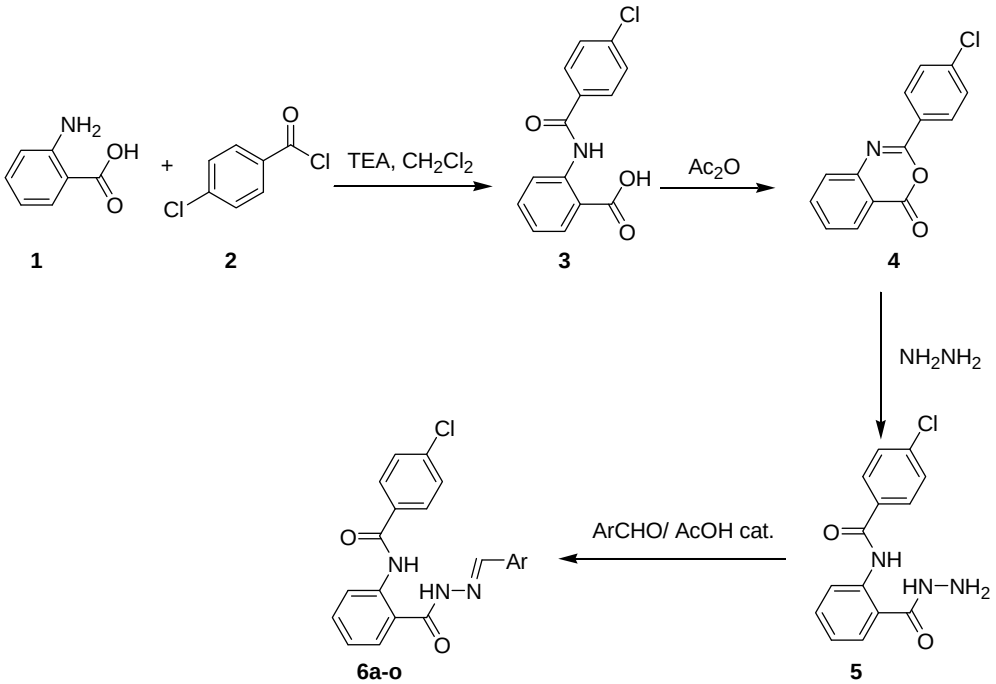
In continuation to our previous efforts towards synthesis of novel biologically active compounds [39–41], we report herein the synthesis of novel hydrazones **6a**–**o** and evaluation of their phospholipases, proteases and bacterial inhibitory activities. The docking simulations of hydrazones **6a**–**o** against GIIA sPLA$_2$, proteinase K and hydrazones **6a**–**e** against glutamine-fructose-6-phosphate transaminase were performed in order to obtain information regarding the mechanism of action.

2. Results and Discussion

2.1. Chemistry

Benzoylation of anthranillic acid **1** with 4-chlorobenzoyl chloride **2** in methylene chloride in the presence of triethylamine afforded the corresponding amido acid **3** which upon boiling with excess of acetic anhydride underwent intramolecular cyclization and afforded benzo[*d*][1,3]oxazin-4-one derivative **4**. Nucleophilic attack by the amino group of hydrazine hydrate on the carbonyl group of the latter benzoxazinone, and subsequent ring opening gives the key intermediate 4-Chloro-*N*-(2-hydrazinocarbonyl-phenyl)-benzamide **5**. Condensation of hydrazino derivative **5** with a variety of aromatic aldehydes yielded the desired hydrazones **6a**–**o** (Scheme 1). The structures of these products were confirmed based on their spectral data and elemental analyses. In general, the IR spectra of compounds **6a**–**o** displayed two absorption bands at ν_{max} 3421–3292 cm^{-1}, which are attributed to the two (NH) groups, and two absorption bands at ν_{max} 1684–1657 cm^{-1} due to the two carbonyl groups. In addition, the (C=N) groups appeared around 1598–1579 cm^{-1}. Moreover, the ^{1}H-NMR spectra of these compounds indicated the disappearance of the spectral line due to NH$_2$

group of the starting hydrazide **5** and appearance of two broad singlet signals at δ 12.37–11.08 ppm corresponding to 2NH groups, singlet signals at δ 8.84–8.30 ppm due to the characteristic azomethines' protons (N=CH) in addition to signals attributed to the aliphatic and aromatic protons at the expected chemical shift values. Analogously, the ^{13}C-NMR spectra proved the presence the two C=O groups at δ_C 165.61–163.86 ppm, azomethine carbons' at 151.46–145.10 ppm and the aliphatic and aromatic carbons at the expected chemical shift values. The mass spectra of all of the synthesized compounds revealed the existence of the parent ion peaks. Finally, the C, H, N elemental analyses of all of the synthesized compounds were in agreement with the proposed structures.



a, Ar = Ph
b, Ar = 4-Cl-C_6H_4
c, Ar = 4-OH,3-OMe-C_6H_3
d, Ar = 3,4,5-$(OMe)_3$-C_6H_2
e, Ar = 2,4-Cl-C_6H_3
f, Ar = 4-OMe-C_6H_4
g, Ar = 4-*N*,*N*-di-Me-C_6H_4
h, Ar = 2-OMe-C_6H_4
i, Ar = 4-Me-C_6H_4
j, Ar = 4-COOH-C_6H_4
K, Ar = CH=CH-C_6H_5
l, Ar = 2-COOH-C_6H_4
m, Ar = 3-OH,4-OMe-C_6H_3
n, Ar = 4-cyclohexyl-C_6H_4
o, Ar = 3-OMe-C_6H_4

Scheme 1. The synthesis of Schiff bases **6a**–**o**.

2.2. Biological Evaluation

2.2.1. Phospholipases Inhibitory Activity

The phospholipase inhibitory activity of hydrazones **6a**–**o** have been detected against two different classes of sPLA$_2$s, namely human group IIA sPLA$_2$ (hG-IIA) and dromedary group IB sPLA$_2$ (DrG-IB). The obtained results revealed that compounds **6c**, **6d**, **6e** and **6l** exhibited selective inhibition against *h*GIIA rather than DrG-IB by 50.67% ± 4.04%, 55.67% ± 4.72%, 72.67% ± 2.51% and 74.33% ± 3.21%, respectively, as shown in Figure 1 and Table S1.

Conversely, the lowest inhibitory activity against this enzyme (9% ± 2%) was displayed by compound **6n**. These results are in agreement with the data obtained in our previous work [42].

As many clinical studies revealed that the levels of sPLA$_2$s are increased in different inflammatory conditions such as rheumatoid arthritis [28], these active hydrazones can be proposed as potential candidates to explore their utility for such ailment.

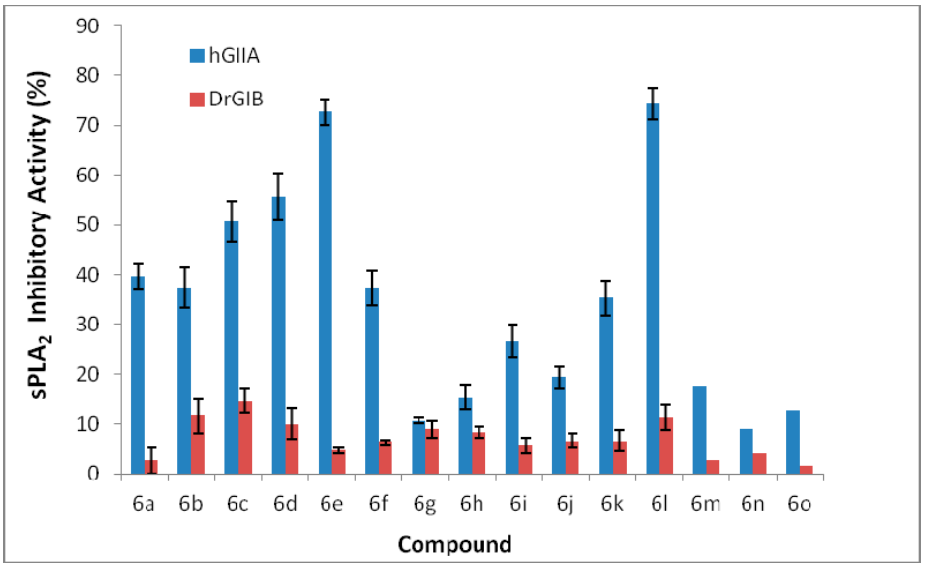


Figure 1. Inhibitory activity (%) of compounds **6a–o** against $sPLA_2$ (hG-IIA and DrG-IB).

2.2.2. Proteases Inhibitory Activity

The synthesized compounds were also screened for in vitro anti-proteases activity against the commercially available protease-esperase, proteinase K and protease obtained from *Bacillus* sp. The screening results shown in Figure 2 and Table S2 revealed that the tested compounds displayed varied degrees of proteases inhibition. The maximum inhibitory activities against proteinase K (86 ± 2.64), protease from *Bacillus* (74.66 ± 2.88) and protease-esperase (39.33 ± 3.21) were exhibited by compound **6l**.

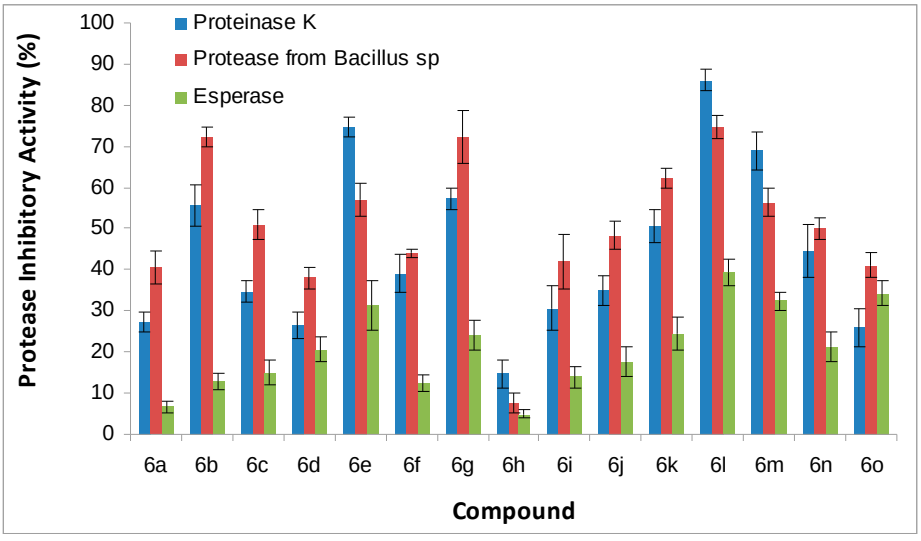


Figure 2. Antiprotease activity (%) of compounds **6a–o** against different protease enzymes.

Furthermore, the next highest inhibitory activities against proteinase K were exhibited by compounds **6e** (74.66% ± 2.51%) and **6m** (69% ± 4.58%), while the next highest inhibitory activities against protease from *Bacillus* sp. were exhibited by compounds **6b** (72.33% ± 2.51%) and **6g** (72.33% ± 6.42%).

It is worth mentioning that most of the compounds showed good antiprotease inhibition against proteinase K and protease from *Bacillus* sp., as depicted in Figure 2. It was also noticed that there was alignment in inhibitory activity against these two enzymes, as any single compound that showed high inhibitory potential against one of them also reacted in a similar fashion towards the other one.

As the anti-inflammatory activities of chemical compounds can be expressed by phospholipase A_2 (hGIIA) and/or through protease inhibitor potentials [42], compound **6l**, which was found to be the most active candidate against both phospholipases A_2 ($sPLA_2$) and protease enzymes under investigation, may be proposed as promising potential anti-inflammatory agent for treatment of ulcerative colitis.

2.2.3. Antibacterial Screening

Finally, compounds **6a**–**o** were further examined for in vitro antibacterial activity. Preliminary screening against eleven strains of Gram-positive and Gram-negative bacteria was performed by adopting standard protocol [43]. The antibacterial potency was determined by measuring the inhibition zones. All tests were performed in duplicates and means of inhibition zones were recorded in mm as presented in Table 1.

Analysis of the screening data revealed that the inhibition activity produced by some of the tested compounds was found to be good to excellent compared to the used reference drug tetracycline. Among the eleven strains that would be considered more susceptible to inhibition by one or more of the synthetic compounds were; *P. aeruginosa*, *Serratia*, *S. aureus*, *S. mutans* and *E. feacalis* with genus *Serratia* being the most sensitive one which was inhibited by nine hydrazones. The highest inhibition towards this pathogen was displayed by compounds **6a**, **6b**, **6d**, **6e**, **6f**, **6l**, **6m**, **6n**, and **6o** with inhibition zones of 15.5 ± 0.0, 12.5 ± 0.0, 12 ± 0.0, 14 ± 1.0, 14 ± 1.0, 13 ± 0.01, 14.5 ± 1.5, 14.5 ± 0.5 and 12.5 ± 0.5, respectively. The highest inhibitory activity against *P. aeruginosa* was exerted by compounds **6a**, **6m**, and **6o** with inhibition zones of 17 ± 1.0, 18.5 ± 0.5 and 18.5 ± 0.5, respectively. Although compounds **6j**, **6l** and **6n** produced the highest inhibition zones against *S. aureus* strain, they were considered to be less effective compared to the reference drug tetracycline. Moreover, the maximum zone of inhibition (24.5 ± 0.5) was exhibited by compound **6k** against *S. mutans*. Finally, the reference drug tetracycline was found to be completely inactive against *E. feacalis*, while compounds **6a**, **6d**, **6e**, **6m**, and **6n** exhibited the maximum inhibition zones of 18.5 ± 0.5, 18.0. ± 1.0, 18.5 ± 0.5, 13.5 ± 1.5 and 18.5 ± 0.5, respectively. The rest of the compounds showed moderate inhibition against all other bacterial strains.

2.3. Molecular Docking Analysis

Based on the data obtained from different biological evaluations, compounds **6a**–**o** were docked against proteinase K, GIIA $sPLA_2$, and compounds **6a**–**e** against glutamine-fructose-6-phosphate transaminase (GlcN6P) synthase (GlmS, L-glutamine: D-fructose-6P amidotransferase, EC 2.6.1.16) in order to provide a conceivable rationale for the observed activities.

2.3.1. Docking Simulations for Compounds **6a**–**o** in Active site of $GIIAsPLA_2$

$GIIAsPLA_2$ is a low molecular weight enzyme (14 kDa) with seven disulfide bonds with a highly conserved Ca^{2+}-binding loop and a catalytic dyad consisting of His47/Asp91 along with active a hydrophobic region lined near the *N*-terminal helix [44].

Table 1. Antibacterial activities of the synthesized hydrazones **6a**–**o**.

Comp #	*Gram-Negative Bacteria*					*Gram-Positive Bacteria*					
	E. coli	***p. aeruginosa***	***K. Pneumoniae***	***Salmonella***	***Serratia***	***S. aureus***	***S. aureus ALA1***	***MRSA ATCC3***	***S. mutans***	***E. feacalis***	***B. subtilis***
6a	0 ± 0	17 ± 1	0 ± 0	8 ± 1	15.5 ± 0	0 ± 0	10 ± 0	12 ± 0	12 ± 0.5	18.5 ± 0.5	0 ± 0
6b	14.5 ± 1.5	12 ± 0	0 ± 0	12.5 ± 0.5	12.5 ± 0.5	8 ± 0.5	0 ± 0	6 ± 0	0 ± 0	9.5 ± 0.5	0 ± 0
6c	1 ± 0	1.5 ± 0	0 ± 0	10.25 ± 1	1.4 ± 1	0 ± 0	0 ± 0	8 ± 0.5	0.6 ± 1.2	1.3 ± 1	0 ± 0
6d	14.5 ± 0.5	10 ± 0	12.2 ± 1	6.5 ± 0	12 ± 0	8.5 ± 0.5	0 ± 0	0 ± 0	10 ± 0.0	18 ± 1	0 ± 0
6e	10 ± 0	12.5 ± 0.1	12.5 ± 0.5	4 ± 0	14 ± 1	8.5 ± 0.5	0 ± 0	14 ± 1	8 ± 1	18.5 ± 0.5	0 ± 0
6f	0 ± 0	10.5 ± 0.1	4.5 ± 0.1	10 ± 0	14 ± 0.1	0 ± 0	0 ± 0	0 ± 0	8 ± 1	0 ± 0	0 ± 0
6g	0 ± 0	10.5 ± 0.5	8 ± 1	0 ± 0	10.5 ± 0.5	8.5 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
6h	8 ± 0	12.5 ± 0.7	0 ± 0	0 ± 0	10 ± 0	8.5 ± 0.7	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
6i	8.5 ± 0.5	10.5 ± 0.5	0 ± 0	0 ± 0	8.5 ± 0.5	10.5 ± 1.5	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
6j	8 ± 1	10 ± 0	0 ± 0	0 ± 0	8.5 ± 0.5	19.5 ± 1.5	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
6k	10 ± 0	13.5 ± 1.5	14.5 ± 1.5	0 ± 0	10 ± 0	10.5 ± 1.5	0 ± 0	0 ± 0	24.5 ± 0.5	0 ± 0	8.5 ± 0.5
6l	14 ± 1	11 ± 0	11 ± 0	8 ± 1	13 ± 0.1	18.5 ± 0.5	0 ± 0	0 ± 0	14 ± 2	0 ± 0	0 ± 0
6m	10 ± 1	18.5 ± 0.5	0 ± 0	4 ± 0	14.5 ± 1.5	8.5 ± 0.5	0 ± 0	8.5 ± 0.5	0 ± 0	13.5 ± 1.5	0 ± 0
6n	10 ± 0	0 ± 0	13 ± 1	0 ± 0	12.5 ± 0.5	14 ± 1	0 ± 0	10 ± 0	15 ± 1	18.5 ± 0.5	0 ± 0
6o	10 ± 0	18.5 ± 0.5	10 ± 0	0 ± 0	12.5 ± 0.5	0 ± 0	0 ± 0	0 ± 0	9 ± 0.6	0 ± 0	0 ± 0
TCN	19 ± 0.1	17 ± 0.2	17 ± 0.5	16 ± 0.1	12 ± 0.3	31 ± 0.6	29 ± 0.4	18 ± 0.3	27 ± 1.2	0 ± 0	15 ± 0.5

Comp # = Compound number; TCN = Tetracycline.

The docking simulations for **6a**–**o** in active site of GIIAsPLA$_2$ are presented in Supplementary Materials, Figure S1. Results of docking simulations for compound **6l**, the most active anti-GIIAsPLA$_2$ enzyme, depicted here as a representative in Figure 3, revealed that it interacts with hydrophobic and polar residues of active site of GIIAsPLA$_2$. Compound **6l** has adopted "U" shape with its central benzene ring oriented towards the polar residues viz. His6, Gly22, Asp48, and Val30. The –CONH–N– moiety is responsible for interactions with Phe5 and His47. The –CO–NH–N= moiety bridging the two benzene rings as a polar linker has incorporated good flexibility to the ligand, hence such a flexible moiety is beneficial for further amendments. The –Cl and –COOH groups are oriented toward Leu2 and Val3 due to polar interactions. The –CO– group of –CONH– group is close to Gly22. Hence, –CONH– group is important group for retention in future optimizations.

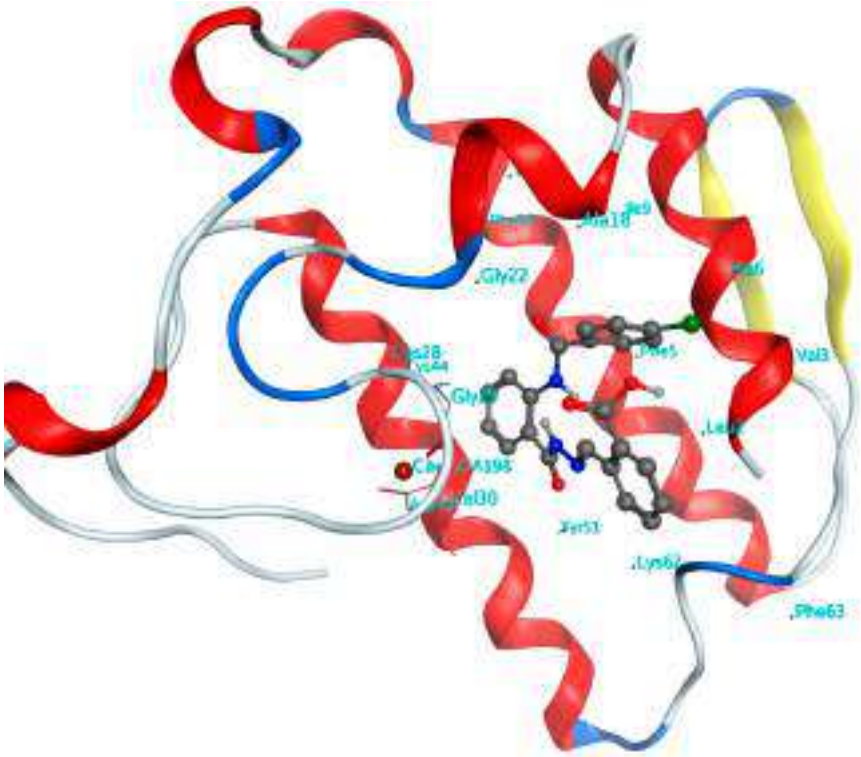


Figure 3. Docking pose for compound **6l** as a representative, in the active site of GIIAsPLA$_2$.

2.3.2. Docking Simulations for Compounds **6a**–**o** in Active Site of Proteinase K

Proteinase K (EC 3.4.21.64, protease K, endopeptidase K, Tritirachium alkaline proteinase, Tritirachium album serine proteinase, and Tritirachium album proteinase K) is a broad-spectrum serine protease belonging to Peptidase family S8 with ability to digest proteins. It is used for the destruction of proteins in cell lysates (tissue, and cell culture cells) and for the release of nucleic acids [45].

The docking simulations for hydrazones **6a**–**o** in active site of proteinase K are presented in Supplementary Materials, Figure S2. Results of docking simulations for compound **6l**, the most active antiproteinase K, depicted here as a representative in Figure 4, revealed that it interacts with hydrophobic and polar residues of active site of proteinase K. Compound **6l** is unable to occupy the complete space of active site of the enzyme. It interacts with polar residues viz. Asn161, Asn162, Ser224 and His69. In addition, it has H-bond formation with H_2O (at distance of 2.86 A°), present inside the active site of Proteinase K, due to the –COOH group present on benzene ring. Hence, the –COOH group is beneficial. Another important interaction is arene-cation interaction between the benzene ring possessing –Cl atom with H_2O (at distance of 4.08 A°), present inside the active site of proteinase K. Interestingly, the compound possesses intramolecular H-bond formation (distance 2.09 A°) between

the –NH– part of –CONH– group with –CO– part of –CONH–N– group. This H-bond is probably responsible for the specific orientation and shape of the molecule inside the active site. The compound **6l** has acquired weird "J" or "L" shape inside the active site. The benzene ring possessing –COOH group is closer to the active site residues. This indicates that the –CONH– and –CONH–N– groups are important for future modifications.

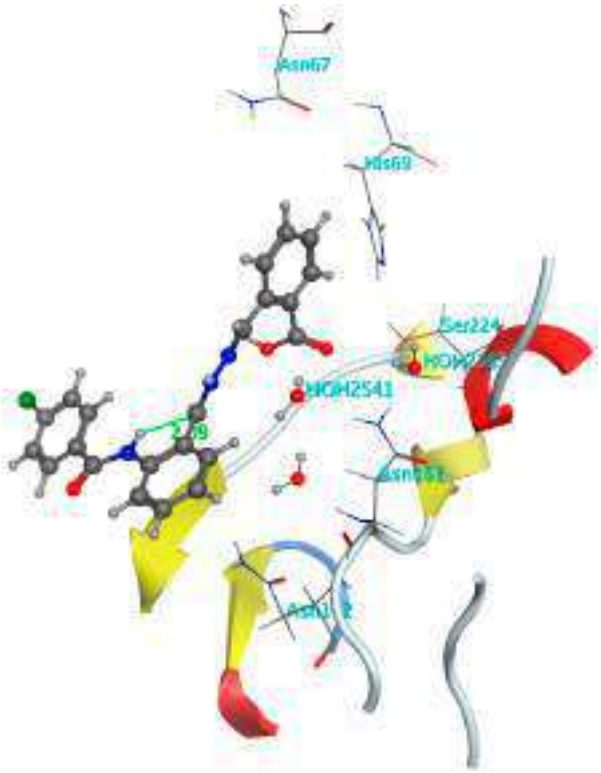


Figure 4. Docking pose for compound **6l** as a representative, in the active site of proteinase K.

2.3.3. Docking Simulations for Compounds **6a**–**e** in Active Site of Glutamine-Fructose-6-Phosphate Transaminase

The molecular mechanism of multifarious reaction catalyzed by glucosamine-6-phosphate (GlcN6P) synthase (GlmS, L-glutamine: D-fructose-6P amidotransferase, EC 2.6.1.16) enzyme comprises both ammonia transfer (L-glutamine to Fru-6-P) and sugar isomerization (fructosamine-6-phosphate to glucosamine-6-phosphate). This reaction is the initiation of the pathway leading to the eventual production of uridine 5′-diphospho-*N*-acetyl-D-glucosamine (UDP-GlcNAc), a product that is present in all class of organisms, but in fungi and bacteria it is utilized to construct macromolecules essential for the cell wall assembly, such as a number of amino sugar-containing macromolecules, comprising chitin and mannoproteins in fungi, and peptidoglycan and lipopolisaccharides in bacteria. In the prokaryotic cell, the inhibition of GlcN6P synthase even for a small time is fatal. Fortunately, because of the longer lifespan of human, the running down of amino sugar pool for a short time is not deadly. Consequently, it has been proposed as a possible target for developing antibacterial and antifungal agents [46–49].

It is evident that recognition of a molecule by a particular enzyme is dependent on the structural properties of that molecule and its distribution of the molecular electrostatic potential (MEP). Furturmore, analysis of ligand–receptor interactions for GlcN-6-P synthase revealed that ligands having primary amido groups can form stable hydrogen bonds with the amino acids residues present in the binding site of the fungal enzyme thus they may serve as "anchors" to lock the inhibitor in the binding pocket of the enzyme. In addition, previous structure–activity relationship experiments

revealed that presence of active electrophilic center at a proper position is required for inactivation of the enzyme to take place [49]. By analogy, hydrazones **6a**–**o** having the same structural features represented by two primary amido groups and electrophilic double bond may serve as inhibitors for bacterial GlcN6P synthase. This hypothesis is examined by docking hydrazones **6a**–**e** in the active site of the bacterial enzyme (these results are presented in Supplementary Materials, Figure S3).

Docking simulations for the most active candidate **6a** which inhibits collectively three bacterial strains and exhibiting inhibition zones larger than those produced by the reference drug tetracycline against two bacterial strains, *Serratia* and *E. feacalis*, depicted here as a representative in Figure 5, revealed that it interacts with a good number of residues of active site of glucosamine-6-phosphate (GlcN6P) synthase. It mainly interacts with polar and hydrophobic residues of the active site. It has adopted weird "J" or "L" shape in the active site. The oxygen atoms of the two amide groups are responsible for the formation of H-bonding with the polar residues Ser A401 (distance 2.61 A°), Gln A348 (distance 1.94 A°) and Ser A349 (distance 1.71 A°). Hence, the amide groups are beneficial for future development. The arene-cation interaction of benzene ring of ligand with the polar residue Arg A26 has strengthened the binding of ligand with the receptor. The chlorine atom on the benzene ring of the ligand has hydrophobic interactions with the hydrophobic residues Trp A74, Ala A602 and Val A399 that constitute the lipophilic region of the cavity. The –CO-NH-N– moiety present between the two benzene rings as a polar linker has furnished high flexibility to the ligand, hence such a flexible moiety is advantageous for further modifications. The benzene ring, which is acting as a bridge between the two –CONH– groups, is oriented toward polar region of the active site, which comprises polar residues such as Ser A401, Cys A300, Ser A303, Ser A347, Thr A352, Gln A348 and Ser A349.

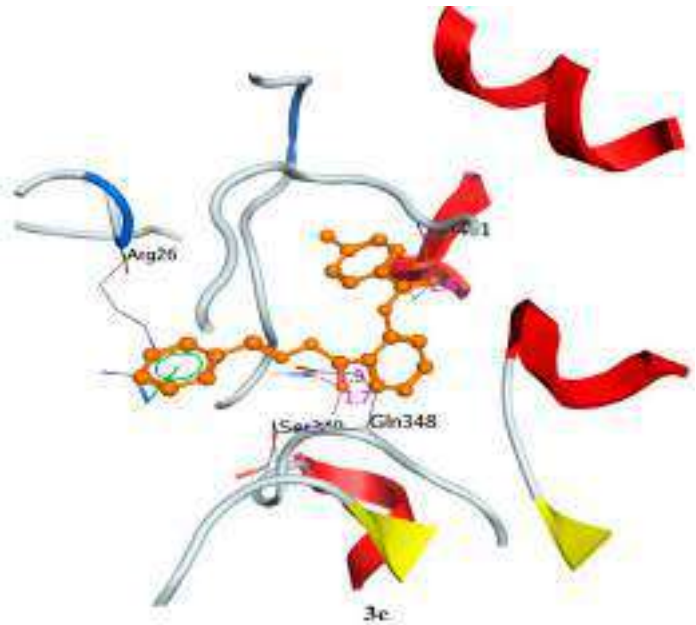


Figure 5. Docking pose for compound **6a**, as a representative, in the active site of glucosamine-6-phosphate (GlcN6P) synthase.

3. Experimental Section

3.1. Chemistry

3.1.1. General

All the chemicals were purchased from various suppliers, and were used without further purification, unless otherwise stated. Melting points were measured on a Gallenkamp melting point

apparatus (Sanyo Gallenkamp, South borough, UK) in open glass capillaries and are uncorrected. Infrared spectra (IR) were recorded using the KBr disc technique using a Perkin Elmer FT-IR spectrophotometer 1000 (PerkinElmer, Waltham, MA, USA). ^{1}H- and ^{13}C-NMR spectra were recorded on a BRUCKER-PLUS NMR (Billerica, MA, USA) operating at 500 MHz in deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts are referred to in terms of ppm and *J*-coupling constants are given in Hz. Mass Spectra were recorded on a Shimadzu GCMS-QP 5000 instrument (Shimadzu, Tokyo, Japan). Elemental analysis was done to evaluate the presence of C, H, and N by Perkin Elmer-series-II and the found results were within ±0.4% of the theoretical values. The biological evaluations of the products were carried out at King Saud University, Riyadh, KSA.

3.1.2. Synthetic Procedures

Compounds **3** and **4** were prepared according to reported procedures [20].

4-Chloro-*N*-(2-(hydrazinecarbonyl)phenyl)benzamide **5**

A mixture of 2-(4-chlorophenyl)-4*H*-benzoyl [*d*][1,3]oxazin-4-one **4** (2.57 g, 10 mmol) and 10 mL of hydrazine hydrate (80%) was refluxed for 1 h. Evaporation of the excess hydrazine under reduced pressure and washing of the remaining solid product with plenty of water afford the title compound in pure form.

Yield (95%); shiny white powder; m.p. 175–177 °C. IR (KBr) ν_{max}: 3316–3128 (NH_2 and 2NH), 1673, 1635 (2 C=O), 1592 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.04 (s, 1H, NHCO), 11.92 (s, 1H, NHCO), 8.51 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.95 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.90 (d, 1H, Ar-H, *J* = 7.6 Hz), 7.76–7.62 (m, 3H, 3 × Ar-H), 7.28 (t, 1H, Ar-H, *J* = 7.5 Hz), 4.52 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6) δ: 165.27 (CO), 164.16 (CO), 138.2, 137.10, 132.43, 129.11, 128.72, 127.80, 125.445, 124.32, 120.93 (12 × Ar-C); MS (ESI): 290 [M^+ + 1], Anal. Calcd. For $C_{14}H_{12}ClN_3O_2$: C (58.04%); H (4.17%); N (14.50%); Found: C (58.08%); H (4.21%); N (14.53%).

Synthesis of Compounds **6a**–**o**

General procedures: A mixture of 4-chloro-*N*-(2-(hydrazinecarbonyl)phenyl)benzamide **5** (2.89 g, 10 mmol) and the appropriate aldehyde (10 mmol) was refluxed in absolute ethanol (15 mL) in presence of few drops of glacial acetic acid as a catalyst for about 4 hour and monitored with TLC (*n*-hexane:EtOAc, 80:20) until the reaction was completed as observed by appearance of a single new spot. The resultant reaction mixture was cooled to room temperature and the solid product obtained in each experiment was collected by filtration and recrystallized from ethanol to afford the desired products **6a**–**o**

N-(2-(2-benzylidenehydrazine-1-carbonyl)phenyl)-4-chlorobenzamide (**6a**) Yield (89%); white crystals; m.p. 244–246 °C; IR (KBr) ν_{max}: 3336–3197 (2 NH), 1673, 1635 (2 C=O), 1592 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.14 (s, 1H, NHCO), 11.94 (s, 1H, NHCO), 8.51 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.47 (s, 1H, N=CH), 7.96 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.92 (d, 1H, Ar-H, *J* = 7.6 Hz), 7.76–7.47 (m, 8H, 8 × Ar-H), 7.30 (t, 1H, Ar-H, *J* = 7.5 Hz); ^{13}C-NMR (DMSO-d_6) δ: 165.39 (CO), 164.00 (CO), 149.53 (N=CH), 139.53, 137.42, 134.49, 133.63, 133.06, 130.86, 129.48, 129.36, 129.10, 127.75, 123.85, 121.85, 121.75, 121.31 (18 × Ar-C); MS (ESI): 379 ($C_{21}H_{16}ClN_3O_2$, [M^+ + 1]; Anal. Calcd. for $C_{21}H_{16}ClN_3O_2$: C (66.76%); H (4.27%); N (11.12%); Found: C (66.72%); H (4.24%); N (11.14%).

4-Chloro-N-(2-(2-(4-chlorobenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6b**) Yield (95%); white powder; m.p. 252–256 °C; IR (KBr) ν_{max}: 3333–3201 (2 NH), 1675, 1639 (2 C=O), 1598 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.19 (s, 1H, NHCO), 11.95 (s, 1H, NHCO), 8.52 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.45 (s, 1H, N=CH), 7.96 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.90 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.77 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.65–7.61 (m, 3H, 3 × Ar-H), 7.52 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.28 (t, 1H, Ar-H, *J* = 7.6 Hz); ^{13}C-NMR (DMSO-d_6) δ: 165.46 (CO), 163.96 (CO), 148.13 (N=CH), 139.62, 137.43, 135.32, 133.58, 133.42, 133.10, 129.67, 129.44, 129.33, 129.07, 123.76, 121.71, 121.08 (18 × Ar-C); MS (ESI): 413

[M^+ + 1], Anal. Calcd. for $C_{21}H_{15}Cl_2N_3O_2$: C (61.18%); H (3.67%); N (10.19%); Found: C (61.20%); H (3.64%); N (10.21%).

4-Chloro-N-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6c**) Yield (85%); white crystals; m.p. 236–238 °C; IR (KBr) ν_{max}: 3341–3201 (2 NH and OH), 1675, 1639 (2 C=O), 1588 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 11.93 (s, 2H, NH and OH), 9.59 (br. s, 1H, NH), 8.46 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.30 (s, 1H, N=CH), 7.90 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.83 (d, 1H, Ar-H, *J* = 7.7 Hz), 7.58 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.54 (d, 1H, Ar-H, *J* = 7.7 Hz), 7.29 (d, 1H, Ar-H *J* = 1.0 Hz), 7.21 (t, 1H, Ar-H, *J* = 7.7 Hz), 7.06 (dd, 1H, Ar-H, *J* = 8.1, 1.0 Hz), 6.80 (d, 1H, Ar-H, *J* = 8.1 Hz), 3.78 (s, 3H, OCH_3); ^{13}C-NMR (DMSO-d_6) δ 165.13 (CO), 163.98 (CO), 150.24, 149.81, 148.55, 139.52, 137.41, 133.65, 132.90, 129.46, 129.01, 125.84, 123.78, 123.06, 121.63, 121.31, 115.93, 109.49 (CH=N and 18 × Ar-C), 56.04 (OCH_3); MS (ESI): 425 [M^+ + 1], Anal. Calcd. for $C_{22}H_{18}ClN_3O_4$: C (62.34%); H (4.28%); N (9.91%); Found: C (62.32%); H (4.24%); N (9.93%).

4-Chloro-N-(2-(2-(3,4,5-trimethoxybenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6d**) Yield (93%); white crystals; m.p. 247–248 °C; IR (KBr) ν_{max}: 3345–3208 (2 NH), 1671, 1644 (2 C=O), 1578 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.11 (s, 1H, NHCO), 11.81 (s, 1H, NHCO), 8.46 (d, 1H, Ar-H, *J* = 8.2 Hz), 8.37 (s, 1H, N=CH), 7.96 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.88 (d, 1H, Ar-H, *J* = 7.6 Hz), 7.67 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.63 (t, 1H, Ar-H, *J* = 8.2 Hz), 7.31 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.04 (s, 2H, 2 × Ar-H), 3.85 (s, 6H, 2 × OCH_3), 3.74 (s, 3H, OCH_3); ^{13}C-NMR (DMSO-d_6) δ: 165.25 (CO), 164.12 (CO), 153.69 (3 × $\underline{C}$-OCH_3), 146.48 (N=CH), 139.32, 137.39, 133.68, 129.97, 129.52, 129.47, 129.15, 123.96, 121.96, 104.96 (15 × Ar-C), 60.60 (OCH_3), 56.50 (OCH_3), 56.46 (OCH_3). MS (ESI): 469 [M^+ + 1], Anal. Calcd. for $C_{24}H_{22}ClN_3O_5$: C (61.61%); H (4.74%); N (8.98%); Found: C (61.32%); H (4.71%); N (9.02%).

4-Chloro-N-(2-(2-(2,4-dichlorobenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6e**) Yield (93%); creamish powder; m.p. 262–264 °C; IR (KBr) ν_{max}: 3421–3268 (2 NH), 1680, 1656 (2 C=O), 1592 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.36 (s, 1H, NHCO), 11.79 (s, 1H, NHCO), 8.82 (s, 1H, N=CH), 8.47 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.04 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.95 (d, 2H, 2 × Ar-H, *J* = 8.4 Hz), 7.91 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.75 (s, 1H, CH-Ar), 7.69–7.64 (m, 3H, 3 × Ar-H), 7.55 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.31 (t, 1H, Ar-H, *J* = 7.6 Hz); ^{13}C-NMR (DMSO-d_6) δ: 165.31 (CO), 164.42 (CO), 148.38 (N=CH), 139.64, 137.93, 135.26, 133.45, 133.39, 133.10, 129.51, 129.49, 129.27, 129.11, 123.80, 121.71, 121.88 (18 × Ar-C). MS (ESI): 447 [M^+ + 1], Anal. Calcd. for $C_{21}H_{14}Cl_3N_3O_2$: C (56.46%); H (3.16%); N (9.41%); Found: C (56.48%); H (3.20%); N (9.42%).

4-Chloro-N-[2-(4-methoxy-benzylidene-hydrazinocarbonyl)-phenyl]-benzamide (**6f**) Yield (88%); white powder; m.p. 260–262 °C; IR (KBr) v_{max}: 3374–3242 (2 NH), 1682, 1646 (2 C=O), 1589 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.06 (s, 1H, NHCO), 12.03 (s, 1H, NHCO), 8.55 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.42 (s, 1H, CH=N), 7.96 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.91 (d, 1H, Ar-H, *J* = 7.6 Hz), 7.69 (d, 2H, 2 × Ar-H, *J* = 8.7 Hz), 7.64 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.60 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.27 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.02 (d, 2H, 2 × Ar-H, *J* = 8.7 Hz), 3.80 (s, 3H, OCH_3); ^{13}C-NMR (DMSO-d_6) δ: 165.25 (CO), 163.91 (CO), 161.55 ($\underline{C}$-OCH_3), 149.54 (N=CH), 139.65, 137.42, 133.60, 132.96, 129.45, 129.42, 128.99, 127.01, 123.69, 121.53, 121.02, 114.82 (17 × Ar-C), 55.75 (OCH_3). MS (ESI): 409 [M^+ + 1], Anal. Calcd. for $C_{22}H_{18}ClN_3O_3$: C (64.79%); H (4.45%); N (10.30%); Found: C (64.78%); H (4.42%); N (10.32%).

4-Chloro-N-(2-(2-(4-(dimethylamino)benzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6g**) Yield (82%); yellow powder; m.p. 249–251 °C; IR (KBr) ν_{max}: 3364–3212 ((2 NH), 1679, 1640 (2 C=O), 1582 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.11 (s, 1H, NHCO), 11.85 (s, 1H, NHCO), 8.56 (d, 1H, Ar-H, *J* = 8.2 Hz), 8.32 (s, 1H, CH=N), 7.96 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.90 (d, 1H, Ar-H, *J* = 7.2 Hz), 7.68 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.62 (t, 1H, Ar-H, *J* = 7.4 Hz), 7.56 (d, 2H, 2 × Ar-H, *J* = 8.8 Hz), 7.28 (t, 1H, Ar-H, *J* = 7.4 Hz), 6.77 (d, 2H, 2 × Ar-H, *J* = 8.8 Hz), 2.99 (s, 6H, 2 × N-CH_3); ^{13}C-NMR (DMSO-d_6) δ: 165.31 (CO), 164.13 (CO), 152.4 ($\underline{C}$-NCH_3), 148.27 (N=CH), 138.2, 137.4, 134.84, 129.53, 129.44, 129.18, 128.8, 127.7, 124.2, 123.74, 119.8, 112.3 (17 × Ar-C), 45.2 (2 × CH_3). MS (ESI): 422 [M^+ + 1], Anal. Calcd. for $C_{23}H_{21}ClN_4O_2$: C (65.63%); H (5.03%); N (13.31%); Found: C (65.59%); H (5.02%); N (13.33%).

4-Chloro-N-(2-(2-(2-methoxybenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6h**) Yield (98%); white powder; m.p. 236–238 °C; IR (KBr) ν_{max}: 3383–3251 ((2 NH), 1680, 1652 (2 C=O), 1589 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.06 (s, 1H, NHCO), 11.97 (s, 1H, NHCO), 8.77 (s, 1H, N=CH), 8.47 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.90 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.88–7.83 (m, 2H, 2 × Ar-H), 7.60 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.58–7.20 (m, 3H, 3 × Ar-H, *J* = 7.5 Hz), 7.05 (d, 1H, Ar-H, *J* = 8.4 Hz), 6.98 (t, 1H, Ar-H, *J* = 7.7 Hz), 3.80 (s, 3H, O-CH_3); ^{13}C-NMR (DMSO-d_6) δ: 165.28 (CO), 163.96 (CO), 158.39 (C-OCH_3), 145.11 (N=CH), 139.63, 137.42, 133.64, 133.05, 132.40, 129.49, 129.46, 129.09, 126.09, 123.77, 122.47, 121.58, 121.23, 120.99, 112.37 (17 × Ar-C), 56.18 (OCH_3). MS (ESI): 409 [M^+ + 1], Anal. Calcd. for $C_{22}H_{18}ClN_3O_3$: C (64.79%); H (4.45%); N (10.30%); Found: C (64.82%); H (4.46%); N (10.33%).

4-Chloro-N-(2-(2-(4-methylbenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6i**) Yield (91%); white crystals; m.p. 256–258 °C; IR (KBr) ν_{max}: 3372-3264 ((2 NH), 1684, 1657 (2 C=O), 1579 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.08 (s, 1H, NHCO), 11.97 (s, 1H, NHCO), 8.52 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.43 (s, 1H, N=CH), 7.98 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.91 (d, 2H, 2 × Ar-H, *J* = 7.7 Hz), 8.68–7.62 (m, 5H, 5 × Ar-H), 7.31–7.28 (m, 3H, 3 × Ar-H), 2.34 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ (ppm): 165.31 (CO), 163.98 (CO), 149.61 (N=CH), 140.77, 139.55, 137.42, 133.62, 133.62, 133.02, 131.78, 129.97, 129.49, 129.46, 129.06, 127.74, 123.81, 121.67, 121.24 (18 × Ar-C), 21.52 (CH_3). MS (ESI): 393 [M^+ + 1], Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: C (67.43%); H (4.63%); N (10.72%); Found: C (64.42%); H (4.66%); N (10.73%).

4-((2-(2-(4-chlorobenzamido)benzoyl)hydrazono)methyl)benzoic acid (**6j**) Yield (85%); creamish powder; m.p. 252–254 °C; IR (KBr) ν_{max}: 3373–3292 (2 NH, OH), 1759, 1680, 1652 (3 C=O), 1581 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.25 (s, 1H, NHCO), 11.92 (s, 1H, NHCO), 8.51 (s, 1H, N=CH), 8.04–7.25 (m, 12H, 12 × Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 167.37 (COOH), 165.58 (CONH), 163.98 (CO), 148.24 (N=CH), 139.63, 138.49, 137.44, 133.56, 133.13, 132.42, 130.26, 129.40, 129.30, 129.09, 127.72, 123.75, 121.75, 121.05 (18 × Ar-C). MS: *m*/*z* 423 [M^+ + 1], Anal. Calcd. for $C_{22}H_{16}ClN_3O_4$: C (62.64%); H (3.82%); N (9.96%); Found: C (62.63%); H (3.86%); N (9.97%).

Chloro-N-(2-(2-(3-phenylallylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6k**) Yield (93%); creamish powder; m.p. 248–250 °C; IR (KBr) ν_{max}: 3391–3271 (2 NH), 1680, 1644 (2 C=O), 1594 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.04 (s, 1H, NHCO), 11.97 (s, 1H, NHCO), 8.51 (d, 1H, Ar-H, *J* = 7.8 Hz), 8.25 (d, 1H, N=CH, *J* = 8.3 Hz), 7.95 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.88 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.68 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.64–7.62 (m, 3H, 3 × Ar-H, *J* = 7.6 Hz), 7.41 (t, 2H, 2 × Ar-H, *J* = 7.3 Hz), 7.36–7.08 (m, 4H, 4 × Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 165.29 (CO), 163.92 (CO), 151.46, 140.39, 139.49, 137.44, 136.26, 129.50, 129.45, 129.34, 129.05, 127.67, 125.84, 123.84, 121.28 (N=C**H**-C**H**=C**H** and 18 × Ar-C). MS: *m*/*z* 405 [M^+ + 1], Anal. Calcd. for $C_{23}H_{18}ClN_3O_2$: C (68.40%); H (4.49%); N (10.40%); Found: C (68.42%); H (4.51%); N (10.44%).

2-((2-(2-(4-chlorobenzamido)benzoyl)hydrazono)methyl)benzoic acid (**6l**) Yield (87%); white powder; m.p. 251–253 °C; IR (KBr) ν_{max}: 3368–3278 (2 NH and OH), 1758 (CO), 1680, 1656 (2 C=O), 1579 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.37 (s, 1H, NHCO), 11.95 (s, 1H, NHCO), 8.74 (s, 1H, N=CH), 8.52 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.09 (d, 1H, Ar-H, *J* = 7.8 Hz) 7.97 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.95–7.62 (m, 6H, 6 × Ar-H), 7.56 (t, 1H, Ar-H, *J* = 7.4 Hz), 7.28 (t, 1H, Ar-H, *J* = 7.4 Hz); ^{13}C-NMR (DMSO-d_6) δ: 168.51 (COOH), 165.61 (CO), 164.02 (CO), 148.38 (N=CH), 139.56, 137.39, 134.82, 133.66, 133.09, 132.49, 131.29, 130.35, 129.47, 129.25, 127.23, 123.78, 121.70, 121.19 (18 × Ar-C). MS (ESI): 423 [M^+ + 1], Anal. Calcd. for $C_{22}H_{16}ClN_3O_4$: C (62.64%); H (3.82%); N (9.96%); Found: C (62.67%); H (3.85%); N (9.88%).

4-Chloro-N-(2-(2-(3-hydroxy-4-methoxybenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6m**) Yield (94%); white powder; m.p. 239–241 °C; IR (KBr) ν_{max}: 3383–3256 (2 NH), 1680, 1657 (2 C=O), 1582 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.04 (s, 1H, NHCO), 11.97 (s, 1H, NHCO), 8.56 (d, 1H, Ar-H, *J* = 8.3 Hz), 8.34 (s, 1H, N=CH), 7.96 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.90 (d, 1H, *J* = 7.7 Hz), 7.67 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.62 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.31 (d, 1H, Ar-H, *J* = 1.6 Hz), 7.28 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.08 (dd, 1H, Ar-H, *J* = 8.3, 1.6 Hz), 6.98 (d, 1H, Ar-H, *J* = 8.3 Hz), 3.82 (s, 3H, O-CH_3); ^{13}C-NMR (DMSO-d_6) δ: 165.16 (CO), 163.93 (CO), 150.53, (C-OCH_3), 149.81 (C-OH), 147.37 (N=CH),

139.58, 137.44, 133.62, 132.62, 129.49, 129.43, 129.01, 127.29, 123.77, 121.55, 121.13, 112.90, 112.29 (16 × Ar-C), 56.04 (OCH_3). MS (ESI): 425 [M^+ + 1], Anal. Calcd. for $C_{22}H_{18}ClN_3O_4$: C (62.34%); H (4.28%); N 00(9.91%); Found: C (62.38%); H (4.26%); N (9.93%).

4-Chloro-N-(2-(2-(4-cyclohexylbenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6n**) Yield (85%); white crystals; m.p. 257–259 °C; IR (KBr) ν_{max}: 3386–3260 (2 NH), 1682, 1654 (2 C=O), 1589 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.03 (s, 1H, NHCO), 11.08 (s, 1H, NHCO), 8.51 (d, 1H, Ar-H, *J* = 8.2 Hz), 8.36 (s, 1H, N=CH), 7.95 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.88 (d, 1H, Ar-H, *J* = 7.7 Hz), 7.65 (d, 2H, 2 × Ar-H, *J* = 8.3 Hz), 7.59 (t, 1H, Ar-H, *J* = 7. 7Hz), 7.31–7.18 (m, 5H, 5 × Ar-H), 3.09–1.55 (m, 11H, cyclohexyl-H); ^{13}C-NMR (DMSO-d_6) δ: 165.54 (CO), 163.86 (CO), 146.14 (N=CH), 139.23, 137.44, 133.55, 132.61, 129.47, 129.39, 128.84, 127.16, 126.60, 123.76, 121.72, 121.49 (18 × Ar-C), 42.85, 41.23, 35.32, 34.39, 33.43, 28.39 (cyclohexyl-C). MS (ESI): 461 [M^+ + 1], Anal. Calcd. For $C_{27}H_{26}ClN_3O_2$: C (70.50%); H (5.70%); N (9.14%); Found: C (70.51%); H (5.71%); N (9.13%).

(Z)-4-chloro-N-(2-(2-(3-hydroxybenzylidene)hydrazine-1-carbonyl)phenyl)benzamide (**6o**) Yield (95%); white powder; m.p. 262–264 °C; IR (KBr) ν_{max}: 3386–3258 (2 NH, OH), 1680, 1652 (2 C=O), 1579 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 12.12 (s, 1H, NHCO), 12.04 (s, 1H, NHCO), 8.84 (s, 1H, N=CH), 8.55 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.97 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.95–7.90 (m, 2H, 2 × Ar-H), 7.67 (d, 2H, 2 × Ar-H, *J* = 8.5 Hz), 7.63 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.46–7.03 (m, 4H, 4 × Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 165.27 (CO), 163.96 (CO), 158.40 (C-OCH_3), 145.10 (N=CH), 139.64, 137.42, 133.64, 133.05, 132.40, 129.50, 129.46, 129.09, 126.09, 123.77, 122.47, 121.48, 121.57, 121.23, 120.99 (17 × Ar-C). MS (ESI): 395 [M^+ + 1], Anal. Calcd. For $C_{21}H_{16}ClN_3O_3$: C (64.05%); H (4.09%); N (10.67%); Found: C (64.07%); H (4.12%); N (10.63%).

3.2. Biological Evalustion

3.2.1. Inhibition of $sPLA_2$ Activity

The test of inhibitory activity of secretory phospholipase A_2 ($sPLA_2$) was performed as described by De Aranjo and Radvany [50]. Briefly, the substrate consisted of 3.5 mM lecithin in a mixture of 3 mM NaTDC, 100 mM NaCl, 10 mM $CaCl_2$ and 0.055 mM red phenol as colorimetric indicator in 100 mL H_2O. The pH of the reaction mixture was adjusted to 7.6 using phosphate buffer. The Human group IIA (hG-IIA) and dromedary group IB (DrG-IIA) $sPLA_2$ were solubilized in 10% acetonitrile at a concentration of 0.05 μg/μL. A volume of 10 μL of these PLA_2 solutions was incubated with 10 μL containing 10 μg of each compound for 20 min at room temperature. Then, 1 mL of the PLA_2 substrate was added, and the kinetic of hydrolysis was followed during 5 min by reading the optical density at 558 nm. The inhibition percentage was calculated by comparison with a control experiment (absence of compound).

3.2.2. Protease Inhibitor Assay

Three commercially available proteases; proteinase K (Sigma-Aldrich, St. Louis, MO, USA, P2308), esperase (Novozyme, Sigma-Aldrich, P5860) and that obtained from *Bacillus* sp. (Sigma-Aldrich, P3111) were evaluated for the effect of the studied compounds on their activities. Protease assays were carried out by adopting Kunitz caseinolytic method [51] using Hammerstein casein as substrate. Respective protease inhibitor activities were assayed under the same conditions with the addition of the inhibitor (0.1 mg/mL) to the respective reaction mixture and pre incubation for 10 min at 37 °C. The assay of the residual enzyme activity was followed by the addition of 2 mL of 1% casein and the resulting mixture was allowed to stand for 30 min at 37 °C. The reaction was stopped by the addition of 2.5 mL of 5% TCA solution. After centrifugation of the reaction mixture (12,000 rpm, 15 min), the absorbance was measured at 280 nm. Protease inhibitor unit is defined as the amount of protease inhibitor that inhibited one unit of respective enzyme activity. The protease inhibitor activity was expressed in

terms of percent inhibition. Appropriate blanks for the enzyme, inhibitor, and the substrate were also included in the assay along with the test.

3.2.3. Antibacterial Activity

Culture of Microbial Strains Preparation

Pure standard microbial isolates collected from King Khaled University Hospital were tested in this study; including *Staphylococcus aureus* ATCC 25923, Methicillin resistant *Staphylococus aureus* ATCC 12498, *Bacillus subtilis* ATCC 6633, *Enterococcus faecalis* ATCC 29212 as Gram-positive and *Escherichia coli* ATCC 25966, *Pseudomonas aeruginosa* ATCC 27853 and *Serratia marcescens* as Gram-negative bacteria. Fresh cultures of each microorganism were grown on nutrient agar plates (Oxoid, Thermo Scientific, Basingstoke, UK); of which small inoculums were suspended in 5 mL nutrient broth for bacterial suspension preparation of 0.5 MacFarland.

Antibacterial Assay

Antimicrobial activity was assayed using well diffusion technique according to given literature [43]. Briefly, small inoculums of each of the microbial suspension prepared were loaded on sterile Muller Hinton agar plates surface (Oxoid) with sterile cotton swabs. Loaded plates were then perforated equidistantly with a sterile 6 mm diameter cork borer, and 70 µL of each compound solution (1 mg/mL) were loaded in their respective wells. DMSO and Tetracycline were used as negative and positive controls, respectively. Plates were kept to rest for 30 min at room temperature and then incubated at 37 °C for 18–24 h. Antimicrobial activity was determined by measuring the inhibition zone. All tests were performed in duplicates and means of inhibition zones were recorded in mm.

3.3. Molecular Docking

In the present work, AutoDock 4.0 (The Scripps Research Institute, La Jolla, CA, USA) was used for molecular docking. The software is freely available and can be used with different molecular viewers like PMV, PyMol, etc. For docking simulations, the structures of the molecules were drawn using ChemSketch 12.0 (Advanced Chemistry Development, Inc., Toronto, ON, Canada) freeware and optimized using the inbuilt methodology. The optimized structures were saved in 3D-format in .mol file format. The structures of proteins GIIA $sPLA_2$ (pdb: 1DB4), proteinase K (pdb: 2PWB) and glutamine-fructose-6-phosphate transaminase (1JXA) were retrieved from www.rcsb.org. The pdb 1DB4, 2PWB, and 1JXA for the proteins were selected on the basis of reasonable X-ray resolution and sequence completion. The proteins structures were optimized before actual docking simulations. Following parameters were set for getting better docking results: Algorithm: genetic Algorithm; Number of runs: 10 GA runs; Number of evaluations: 250,000 evaluation/run; population size: 150.

4. Conclusions

In conclusion, fifteen novel hydrazone derivatives **6a–o** were synthesized, fully characterized and examined to evaluate their inhibitory activity against two phospholipases A_2, three protease enzymes and a panel of Gram-negative and Gram-positive bacterial strains. Among the investigated compounds; **6e** and **6l** selectively exhibited $sPLA_2$ the highest inhibitory activity against *h*G-IIA isoform. It is quite interesting to report that compound **6l** also displayed the highest antiprotease inhibition against all used protease enzymes.

Moreover, the series under investigation showed varied antibacterial inhibitory activity. Thus, while similar inhibition to that produced by the reference drug tetracycline was displayed by compound **6a** against *P. aeruginosa*, compounds **6m** and **6o** exhibited higher inhibition. In addition, the most susceptible bacterial strain to the synthesized compounds was genus *Serratia*, which was inhibited by nine of them, with compound **6a** being the most powerful inhibitory agent. Furthermore, the maximum inhibitory activities were exhibited by compounds **6j**, **6l**, and **6n** against *S. aureus* and by compound

6k against *S. mutans*. Finally, compounds **6a**, **6d**, **6e**, **6m** and **6n** were found to be more potent than the used reference drug against *E. feacalis*. The docking simulations of compounds **6a**–**o** with GIIA $sPLA_2$, proteinase K and compounds **6a**–**e** GlcN6P were carried out in order to investigate the mode of action.

Supplementary Materials: Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/21/12/1664/s1.

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Sample Availability: Samples of the compounds are available from the authors.



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PRELIMINARY PHYTOCHEMICAL ANALYSIS OF *MILIUSA TOMENTOSA* (ROXB.) J. SINCLAIR BY USING VARIOUS ORGANIC SOLVENTS

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ABSTRACT
The present study was to evaluate the phytochemical compound from six different solvent of dried leaves and stem of *Miliusa tomentosa* belongs to family Annonaceae. Qualitative preliminary phytochemical analysis of this plant contains carbohydrate, protein, cardiac glycoside, glycosides, alkaloids, flavonoids, saponins, steroids, anthraquinones, tannins, quinines and inorganic compound. The presence of these phytochemicals can be correlated with medicinal potential of these plants.

KEYWORDS: *Miliusa tomentosa*, Phytochemical screening; Quantitative analysis.

INTRODUCTION
Higher and aromatics plants have traditionally been used in folk medicine as well as to extend the shelf life of foods, medicinal plant use for inhibition against bacteria, fungi and yeasts. Annonaceae is a pantropical family of shrubs, trees and lianas. The family consists of about 130 genera and 2300 species. Although the position of Annonaceae within the Angiosperms and order Magnoliales and its family circumscription is clear and undisputed.[1] The plants belonging to family Annonaceae are used as antibacterial, anticancer, anthelmintic, antiparasitic and pesticidal agents.[2] The genus *Miliusa* (Annonaceae family) consists about 40 species which grows in tropical rainforest of India, Thailand, South China and North Australia.[3] The different species of *Miliusa* are invariably small to large trees and are found in a wide range of rainforest communities. Only three species of Genus *Miliusa* occur in Australia, which are endemic to there and contain two essential oils.[4] The plant is used in folk medicine for different symptom such as gastropathy and glomerulonephropathy.[5] In Chinese traditional medicine *Miliusa tomentosa* oil has been found to have both antibacterial and analgesic properties.[6]

Knowledge of the chemical constituents of plants is desirable because such information will be valuable for synthesis of complex chemical substances.[7] Two new isoquinoline alkaloids, 2,10- dimethoxy-3,11-dihydroxy-5,6-dihydroprotober -berine and 1,9-dihydroxy-2,11 -dimethoxy-4,5- dihydro-7-oxoaporphine, together with thirteen known alkaloids, were isolated from the ethanolic extracts of the stem and leaves of *M. cuneata* (Graib).[8] Since *Miliusa tomentosa* (Roxb.) J Sinclair is one of them, its traditional uses are not reported but its fruits are eaten in some parts of India and its tree yields a pale yellow gum known as karee gum.[9] Thus, main objective of this research work is to consider the photochemical screening of the content which is present in different crude extracts.

MATERIAL AND METHODS
Collection of plant materials
Fresh plant parts of *Miliusa tomentosa* (Roxb.) J. Sinclair were collected from naturally growing populations located in Melghat region Maharashtra, India, during February-March 2016. The samples were identified at the herbarium section of the Department of Botany, Vidya Bharati Mahavidyalaya, Amravati. The fresh plant part samples were washed by tap water, air dried in shadow at room temperature milled well into a fine powder in a mixer grinder and stored until for further analysis.

Preparation of plant extracts in aqueous and different organic solvent
5 gm of dried powder was macerated with 100 ml of aqueous, petroleum ether, chloroform, toluene, butanol and benzene in a conical flask and shaken at room temperature for 24 hours and filtered through Whatman No.1 filter paper. The concentrated extracts were taken in colour amber bottles and kept in refrigerator for further analysis using the standard methods.[10]

Calculation of Extraction Yield (% Yield)
The yield (%, w/w) from dried extract was calculated as:
Yield (%) = $(W_1 \times 100) / W_2$

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W_1 is the weight of the extract after lyophilization of solvent and W_2 is the weight of the powdered material.

Phytochemical screening

Phytochemical screening tests for the identification of protein, sugar, amino acid, alkaloids, flavonoids, steroids, cardiac glycosides, tannins, phenols, quinines & inorganic tests were carried out for all the extracts by the standard methods.[11][12]

Tests for carbohydrates

Fehling's Test

1ml Fehling's A solution and 1 ml of Fehling's B solution were mixed and boiled for one minute. Now the equal volume of test solution was added to the above mixture. The solution was heated in boiling water bath for 5-10 minutes. First a yellow, the brick red precipitate was observed.

Benedict's reagent

Equal volumes of Benedict's reagent and test solution were mixed in a test tube. The mixture was heated in boiling water bath for 5 minutes. Solution appeared green showing the presence of reducing sugar.

Molisch's test

Equal volumes of Molisch's reagent and test solution were mixed in a test tube. The mixture was heated in boiling water bath for 5 minutes. Appearance of violet or purple colour ring showing the presence of reducing sugar.

Standard Test for combine sugar

In 1 ml extract 5 ml conc. Hcl added and hydrolyzed by boiling and neutralized by adding NaOH and repeat the fehling test, Brick red ppt indicate result.

Keton's test

2 ml extract add with few crystal of resorcinol and equal voloume of conc. Hcl and heat over sprit lamp observed rose coloration indicate presence of keton.

Test for proteins

Burette Test

To the small quantity of extract 1-2 drops of burette reagent was added. Formation of violet colour precipitate showed presence of proteins.

Million's Test

To the small quantity of extract 1-2 drops of Million's reagent was added Formation of white colour precipitate showed presence of proteins.

Test for Xanthoprotein

In 2ml of test solution a few drops of conc. nitric acid and 3ml of ammonia were added appearance of red precipitate indicate the presence of xanthoprotien.

Tests for Anthroquinone glycosides

Borntrager's Test

To the 3 ml of extracts, dil. H_2SO_4 was added. The solution was then boiled and filtered. The filtrate was cooled and to it equal volume of benzene was added. The solution was shaken well and the organic layer was separated. Equal volume of dilute ammonia solution was added to the organic layer. The ammonia layer turned pink showing the presence of glycosides.

Tests for Cardiac glycosides

Keller-Killiani test

5ml of extract, 1ml of conc.H_2SO_4, 2 ml of Glacial acetic acid and 1 drop of $FeCl_3$ solution was added. Appearance of brown ring shows the presence of cardiac glycosides.

Test for steroids

Salkowski test

To 2 ml of extract, 2ml of chloroform and 2ml of conc.H_2SO_4 was added. The solution was shaken well. As a result chloroform layer turned red and acid layer showed greenish yellow fluorescence.

Test for alkaloids

Hager's test

2-3 ml of filtrate, few drops of dil.HCl and Hager's reagent was added and shake well. Yellow precipitate was formed showing the presence of alkaloids.

Mayer's test

2-3 ml of filtrate, dil. HCl and Mayer's reagent was added and shake well. Yellow precipitate was formed showing the presence of alkaloids.

Dragendroff's test

2-3 ml of filtrate, few drops of dil.HCl and Dragendroff's reagent was added and shake well. Formation of orange-brown precipitate showed the presence of alkaloids.

Wagners test

2 ml extract add the reagent reddish brown ppt show indicates the presence of alkaloids.

Tests for flavonoids

Lead Acetate test

To the small quantity of extract lead acetate solution was added. Formation of yellow precipitate showed the presence of flavonoids.

Alkaline test

To the test solution add few drops o NaOH solution formation of intence yellow color which turn to colorless solution after addition of dil. Acetic acid indicate presence of flavonoids.

NaOH test

Small amount of extract was treated with NaOh and Hcl observe formation of yellow Orange color.

H_2SO_4
Fraction of extract treated with Conc.H_2SO_4 and observe formation of orange color.

Test for Tannins and Phenolics compound
$FeCl_3$ solution Test
On addition of 5% $FeCl_3$ solution to the extract, deep blue black colour appeared.

Lead Acetate test
On addition of lead acetate solution to the extract white ppt appeared.

Phlobotannins
2 ml extract add dil.HCl observe red ppt.

Gelatin test
To the test solution add few drops of 10% gelatin solution white ppt indicate the result.

Test for Saponin
Foam Test
1 ml extract 20 ml distilled water was added and shakes well in measuring cylinder for 15 min. Then 1 cm layer of foam was formed.

Frothing test
3 ml extract with 10 ml D/W in test tube and plug the Stoppard and shake vigorously for 5 min. it allow to stand 30 min observe the honey comb forth indicate result.

Test for Glycosides
The extract was mixed with a little anthrons on a watch glass. One drop of conc. sulphuric acid was added and made into a paste and warmed gentle over the water bath. Dark green coloration indicates the presence of glycosides.

Test for Quinone
2 ml test solution was treated with a few drops of conc. H_2SO_4 or aq. NaOH solution. Colour formation indicates the presence of quinoid compound.

Test for fixed oil
A small quantity of powder was pressed between the filter paper. Formation of grease spot indicates the presence of fixed oil and fats.

RESULT
The preliminary phytochemical analysis of leaf and stem of *Miliusa tomentosa* in this study revealed the presence of glycosides, steroid, saponins, flavonoids, tannins, alkaloids, phenolic compounds, quinine, anthraquinone and inorganic test (Table-1 and Table-2). Using different solvent (aqueous, benzene, butanol, chloroform, toluene, and petroleum ether) extract. This study revealed the presence of glycosides maximum in benzene, butanol and petroleum ether, where as steroids were present in all solvents except water. Alkaloids presence maximum in water and chloroform. Flavonoids minimum presence in benzene, butanol, toluene and water while phenolic compounds found in butanol and water extracts only but tannins were absent in all extracts. Saponins were maximum present in chloroform and anthraquinone absent in all extracts while as inorganic tests showed positive results in chloroform extracts. In contrast to all this carbohydrate are maximum in butanol extract and protein in aqueous solvent extracts of leaf.

The phytochemical analysis of stem extracts show the presence of glycosides, saponins maximum in chloroform extract while alkaloids, phenol, inorganic test in butanol extract. Flavonoids and steroid recorded in petroleum extract only. Interestingly, tannin and anthraquinone absent in all extract (Table-1 and Table-2). Extractive values of leaf and stem extract by various solvents shown in (Table -3). Extractive values are varies according to solvents systems.

Table 1: Phytochemicals analysis in the stem extracted by various solvents

Sr.No	Phytochemicals	Test Name	Benzene	Butanol	Chloroform	Toluene	Petroleum Ether	Water
1	Carbohydrate	Fehling	-	-	+	-	+	-
		Benedict	-	-	-	-	-	+
		Molisch	-	-	-	-	-	-
		Combine Sugar	-	+	-	-	-	+
		Keton	+	+	-	-	-	+
2	Proteins	Biurett	-	-	-	-	-	-
		Millions	-	-	+	-	-	-
		Xanthoprotein	-	+	-	-	-	+
3	Glycosides	Cardiac	+	+	+	+	+	+
		Keller-Killani	-	-	+	-	-	-
5	Steroid	Salkowski test	-	-	-	+	+	+
		Lieberman-Buchnard	-	-	-	-	-	-
		H_2SO_4	-	-	+	-	-	-
6	Alkaloids	Hager's	-	-	-	-	-	+
		Mayer's	-	+	+	+	-	-

		Dragendroff's	+	+	-	-	-	+
		Wagner's	+	-	-	+	+	+
7	Flavonoids 8	Lead acetate	+	+	+	+	+	+
		Alkalin	+	-	-	+	+	-
		NaOH	-	-	-	-	-	-
		H_2SO_4	-	+	+	-	+	+
8	Phenolic	$FeCl_3$	-	+	-	-	-	+
		Lead acetate	+	+	+	+	+	+
9	Tannin	Gelatin	-	-	-	-	-	-
		Phlobotannin	-	-	-	-	-	-
10	Saponin	Foam	-	-	+	+	+	+
		Frothing	-	-	+	-	-	+
11	Quinone	quinone	+	+	+	+	-	-
12	Anthraquinone	Anthraquinone	-	-	-	-	-	-
13	Inorganic	Sulphate test	+	+	+	+	-	-
		Carbonate test	+	+	+	+	+	-

(+) Present (-) Not detected

Table 2: Phytochemicals analysis in the Leaf extracted by various solvents

Sr.No	Phytochemicals	Test Name	Benzene	Butanol	Chloroform	Toluene	Petroleum Ether	Water
1	Carbohydrate	Fehling	+ +	+ +	+ +	- -	+ +	+ +
		Benedict	-	+	-	-	-	+
		Molisch	-	-	-	-	-	-
		Combine Sugar	-	+	-	-	-	+
		Keton	-	+	-	-	-	+
2	Proteins	Biurett	-	-	-	-	-	-
		Millions	-	-	-	-	-	+
		Xanthoprotein	-	+	-	+	+	+
3	Glycosides	Cardiac	+	+	-	-	+	+
		KellerKillaiani	+	+	-	+	+	-
5	Steroid	Salkowski	+	+	+	+	+	-
		Lieberman-Buchnard	+	+	+	+	+	-
		H_2SO_4	+	+	+	-	+	-
6	Alkaloids	Hager's	-	-	-	-	-	-
		Mayer's	-	-	+	-	-	-
		Dragendroff's	-	-	-	-	-	+
		Wagner's	+	+	+	+	+	+
7	Flavonoids	Lead acetate	+	+	+	+	+	+
		Alkalin	-	-	-	-	-	-
		NaOH	-	-	-	-	-	-
		H_2SO_4	+	+	-	+	-	+
8	Phenolic	$FeCl_3$	-	+	-	-	-	+
		Lead acetate	+	+	+	+	+	+
9	Tannin	Gelatin	-	-	-	-	-	-
		Phlobotannin	-	-	-	-	-	-
10	Saponin	Foam	+	-	+	-	-	+
		Fothing	-	-	+	-	-	-
11	Quinone	quinone	+	+	+	+	+	-
12	Anthraquinone	Anthraquinone	-	-	-	-	-	-
13	Inorganic	Sulphte test	-	-	+	+	+	-
		carbonate test	-	+	+	-	+	-

(+) Present (-) Not detected

Table 3: Extractive values of leaf and stem extract by various solvents

Sr. No.	Solvent Name	Leaf extract colour	Extractive of Leaf	Stem extract colour	Extractive value of Stem
1	Benzene	Blackish green	0.13	Green	0.07
2	Butanol	Green	0.04	Light green	0.45
3	Chloroform	Dark Green	0.08	Light green	0.012
4	Toluene	Yellowish Green	0.09	Light green	0.01
5	Pet. Ether	Yellowish Green	0.07	Light green	0.11
6	Water	Orange	0.19	Red Orange	0.11

DISCUSSION

The phytochemical screening revealed the presence glycosides, steroids, alkaloids, flavonoids, phenolics, tannins, saponins, quinines, anthraquinones and inorganic compounds. The leaf extract detected the phytochemicals including Flavonoids, Steroids, Saponins and Alkaloids which have been supported by some other workers also.[13] The crude extract of leaf and stem showed the absence of phytochemical constituents such as tannins and anthraquinones. Similar results have been found by other workers[14] hence supporting present work. Alkaloids tend to be organic and natural ingredients that have nitrogen and are also physiologically active together with sedative and analgesic roles.[15] Phenolic compounds are some of the most widespread molecules among plant secondary metabolites, are known to act as natural antioxidants.[16] Cardiac glycosides are the compounds used to treat congestive heart failure and cardiac arrhythmea. These compounds work by inhibiting the Na+/K+ pump.[17] Saponins are high molecular weight compounds in which a sugar molecule is combined with triterpene or steroid aglycon, so there are two major groups of saponins; triterpene saponins and steroid saponins. These are therapeutically important as they show hypolipidemic and anticancer activity of cardiac glycosides.[18] Flavonoids enhance the effects of Vitamin C and function as antioxidants. They are also known to be biologically active against liver toxins, tumors, viruses and other microbes.[19] The yield of extracts depending on the solvent and plant material used.[20] Hence the preliminary phytochemical investigation are actually obliging in finding chemical ingredients in the plant that may help to their quantitative evaluation and also in locating the source of pharmacologically active principle.

CONCLUSION

The results of the phytochemical analysis showed the leaves and stem extracts indicate their potential as a source of bioactive principles that may supply drugs for modern medicines. Further studies are therefore required to validate their antimicrobial, antihyperglycemic, anti-inflammatory and anthelminthic activities. In addition, isolation, purification and characterization of the active chemicals are necessary to ensure that the plant has novel chemicals which will be helpful in future studies.

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LRS Bianchi Type –I Magnetized Anisotropic Dark Energy Models with Variable Equation of State

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ABSTRACT

We discuss two dark energy models on LRS Bianchi Type-I magnetized anisotropic space –time with a variable equation of state (EoS). The EoS for dark energy ω is found to be time dependent and its existing range for derive models is in good agreement with the recent observations. Using the suitable condition, the anisotropic models approach to isotropic scenario. We also find that during the evolution of the universe, the EoS parameter for DE changes from $\omega > -1$ to $\omega = -1$ in first model whereas from $\omega > -1$ to $\omega < -1$ in second model which is consistent with recent observations. The cosmological constant Λ is found to be a positive decreasing function of time and it approaches a small positive value at late time (i.e. the present epoch) which is corroborated by results from recent supernovae Ia observations. The physical and geometric properties are also discussed.

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Introduction

The nature of the dark energy component of the universe [1-3] remains one of the deepest mysteries of cosmology. There is certainly no lack of candidates: cosmological constant, quintessence [4-6], k-essence [7-9], phantom energy [10-12]. Modifications of the Friedmann equation such as Cardassian expansion [13,14] as well as what might be derived from brane cosmology [15-17] have also been used to explain the acceleration of the universe. A particular case of the linear Equation of state has used in the cosmological context by Xanthopuolos [18], he considered space-times with two hypersurface orthogonal, space-like, commuting killing fields.

The current standard model of cosmology implies the existence of dark energy which accounts for about 70% of the total energetic content of the universe, which ac-cording to the observations is spatially flat [19]. Several models have been proposed to explain dark energy [20-26]. An alternative consists of to consider a phenomenological decaying dark energy density with continuous creation of matter [26] or photons [27,28].The dark energy might decay slowly in the course of the cosmic evolution and thus provide the source term for matter and radiation. Different such models have been discussed and strong constraints come from accurate measurements of the CMB. Although some authors [29] have suggested cosmological model with anisotropic and viscous dark energy in order to explain an anomalous cosmological observation in the cosmic microwave background (CMB) at the largest angles.

Bianchi type models have been studied by several authors in an attempt to understand better the observed small amount of anisotropy in the universe. The same models have also been used to examine the role of certain anisotropic sources during the formation of the large-scale structures we see in the universe today. Some Bianchi cosmologies, for example, are natural hosts of large-scale magnetic fields and therefore, their study can shed light on the implications of cosmic magnetism for galaxy formation. The simplest Bianchi family that contains the flat FRW universe as a special case are the type-I space-times.

Measuring the equation of state for dark energy is one of the biggest efforts in observational cosmology today. The DE model has been characterized in a conventional manner by the equation of state (EoS) parameter $\omega = \frac{p}{\rho}$ which is not necessarily constant, where ρ is the energy density and p is the fluid pressure [9]. The present data seem to slightly favour an evolving dark energy with EoS $\omega < -1$ around the present epoch and $\omega > -1$ in the near past. Obviously, ω cannot cross -1 for quintessence or phantom alone. Some efforts have been made to build a dark energy model whose EoS can cross the phantom divide. The simplest DE candidate is the vacuum energy ($\omega = -1$), which is mathematically equivalent to the cosmological constant (Λ). The other conventional alternatives, which can be described by minimally coupled scalar fields, are quintessence ($\omega > -1$) [30], phantom energy ($\omega < -1$) [31] and quintom (that can across from phantom region to quintessence region as evolved) and have time dependent EoS parameter. Some other limits obtained from observational results coming from SNe Ia data [32] and combination of SNe Ia data with CMBR anisotropy and galaxy clustering statistics [33] are [illegible] respectively. The latest results in 2009, obtained after a combination of cosmc

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luminosity distances of high redshift type Ia supernovae and galaxy clustering, constrain the dark energy EoS to $-1.44 < \omega < -0.92$ at 68% confidence level [34,35], However, it is not at all obligatory to use a constant value of ω. Due to lack of the observational evidence in making a distinction between constant and variable ω, usually the equation of state parameter is considered as a constant [36,37,4] with phase wise value $-1, 0, -\frac{1}{3}, and +1$ for vacuum fluid, dust fluid, radiation and stiff dominated universe respectively. But in general, ω is a function of time or redshift [38,39,40]. Some literature are also available on models with varying fields, such as cosmological models with variable EoS parameter in Kaluza-Klein metric and wormhole [41,42]. In recent years various form of time dependent ω have been used for variable Λ models by Mukhopadhyay et al. [43]. In well –known reviews on modified gravity [44,45],it is clearly indicated that any modified gravity may be represented as effective fluid with time dependent ω.

In Principle, once the metric is generalized to Bianchi types, the EoS parameter of the fluid can be generalized in a way conveniently to wield anisotropy with the considered metric . In such model, where both the metric and EoS parameter of the fluid are allowed to exhibit an anisotropic character, the universe can exhibit non-trivial isotropization histories and it can be examined whether the metric and/or the EoS parameter of fluid evolve toward isotropy. We may say about two main classes of such models; according to whether this anisotropization occurs at an early time or at late times of the universe, The former class can be related with the inflation field , which drives the inflation, which drives the late time acceleration of the universe. In the context of the former class, the generic inflationary model can be modified in a way to end inflation with a slightly anisotropic spatial geometry.

Bianchi type-I universe is the prime candidate for studying the possible effects of an anisotropy in the early universe on present-day observations, there are few other models (for example, $B-VI_0$), which describe an anisotropic space-time and generate interest among physicists.[46-49]. Pradhan and Bali [50] and Bali et al. [51] have studied $B-VI_0$ space time in connection with massive strings. Recently Amirhashchi et al.[52] presented dark energy models in an anisotropic $B-VI_0$ space –time by considering constant deceleration parameter. In this paper, we have investigated two new LRS Bianchi type-I magnetized dark energy models with variable equation of state . The discussion of the paper is as follows:

In section.2, the metric and the field equations are described. In section 3 deals with the solutions of the field equations in two different cases .Section 4 deals with physical and geometric behavior of the models. In section 5, we describe an other dark energy model and its physical aspects. Finally, conclusions are summarized in the last Section 6.

2. Metric and Field Equations:

We consider the LRS Bianchi Type-I metric in the following form

$$ds^2 = -dt^2 + a^2 dx^2 + b^2 (dy^2 + dz^2) \tag{1}$$

where the scale factors a and b are functions of cosmic time only.

The energy momentum tensor for anisotropic dark energy with magnetic field is given by

$$T_j^i = {}^{DE}T_j^i + {}^{EM}T_j^i \tag{2}$$

where

$${}^{DE}T_j^i = (\rho_{ED} + p_{ED}) u_i u^j + p g_j^{\ i} \tag{3}$$

where u^i is the flow vector satisfying

$$g_{ij} u^i u^j = -1 \tag{4}$$

${}^{EM}T_j^i$ is the electromagnetic field tensor which is given by

$${}^{EM}T_{ij} = \frac{1}{4\pi}\left[F_{i\alpha} F_{j\beta} g^{\alpha\beta} - \frac{1}{4} g_{ij} F^{\alpha\beta} F_{\alpha\beta} \right] \tag{5}$$

where F_{ij} is the electromagnetic field tensor which satisfies the Maxwell equations

$$F_{[ij;\alpha]} = 0, \qquad (F^{ij}\sqrt{-g}) = 0 \tag{6}$$

In commoving coordinates, the incident magnetic field is taken along x-axis, with the help of Maxwell equations (6), the only non-vanishing component of F_{ij} is

$$F_{23} = const = M. \tag{7}$$

By preserving the diagonal form of the energy momentum tensor in a consistent way with the above metric, the simplest generalization of EoS parameter of perfect fluid may be to determine it separately on each spatial axis. Therefore the energy momentum tensor of perfect fluid is taken as

$$T_i^j = diag[T_0^0, T_1^1, T_2^2, T_3^3] \tag{8}$$

Thus, one may parameterize it as follows

$$T_i^j = dia[-\rho + \frac{M^2}{8\pi b^4}, p_x - \frac{M^2}{8\pi b^4}, p_y + \frac{M^2}{8\pi b^4}, p_z + \frac{M^2}{8\pi b^4}]$$

$$= dia[-(\rho + \frac{M^2}{8\pi b^4}), (\omega_x \rho - \frac{M^2}{8\pi b^4}), (\omega_y \rho + \frac{M^2}{8\pi b^4}), (\omega_z \rho + \frac{M^2}{8\pi b^4})]$$
$$= dia[-(\rho + \frac{M^2}{8\pi b^4}), (\omega\rho - \frac{M^2}{8\pi b^4}), (\omega + \delta)\rho + \frac{M^2}{8\pi b^4}, (\omega + \delta)\rho + \frac{M^2}{8\pi b^4}] \quad (9)$$

where ρ is the energy density of the fluid p_x, p_y, p_z are the pressures and $\omega_x, \omega_y, \omega_z$ are the directional EoS parameters along the x, y, z respectively, $\omega(t) = p/\rho$ is the deviation free EoS parameter of the fluid. We have parameterized the deviation from isotropy by setting $\omega_x = \omega$ and then introducing skewness parameter δ which is the deviation from ω along both *y* and *z*-axes. ω and δ are not necessarily constants and might be function of the cosmic time t.

The Einstein's field equations are

$$R_{ij} - \frac{1}{2} R g_{ij} = -8\pi T_{ij} \quad (10)$$

where the symbols have their usual meaning.

By adopting commoving coordinates, Einstein's field equation (10), for the Kontowski-Sachs space-time, the field equations take the form

$$\frac{2a_4 b_4}{a\,b} + \frac{b_4^2}{b^2} = 8\pi\rho + \frac{M^2}{b^4} \quad (11)$$

$$\frac{a_{44}}{a} + \frac{b_{44}}{b} + \frac{a_4 b_4}{ab} = -8\pi(\omega + \delta)\rho - \frac{M^2}{b^4} \quad (12)$$

$$\frac{2b_{44}}{b} + \frac{b_4^2}{b^2} = -8\pi\omega\rho + \frac{M^2}{b^4} \quad (13)$$

where a subscript 4 indicates differentiation with respect to t.

3. Solutions of the field equations

The spatial volume for the model (1) is given by

$$V = R^3 = ab^2 \quad (14)$$

where *R* is the mean scale factor. The mean Hubble parameter *H* is given as

$$H = \frac{R_4}{R} = \frac{1}{3}\frac{V_4}{V} = \frac{1}{3}\left(\frac{a_4}{a} + 2\frac{b_4}{b}\right) \quad (15)$$

The directional Hubble parameters in the directions of *x,y and z* respectively may be defined as

$$H_x = \frac{a_4}{a} \qquad and \quad H_y = H_z = \frac{b_4}{b} \quad (16)$$

The volumetric deceleration parameter q, the scalar expansion θ, shear scalar σ^2 and the average anisotropy parameter A_m are defined by

$$q = -RR_{44}/R_4^2 \quad (17)$$

$$\theta = \frac{a_4}{a} + 2\frac{b_4}{b} \quad (18)$$

$$\sigma^2 = \frac{1}{3}\left(\frac{a_4}{a} - \frac{b_4}{b}\right)^2 \quad (19)$$

$$A_m = \frac{1}{3}\sum_{i=1}^{3}\left(\frac{H_i - H}{H}\right)^2 \quad (20)$$

where $H_i (i = x, y, z)$ represents the directional Hubble parameter in the direction of $x,y\,and\,z$, respectively. $A_m = 0$ corresponds to isotropic expansion.

Initially we apply the law of variation for Hubble parameter for the LRS Bianchi Type –I metric may be given by

$$H = D(ab^2)^{-\frac{n}{3}} \quad (21)$$

where $D > 0$ *and* $n \geq 0$ are constants. Such type of relations have firstly been considered by Berman [53], Berman and Gomide [54] for solving FRW models. Letter on many authors have used this law to study FRW and Bianchi type models.

On integrating, after equating (15) and (21), we obtain

$$ab^2 = (nDt + c_1)^{\frac{3}{n}} \qquad for \quad n \neq 0 \tag{22}$$

here c_1 is positive constants of integration. The values for the deceleration parameter for the mean scale factor as:

$$q = n - 1 \tag{23}$$

which is constant. The sign of q indicates where the model inflates or not. The positive sign of q i.e. $0 \leq n < 1$ indicates inflation. It is remarkable to mention here that through the current observations of SNe Ia and CMBR favors accelerating models $(q < 0)$, but both do not altogether rule out the deceleration ones which are also consistent with these observations [55]

Now we assume that the expansion (θ) is proportional to shear (σ), this condition lead to

$$\frac{a_4}{a} - \frac{b_4}{b} = \alpha_0 \sqrt{3}\left(\frac{a_4}{a} + 2\frac{b_4}{b}\right)$$

which yields to

$$\frac{a_4}{a} = m\frac{b_4}{b}$$

where $m = \dfrac{2\alpha_0\sqrt{3}+1}{1-\alpha_0\sqrt{3}}$ and α_0 are arbitrary constants. Above equation, after integration, reduces to

$$a = \beta b^m$$

where β is an integrating constant. Here , for simplicity and without any loss of generality, we assume $\beta = 1$. Hence we have

$$a = b^m \tag{24}$$

The motivation behind assuming this condition is explained with reference to Thorne[56], the observations of the velocity-red-shift relation for extragalactic sources suggest that Hubble expansion of the universe is isotropic today within ≈ 30 percent [57,58]. To put more precisely, red- shift studies place the limit

$$\frac{\sigma}{H} \leq 0.3,$$

On the ratio of shear σ to Hubble constant *H* in the neighborhood of our Galaxy today. Collins et al. [59] have pointed out that for spatially homogeneous metric, the normal congruence to the homogeneous expansion satisfies that the condition $\dfrac{\sigma}{\theta}$ is constant.

Using (24) (14) in (15), we obtain the expressions for metric function as follows

$$b = (nDt + c_1)^{\frac{1}{ml}} \tag{25}$$

$$a = (nDt + c_1)^{\frac{1}{l}} \tag{26}$$

where c_1 is an integrating constant

Hence the model (1) reduces to

$$ds^2 = -dt^2 + (nDt + c_1)^{\frac{2}{l}} dx^2 + (nDt + c_1)^{\frac{2}{ml}} (dy^2 + dz^2) \tag{27}$$

4. Physical aspects of dark energy model

The expressions for the Hubble parameter H, scalar of expansion θ ,shear scalar σ and the average anisotropy parameter A_m for the model (27) are given by

$$\theta = 3H = \frac{3L}{(nDt + c_1)} \tag{28}$$

$$\sigma^2 = \frac{1}{3}\left[\frac{nD(m-1)}{ml}\right]^2 (nDt + c_1)^{-2} \tag{29}$$

$$A_m = \frac{(m^2+2)(nD)^2 - 2nDLml(m+2)}{3m^2l^2L^2} + 1 \tag{30}$$

Using equation (11) , the energy density of the fluid is obtain as

$$8\pi\rho = (2m+1)\frac{(nD)^2}{(ml)^2}(nDt+c_1)^{-2} - M^2(nDt+c_1)^{-4/ml} \tag{31}$$

Using equation (13) , the EoS parameter is obtained as

$$\omega = \frac{(2ml-3)\left(\frac{nD}{ml}\right)^2(nDt+c_1)^{-2} + M^2(nDt+c_1)^{-4/ml}}{(2m+1)\left(\frac{nD}{ml}\right)^2(nDt+c_1)^{-2} - M^2(nDt+c_1)^{-4/ml}} \tag{32}$$

Using equation (12), the skewness parameter δ are computed as

$$\delta = \frac{\left[2+l(m-1)-m(m+1)\right]\left(\frac{nD}{ml}\right)^2(nDt+c_1)^{-2} - 2M^2(nDt+c_1)^{\frac{-4}{ml}}}{(2m+1)\left(\frac{nD}{ml}\right)^2(nDt+c_1)^{-2} - M^2(nDt+c_1)^{-4/ml}} \tag{33}$$

From (32), it is observed that the equation of state parameter ω is time dependent, it can be function of redshift z or scale factor R as well. The redshift dependence of ω can be linear like

$$\omega(z) = \omega_0 + \omega' z \tag{34}$$

with $\omega' = \left.\frac{d\omega}{dz}\right|_{z=0}$ (see [60,61]) or nonlinear as

$$\omega(z) = \omega_0 + \frac{\omega_1 z}{1+z} \tag{35}$$

[62,63]. So as for as the scale factor dependence of ω is concern. The parametrization

$$\omega(R) = \omega_0 + \omega_R(1-R) \tag{36}$$

where ω_0 is the present value $(R=1)$ and ω_R is the measure of the time variation ω' is widely used in the literature [64]

So, if the present work is compare with experimental results [31,32,33,34], then one can conclude hat the limit of ω provided by (32) may accommodated with the acceptable range of EoS parameter . Also it is observed that at $t = t_c$, ω vanishes, where t_c is a critical time given by

$$t_c = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{2ml-3}{M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{37}$$

Thus, for this particular time , our model represents a dusty universe. We also note that earlier real matter at $t \le t_c$, where $\omega \ge 0$ later on at $t \ge t_c$, where $\omega > 0$ converted to the dark energy dominated phase of universe.

For the value of ω to be in consistent with observation [31], we have the following general condition

$t_1 < t < t_2$,

where

$$t_1 = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{3\left[m\left(\frac{2}{3}l+3.34\right)+0.67\right]}{2.67M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{38}$$

$$t_2 = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{3\left[m\left(\frac{2}{3}l+1.24\right)-0.38\right]}{1.62M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{39}$$

For this constrain, we obtain $-1.67 < \omega < -0.62$ which is in good agreement with the limit obtained from observational results coming from SNe Ia data [31].

For the value of ω to be in consistent with observation [12] , we have the following general condition

$$t_3 < t < t_4, \tag{40}$$

where

$$t_3 = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{3\left[m\left(\frac{2}{3}l+2.66\right)+0.33\right]}{2.33M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{41}$$

$$t_4 = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{3\left[m\left(\frac{2}{3}l+1.58\right)-0.21\right]}{1.79M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{42}$$

For this constrain, we obtain $-1.33 < \omega < -0.79$ which is in good agreement with the limit obtained from observational results coming from SNe Ia data [31] with CMB anisotropy and galaxy clustering statistics [32].

For the value of ω to be in consistent with observation [33,34] , we have the following general condition

$$t_5 < t < t_6,$$

$$t_5 = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{3\left[m\left(\frac{2}{3}l+2.88\right)+0.44\right]}{2.44M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{43}$$

$$t_6 = \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{3\left[m\left(\frac{2}{3}l+1.84\right)-0.08\right]}{1.92M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{44}$$

For this constrain, we obtain $-1.33 < \omega < -0.79$ which is in good agreement with the limit obtained from observational results [33,34].

From (31), we note that energy density of the fluid $\rho(t)$ is a decreasing function of time and $\rho \geq 0$ when

$$t \leq \frac{1}{nD}\left(\frac{nD}{ml}\sqrt{\frac{2m+1}{M^2}}\right)^{\frac{ml}{ml-2}} - \frac{c_1}{nD} \tag{45}$$

Here ρ is a positive decreasing function of time and it approaches to zero as $t \to \infty$.

In absence of any curvature, matter energy density Ω_m and dark energy Ω_Λ are related by the equation

$$\Omega_m + \Omega_\Lambda = 1 \tag{46}$$

Where $\Omega_m = \frac{\rho}{3H^2}$ and $\Omega_\Lambda = \frac{\Lambda}{3H^2}$. Thus , (46) reduces to

$$\frac{\rho}{3H^2} + \frac{\Lambda}{3H^2} = 1 \tag{47}$$

Using (28) and (31) in (47), the cosmological constant is obtained as

$$\Lambda = \left[3L^2 - \frac{1}{8\pi}(2m+1)\left(\frac{nD}{ml}\right)^2\right](nDt+c_1)^{-2} + \frac{M^2}{8\pi}(nDt+c_1)^{-\frac{4}{ml}} \tag{48}$$

From (48), we observe that Λ is decreasing function of time and it is always positive when

$$t > \frac{1}{nD}\left[M^2(24\pi L^2 - (2m+1)\left(\frac{nD}{ml}\right)^2) \right]^{\frac{ml}{2(ml-2)}} + \frac{c_1}{nD} \tag{43}$$

We observe that cosmological parameter is decreasing function of time and it approaches a small positive value at late time (i.e. At present epoch). Recent cosmological observations[65,2]; [3,66,67] suggest the existence of a positive cosmological constant Λ with the magnitude $\Lambda\left(Gh/c^3\right) \approx 10^{-123}$. These observations on magnitude and red-shift of type Ia supernova suggest that our universe may be an accelerating one with induced cosmological density through the cosmological Λ - term. Thus, the nature of Λ in our derive DE model is supported by recent observations.

From (28)-(29) , it can be seen that all the kinematical parameters $H, \theta, and\ \sigma$ diverge at the initial singularity. There is a Point Type singularity [48] at $t = -\frac{c_1}{nD}$ in the model . The mean anisotropic parameter is constant and it increases. Thus, the dynamics of the mean anisotropy parameter depends on the value of n . Since $\frac{\sigma^2}{\theta^2} = cons\tan t,$ the models does not approach isotropy through the whole evolution of the universe.

5. Other dark energy model

Now we take the following ansatz for the scale factor, where the increase in terms of time evolution is

$$R(t) = te^t \tag{50}$$

By the above choice of scale factor yields a time dependent deceleration parameter. We define the deceleration parameter q as usual,

$$q = -\frac{R_{44}R}{R_4^{\,2}} = -\frac{R_{44}}{RH^2} \tag{51}$$

Using (50) into (51), we find

$$q = -1 + \frac{1}{(1+t^2)} \tag{52}$$

Using (24) and (51) in (15), we obtain the expressions for metric functions as follows

$$a = \left(te^t\right)^{\frac{3m}{2+m}} \tag{53}$$

$$b = (te^t)^{3/2+m} \tag{54}$$

Hence the model (1) reduces to

$$ds^2 = -dt^2 + (te^t)^{\frac{6m}{m+2}}dx^2 + (te^t)^{\frac{6}{m+2}}(dy^2 + dz^2) \tag{55}$$

The expressions for the Hubble parameter H , scalar of expansion θ, shear σ and the average anisotropy parameter A_m for the model (55) are given by

$$\theta = 3H = 3\left(\frac{R_4}{R}\right) = 3\left(\frac{t+1}{t}\right) \tag{56}$$

$$\sigma^2 = \frac{(m-1)^2}{m^2r^2}\left(\frac{t+1}{t}\right)^2 \tag{57}$$

$$A_m = \frac{(m^2+2) - 2mr(m+2)}{3mr^2} + 1 \tag{58}$$

Where $r = \frac{m+2}{3m}$. Since $\frac{\sigma^2}{\theta^2} \neq 0$ for all values of m except for $m = 1$, hence the model is anisotropic except for $m = 1$.

The dynamics of the mean anisotropic parameter depends on the value of m. The mean anisotropic parameter is constant. We observed that when $m = 0,\ A_m \to \infty$ and for $m = 1,\ A_m = 0$. Thus, the observed isotropy of the universe can be achieved in phantom model.

The energy density of the fluid can be find by using (53) and (54) in (11)

$$8\pi\rho = \frac{(2m+1)}{m^2r^2}\left(\frac{t+1}{t}\right)^2 - M^2(te^t)^{\frac{-4}{rm}} \tag{59}$$

Using (53) , (54) and (59) in (13) , the EoS parameter ω is obtained as

$$\omega = -\frac{\left[\frac{3(t+1)^2 - 2mr}{t^2 m^2 r^2} - M^2 (te^t)^{-\frac{4}{rm}}\right]}{\frac{(2m+1)}{r^2 m^2}\left(\frac{t+1}{t}\right)^2 - M^2 (te^t)^{-\frac{4}{rm}}} \tag{60}$$

Using (53), (54), (59) and (60) in (12), the skew parameter δ are computed as

$$\delta = -\frac{\left[\frac{(m^2+m-2)}{m^2 r^2}\left(\frac{t+1}{t}\right)^2 + \frac{(1-m)}{mrt^2} + 2M^2 (te^t)^{\frac{-4}{rm}}\right]}{\frac{(2m+1)}{r^2 m^2}\left(\frac{t+1}{t}\right)^2 - M^2 \left(te^t\right)^{-\frac{4}{rm}}} \tag{61}$$

So, if the present work is compared with experimental results [31,32,33,34], then one can conclude that the limit of ω provided by (60) may accommodated with the acceptable range of EoS parameter. Also it is observed that at $t = t_c$, ω *vanishes* , where t_c is a critical time given by the following relation

$$\frac{3(t+1)^2 - 2mr}{m^2 r^2 {t_c}^2} - M^2 (t_c e^{t_c})^{-\frac{4}{rm}} = 0 \tag{62}$$

Thus for this particular time, our model represents a dusty universe, We also note that the earlier real matter at $t \le t_c$, where $\omega \ge 0$ later on at $t > t_c$, where $\omega < 0$ converted to the dark energy dominated phase of universe.

From (59), we note that energy density of the fluid $\rho(t)$ is a decreasing function of time and $\rho \ge 0$ when

$$(te^t)^{4/rm}\left(\frac{t+1}{t}\right)^2 \ge \frac{M^2 m^2 r^2}{2m+1} \tag{63}$$

Here ρ is a positive decreasing function of time and it approaches to zero as $t \to \infty$.

Using (56),(59) in (47), the cosmological constant is obtained as

$$\Lambda = \left[3 - \frac{9(2m+1)}{8\pi(m+2)^2}\right]\left(\frac{t+1}{t}\right)^2 - \frac{M^2}{8\pi}(te^t)^{\frac{-4}{rm}} \tag{64}$$

From (64), we observe that Λ is a decreasing function of time and it is always positive when

$$\left(\frac{t+1}{t}\right)\left(te^t\right)^{\frac{12}{m+2}} \ge \frac{M^2 (m+2)^2}{24\pi(m-1)^2} \tag{65}$$

We observe that cosmological parameter is decreasing function of time and it approaches a small positive value at late time. Thus ,the nature of Λ in this derived DE model is also in good agreement with recent observations [1,2,68,69,70].

6. Conclusion

On getting motivated from increasing evidence for the need of a geometry that resembles Bianchi morphology to explain the observed anisotropy in the Wilkinson microwave anisotropy probe (WMAP) data, we have discussed some features of the Bianchi type- VI_0 universes in the presence of a fluid that wields an anisotropic EoS parameter in general relativity. A new class of anisotropic LRS Bianchi type –I magnetized Dark energy models with variable EoS parameter ω has been investigated by using time dependent deceleration parameter. In literature it is a plebeian practice to consider constant deceleration parameter. Now for a universe which was decelerating in past and acceleration at present epoch, the DP must show signature flipping as already discussed in Section 2 . Therefore our consideration of DP to be variable is physically justified.

Our Power law solution represents the singular model where the spatial scale factors and volume scalar vanish at $t = -\frac{c_2}{nD}$. All the physical parameters are infinite at this initial epoch and tend to zero as $t \to \infty$. There is a point Type singularity [48] at $t = -\frac{c_2}{nD}$ in the model.

It is observed that, in early stage, the EoS parameter ω is positive i.e. the universe was matter dominated in early stage but in late time, the universe is evolving with negative values i. e. the present epoch . DE model presents the dynamics of EoS parameter ω provided by (32) whose range is in good agreement with the acceptable range by the recent observations [31-34].

The existence of DE, in whatever form , is needed to reconcile the measured geometry of space with the total amount of matter in the universe, DE models present the dynamics of EoS parameter ω provided by (32) and (60) whose range is in good agreement with the acceptable range by the recent observations [31-34] .It can be easily seen that in both DE models . Thus , our both anisotropic parameter vanishes at $m = 1.$ Thus, our both anisotropic models approach to isotropy at $m = 1.$ It is already

discussed in previous section , we obtain cosmological constant dominated universe, quintessence and phantom fluid dominated universe [45], representing different phases of the universe through- out the evolving process.

Our DE model is of great importance in the sense that the nature of decaying vacuum energy $\Lambda(t)$ is supported by recent cosmological observations. Though there are many suspects (candidates) such as cosmological constant, vacuum energy, scalar field, brane world, cosmological nuclear-energy, etc. as reported in the vast literature for DE, the proposed model in this paper favors EoS parameter as a possible suspect for the DE.

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QSAR analysis for 6-arylpyrazine-2-carboxamides as *Trypanosoma brucei* inhibitors

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ABSTRACT

Human African trypanosomiasis (HAT) is prevalent in African countries, covering 37 countries, mostly sub-Saharan. A limited number of drugs are available to cure this neglected disease. In the present work, quantitative structure–activity (toxicity) relationships (QSA(T)R) analysis has been performed for a dataset of 54 6-arylpyrazine-2-carboxamides as *Trypanosoma brucei* inhibitors to identify the important structural features required for future optimization of lead candidates. The QSA(T)R models satisfy OECD guidelines and have high statistical robustness. The QSA(T)R models are based on easily interpretable molecular descriptors. The QSA(T)R models indicate that *Trypanosoma brucei* inhibitory activity of 6-arylpyrazine-2-carboxamides has correlation with the presence of *N-sec*-butylformamide and substituted benzene. The results could be beneficial for further optimization of 6-arylpyrazine-2-carboxamides as *Trypanosoma brucei* inhibitors. Some potential candidate molecules have been proposed.

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Introduction

Sleeping sickness, also known as Human African trypanosomiasis (HAT), is a neglected disease, which is mostly transmitted by the bite of the blood-sucking tsetse fly of the genus *Glossina* [1–3]. According to a report from the World Health Organization this disease has high occurrence in sub-Saharan countries, with 70 million people at risk of contracting HAT and about 8000 new HAT cases each year [1–4]. This vector-borne parasitic disease, caused by protozoan parasites of the genus *Trypanosoma*, has two main stages: (a) the peripheral infection, which has non-specific symptoms, and (b) central nervous system invasion [1–6]. If untreated, this disease is eventually incurable in practically all cases, and due to toxicity and poor efficacy, limited drugs are presently available for its effective treatment [1–6]. Fortunately, the genome sequence of the parasite has been determined and various proteins have been identified as potential targets for drug development. But further investigation of the genome sequencing has disclosed that *Trypanosoma brucei* has over 800 genes that

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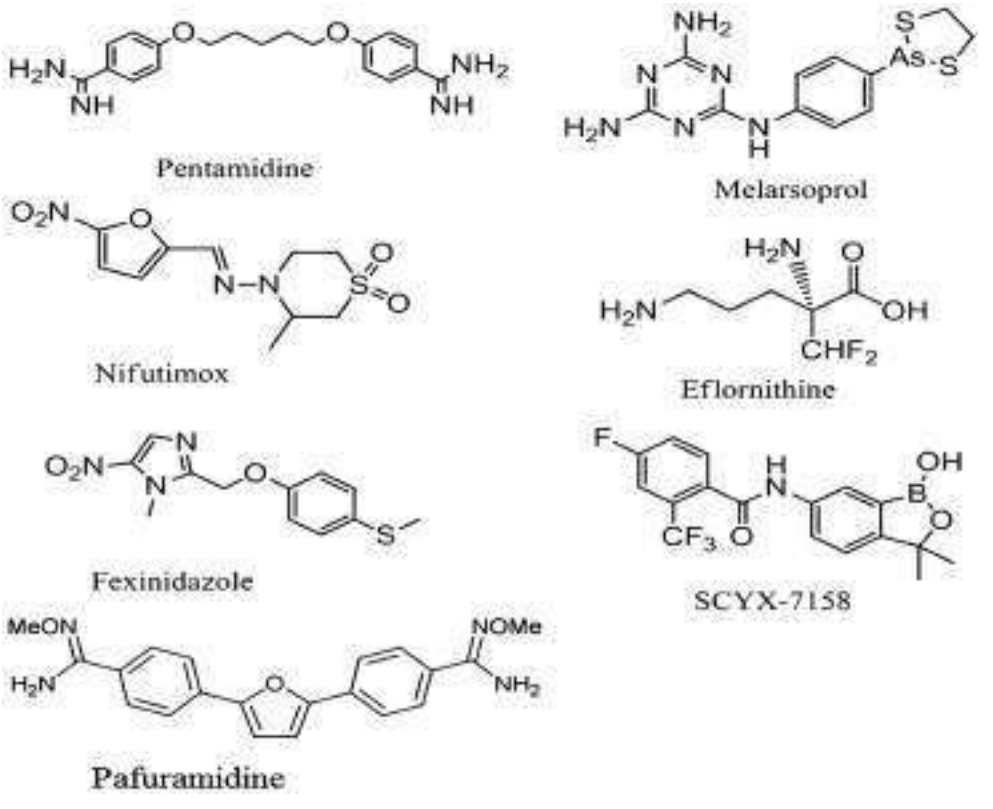


Figure 1. Some commercial and clinical stage drugs for treating HAT.

encode variant surface glycoproteins, resulting in parasite protein 'mixes and matches' to evade immune system detection; subsequently, developing a vaccine for this disease is rightly challenging [1–7]. In addition, the type of treatment varies with the stage of the disease. The drugs employed in the first stage of the disease have little toxicity and are easy to administer. The prospects of a cure are better if the disease is identified in its earlier stage. But, in most of the cases, the disease is identified at a later stage. The success of treatment in the second stage relies significantly on a drug that can cross the blood–brain barrier to reach the parasite. Unfortunately, such drugs are mostly toxic and difficult to administer. In Figure 1, the commercial drugs and drugs in clinical stages have been illustrated [1–10].

To overcome these problems, Rahmani et al. [3] used high-throughput screening against *T. brucei* using a library of 87,296 compounds, and identified 6-arylpyrazine-2-carboxamide as a promising scaffold for developing therapeutics against *T. brucei*. Further, they synthesized a good number of 6-arylpyrazine-2-carboxamide derivatives and screened for *in vitro* activity, microsome stability, solubility, etc. The analysis revealed that the compounds possess activity in the μM range with low microsome stability. Hence, further improvements are essential to achieve the goals with retention or augmentation of HAT healing activity and metabolic profiles. In this scenario, computer-aided drug design (CADD) is an attractive tool for further lead optimization.

In past decades, computer-aided techniques have appeared as promising alternatives to the conventional 'trial and error' methodology of drug design/discovery to unveil the secrets

of the biochemistry of drug action with absorption, distribution, metabolism, excretion and toxicity (ADMET) optimization. CADD is a rapid, cost-effective and impressively successful result-oriented contemporary technique comprising unification of various fields, with a main emphasis on mapping how diverse biological important molecules interact, to understand the mechanisms of disease and to find the pharmacophoric patterns linked with activity/toxicity [7,11–15]. The commonly employed CADD methods – quantitative structure–activity relationships (QSAR), molecular docking, pharmacophore modelling – when used concomitantly result in particularly effective analysis, providing maximal information desired for lead (and drug) optimization. These methods offer in-depth knowledge about the pharmacophoric patterns that control the specific activity/toxicity of a drug candidate and enhanced intuition for the mechanism of drug action.

Molecular docking is generally preferred when sufficient knowledge and evidence are available about the target protein (receptor or bio-polymer) with which the drug interacts. As the target protein with which 6-arylpyrazine-2-carboxamides interact is unidentified [3], QSAR (a ligand-based drug design technique) was performed to identify the structural features that have good correlation with the HAT healing activity of 6-arylpyrazine-2-carboxamides.

Experimental methodology

Experimental dataset

In the present work, anti-HAT activity values of a diverse dataset of 54 6-arylpyrazine-2-carboxamide derivatives encompassing different heterocyclic rings and a variety of substituents, previously reported by Rahmani et al. [3], were subjected to QSAR analysis (see Figure 2 and Table 1). The substituents are highly varied; consequently, the present dataset comprises isomers such as positional, functional, etc. Thus, the dataset covers a good chemical space.

A separate quantitative structure–toxicity relationships (QSTR) model has been developed for the cytotoxicity data of 13 arylpyrazine-2-carboxamide derivatives. The reported EC_{50} (μM) activity values for anti-HAT and rat skeletal myoblast cell L-6 strain were converted to

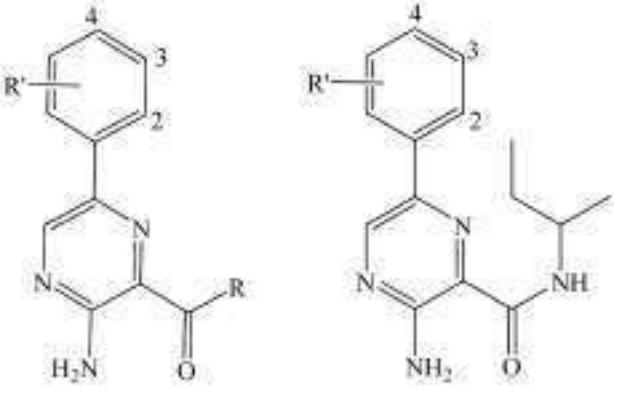


Figure 2. 6-arylpyrazine-2-carboxamide derivatives used in the present work.

Table 1. Substituents, experimental EC_{50} and pEC_{50} for anti-HAT activity of 6-Arylpyrazine-2-carboxamide derivatives.

S.N.		R	R′	EC_{50} (μM) Anti-HAT	pEC_{50} (M) anti-HAT	EC_{50} (μM)L-6 strain	pEC_{50} (M)L-6 strain
1	1a-9		H	0.49	5.690	18	7.744
2	1b-10		H	2.6	6.415	–	–
3	1c-11		H	0.26	5.415	20	7.699
4	1d-12		H	0.32	5.505	–	–
5	1e-14		H	1.7	6.230	–	–
6	1f-15		H	0.53	5.724	–	–
7	1g-16		H	7.3	6.863	–	–
8	1h-21		H	2.6	6.415	–	–
9	1i-22		H	3	6.477	–	–
10	1j-24		H	6.1	6.785	–	–
11	1k-25		H	4.6	6.663	–	–
12	1l-27	2-F	H	0.75	5.875	–	–
13	1m-28	2-Cl	H	1.1	6.041	–	–
14	1n-30	2-OCH_3	H	5.4	6.732	–	–
15	1p-31	2-NO_2	H	0.89	5.949	–	–
16	1o-33	2-$COCH_3$	H	10	7.000	–	–
17	1q-34	2-Me	H	1.2	6.079	–	–
18	1r-35	2-CN	H	0.35	5.544	18	7.744
19	1s-36	3-F	H	0.82	5.914	–	–
20	1t-37	3-Cl	H	0.48	5.681	39	7.409
21	1u-38	3-Br	H	0.57	5.756	–	–
22	1v-39	3-OCH_3	H	0.41	5.613	–	–
23	1w-40	3-NO_2	H	0.45	5.653	–	–
24	1x-41	3-NH_2	H	1.1	6.041	–	–
25	1y-43	3-CH_3	H	0.17	5.230	43	7.366
26	1z-44	3-CN	H	2.7	6.431	–	–
27	2a-45	4-F	H	0.4	5.602	17	7.769
28	2b-46	4-Cl	H	0.68	5.833	–	–
29	2c-47	4-Br	H	2.2	6.342	–	–
30	2d-48	4-OCH_3	H	1.3	6.114	–	–
31	2e-49	4-NO_2	H	4.5	6.653	–	–
32	2f-50	4-NH_2	H	2.9	6.462	–	–
33	2g-51	4-$COCH_3$	H	4.7	6.672	–	–
34	2h-52	4-CH_3	H	3.74	6.573	–	–
35	2i-53	4-CN	H	2.7	6.431	–	–
36	2j-54		2-CN	0.17	5.230	10	8
37	2k-55		3-Me	0.11	5.041	20	7.699
38	2l-56		3-Me and 5-Me	0.48	5.681	–	–

(*Continued*)

Table 1. (*Continued*)

S.N.		R	R′	EC_{50} (μM) Anti-HAT	pEC_{50} (M) anti-HAT	EC_{50} (μM)L-6 strain	pEC_{50} (M)L-6 strain
39	2m-57		4-F	0.08	4.903	28	7.553
40	2n-58		3-Me and 4-F	0.025	4.398	24	7.620
41	2o-59		2-CN and 4-F	0.1	5.000	20	7.699
42	2p-60		3-CF_3	0.26	5.415	–	–
43	2q-61		3-Cl	0.36	5.556	–	–
44	2r-62		3-Cl and 5-Me	0.77	5.886	–	–
45	2s-63		3-Cl and 4-F	0.22	5.342	–	–
46	2t-64		2-CN	0.2	5.301	11	7.958
47	2u-65		3-Me	0.035	4.544	42	7.376
48	2v-66		4-F	0.071	4.851	–	–
49	2w-67		3-Me and 4-F	0.024	4.380	–	–
50	2x-68		2-CN and 4-F	0.057	4.756	–	–
51	2y-69		3-CF_3	0.15	5.176	–	–
52	2z-70		3-Cl	0.24	5.380	–	–
53	3a-71		3-Cl and 5-Me	0.5	5.699	–	–
54	3b-72		3-Cl and 4-F	0.11	5.041	–	–

pEC_{50} ($pEC_{50} = -\log_{10}EC_{50}$) before quantitative structure–activity (toxicity) Relationships (QSA(T)R) analysis. The EC_{50}, pEC_{50} along with the substituents are shown in Table 1.

Modelling and molecular descriptors' calculation

In the present work, for successful QSA(T)R analysis, OECD guidelines and a standard protocol recommended and used by different researchers have been followed [12,16–25]. The structure drawing was accomplished using ChemSketch 12 freeware, followed by energy

minimization by means of MMFF94 force field available in TINKER. The energy-minimized 3D structures were used for calculation of a large number of descriptors (>29,000) using PaDEL 2.21 and *PyDescriptor* as a molecular descriptor calculator. This huge molecular descriptor pool of more than 29,000 descriptors covers mono-dimensional (1D) to three-dimensional (3D), electro-topological, finger-prints and other molecular descriptors. Since all the calculated descriptors do not contain relevant information, henceforward, objective feature selection (OFS) was performed using QSARINS-Chem 2.2.1 [24,26] to eliminate a large number of redundant molecular descriptors. Prior to subjective feature selection (SFS) performed using QSARINS-Chem 2.2.1 [24,26], constant, near constant (>98%) and highly correlated ($|R|$ >90%) descriptors were rejected. OFS caused significant reduction of descriptor pool to a cluster of 1200 and 865 molecular descriptors only for QSAR and QSTR models, respectively, still covering a wide structural and chemical space, including constitutional (0D), 1D, bi-dimensional (2D) and 3D [7,11,12,20–25,27,28].

Model development

The main objectives for QSA(T)R models analysis are (1) to identify the structural features that influence the activity/toxicity profile of a congeneric series of molecules, and (2) to predict the activity/toxicity for a compound prior to its actual synthesis and/or biological screening. To obtain maximum information about pharmacophoric features, QSAR models were derived using a divided and undivided dataset. The dataset was randomly split into training (80%) and prediction (20%) set earlier to descriptor selection. Multiple splitting was carried out to derive multiple QSAR models. A compound may or may not be in the training set of two different splittings. The genetic algorithm (GA) module of QSARINS-Chem 2.2.1 [24] was employed for selection of optimum number and cluster of molecular descriptors. The heuristic search of molecular descriptors was restricted to four descriptors using the defaults settings in QSARINS-Chem 2.2.1 to avoid over-fitting and have simplicity in understanding the developed QSAR models. Q^2_{loo} was considered as a fitness function to circumvent the problem of naïve Q^2.

As the dataset for toxicity is small, for QSTR model development the complete dataset was used. The heuristic search of molecular descriptors was constrained to two descriptors using the defaults settings in QSARINS-Chem 2.2.1 to circumvent the problem of over-fitting and complexity.

Model validation

QSA(T)R model development is incomplete without appropriate model validation. Appropriate QSA(T)R model validation ensures the external predictive ability of a model. Hence, the statistical qualities and strength of the genetic algorithm–multiple linear regression (GA–MLR) equations were assessed on the basis of: (a) cross-validation (CV) by leave-one-out (LOO) and leave-many-out (LMO) procedures (i.e. internal validation); (b) using the prediction set; (c) data randomization, i.e. Y-scrambling, and (d) observing if the following criteria are fulfilled: $r^2_{tr} \geq 0.6$, $Q^2_{loo} \geq 0.5$, $Q^2_{LMO} \geq 0.6$, $r^2 > Q^2$, $r^2_{ex} \geq 0.6$, $RMSE_{tr} < RMSE_{cv}$, $\Delta K \geq 0.05$, CCC ≥ 0.80, $Q^2 - F^n \geq 0.60$, $r^2_m \geq 0.6$, $(1-r^2/r_o^2) < 0.1$, $0.9 \leq k \leq 1.1$ or $(1-r^2/r'_o{}^2) < 0.1$, $0.9 \leq k' \leq 1.1$, $|r_o^2 - r'_o{}^2| < 0.3$ with RMSE and MAE close to zero [7,11–13,28]. A GA–MLR model that satisfies the threshold values of these parameters possesses statistical robustness and

external predictive ability. Therefore, the models that do not satisfy above mentioned criteria were consequently excluded [7].

Results and discussion

QSAR models

The selected dataset considered in the present study is of moderate size with the molecules either being positional or constitutional isomers, consequently covering a good chemical space. We have earlier proved that for small or moderate-size datasets at least one QSAR model must be constructed using an undivided whole dataset to determine maximal significant descriptors, which in turn not only affords valuable information for future variations but is also beneficial for comparison and evaluation of QSAR models built using divided datasets. Hence, in the present work, QSAR models were developed using divided and undivided datasets.

During the QSAR analysis, normally stepwise regression, GA, etc. algorithms are considered for SFS. SFS gives rise to a good number of MLR models with almost equivalent statistical performance but often comprising different descriptors. Generally, in such a situation, only one MLR model is chosen on the basis of its statistical robustness. The weaknesses, however, of this 'first among equals' approach are (1) if the chosen model comprises complex/esoteric descriptors then simple and straightforward correlation of descriptors with proper structural features is relatively difficult, (2) a single QSAR model may be swayed by (i) the method of splitting, constitution of training and prediction sets, method adopted for descriptor selection, and (ii) some more influencing molecules in the training/prediction dataset [7,11,12,14]. A simple and potential answer to outwit the shortcomings of the 'first among equals' approach is to construct multiple QSAR models using multiple splitting. A further advantage of this solution lies in identification of underprivileged yet valuable pharmacophoric features that control the anti-HAT activity [7,11,12,14]. Therefore, in the present study, multiple QSAR models were constructed. Interestingly, univariate statistical analysis revealed that anti-HAT activity has good but negative correlation with $R = 0.771$ with a finger print descriptor KRFPC3662, which signifies the presence of SMILES notation CCC(C)NC=O that corresponds to *N-sec*-butylformamide fragment. The developed multi-linear GA–MLR QSAR models are as follows:

Full set model Model 1:

pEC_{50} = + 5.598 (± 1.92) + 8.333 (± 0.343) * KRFPC1609 + 0.608 (± 0.128) * KRFPC3662 – 0.021 (± 0.009) * byring allplus_AbSA + 0.221 (± 0.075) * fHF4B

Full set model Model 2:

pEC_{50} = + 5.505 (± 0.184) – 0.460 (± 0.222) * AD2D627 + 0.701 (± 0.357) * KRFPC1609 + 0.514 (± 0.133) * KRFPC3662 + 0.202 (± 0.078) * fHF4B

Model 3:

pEC_{50} = + 5.539 (± 0.202) + 0.826 (± 0.340) * KRFPC1609 + 0.595 (± 0.135) * KRFPC3662 – 0.016 (± 0.010) * byring allplus_AbSA + 0.226 (± 0.075) * fHF4B

Model 4:

pEC_{50} = + 5.994 (± 0.473) + 0.773 (± 0.372) * KRFPC1609 + 0.484 (± 0.165) * KRFPC3662 + 1.934 (± 1.294) * O_all_3Bc + 0.219 (± 0.084) * fHF4B

From the derived models it is clear that KRFPC1609 (a Klekota–Roth finger print descriptor that corresponds to di-substituted benzene with one of the substituents at the meta position), KRFPC3662 (a Klekota–Roth finger print descriptor that corresponds to *N-sec*-butylformamide fragment) and fHF4B (frequency of occurrence of hydrogen within 4 Å from fluorine atom) are common in all the newly derived MLR–QSAR models. Their coefficients are positive in all the models; hence, the higher the values of these fragments, the higher the activity. In models 1 and 3, the descriptor byring allplus_AbSA, which represents absolute surface area of positively charged atoms of rings, has negative coefficient, therefore, its value must be as low as possible. For this, electron-withdrawing groups on rings and heterocyclic rings must be avoided.

The descriptor KRFPC3662 (representing the fragment *N-sec*-butylformamide) has encouraging correlation with the activity, which is supported by comparing the activity of following pairs of compounds: **1** (IC_{50} = 0.49 μM) and **2** (IC_{50} = 2.6 μM), **15** (IC_{50} = 0.53 μM) with **14** (IC_{50} = 1.7 μM), and **1** (IC_{50} = 0.49 μM) with **9** (IC_{50} = 3 μM). In general, molecules lacking the *N-sec*-butylformamide fragment have lower activity profile compared with their analogues with the *N-sec*-butylformamide fragment. The descriptor KRFPC1609 has significant influence in deciding the activity, as evident from the comparison of activity values of the following pairs of compounds: **13** (IC_{50} = 1.1 μM) and **20** (IC_{50} = 0.49 μM), **30** (IC_{50} = 5.4 μM) and **22** (IC_{50} = 0.41 μM), **17** (IC_{50} = 1.2 μM) and **25** (IC_{50} = 0.17 μM), and **15** (IC_{50} = 0.89 μM) and **23** (IC_{50} = 0.45 μM). Surprisingly, the compound number **19** (IC_{50} = 0.82 μM) even though it possesses –F at the meta position on the benzene ring, it has lower activity than **12** (IC_{50} = 0.75 μM) and **27** (IC_{50} = 0.40 μM). A plausible explanation for this abnormal observation was obtained after derivation of above QSAR models. The above QSAR models revealed that the descriptor fHF4B has positive correlation with the activity. In the case of compound **12** and **27**, the value of the descriptor fHF4B is higher than compound number **19** (see the supporting information, available via the Supplementary Content tab on the article's online page at ####). Hence, in future optimizations of 6-arylpyrazine-2-carboxamides as *T. brucei* inhibitors with –F as one of the substituents, the value of the descriptor fHF4B must be given significant importance.

The descriptor AD2D627, which stands for the presence of carbon and oxygen atoms at a topological distance of 9 from each other, has negative coefficient in model 2. Hence, such a combination of C and O must be avoided to have better activity. This is supported by the difference in the activity of compound **5** (IC_{50} = 1.7 μM) and **7** (IC_{50} = 7.8 μM), **30** (IC_{50} = 1.3 μM) and **14** (IC_{50} = 5.4 μM), and **18** (IC_{50} = 0.35 μM) and **35** (IC_{50} = 2.7 μM).

The statistical parameters for all the derived models have been tabulated in Table 2. In Table 3, experimental and predicted pEC_{50} by various models along with the status of the molecule are shown.

The GA heuristic search for undivided whole dataset resulted in many QSAR models, but only two models (models 1 and 2) were observed to accomplish the threshold values for different statistical parameters. From Table 2, it is evident that the derived QSAR models fulfil threshold values for many of the internal and external validation parameters. A comparative analysis of various statistical parameters for different models points out that the models are statistically acceptable because of good external predictive ability. For all the derived models, the close value of r^2_{adj} to r^2_{tr} indicates that the models consist of a sufficient number of descriptors and the problem of over-fitting is absent. The low value of RMSE and MAE (fitting,

Table 2. Different statistical parameters for goodness of fit, internal validation and external predictive ability for models 1–4.

S. No.	Statistical parameter	Model-1	Model-2	Model-3	Model-4
1.	N_{tr}	54	54	44	44
2.	N_{ex}	00	00	10	10
3.	*Number of descriptors*	04	04	04	04
Fitting criteria					
4.	r^2_{tr}	0.8351	0.8218	0.8459	0.8141
5.	r^2_{adj}	0.8216	0.8072	0.8301	0.7950
6.	$r^2_{tr} - r^2_{adj}$	0.0135	0.0145	0.0158	0.0191
7.	*LOF*	0.0967	0.1045	0.0973	0.1159
8.	K_{xx}	0.2004	0.1973	0.2133	0.2042
9.	ΔK	0.1458	0.1926	0.1395	0.1902
10.	$RMSE_{tr}$	0.2648	0.2753	0.2552	0.2786
11.	MAE_{tr}	0.2120	0.2216	0.2032	0.2228
12.	RSS_{tr}	3.7875	4.0931	2.8660	3.4143
13.	CCC_{tr}	0.9101	0.9022	0.9165	0.8975
14.	*s*	0.2780	0.2890	0.2711	0.2959
15.	*F*	62.0275	56.4818	53.5289	42.6884
Internal validation criteria					
16.	r^2_{cv} (Q^2loo)	0.8067	0.7854	0.8057	0.7809
17.	$r^2 - r^2_{cv}$	0.0284	0.0363	0.0402	0.0331
18.	$RMSE_{cv}$	0.2867	0.3021	0.2866	0.3024
19.	MAE_{cv}	0.2321	0.2435	0.2290	0.2461
20.	$PRESS_{cv}$	4.4393	4.9275	3.6144	4.0227
21.	CCC_{cv}	0.8943	0.8821	0.8941	0.8788
22.	Q^2_{LMO}	–	–	0.7980	0.7822
23.	r^2_{Yscr}	–	–	0.0924	0.0958
24.	Q^2_{Yscr}	–	–	-0.1713	-0.1686
External validation criteria					
25.	θ^*	–	–	-11.1670°	-9.0760°
26.	$RMSE_{ex}$	–	–	0.3190	0.3897
27.	MAE_{ex}	–	–	0.2716	0.2823
28.	$PRESS_{ext}$	–	–	1.0175	1.5185
29.	r^2_{ex}	–	–	0.7473	0.7231
30.	Q^2_{F1}	–	–	0.7724	0.6757
31.	Q^2_{F2}	–	–	0.7387	0.6430
32.	Q^2_{F3}	–	–	0.7593	0.6362
33.	CCC_{ex}	–	–	0.8369	0.8023
34.	r^2-*ExPy*	0.8068	0.7858	0.8060	0.7811
35.	r'^2_o	0.7671	0.7391	0.7678	0.7292
36.	k'	0.9980	0.9978	0.9983	0.9978
37.	$1 - (r^2/r'^2_o)$	0.0493	0.0595	0.0474	0.0665
38.	r'^2m	0.6460	0.6159	0.6484	0.6031
39.	R^2_o	0.8067	0.7854	0.8057	0.7809
40.	k	0.9999	0.9999	0.9996	0.9999
41.	$1 - (r^2 - ExPy/r^2_o)$	0.0002	0.0005	0.0003	0.0003
42.	r^2m	0.7972	0.7706	0.7930	0.7697

CV and external validation) indicates that the models have statistical acceptability. The high value of internal validation parameters r^2_{cv} (Q^2loo) and Q^2_{LMO} indicates that the derived models are statistically robust. Models 3 and 4 possess high external predictive ability as indicated by high value of CCC_{ex} (> 0.80); this is further supported by high values of Q^2_{F1}, Q^2_{F2}, and Q^2_{F3} (> 0.60). The high predictive ability is vindicated by a high value of r^2_{ex} for Models 3 and 4.

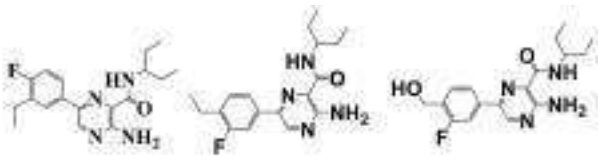
Table 3. Experimental and predicted pEC_{50} by various models along with the status of the molecule.

S.N.	Exp. pEC_{50}	Status for model 1 and 2	Pred. model 1	Pred. model 2	Status model 3	Pred. model 3	Status model 4	Pred. model 4
1	6.3100	Training	5.9519	6.0187	Training	5.9383	Training	5.9561
2	5.5850	Training	5.5679	5.5052	Training	5.5152	Prediction	5.4923
3	6.5850	Training	6.6599	6.5323	Training	6.6100	Training	6.4552
4	6.4950	Training	6.6220	6.5323	Training	6.5810	Training	6.4337
5	5.7700	Training	5.4075	5.5052	Training	5.3920	Training	5.4370
6	6.2760	Training	6.0342	6.0187	Prediction	6.0014	Training	5.9615
7	5.1370	Training	5.5607	5.0451	Training	5.5096	Prediction	5.2072
8	5.5850	Training	5.3093	5.5052	Training	5.3166	Training	5.5381
9	5.5230	Training	5.5121	5.5052	Training	5.4723	Training	5.5824
10	5.2150	Training	5.4076	5.5052	Training	5.3921	Training	5.1697
11	5.3370	Training	5.2272	5.5052	Prediction	5.2536	Prediction	5.1611
12	6.1250	Training	6.3324	6.4226	Training	6.3420	Training	6.4218
13	5.9590	Training	5.8078	6.0187	Training	5.8276	Training	5.9913
14	5.2680	Training	5.6895	5.5586	Prediction	5.7368	Training	5.4268
15	6.0510	Training	5.5574	5.5586	Training	5.6354	Training	5.6678
16	5.0000	Training	5.3445	5.5586	Training	5.4720	Training	5.7388
17	5.9210	Training	5.6280	6.0187	Training	5.6895	Training	6.0005
18	6.4560	Training	6.0655	6.0187	Prediction	6.0255	Prediction	6.0356
19	6.0860	Training	6.2159	6.2206	Training	6.1967	Prediction	6.1824
20	6.3190	Training	5.9965	6.0187	Prediction	5.9724	Training	5.9669
21	6.2440	Training	5.9618	6.0187	Training	5.9458	Training	5.9711
22	6.3870	Training	5.9697	5.5586	Training	5.9519	Training	5.7853
23	6.3470	Training	5.9905	6.0187	Training	5.9679	Prediction	5.3715
24	5.9590	Training	6.1657	6.0187	Training	6.1024	Training	5.9481
25	6.7700	Training	6.6703	6.7193	Training	6.6757	Training	6.7215
26	5.5690	Training	5.5158	6.0187	Prediction	5.6035	Training	5.9775
27	6.3980	Training	6.5026	6.4226	Training	6.4727	Training	6.4026
28	6.1670	Training	5.9992	6.0187	Training	5.9745	Training	5.9535
29	5.6580	Training	5.9637	6.0187	Training	5.9473	Training	5.9717
30	5.8860	Training	5.9366	6.0187	Prediction	5.9265	Training	5.7398
31	5.3470	Training	5.9654	5.5586	Training	5.9486	Training	5.3967
32	5.5380	Training	6.1523	6.0187	Training	6.0921	Training	5.9454
33	5.3280	Training	5.8321	5.5586	Prediction	5.8463	Prediction	5.5336
34	5.4270	Training	5.8992	5.5586	Training	5.8978	Training	5.9472
35	5.5690	Training	5.5359	5.5586	Training	5.6189	Training	5.9876
36	6.7700	Training	6.5957	6.5323	Training	6.5607	Training	6.4788
37	6.9590	Training	7.2413	7.2328	Training	7.2423	Training	7.2173
38	6.3190	Training	6.1893	6.5323	Training	6.2488	Prediction	6.4349
39	7.0970	Training	6.9895	6.9361	Training	6.9748	Training	6.8834
40	7.6020	Training	7.5257	7.5418	Training	7.5540	Training	7.5331
41	7.0000	Training	6.9134	6.7342	Training	6.8605	Training	6.7013
42	6.5850	Training	6.7637	6.9361	Prediction	6.8015	Training	6.9037
43	6.4440	Training	6.4919	6.5323	Training	6.4811	Training	6.4471
44	6.1140	Training	6.2654	6.5323	Training	6.3072	Training	6.4492
45	6.6580	Training	6.8804	6.9361	Training	6.8910	Training	6.8946
46	6.6990	Training	6.7132	6.5323	Training	6.6509	Prediction	6.5316
47	7.4560	Training	7.2735	7.2328	Training	7.2670	Training	7.2462
48	7.1490	Training	7.0749	6.9361	Training	7.0404	Training	6.9132
49	7.6200	Training	7.5350	7.5418	Training	7.5612	Training	7.5651
50	7.2440	Training	7.0186	6.7342	Prediction	6.9413	Prediction	6.7414
51	6.8240	Training	6.8358	6.9361	Training	6.8568	Training	6.9291
52	6.6200	Training	6.5221	6.5323	Training	6.5043	Training	6.4587
53	6.3010	Training	6.3190	6.5323	Training	6.3483	Training	6.4570
54	6.9590	Training	6.9099	6.9361	Training	6.9137	Training	6.9055

QSTR model

The derived QSTR model along with its statistical parameters is as follows:

$$pEC_{50} = + 1.266\ (\pm\ 1.401) + 0.268\ (\pm\ 0.107) * C_don_7A - 0.305\ (\pm\ 0.153) * RDF135s$$



pEC_{50}: Model-3 (μM):	0.052	0.088	0.094
Model-4 (μM):	0.048	0.078	0.096
QSTR Model (μM):	309.72	79.23	1499.85

Figure 3. Plausible 6-arylpyrazine-2-carboxamide derivatives with low toxicity (predicted by the QSTR model) and high activity (predicted by models 3 and 4).

N_{tr} = 13, Q^2_{loo} = 0.675, r^2_{tr} = 0.824, r^2_{adj} = 0.789, K_{xx} = 0.089, ΔK = 0.366, $RMSE_{tr}$ = 0.081, $RMSE_{cv}$ = 0.109, F = 23.399, CCC_{tr} = 0.904, CCC_{cv} = 0.832, MAE_{tr} = 0.064, MAE_{cv} = 0.087, RSS_{tr} = 0.084, $PRESS_{cv}$ = 0.155, s = 0.092

From the various statistical parameters, it is clear that the developed QSTR model is statistically robust with acceptable predictive ability, and satisfies the threshold values for many statistical parameters. The descriptor C_don_7A stands for the presence of a donor atom and carbon atom within 7 Å of each other. The positive coefficient for C_don_7A indicates that the presence of the donor atom and carbon atom within 7 Å of each other has strong correlation with the toxicity. RDF135s, a radial distribution function descriptor, which stands for radial distribution function – 135 / weighted by relative I-state, has negative correlation with toxicity. Its value must be lowered to reduce the cytotoxicity. The molecular descriptor values have been tabulated in Table S3 in the online supplementary material.

To summarize, QSA(T)R analysis reveals that for better *T. brucei* inhibitory activity and reduced toxicity the following 6-arylpyrazine-2-carboxamide derivatives could be plausible synthetic targets (see Figure 3).

Conclusions

In conclusion, the QSAR analysis reveals that the anti-HAT activity of 6-arylpyrazine-2-carboxamides has correlation with the frequency of occurrence of C and O at a topological distance of nine and the *N-sec*-butylformamide fragment. The QSA(T)R models are statistically robust with high external predictive ability. In addition, the idea of developing multiple QSAR models helped in identifying more significant descriptors. The developed models could be useful for future optimization of lead candidates.

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Synthesis, Characterization and Antimicrobial Activity of Newly Substituted 3-Aroyl Flavanones

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ABSTRACT

One of the intention of medicinal chemistry research is to develop compounds that show desirable biological activity and easily accessible. Newly substituted 3 Aroyl flavanones were synthesised by using β- Diketones. The structure of compounds were elucided by specral analysis (IR and NMR). The synthesised compounds were screened for their amtimicrobial activity.

Keywords: 3-aroyl flavanone, β- Diketone, antimicrobial activity.

INTRODUCTION

Flavanoids are naturally occurring polyphenolic compounds with flavones nucleus having anti-oxidant, anti-tumor, anti-ulcer, anti-inflammatory activities. They are available as flavanone, flavanol, isoflavane ,flavones and their derivatives. The flavanoides basically possess 15 carbon skeleton (C6-C3-C6). Flavanoides are mainly found in onions, apples, red wine, blueberries, grapes and tea (Bylka *et al*., 2004). Flavanones are the important class of flavanoids containing a 2-phenyl-benzopyran-4-one skeleton, Flavanones are commonly found in various citrus fruits and vegetables.[1-3]Synthetic flavanones have attracted considerable attention because of their various pharmacological properties including antifungal[4,5], antibacterial[4,6,7], analgesic[7], antioxidant[7].

MATERIALS AND METHODS

All the laboratory chemicals and solvents required for the study were of highest purity commercially available. Melting points of all synthesised compounds were determined by melting point apparatus. The purity of synthesised compounds was checked by Thin layer chromatography on silica –G layers. IR spectra were recorded on FTIR spectrophotometer using KBR pallets. NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer.

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Preparation of 5-chloro-2-hydroxy-4-methyl acetophenone (1)

p-chloro -m-cresyl acetate was prepared by acetylation of p-chloro-m-cresol. Then by Fries migration 5-chloro-2-hydroxy-4-methyl acetophenone was obtained.

Preparation of substituted 2-benzoyloxy acetophenones (2 a-b)

5-chloro- 2-hydroxy-4-methyl acetophenone (1) (0.04 mol) and aromatic carboxylic acid (0.05 mol) were dissolved in pyridine and $pocl_3$ is added drop by drop with constant stirring till the viscous mass is obtained. Maintain the temperature below 10^0c during the addition of $pocl_3$ to the reaction mixture. The reaction mixture is allow to stand for overnight at room temperature .The reaction mixture is decomposed by 10% HCl. The product thus separated was filtered, washed with water followed by sodium bicarbonate (10% solution) and then again washed with water. The solid product was crystallised from ethanol to obtained corresponding substituted 2-benzoyloxy acetophenones.

5-chloro-2-(4' chloro benzoyloxy)-4-methyl acetophenone (2a) was prepared by above method by using 4-chloro benzoic acid. Similarly 5-chloro-2-(4' methoxy benzoyloxy) -4-methyl acetophenone (2b) was prepared by using p-methoxy benzoic acid.

Preparation of 1-(2'-hydroxy phenyl)-3-phenyl propan-1,3-diones (3 a-b)

2-substituted benzoyloxy acetophenones (2a-b) (0.05 mol) was dissolved in dry pyridine (40 ml) . The solution was warmed up to about 60^0c and pulverised KOH (0.15 mol) was added slowly with constant stirring. After four hours the reaction mixture was acidified by adding ice cold dilute HCl (1:1). The solid product thus separated was filtered, washed with sodium bicarbonate solution (10%) and finally with water. It is then crystallised from ethanol acetic acid mixture to get 1-(2'-hydroxy phenyl)-3-phenyl propane 1,3--diones (3 a-b)

Preparation of some new substituted 3-aroyl flavanones (4 a-d)

Under microwave irradiation

Synthesis of flavanone was carried out by mixing appropriate amount of 1-(2'-hydroxy phenyl)-3-phenyl propane-1,3-diones (3 a-b) (2.69 m. mol) and aromatic aldehydes (2.69 m. mol) in presence of catalytic amount of aqueous KOH in methanol and irradiating in microwave at 100 W for two minutes. The reaction mixture was cooled, poured into crushed ice and then conc. HCl was added. The mixture was left to stay at 2-3^0c overnight and the separated solid was collected by filtration, washed with water and recrystalized from methanol to give desired product.

2 (4' chloro)-3-(4'-chloro benzoyl)-6-chloro-7-methyl flavanone (4a) was prepared by above method by using 1 -(2'hydroxy-4'methyl-5' chloro phenyl)-3(4' chloro phenyl) propane 1-3-dione (3a) and p-chloro benzaldehyde. 2 (4' methoxy)-3-(4'-chloro benzoyl)-6-chloro-7-methyl flavanone (4b) was prepared by above method by using (3b) and p-methoxy benzaldehyde. Similarly 2 (4'chloro)-3(4'-methoxy benzoyl)-6-chloro-7-methyl flavanone (4c) and 2(2'chloro)-3(4'methoxy benzoyl)-6-chloro-7 methyl flavanone (4d)were prepared

by using 1-(2'hydroxy -4'methyl-5' chloro phenyl)-3(4'methoxy phenyl) propane 1-3-dione (3b) and p-chloro benzaldehyde and o-chloro benzaldehyde respectively.

Table 1: Chemical data of substituted acetophenones and diones

Compound code	R_1	R_2	Mol. Formulae	M.P.(^{0} C)	Yield (%)
2a	Cl	H	$C_{16}H_{12}Cl_2O_3$	120	63%
2b	OCH_3	H	$C_{17}H_{15}ClO_4$	80	50%
3a	Cl	H	$C_{16}H_{12}Cl_2O_3$	162	72%
3b	OCH_3	H	$C_{17}H_{15}ClO_4$	142	57%

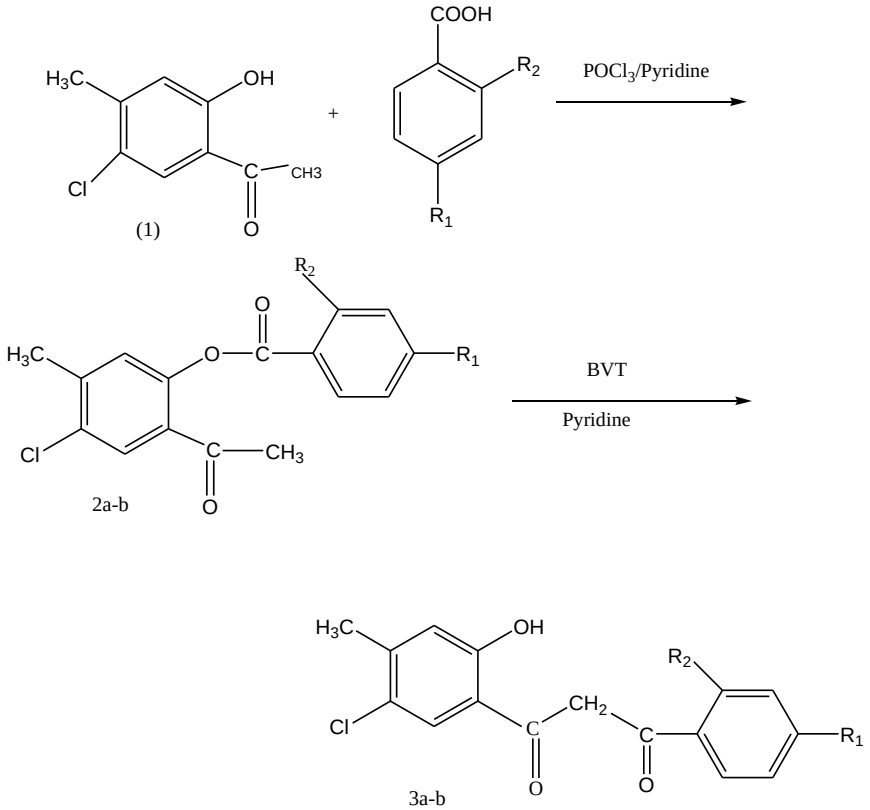


Fig.1: Experimental scheme for the synthesis of 1-(2'-hydroxy phenyl)-3-phenyl propane-1,3-diones (3 a-b)

Table 2: Chemical data of newly synthesised flavanones

Compound code	Name of compounds	Mol. Formulae	M.P (^{0}c)	% Yield
4a	2 (4' chloro)-3-(4'-chloro benzoyl)-6-chloro-7-methyl flavanone	$C_{23}H_{15}O_3Cl_3$	120	71%
4b	2 (4' methoxy)-3-(4'-chloro benzoyl)-6-chloro-7-methyl flavanone	$C_{24}H_{18}O_4Cl_2$	130	61%
4c	2 (4'chloro)-3(4'-methoxy benzoyl)-6-chloro-7-methyl flavanone	$C_{24}H_{18}O_4Cl_2$	145	55%
4d	2(2'chloro)-3(4'methoxy benzoyl)-6-chloro-7 methyl flavanone	$C_{24}H_{18}O_4Cl_2$	152	59%

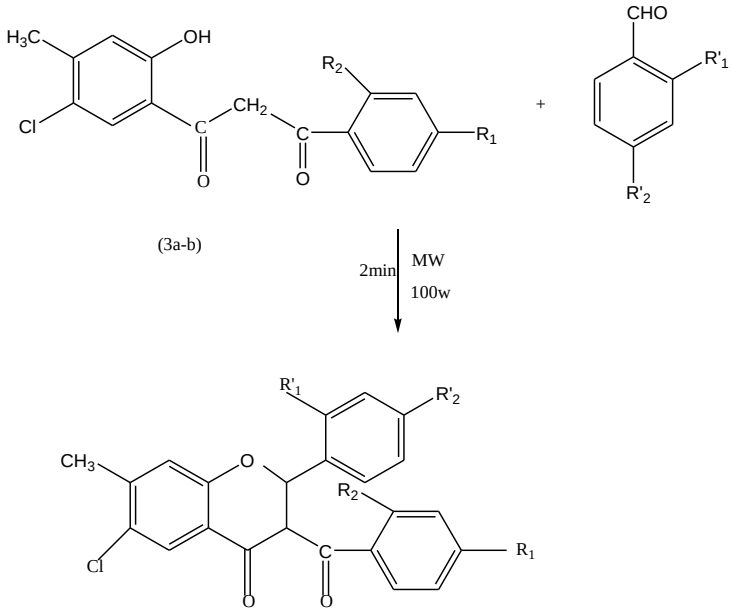


Fig.2: Experimental scheme for the synthesis of substituted 3-aroyl flavanones (4 a-d).

Spectral data of flavanones

Spectral data of 4a:

IR: 3071 cm^{-1} (Aromtic C-H stretch), 1748 cm^{-1}(C=O stretch), 1498 cm^{-1} (Aromatic C=C stretch), 2948 cm^{-1}(C-H stretch of methyl group), 1197 cm^{-1}(C-O-C stretch), 796 cm^{-1} (Aromatic substitution C-Cl), H NMR: δ 2.38 (S, 3H of CH_3), δ 4.5 (S, 1H of CH attached to C=O), δ 1.2(S,1H of CH attached to O), δ 6.8-8.0 (m,10H of Ar-H), δ 11.9 (tautomerism).

Spectral data of 4b:

IR: 3053 cm^{-1} (Aromtic C-H stretch), 1691 cm^{-1}(C=O stretch), 1567 cm^{-1} (Aromatic C=C stretch), 2970 cm^{-1}(C-H stretch of methyl group), 1196 cm^{-1}(C-O-C stretch), 795 cm^{-1} (Aromatic substitution C-Cl), H NMR: δ 2.38 (S, 3H of CH_3), δ 4.6 (S, 1H of CH attached to C=O), δ 1.3(S,1H of CH attached to O), δ 3.8 (S,3H of O CH_3), δ 6.6-7.8 (m,10H of Ar-H), δ 11.8 (tautomerism).

Spectral data of 4c:

IR: 3017 cm^{-1} (Aromtic C-H stretch), 1748 cm^{-1}(C=O stretch), 1565 cm^{-1} (Aromatic C=C stretch), 2840 cm^{-1}(C-H stretch of methyl group), 1205 cm^{-1}(C-O-C stretch), 794 cm^{-1} (Aromatic substitution C-Cl), H NMR: δ 2.38 (S, 3H of CH_3), δ 4.5 (S, 1H of CH attached to C=O), δ 2.4(S,1H of CH attached to O), δ 3.8 (S,3H of O CH_3), δ 6.6-7.9 (m,10H of Ar-H), δ 11.8 (tautomerism).

Spectral data of 4d:

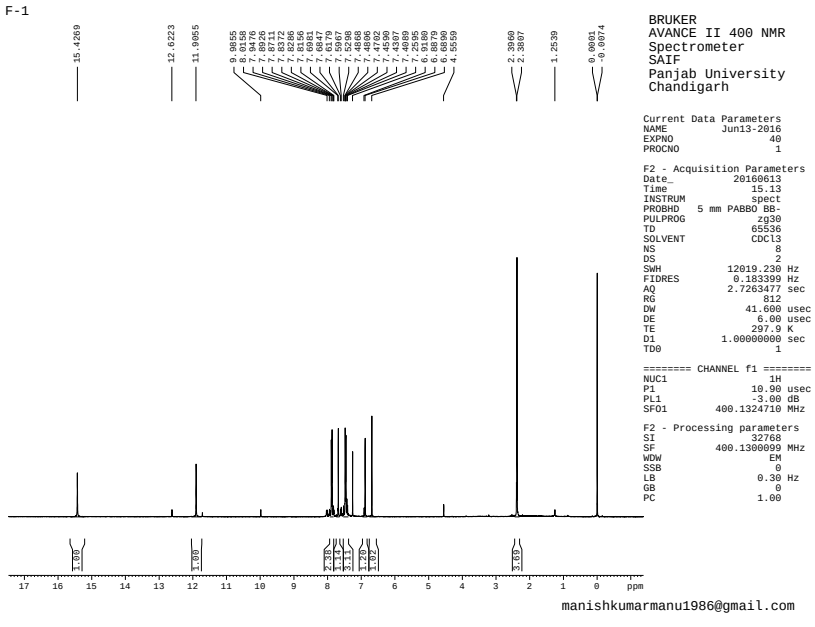
IR: 3065 cm^{-1} (Aromtic C-H stretch), 1737 cm^{-1}(C=O stretch), 1612cm^{-1} (Aromatic C=C stretch), 2995cm^{-1}(C-H stretch of methyl group), 1179 cm^{-1}(C-O-C stretch), 729 cm^{-1} (Aromatic substitution C-Cl), H NMR: δ 2.39 (S, 3H of CH_3), δ 4.5 (S, 1H of CH attached to C=O), δ 3.1(S,1H of CH attached to O), δ 3.8 (S,3H of O CH_3), δ 6.6-7.9 (m,10H of Ar-H), δ 12.5 (tautomerism).

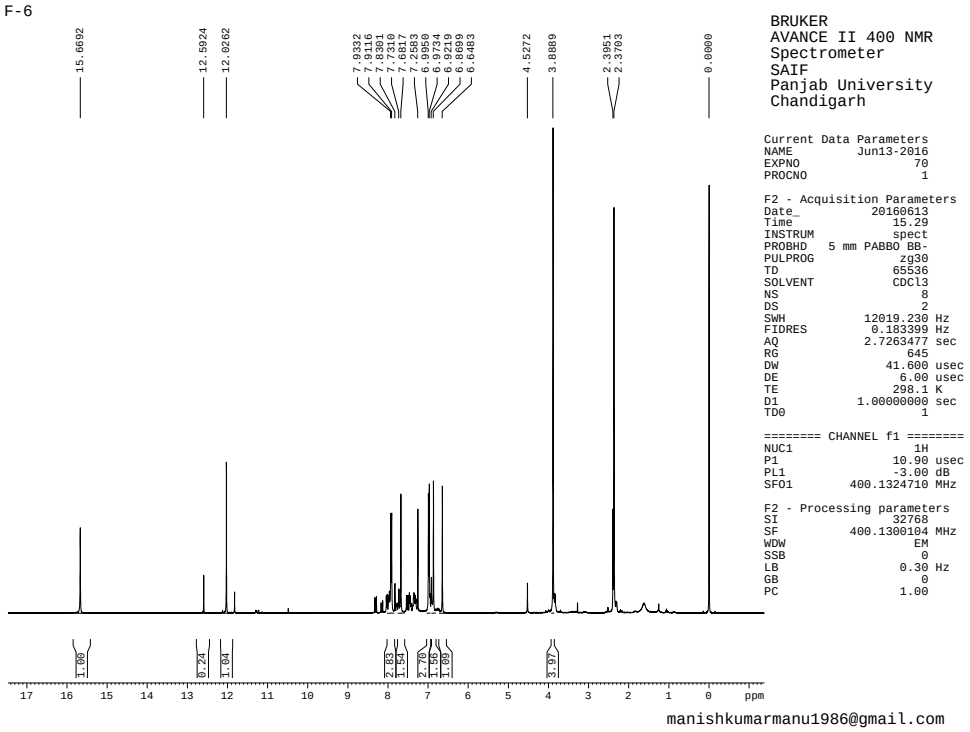
Antibacterial activity

All the synthesised flavanones were screened for their antibacterial activity against S. Aureus, E. Coli and S. typhi using ciprofloxacin as a standard drug. Agar diffusion method was employed to study the activity. Initially, the stock culture of bacteria were revived by inoculating on broth media and grown at 37^0c for 18 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 hr. old culture and spread evenly on the plate. After 20 min, the wells were filled with the compound and antibiotic at different concentrations. All the plates were incubated at 37^0c for 24 hr. and the diameter of inhibition zone were noted.

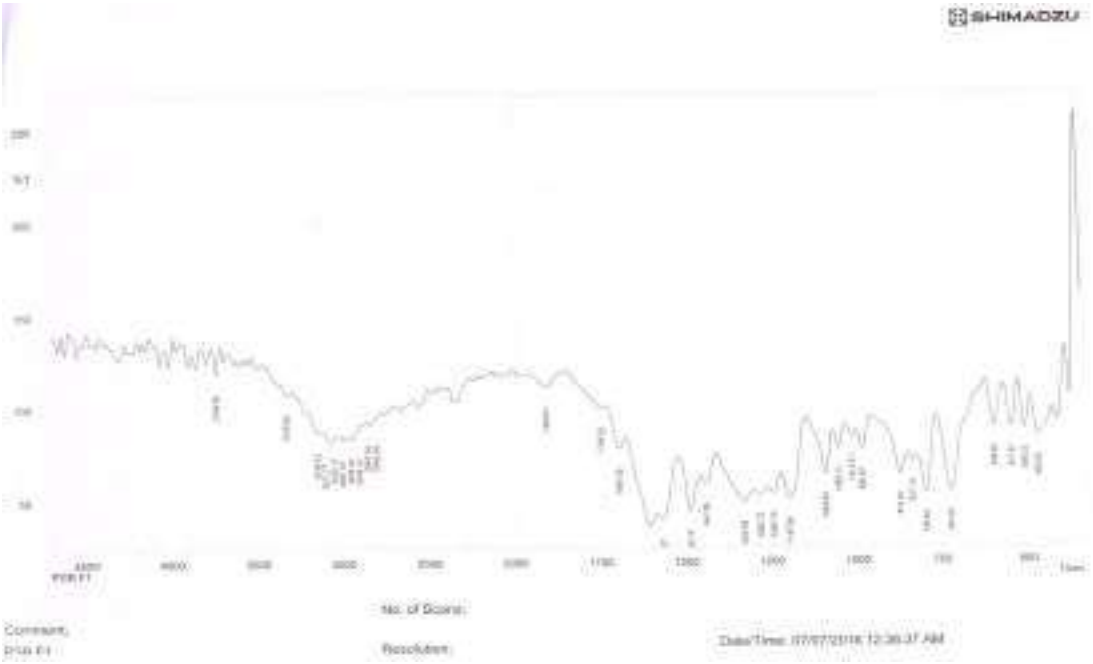
Table 3: Antimicrobial activity of newly synthesised flavanones(4a-d)

Sr. NO.	Compound codes	Antibacterial activity inhibition zone (mm)		
		S.aureus	E.coli	S.typhi
1	4a	7	10	7
2	4b	5	8	6
3	4c	5	5	6
4	4d	6	8	11





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RESULT AND DISCUSSION

In this work, total four flavanones namely 4a-d are synthesised from different aromatic aldehydes. All the synthesised flavanones were screened for their antibacterial activity against S. Aureus, E. Coli and S. Typhi. From the data on Antibacterial activities given in table 3, it was observed that, compound 4a showed moderate activity against E. Coli while week activity against S. Aureus and S. Typhi. Compound 4b showed moderate activity against E. Coli and week activity against S. Aureus and S.Typhi. Compound 4c showed comparatively week activity against all the three bacteria. Compound 4d showed moderate activity towards S.Typhi. While week activity against S. Aureus, E. Coli.

CONCLUSION

From the above data it is conclude that 4a is found to be lead compound against E. Coli. And 4d is found to be lead compound against S. Typhi, as these compounds showed moderate antibacterial activity against E. Coli and S. Typhi respectively.

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pH Metric Study of Synthesised Substituted Propane -1,3-Diones with CU(II), CO(II) and NI(II) Cataions at 0.1 M Ionic Strength

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ABSTRACT

A newly synthesised propane-1,3- dione (β- Diketones) are synthesised from substituted 2-hydroxy acetophenone and different sustituted benzoic acids and are characterised by IR and NMR spectra. The stability constants of ligand complexes with transition metal ions Cu(II), Co(II) and Ni(II) were determined pH metrically. The stability constants of ligands and metals have been calculated.

Keywords: IR and NMR spectra, ions Cu(II), Co(II) and Ni(II), pH metrically.

INTRODUCTION

pH metric technique is simple, rapid, most versatile, cheap and do not need any sophisticated instruments, which is very much used for investigating the physical properties such as proton ligand and metal ligand stability constants of organic drugs. This technique has been extensively used by J. Bjerrum[1] and Irving-Rossotti[2]. Propane-1,3- dione are very important compound in organic synthesis, because they exhibits some biological activity such as antioxidant[3], antitumor[4], antibacterial[5] activities. B- Diketones have gained a lot of interest due to their importance as good ligands[6] and its complexes have been widely used in diverse area.

MATERIALS AND METHODS

All the laboratory chemicals and solvents required for the study were of highest purity commercially available. Metal ion concentration were determined by using EDTA with suitable indicator and used as a chelating reagent. B- Diketones were synthesised by using Baker Venkatraman reaction. The purity of synthesised compounds was checked by thin layer chromatography on silica –G layers. IR spectra were recorded on FTIR spectrophotometer using KBR powder. NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer.

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SYNTHESIS OF B-DIKETONE

The synthesis involves following steps:

Preparation of 5-chloro-2-hydroxy-4-methyl acetophenone(1):

p-chloro-m-cresyl acetate was prepared by acetylation of p-chloro-m-cresol.

Then prepared p-chloro-m-cresyl acetate (50ml) and anhydrous aluminium chloride (120 g) were heated at 120^0c for 60 min. in an oil bath. The reaction mixture was cooled and decomposed with ice-cold water containing a little HCl (10%) to get Ketone.

Preparation of substituted 2-benzoyloxy acetophenones (2a,b,c) :

5-chloro-2-hydroxy-4-methyl acetophenone (1)(0.04 mol) and aromatic carboxylic acid (0.05 mol) were dissolved in pyridine and $pocl_3$ is added drop by drop with constant stirring till the viscous mass is obtained. Maintain the temperature below 10^0c during the addition of $pocl_3$ to the reaction mixture. The reaction mixture is allowed to stand for overnight at room temperature. The reaction mixture is decomposed by 10% HCl. The product thus separated was filtered, washed with water followed by sodium bicarbonate (10% solution) and then again washed with water. The solid product was crystallised from ethanol to obtained corresponding substituted 2-benzoyloxy acetophenones.

5-chloro-2-(4' chloro benzoyloxy)-4-methyl acetophenone (2a) was prepared by above method by using 4-chloro benzoic acid. 5 chloro- 2-(2'-4'dichloro benzoyloxy) -4-methyl acetophenone (2b) was prepared by using 2-4 dichloro benzoic acid. Similarly 5 chloro -2-(4' methoxy benzoyloxy) -4-methyl acetophenone (2c) was prepared by using p-methoxy benzoic acid.

Preparation of 1-(2'-hydroxy phenyl)-3-phenyl propan-1,3-diones (3 a,b,c) :-

2-substituted benzoyloxy acetophenones (2a-b) (0.05 mol) was dissolved in dry pyridine (40 ml). The solution was warmed up to about 60^0c and pulverised KOH (0.15 mol) was added slowly with constant stirring. After four hours the reaction mixture was acidified by adding ice cold dilute HCl (1:1). The solid product thus separated was filtered, washed with sodium bicarbonate solution (10%) and finally with water. It is then crystallised from ethanol acetic acid mixture to get 1-(2'-hydroxy phenyl)-3-phenyl propan-1,3-diones (3 a,b,c) .

Spectral data of β- diketones:

Spectral data of 3a (L_1):

IR: 3424 cm^{-1} (Phenolic -OH stretch), 3093 cm^{-1} (Aromtic C-H srretch), 1685 cm^{-1} (C=O stretch), 1611 cm^{-1} (Aromatic C=C stretch), 2927 cm^{-1}(C-H stretch of methyl group), 761 cm^{-1}(Aromatic substitution C-Cl), H NMR: δ 3.54 (S, 1H of OH), δ 2.49 (S, 3H of CH_3), δ 2.61 (S, 2H of CH_2), δ 6.8-8.1 (m,6H of Ar-H), δ 11.94 (tautomerism).

Spectral data of 3b (L_2):

IR: 3444 cm^{-1} (Phenolic -OH stretch), 3095 cm^{-1} (Aromtic C-H srretch), 1749 cm^{-1}(C=O stretch), 1610 cm^{-1} (Aromatic C=C stretch), 2924 cm^{-1}(C-H stretch of methyl group),734 cm^{-1}

(Aromatic substitution C-Cl), H NMR: δ 4.52 (S, 1H of OH), δ 2.37 (S, 3H of CH_3), δ 2.52 (S, 2H of CH_2), δ 6.6-8.1 (m,5H of Ar-H), δ 11.8 (tautomerism).

Spectral data of (L_3):

IR: 3470 cm^{-1} (Phenolic -OH stretch), 3005 cm^{-1} (Aromtic C-H srretch), 1686 cm^{-1}(C=O stretch), 1605 cm^{-1} (Aromatic C=C stretch), 2939 cm^{-1}(C-H stretch of methyl group),794 cm^{-1} (Aromatic substitution C-Cl), H NMR: δ 4.68 (S, 1H of OH), δ 2.44 (S, 3H of CH_3), δ 3.80 (S, 2H of CH_2), δ 3.89(S,3H of O CH_3), δ 6.8-8.0 (m,6H of Ar-H), δ 11.56 (tautomerism).

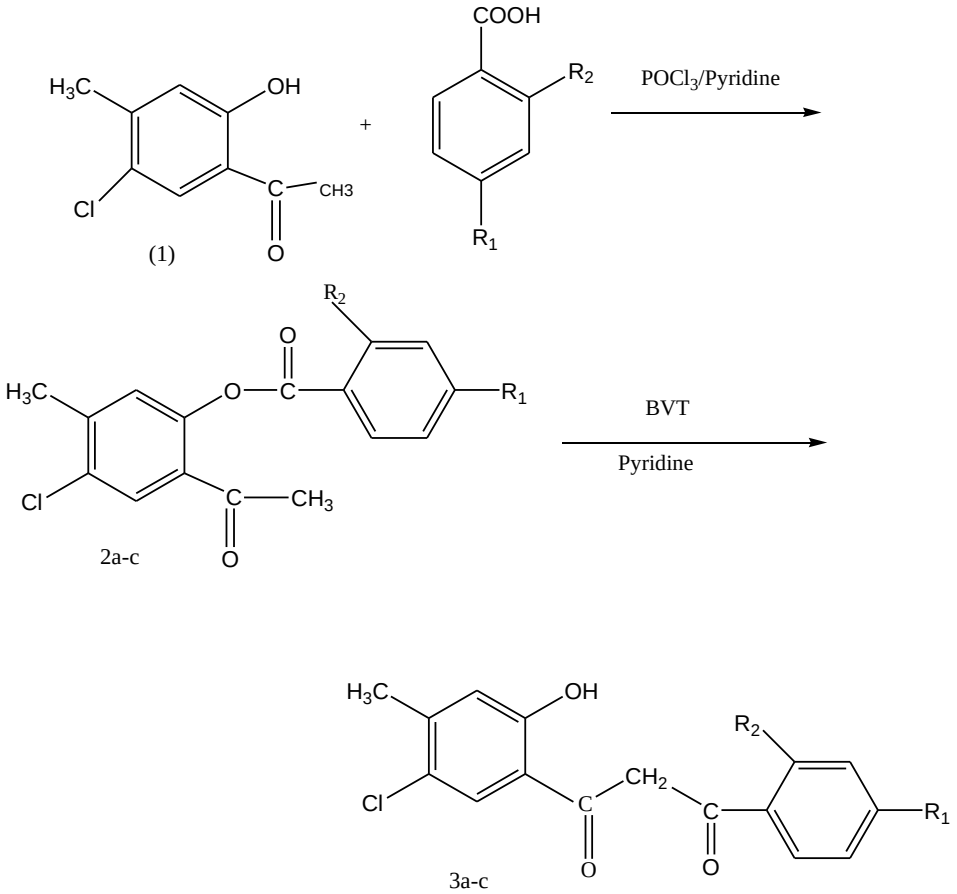


Fig.1: Experimental scheme for the synthesis of 1-(2'-hydroxy phenyl)-3-phenyl propan-1,3-diones (3 a-c)

Table 1: Physical data of β-diketones

Ligand	R_1	R_2	M.F	M.P °c	colour	%Yield
3a	Cl	H	$C_{16}H_{12}Cl_2O_3$	162-164	Yellow	72
3b	Cl	Cl	$C_{16}H_{11}Cl_3O_3$	125-126	Yellow	69
3c	OCH_3	H	$C_{17}H_{15}ClO_4$	142-144	Yellow	57

pH metric analysis :

The potentiometric titrations are performed by using systronic digital pH meter with accuracy in 0.01 unit with combined glass electrode. The electrode was activated by immersing 24 hours in 0.1 N hydrochloric acid and then 24 hours in distilled water. For smooth handling of electrodes all the precautions suggested by Albert and Sergent[7], Bates[8] were adopted. All titrations were carried out under inert atmosphere by bubbling nitrogen gas through an assembly. Instrument was calibrated with buffer solution of pH 7.00 and 9.20 at 30^0c before titration. The ligand solutions were prepared in 70% methanol-water which was used for further titrations i.e. without and with transition metals Cu(II),Co(II) and Ni(II). The 1-(2'-hydroxy phenyl)-3-phenyl propan-1,3-diones was monobasic acids having only one dissociable H^+ ion from OH group.

pH metric titration was utilized for determination of proton ligand stability constant and metal ligand stability constant. The respective pH metric data given in table 2 and table 3. The plot of pH vs. Volume of NaOH given in fig.2

RESULT AND DISCUSSION:

The dissociation constant of substituted diketones were determined pH-metrically. The ligands used in present work are monobasic acid having only one dissociable H^+ ion from –OH group and therefore represented as,

$$HL \rightleftharpoons H^+ + L^-$$

Proton ligand stability constant:

The titration curve of acid and ligand deviates at about pH- 3. The deviation between acid curve from ligand for all system showed the dissociation of H^+ ion from –OH group of ligands. The proton ligand formation number ($\bar{n}_A$)

$$\bar{n}_A = \gamma - \frac{(E°+N)\Delta V}{(V°+V1)T°L}$$

Where,

V^0 - Initial volume of solution

N - Normality of sodium hydroxide

T^0_L - Concentration of ligand

γ – Number of dissociable proton s from ligand

ΔV - volume of alkali consumed by acid and ligand on the same pH.

The pK values calculated from the formation curves between pH V_s $\bar{n}_A$. The half integral method was employed for the determination of proton ligand stability constant. The proton ligand stability constant were calculated from formation curve. The value of pH at $\bar{n}_A$ =0.5 corresponding to the value of pK.

Metal ligand stability constant:

Metal ligand formation number ($\bar{n}$) was calculated by following expression.

$$\bar{n} = \frac{(E+N)\Delta V}{(V°+V2)T°M}$$

The metal ligand formation curve were plotted between pH V_s $\bar{n}$. The metal ligand stability constant were determined by half integral methd.log K_1 and K_2 values are calculated from formation curves.

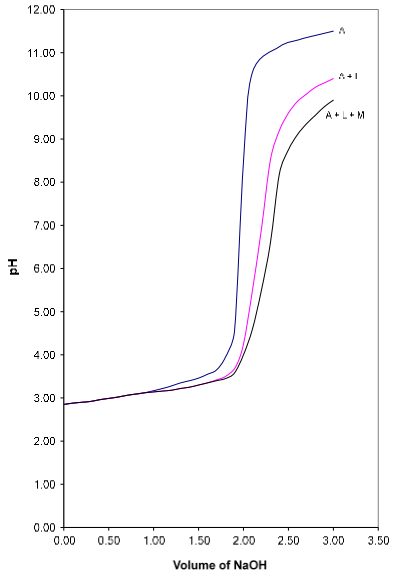


Fig. 2: Titration curve

Table 2: Proton-Ligand Stability Constants (pK)

No.	Ligands	pK Value
L_1	1-(5'-Chloro-2'-hydroxy-4'-methylphenyl)-3-(4'-chloro phenyl)-propane-1-3-dione	7.72
L_2	1-(5'-Chloro-2'-hydroxy-4'-methylphenyl)-3-(2',4'-dichloro phenyl)-propane-1-3-dione	7.58
L_3	1-(5'-Chloro-2'-hydroxy-4'-methylphenyl)-3-(4'-methoxy phenyl)-propane-1-3-dione	7.76

Table 3: Metal-Ligand Stability Constants (Log K)

System	Metal-Ligand Stability Constants (Log K)	
	Log K_1	Log K_2
L_1-Cu(II)	6.49	3.17
L_1-Co(II)	6.48	3.15
L_1-Ni(II)	7.03	4.17
L_2-Cu(II)	4.83	2.01
L_2-Co(II)	5.48	3.01
L_2-Ni(II)	6.34	3.50
L_3-Cu(II)	5.01	3.13
L_3-Co(II)	5.99	2.67
L_3-Ni(II)	6.52	1.68

CONCLUSION

The titration curve for all the system started from pH=3. This indicated the complex formation. Also change in the colour from yellow to red in the range 3to 10 during titration showed complex formation between metal and ligand. It is observed from the table- 3 that the difference between the values of log K_1 and K_2 is sufficiently large. This indicates stepwise complex formation between ligand and metal ion. For ligand-1,the difference between the values of log K_1 and K_2 is higher in Co(II) complex than Cu(II) and Ni(II).This indicated that Co(II) forms more stable complex with ligand-1 than Cu(II) and Ni(II).For ligand-2 the difference between the values of log K_1 and K_2 is higher in Ni(II) than Cu(II) and Co(II).And for ligand-3 also the difference between the values of log K_1 and K_2 is higher in Ni(II) than Cu(II) and Co(II).This indicates that ligand-2 and ligand-3 form more stable complex with Ni(II) than Cu(II) and Co(II).

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STUDY OF METAL-LIGAND STABILITY CONSTANTS OF La (III), Sm(III) & Nd(III) METAL ION COMPLEXES WITH SUBSTITUTED SCHIFF'S BASES AT 0.1 M IONIC STRENGTH PH- METRICALLY

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ABSTRACTS

In present work, the interaction of **La(III), Sm(III)** and **Nd(III)** metal ion with 6,6'((ethane1,2diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-methyl-2-nitrophenol) [$\mathbf{L_1}$] and 6,6'((ethane1,2diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis (4-chloro -2-nitrophenol [$\mathbf{L_2}$] was investigated at 0.1 M ionic strength (27 ± 0.1 ^{0}C) in 70% DMF- water mixture by Bjerrum method as adopted by Calvin and Wilson . It is observed that La (III), Sm(III) and Nd(III) metal ions forms 1:1 & 1:2 complexes with Schiff base ligand . The substituted Schiff bases show formation of simultaneous complexes. From estimated data (pK & log K), the effect of substituents were studied.

KEYWORDS: Schiff base, Metals ions La (III), Sm(III) and Nd(III) , DMF-Water mixture , Stability constant.

INTRODUCTION

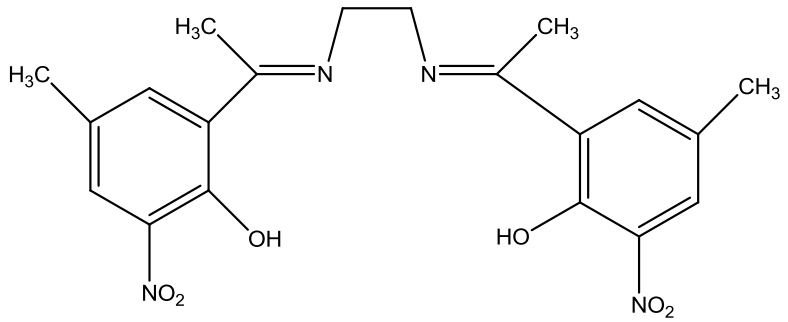
The stability of metal complexes with medicinal drugs plays a most important role in the biological & chemical activity.[1-2] Generally metal complexes play a very major role in biological process such as metalloproteins, metalloenzymes, storage, transport, detoxification etc. The physico-chemical properties of organic reagents are necessary to understand their nature, reactivity and analytical applicability. Schiff bases are versatile complexing reagents. Studies on the metal complexes of the Schiff bases require the knowledge of their ionization constants. The ionization constants in particular are essential for the metal-ligand stability constants and to have knowledge of selectivity of the relevant analytical reactions. Schiff's Bases and their derivatives possess effective antibacterial[3], antitumour[4], antimicrobial[5] properties. Schiff bases and their complexes shows a high variety of applications in biological clinical and analytical fields.[6-8] Narwade *et al*[9] have investigated the equilibrium constants of Cu(II) complexes with some substituted chalcones at 0.1M ionic strength pH metrically. Deshmukh has studied proton –ligands stability constants with dichlrosubstituted pyrazolines, is oxazolines, pyrazoles and isoxazoles.[10] Recently Khambre and Narwade have studied stability constant of Cu(II),Ni(II),Co(II) complexes of substituted schiff's bases.[11] Mandakmare *et al* have investigated the interaction between UO2 (II) and substituted coumarins at 0.1M ionic strength potentiometrically and spectrophotometrically.[12] Looking into wide range of activities of Schiff bases and their metal complexes, the present work describe the interaction between La(III), Sm(III) and Nd(III) metal ions with substituted Schiff base complexes in mixed solvent at 0.1M ionic strength that are studied pH-metrically by Calvin- Bjerrum titration technique.

EXPERIMENTAL

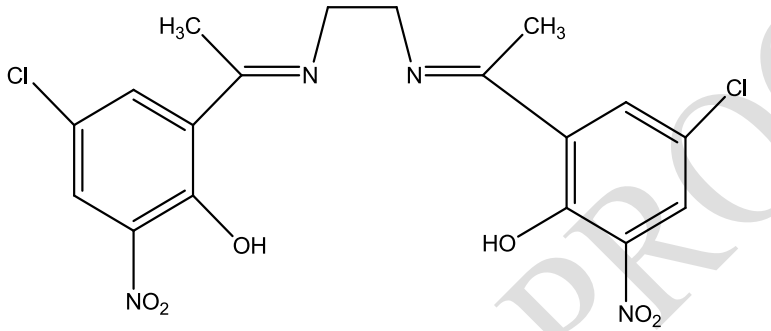
MATERIALS AND METHOD

Substituted Schiff's base ligand 6,6'((ethane1,2diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-methyl-2-nitrophenol [L_1] and 6,6'((ethane1,2diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis (4-chloro -2-nitrophenol [L_2] were synthesized in the laboratory by known literature method & their purity was checked by TLC on microscopic slides with silica gel-G layer thickness 0.3mm. The structure was confirmed by IR, NMR spectra and melting point. All the chemicals used were of AR grade. The solution of ligands was prepared in DMF. DMF (A.R.) was purified by the method described by Vogel.[13] All solutions were prepared in double distilled, CO_2 free water. Metal ion solutions were prepared by dissolving the requisite quantities of metal nitrate in double distilled water and standardized by using conventional procedures. Sodium hydroxide solution was prepared in deionised water and solution were standardized before use by known methods & used as afresh.

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L_1 : 6,6'-((ethane-1,2-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-methyl-2-nitrophenol)



L_2 : 6,6'-((ethane-1,2-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-chloro-2-nitrophenol)

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Measurements

All the pH measurements and titrations were carried out with Systronic microprocessor based pH meter with magnetic stirrer (accuracy ± 0.01 units) using glass electrode & calomel electrode at 27 ± 0.1 ^{0} C. pH meter was calibrated by standard buffer solution (pH 4.0,7.00 & 9.2).

The experimental procedure involved the titrations of

(i) Free acid HNO_3 (0.01 mol.dm^{-3})

(ii) Free acid HNO_3 (0.01 mol.dm^{-3}) and ligand (2 x 10 $^{-3}$ mol.dm^{-3})

(iii) Free acid + ligand (2 x 10 $^{-3}$ M) + metal ion titration (4 x 10 $^{-4}$M) with standard NaOH solution (0.13 mol.dm^{-3}) in presence of an inert atmosphere by bubbling a constant flow of nitrogen gas. The ionic strength of all these systems was maintained constant 0.1M by adding appropriate amount of KNO_3 solution.

RESULTS AND DISCUSSION

The substituted Schiff bases L_1 and L_2 having replaceable H^+ ion in phenolic hydroxy group may be ionized as i.e.

$$HL \text{ -------> } H^+ + L^-$$

The titration data were obtained used to constuct the formation curves [acid curve (A), acid + ligand curve (A + L) and acid + ligand + metal ion curve (A + L + M)] by plotting pH Vs volume of NaOH . It is observed from titration curves that for all systems ligand start deviating from the free acid curves at pH = 2.9 and deviation continuous up to pH = 12. The deviation presents dissociation of proton in Schiff base. The average number of proton dissociated from the ligand (n**A**) was determined from free acid and acid - ligand titration curves by employing the equation (1) proposed by Irving and Rossotti .(Table 1)

$$n_A = \gamma - \frac{(E^\circ + N) \times (V_2 - V_1)}{(V^\circ + V1) \times T^\circ_L} \quad \ldots\ldots\ldots\ldots (1)$$

Where, γ is the number of replaceable H^+ ions, V° is the total volume of the solution, E° & T°_L are the total concentrations of Nitric acid & ligand respectively, V_1 &V_2 are volume of alkali added to reach the same pH reading during titration of free acid and free acid plus ligand respectively.V_2-V_1 is the horizontal difference in the volume at the given pH and N is the concentration of sodium hydroxide (0.13 mol.dm^{-3}).

The pK_1 and pK_2values were determined from formation curves by half integral method (n**A** V/s pH) by noting the pH at which n**A** = 1.5 and n**A**= 0.5 respectively. The accurate values of pK_1 and pK_2 were calculated by point wise calculations which are presented in Table 1.

Table 1: Proton ligand formation number at (27 ± 0.1 ^{0} C) and at ionic strength μ = 0.1 mol dm-3

Medium: 70% DMF -water	**μ** =0.1M	**T ^{0}L** = 2 x 10 $^{-3}$M
T ^{0}M = 4 x 10 $^{-4}$M	**N** = 0.13N	**V_0** = 25 ml
E^o = 1 x 10^{-2}	**Temp.** = 27 ± 0.1 ^{0}C	

System: Ligand 1

pH	V_1	V_2	ΔV	nA
5.6	3.41	3.49	0.08	1.845125
5.8	3.45	3.56	0.11	1.797346
6	3.49	3.61	0.12	1.75834
6.2	3.5	3.69	0.19	1.633333
6.4	3.51	3.75	0.24	1.537005
6.6	3.54	3.82	0.28	1.460406
6.8	3.55	3.88	0.33	1.394273
7	3.58	3.93	0.35	1.356452
7.2	3.6	3.96	0.36	1.307692
7.4	3.63	4	0.37	1.289207
7.6	3.66	4.04	0.38	1.270761
7.8	3.69	4.08	0.39	1.252353
8	3.7	4.1	0.4	1.233449
8.2	3.74	4.15	0.41	1.215379
8.4	3.76	4.18	0.42	1.196801
8.6	3.79	4.22	0.43	1.178534
8.8	3.8	4.25	0.45	1.140625
9	3.83	4.29	0.46	1.122442
9.2	3.86	4.33	0.47	1.104297
9.4	3.88	4.36	0.48	1.085873
9.6	3.91	4.43	0.52	1.050723
9.8	3.95	4.48	0.53	0.999092
10	4	4.54	0.54	0.975862
10.2	4.03	4.58	0.55	0.957975
10.4	4.08	4.64	0.56	0.940853
10.6	4.12	4.69	0.57	0.92342
10.8	4.16	4.75	0.59	0.887174
11	4.21	4.83	0.62	0.832592
11.2	4.26	4.91	0.65	0.778195
11.4	4.35	5.05	0.7	0.688245
11.6	4.44	5.24	0.8	0.505435
11.8	4.5	5.43	0.93	0.266102
12	4.6	5.55	0.95	0.234797

System: Ligand 2

pH	V_1	V_2	ΔV	nA
5.2	3.35	3.4	0.05	1.902998
5.4	3.39	3.48	0.09	1.815643
5.6	3.41	3.53	0.12	1.767687
5.8	3.45	3.58	0.13	1.748682
6	3.48	3.62	0.14	1.729635
6.2	3.5	3.65	0.15	1.710526
6.4	3.52	3.7	0.18	1.652875
6.6	3.54	3.74	0.2	1.614576
6.8	3.55	3.8	0.25	1.538389
7	3.57	3.83	0.26	1.499475
7.2	3.6	3.87	0.27	1.480769
7.4	3.62	3.9	0.28	1.461915
7.6	3.65	3.95	0.3	1.424084
7.8	3.69	4	0.31	1.400716
8	3.7	4.05	0.35	1.349268
8.2	3.73	4.09	0.36	1.310825
8.4	3.76	4.15	0.39	1.269172
8.6	3.79	4.2	0.41	1.226742
8.8	3.82	4.24	0.42	1.198473
9	3.85	4.28	0.43	1.180243

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9.2	3.86	4.31	0.45	1.142412
9.4	3.9	4.37	0.47	1.105536
9.6	3.93	4.42	0.49	1.068441
9.8	3.96	4.47	0.51	1.031423
10	4	4.52	0.52	1.013793
10.2	4.05	4.58	0.53	0.996558
10.4	4.09	4.65	0.56	0.951217
10.6	4.13	4.7	0.57	0.92379
10.8	4.17	4.76	0.59	0.887556
11	4.23	4.85	0.62	0.83339
11.2	4.27	4.95	0.68	0.732241
11.4	4.35	5.05	0.7	0.688245
11.6	4.43	5.14	0.71	0.673123
11.8	4.5	5.23	0.73	0.638983
12	4.57	5.35	0.78	0.566921
12.2	4.7	5.49	0.79	0.537037
12.4	4.8	5.65	0.85	0.431208

Table 2: Determination of proton-ligand stability constant (pK) of Schiff base at 0.1 M ionic Strength

System	Constants (pK)			
	Half integral method		Pointwise calculation	
Schiff Base L1	pK_1	pK_2	pK_1	pK_2
	6.50	11.52	6.61	11.49
Schiff Base L2	7.18	12.42	7.07	12.32

Determination of Metal-Ligand Stability Constant (Log k) of Schiff base at 0.1 M ionic Strength

Metal-ligand stability constant of metal chelates with Schiff bases of L_1 and L_2 were determined by employing Calvin -Bjerrum pH- metric titration method as adopted equation (2) by Irving and Rossotti . The formation of chelate between metal ions with Schiff bases L_1 and L_2 were indicated by the significant separation starting from pH =2.9 for all complexes.

$$n = \frac{(E°+ N) X (V_3 - V_2)}{(V°+ V_2) x T°m} \quad \text{---------- (2)}$$

Where E° is the concentration of acid, N is the normality of the NaOH, T°m is the concentration of metal, V° is the total volume and V_3- V_2 is the horizontal difference in the volume at the given pH.

The metal ligand stability constants for La(III), Sm(III) and Nd(III) with Schiff base ligands L_1 and L_2 in 70% DMF-water can be found by the half integral method and pointwise calculation method (Table -3).

Table 3: Determination of LogK1 & LogK2 Value

Medium: 70% DMF-water **μ** = 0.1M **T ^{0}L** = 2 x $^{-3}$M
T ^{0}M = 4 x 10^{-4}M **N** = 0.13N **V ^{0}** = 25 ml
E ^{0} = 1 x 10^{-2} M **Temp.** = 27 ± 0.1^0 C

System	Metal ligand stability constants (log K)			
	Half Integral		Pointwise Calculation	
	Log K1	Log K2	Log K1	Log K2
La(III)-L1 Complex	9.38	7.39	9.18	7.29
Sm(III)-L1 Complex	9.12	7.52	8.908	7.379
Nd(III)-L1 Complex	9.48	7.53	9.383	7.390
La(III)-L2 Complex	3.39	3.11	3.610	3.047
Sm(III)-L2 Complex	3.62	3.01	2.816	2.748
Nd(III)-L2 Complex	4.68	3.41	4.307	3.494

Table: 4 Metal-Ligand Stability constants (Log K).

System	Log K1	Log K2	Log K1-Log K2	Log K1/Log K2
La(III)-L1 Complex	9.38	7.39	1.99	1.269
Sm(III)-L1 Complex	9.12	7.52	1.6	1.212
Nd(III)-L1 Complex	9.48	7.53	1.95	1.258

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La(III)-L2 Complex	3.39	3.11	0.28	1.090
Sm(III)-L2 Complex	3.62	3.01	0.61	1.202
Nd(III)-L2 Complex	4.68	3.41	1.27	1.372

CONCLUSION

In the present study, it is observed from titration curve that the extent of deviations confirms complete dissociation of –OH group .The deviation between acid+ligand curve and acid+ligand+metal curve indicates the commencement of complex formation. The change in colors during titration with respect to pH also indicates the complex formation between ligand and metal ions.

Proton-Ligand stability constant (pK)

It could be observed from Table No. 2 that there is good agreement of Proton-liand stability constants between half integral method and pointwise calculation method. The pK values for ligand depend on structures and resonance stabilization of ligands. The ligand L_2 shows higher pK values than L_1.This indicates that the chlorine atom present at para position to the phenolic hydroxy group, is exhibiting strong electron donating positive resonance effect than the electron donating hyperconjugation effect of methyl group in ligand L_1,in the DMF-water system. Symmetrical and asymmetrical structures for ligands are also responsible for the pK values for the ligands.

Metal-Ligand stability constant(Log K)

Determination of metal-ligand stability constants requires the accurate value of proton-ligand stability constant. Higher values of log K_1 and log K_2 showed that ligand are stronger chelating agents and vice versa. In the present investigation values of log K_1 and log K_2 have been calculated with half integral and pointwise calculation methods. The values obtained are in good agreement (shows in Table No. 3). The difference between log K_1 and log K_2 values are studied for all the systems and is represented in Table No.4.

The difference between log K_1 and log K_2 values are less. The difference between log K_1 and log K_2 values indicated the simultaneous formation of 1:1 and 1:2 complexes in the solution. They showed the linear relationships between log K and pK values of ligands suggesting identical binding sites in all ligands.

The higher value of ratio (Log K_1/ Log K_2) for La(III)-Ligand- L_1 & Nd(III)-ligand- L_1 & L_2 complex indicates the more stable simultaneous complex formation as compare to Sm(III) –Ligand-L_1 & L_2 and La(III)-Ligand L_2 complexes. Stability constants depend upon the size of cation.

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RESEARCH ARTICLE

A floristic survey of flowering plants from Vidyabharati Mahavidyalya Campus, Amravati (Maharashtra) India

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ABSTRACT

One of the grand tasks of current taxonomy is to prepare a checklist of plants of the globe. This work is largely based on collecting information from regional floras and databases. Till this date, the progress is relatively slow, as the number of common names, synonyms, poorly resolved aggregates is high. For this purpose regional flora, checklists and databases with reliable taxonomy and complete coverage of critically examined data are required. The majority of novelties come from the tropics; but certain areas remain poorly explored as well, and numerous species in these areas still await recognition. In the present work, the studied area is Vidyabharati Mahavidyalaya campus which is situated in the prime location of the Amravati city. Amravati is a district in the state of Maharashtra with its district headquarters situated at 20°55'33' N and 77° 45'53' E. The district is situated at 343m (1,125ft.) asl. The present study deals with the floristic diversity of campus in the former sense, i.e., the number of individual species in the area. The present paper attempts to highlight the diversity of vast plant resources of the campus in a conservation perspective. A total of 91 species of flowering plants are documented in which 43 were herbs, 25 shrubs, and 24 angiospermic trees distributed in 22, 13, and 12 families respectively.

Key words: taxonomy, explored, survey, diversity, conservation

INTRODUCTION

From the very beginning of inception of human beings on the earth man has relied on plants to fulfill his basic needs for his survival. Plants provide food, shelter and health. It is estimated

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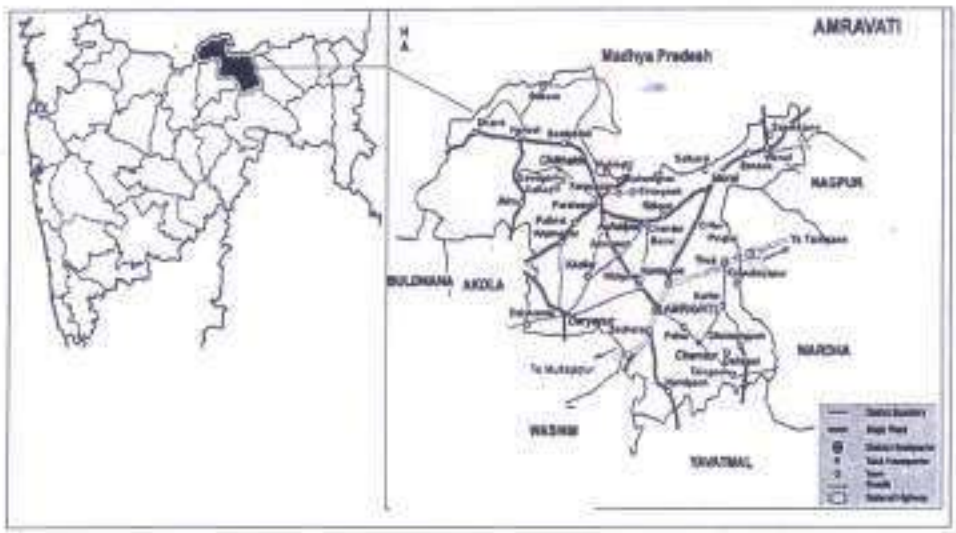
PRINCIPAL VIDYA BHARATI MAHAVIDYALAYA AMRAVATI

that about ten million species of plants inhabit the planet earth of which, however only 1.7 million species are known to science. It is therefore the need of the hour to explore the floristic wealth of the earth so as to know what we have. The plant diversity however is under serious threat due to various anthropogenic factors and many plant species are disappearing. Many species are becoming extinct even before their discovery. This scenario necessitates the urgent need of conservation of this diversity. To formulate various strategies for this purpose, the first important step is to explore and inventories the flora. Keeping this perspective in view the present studies were conducted to explore and inventorize the plant species. Therefore an attempt has been made to study the plant species present in the campus. Different Morphological characters are being studied like habit, height, leaf, inflorescence, flowers, and fruits etc representing diversity of plants in the campus of Vidyabharati Mahavidyalaya college.

Floristic diversity can be defined as the variety and variability of plants in a given region. It refers to the number of types or taxa in a given region or group. Floristic diversity can be measured at any level from overall global diversity to ecosystem, community, species, populations, individuals and even to genes within a single individual. The present survey deals with the floristic diversity of college campus in the former sense, i.e., the number of individual species in the area. The present paper attempts to highlight the diversity of vast plant resources of the college campus in a conservation perspective. In this survey we have focused only on the flowering plants of the campus Although the lower groups of plants (Pteridophytes, Lichens, Bryophytes) form a important part of vegetation and contribute significantly to the floristic diversity, they have been excluded in the present discussion.

Area of study:

Amravati is a district in the state of Maharashtra with its district headquarters situated at 20°55'33" N and 77° 45'53" E. The district is situated at 343m (1,125ft.) asl. The Amravati district has an area of 270 km². Vidyabharati College is situated in the prime location of the Amravati city. It has a set of beautiful buildings along with a play ground & Gardens situated over the 7.77 acres of a piece of a land. The total area under the gardens is about 30,000 sq.feet. The study area has well demarcated four seasons as a hot summer, heavily raining monsoon, a brief autumn and a mild winter. The area has sub tropical climatic conditions with ample rainfall in the monsoon resulting in a rich diversity of vascular plants.



Map: Amravati a district in the state of Maharashtra

MATERIAL AND METHODS

Plants were observed during all seasons of the year 2012-13. During observation field notes were recorded in field notebooks and voucher specimens of these species were collected. The collected specimens were processed using usual taxonomic methods of drying and mounting. The specimens were identified with the help of existing literature (Bentham & Hooker, 1862-83 ; Cooke, 1901-1908; Dhore, 1986; Naik, 1966,1977,1998; Singh *et al*.,2000; Singh *et al*; 2001) and have been preserved in the herbarium of Department of Botany, Vidya Bharati Mahavidyalya, Amravati.

RESULTS AND DISCUSSION

The Present study deals with the documentation of the total number of herbs, shrubs and angiospermic trees, which are the native of different countries. Some of these plants have been brought here from different areas of the country & cultivated over here in the garden, and some grow wildly in this area. A list of plant species in the catchment area starting by herbs, then shrubs, and at last angiospermic trees. A total of **91** species of flowering plants are documented in which **43** were herbs, **25** shrubs, and **24** angiospermic trees distributed in **22**, **13**, and **12** families respectively.

Table 1 : list of herbs

Sr. No.	Botanical Name	Family
1	*Vernonia cineria* (L.)Less.	Asteraceae
2	*Calendula officinalis* L.	Asteraceae
3	*Zinnia peruviana* (L)	Asteraceae
4	*Zinnia angustifolia* kunth.	Asteraceae
5	*Blainvillea acmella* L.	Amaranthaceae
6	*Aerva Lanata* (L.) Juss.	Amaranthaceae
7	*Achyranthus aspera* L.	Amaranthaceae
8	*Amaranthus poligonides* L.	Amaranthaceae
9	*Andrographis paniculata* (Burm.f.)Wall ex Ness	Acanthaceae
10	*Diplocyclous palmatus* L.	Cucurbitaceae
11	*Cocculus hirsutus* (L.) Deils	Menisparnaceae
12	*Oxalis corniculata* L.	Oxalideaceae
13	*Colocasia esculanta* (L.) Schott	Araceae
14	*Ocimum sanctum* L.	Lamiaceae
15	*Catharanthus roseus* (L.)	Apocynaceae
16	*Datura metal* L.	Solanaceae
17	*Withania somnifera* (L) Dunal.	Solanaceae
18	*Acalypha indica* L.	Euphorbiaceae
19	*Curcuma longa* L.	Zingiberaceae
20	*Zingiber officinale* Rosc.	Zingiberaceae
21	*Ipomoea cairica* (L.) Sweet.	Convolvulaceae
22	*Passioflora edulis* Sims.	Passifloraceae
23	*Aloe vera* L.	Liliaceae
24	*Asparagus racemosus* (L.) Willd.	Liliaceae
25	*Cissus qudrangularis* L.	Vitaceae
26	*Agave americana* (L.)A.L.Juss. ex Schutt	Agavaceae
27	*Hymenocallis littoralis* (Jacq.)	Amaryllidaceae

Table No.1 : Continued...

Sr. No.	Botanical Name	Family
28	*Jasminum auriculatum* Roxb.	Oleaceae
29	*Dianthus chinensis* L.	Caryophyllaceae
30	*Trigonella foenumgraecum* L.	Fabaceae
31	*Cynodon dactylon* (L.)Pers	Poaceae
32	*Dicanthium annulatum* (Hook.f.) Blatt. & Mc C.	Poaceae
33	*Lophopogon tridentatus* Hack.	Poaceae
34	*Andropogon pumilus* Roxb.	Poaceae
35	*Aristida hystrix* L.F.	Poaceae
36	*Chloris virgata* Swartz.	Poaceae
37	*Dactylotenium aegyptium* (L) P.Beauv.	Poaceae
38	*Eleusine indica*(L.)Gaertn.	Poaceae
39	*Setaria pumilla* (poir)R.	Poaceae
40	*Melanocenchris jacquemontii* Jaub.and Spach.	Poaceae
41	*Alpuda mutica*	Poaceae
42	*Eragrostis namaquensis* Schard var.*diplachnoides* (Steud)	Poaceae
43	*Eragrostis tanella*	Poaceae

Table No. 2: List of Shurbs

Sr. No	Botanical name	Family
1	*Hibiscus rosa-sinensis* L.	Malvaceae
2	*Abelmoschus moschatus* L.	Malvaceae
3	*Lawsonia inermis* L.	Lithraceae
4	*Murraya koenigii* (L.) Spr.	Rutaceae
5	*Citrus aurantiifolia* (Christm.) Sw.	Rutaceae
6	*Hamelia patens* Jacq.	Rubiaceae
7	*Ixora coccinea* L.	Rubiaceae
8	*Coffee arabica* Ritter Ron.	Rubiaceae
9	*Nyctanthes arbortristis* L.	Oleaceae
10	*Nerium oleander* L.	Apocynaceae
11	*Tabernaemontana divaricata* (L.) R. Br.	Apocynaceae
12	*Calotropis procera* (Ait) R. Br.	Asclepiadaceae
13	*Solanum nigrum* L.	Solanaceae
14	*Barleria cristata* L. var. *cristata*	Acanthaceae
15	*Adhatoda beddomei* Hong Gao	Acanthaceae
16	*Vitex trifolia* L.	Verbenaceae
17	*Lantana camara* L. var. *aculeatea*(L.) Mold	Verbenaceae
18	*Jatropha curcas* L.	Euphorbiaceae
19	*Ricinus communis* L.	Euphorbiaceae
20	*Acalypha wilkesiana* Muell. Arg.	Euphorbiaceae
21	*Euphorbia tithymaloides* L.	Euphorbiaceae
22	*Cajanus cajan*(L.)Millsp DC.nom. cons.	Fabaceae
23	*Calliandra calothyrsus* (Meisn.)	Fabaceae: Mimosoideae
24	*Indigofera tinctoria* L.	Fabaceae: Papilionaceae
25	*Punica granatum* L.	Punicaceae

Table No. 3: List of Angiospermic Trees

Sr. No	Botanical name	Family
1	*Azardirecta indica* A. Juss.	Meliaceae
2	*Ficus benghalensis* L.	Moraceae
3	*Ficus religiosa* L.	Moraceae
4	*Ficus glomerata* Roxb.	Moraceae
5	*Aegle marmelos* (L.) Corr.	Rutaceae
6	*Feronia limonia* L.	Rutaceae
7	*Mangifera indica* L.	Anacardiaceae
8	*Emblica officinalis* Gaertn.	Euphorbiaceae
9	*Psidium guajava* L.	Myrtaceae
10	*Santalum album* L.	Santalaceae
11	*Tectona grandis* L. f.	Verbenaceae
12	*Cocos nucifera* Linn.	Arecaceae
13	*Ziziphus mauritiana* L.	Rhamnaceae
14	*Butea monosperma* (Lam.) Taub.	Fabaceae
15	*Gliricidia sepium* (Jacq.)Walp.	Fabaceae
16	*Pongamia pinnata* (L.) pierre	Fabaceae



Catharanthus roseus



Hymenocallis littoralis



Calliandra calothyrsus



Nyctanthes arbortristis



Butea monosperma



Delonix regia



Eleusine indica



Themada quadrivalvis



Eragrostis namaquensis



Dianthus chinesis



Barleria cristata



Acalypha wilkesiana

Fig. 1:

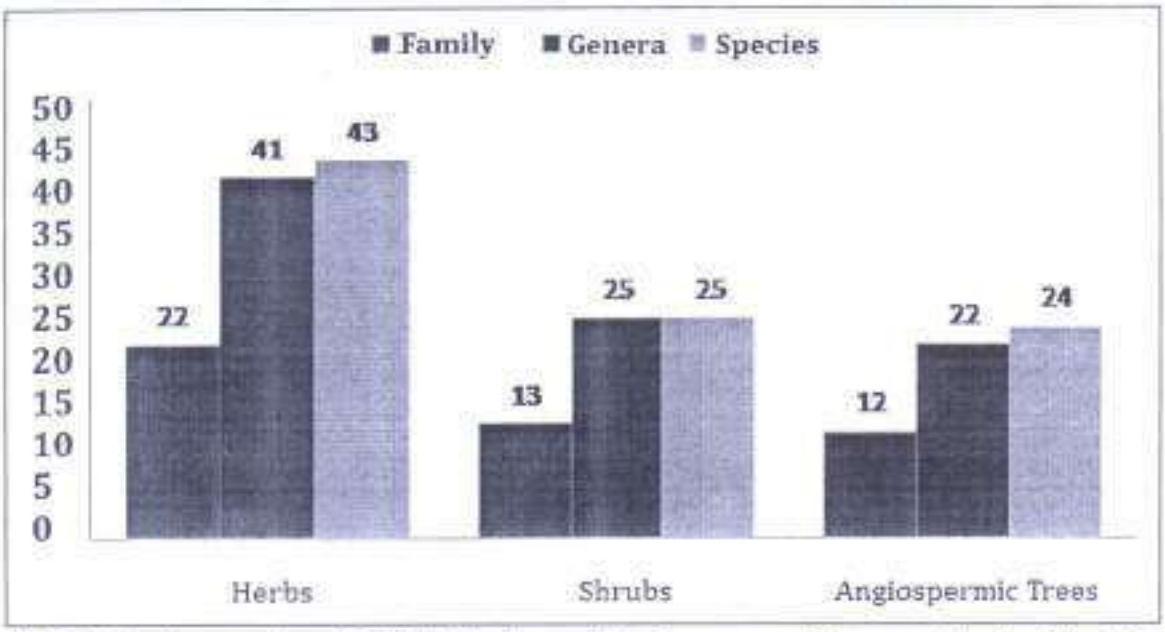


Fig. 2: showing number of Herbs, Shrubs, and Angiosperms with respect to their families, genera and species in the studied area

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प्रेषक
डॉ. सुखदेव ढाणके, 'सर्वमंगल', ४२ - सहजानंद नगर,
मोर्शी रोड, अमरावती. ४४४ ६०३

हा अंक संपादक, मुद्रक, प्रकाशक, पालक डॉ. सुखदेव ढाणके यांनी बोके प्रिंटर्स, गांधी नगर, अमरावती येथे छापून 'सर्वमंगल', ४२, सहजानंद नगर, मोर्शी रोड, अमरावती. ४४४ ६०३, येथे प्रसिद्ध केला.



ज्ञानपीठ या सर्वोच्च पुरस्काराने सन्मानित
डॉ. भालचंद्र नेमाडे

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केतन पिंपळापुरे यांच्या कवितेतील सामाजिकता आणि सौंदर्य

डॉ. गजानन बनसोड

आधुनिक मराठी काव्यविश्वातील प्रतिभावंत कवी म्हणून केतन पिंपळापूरे यांचा उल्लेख होतो. 'सूर्यकंकण', 'मार्शलरेस', 'डेमोफून', 'मकाबी' आणि 'हेमलॉक' या कवितासंग्रहातील कवितातून त्याच्या संवेदनशीलतेची व सर्जनशीलतेची साक्ष पटते. जीवनविषयक मूल्यसंघर्षाची जाण असणाऱ्या या कवीला समकालीन सामाजिक वास्तवाचे तर्कशुद्ध भान आहे. केतन आपल्या कवितेतून समताधिष्ठित कल्याणकारी राज्याची स्वप्ने लोकांच्या पुढ्यात ठेवतो. शब्दाला वाकविण्याची जबरदस्त ताकद या कवीजवळ असून तितकीच विवेकशील ऋजुता त्याच्या कवितेत जाणवते.

समाजजीवनात वावरतांना आलेल्या अनुभवाचं, पाहिलेल्या वास्तवातून आलेल्या अस्वस्थेतेचं प्रतिबिंब त्याच्या कवितेत उमटते. धकाधकीच्या काळातील बदलत्या सामाजिक प्रश्नांची उकल तो आपल्या कवितेत करतो आणि म्हणूनच कवी केतन पिंपळापुरे म्हणतो,

> ''मावळेल जिथे अंधार आणि प्रकाशेल आयुष्य नव्याने
> असे आपलेही एक क्षितिज असेल.'' (मार्शलरेस पृ. २२)

अशी समष्टीची संवेदना व्यक्त करतांना कवी कमालीचा आशावादी झालेला आहे. अस्पृश्य म्हणून ज्यांना हजारो वर्षापासून छळले, त्यांचे जगणे असह्य केले. अशा वेदनांकित जीवनातील काळोख नाहिसा व्हावा असे कविला वाटते. महात्मा फुले, शाहू महाराज व डॉ. आंबेडकरांच्या प्रेरणेने प्रेरित झालेला हा कवी म्हणतो,

> ''मी चैत्यभूमीच्या निद्रिस्त ज्वालामुखीच्या काळजावर
> हात ठेवून घेतली आहे टेनिस कोर्टाची शपथ
> आणि बाबासाहेबांच्या डोळ्यातील स्वप्नांच्या दिशेने
> मी दौडवित नेईन माझ्या युगाचा क्रांतिरथ'' (मार्शलरेस पृ. २१)

मानवी स्वातंत्र्याची बीजं ज्या फ्रान्सच्या भूमित रूजली. त्या मातीशी कवी आपली नाळ जोडतो. तिथल्या 'टेनिसकोर्टच्या शपथेची' आठवण करून देतो. युगपुरूष सिद्धार्थ गौतम बुद्धांपासून तर डॉ. बाबासाहेब आंबेडकरांपर्यंत मानवी स्वातंत्र्यांचा

पुरस्कार अनेक युगनायकांनी केला. तरीही विसाव्या शतकापर्यंत वर्णव्यवस्थेची पकड मजबूत राहिली. या व्यवस्थेने अस्पृश्यांचे अपरिमित नुकसान केले. परंतु डॉ. बाबासाहेब आंबेडकरांनी मानवमुक्तीचे लढे उभारले. संविधानातून समता, स्वातंत्र्य, न्याय, बंधुत्वतेचे मूल्य रूजविले, म्हणूनच कवीला डॉ. आंबेडकरांनी दाखविलेल्या स्वप्नांच्या दिशेने या युगाचा रथ पुढे न्यायचा आहे. कवी समस्त मानवाच्या दु:खमुक्तीच्या लढ्यांचा गौरव करतो.

समाज परिवर्तनाचा आग्रह धरणारी केतन पिंपळापुरेंची कविता आहे. तिच्यामध्ये वैश्विक सामाजिक भान आहे. हिटलर, मुसोलिन, स्टॅलिन, ग्लासनोस्त, पेरेस्त्रोईका, लेनिन ह्या पाश्चात्यांचा समाचार तो कवितेत घेतो. तो फक्त भारतातील वंचितांचे प्रश्न कवितेतून मांडत नाही. तर जागतिक मानवी जीवनातील शोषणाचे पडसादही त्यांच्या कवितेत उमटतात. आंबेडकरी समुदायांच्या सामाजिक जाणिवेच्या संदर्भात प्रा.रा.ग. जाधव म्हणतात की, ''सामाजिक जाणिवांची ही जन्मसिद्ध अंतसृष्टी नाना कळांची, नाना रूपांची आहे. तिच्यात इतिहास पुराणांचे जग जसे सामावते, तसेच सद्य:कालीन वास्तवही वावरते. तिच्याच दलित व्यक्तीची व्यक्ती म्हणून असणारी चित्रविचित्र अनुभव सृष्टी जशी आढळते. तशीच दलित दलितेतर संबंधातील सामाजिक ताणाबाणांची रहदारीही दिसते.''(१) मूळात माणूस ऐतिहासिक घटनांचा मागोवा घेत भविष्याचा वेध घेण्याचा प्रयत्न करतो. सद्याच्या वास्तववादी साहित्यात एकोणिसाव्या शतकातील प्रबोधन व विसाव्या शतकातील राजकीय, सामाजिक चळवळी याचे पडसाद उमटले दिसतात. कवी हा कार्यकर्त्यांची भूमिका वठवतो त्यामुळेच त्याच्या काव्यात सामाजिक जाणिवेचा आविष्कार होतो.

रिडल्स आणि नामांतर आंदोलनाच्या वेळी आंबेडकरी जनतेची झालेली गळचेपी कवी व्यक्त करतो. नामांतराच्या लढ्यात पोचिराम कांबळे, चंदरचा झालेला खून अशा घटना अजूनही घडतांना कविला दिसतात. खैरलांजीची धग शांत होत नाही तर खर्ड्याला शाळकरी विद्यार्थ्यांची हत्या घडते. जातियवादी मानसिकेतून, श्रमजीवी माणसांचा, वंचिताचा आवाज नेहमीच दडपल्या जातो. सत्ता आणि संपत्तीच्या बळावर माणूसकीचा मुडदा पाडल्या जातो. सद्य:स्थितीतील हे जळजळीत वास्तव कवी अधोरेखित करतो.

सिद्धार्थ गौतम बुद्धांनी अडीच हजार वर्षांपूर्वी जी धर्मचिकित्सा केली. मानवाचे मूल्य अंकित केले. तरीही धर्मग्रंथाच्या नावावर पुराणकर्त्यांनी विषमता टिकवून ठेवली. माणसांमाणसांत भेदाभेद केले. विषमतेमुळे शुद्र अतिशूद्रांचे हजारो वर्ष शोषण झाले.

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त्यांना मानवी अधिकार नाकारले गेले. जो ईश्वर शोषणाची व्यवस्था निर्माण करतो. त्या ईश्वराविषयी कवी केतन पिंपळापुरे प्रश्नचिन्ह उभे करतो. ईश्वर नावाची संकल्पना रूजविलेल्याच्या सडक्या, कुजलेल्या मेंदूची शवचिकित्सा करण्यासाठी कवी सज्ज झाला आहे. एका सजग कार्यकर्त्याची भूमिका निभावण्याचा प्रयत्न कवी करतो आहे. आंबेडकरी काव्यातील सामाजिकतेविषयी आपले मत नोंदवतांना, प्रा.रा.ग. जाधव म्हणतात की, ''मराठी साहित्यात सामाजिक जाणिवांचे सौंदर्य निर्माण करण्याची ताकद आज तरी फक्त दलित साहित्यिकांतच आहे, असे मला वाटते. कारण सामाजिक जाणिवांचा अस्सलपणा व सखोलता अनुभवण्याचा भोगवटा दलितांच्या वाट्याला आलेला आहे. तो मूलगामी व म्हणूनच विलक्षण सौंदर्यक्षम व सर्जनक्षम आहे.''(२)

कविला मानवी संवेदना बोथट होतांना दिसतात. सत्ता संपली आणि प्रतिष्ठेसाठी नीती, अनीतीचा व्यवहार होतांना दिसतो. तेव्हा उद्विग्न होऊन कवी म्हणतो,

''जात, धर्म, पंथ, संप्रदाय आणि वंशवादाच्या सूडचक्रात
भोळ्याभाबड्या अज्ञ पामरांना ओरबाडणाऱ्या
या रथयात्रा कुणाच्या?
महागाई, भूक, बेरोजगारी, लूट, दंगली आणि
छिनाल राजकारणासाठी चाललेल्या या मतयात्रा कुणाच्या?''
(मकाबी पृ. १५)

धर्मांध राजकारणामुळे वंचितांच्या आयुष्याचा वाळवंट होतांना कवी पाहतो, तेव्हा त्याचे मन गलबलून जाते. त्याला धर्मसंस्कृतीचे संदर्भ गडद होतांना दिसतात. गुलामगिरीतून मुक्ती मिळविण्यासाठी माणसांची चाललेली धडपड कवी पाहतो. ग्रंथपंथाच्या तार्किक घोटाळ्यात अडकलेल्या माणसाची सहीसलामत सुटका करण्याचा तो प्रयत्न करतो. ज्या महामानवांनी अमानुषतेच्या अरण्यातून सर्व शोषितांना मुक्त केले. त्यांना वंदन करतांना कवी म्हणतो,

''मी तथागतांच्या डोळ्यातील स्वप्नांचा राजहंस आहे
मी शील आहे, मी विवेक आहे, मी आहे अमर्याद करूणा
द्वेष, मत्सर, विकार, विकृती व हिंसेची तीव्र घृणा...
माझ्या स्पर्शाने पाषाणाचे होत असतात सुवर्णशिल्प
माझ्या अस्तित्वाने काळोखाचे साम्राज्य ठरते 'अल्प'
(मार्शलरेस पृ.१५)

केतन पिंपळापुरेंच्या कवितेतूनच त्याची भूमिका अधिकाधीक स्पष्ट होते. स्वत:ला कवी विश्वशांतीचा पहाटपक्षी म्हणतो व या शतकातल्या बांधावर करूणेचे झाड लावण्याची प्रतिज्ञा करतो डॉ. बाबासाहेब आंबेडकरांच्या समग्र समाजक्रांतीचे धम्मध्येय पूर्ण होऊ शकले नाही ही खंत कवी, 'मी तथागताच्या डोळ्यातील विश्वशांतीचा राजहंस आहे' या कवितेत मांडतो.

''आपण आपल्या खोपटात सूर्य बंदिस्त करू नये
दारं, खिडक्या उघडून प्रकाश बाहेर जाऊ द्यावा
प्रज्ञेचा झरा आपण आपल्यापूरता अडवू नये
कुण्या अंधारयात्रिकांना उजेड पिऊ द्यावा
आणि त्यांच्या तृप्त आयुष्याचा दुवा घ्यावा'' (सूर्यकंकण पृ. १०)

विचारसंपृक्त अशी वाक्यरचना केतन पिंपळापुरेंच्या कवितेची आहे. काही कवितेत पल्लेदार वाक्य असूनही त्या कवितेतील सौंदर्यात्मकता अबाधित राहते. कवी 'स्व' पेक्षा 'आम्ही' ची भाषा वापरतो. बाबासाहेबांनी दिलेला प्रज्ञेचा वारसा घराघरात पोहचविण्याचा इरादा कवी करतो. सर्वच अंधार यात्रिकांचे जीवन बदलावे असे कविला वाटत असून शोषितांच्या मुक्तीचे गाणे गाणारा हा कवी आहे.

ज्यांच्या स्वप्नांची भ्रूणहत्या होते त्या आदिम, कष्टकरी माणसांच्या व्यथा-वेदनेला कवी मुखर करतो. ऊनवारा, पाऊस सोसत घाम गाळणाऱ्या श्रमीकांची वेदना कवी व्यक्त करतो. जात धर्म, पंथ, वर्ण, वर्ग व लिंग ही सर्व शोषणाची अस्त्रे आहेत. राजकीय, सामाजिक शैक्षणिक, सामाजिक घटकांच्या माध्यमातून मारसाची लूट होते. याची जाणीव कवीला आहे. केतन पिंपळापुरेंच्या कवितेतील सौंदर्य जाणिवेविषयी आपले मत नोंदवतांना डॉ.मा.प. थोरात म्हणतात, 'सुंदरमानव समाज उत्पन्न करणारी जाणीव 'सौंदर्य' जाणीव होय'(३) पुढील ओळीतून केतनच्या काव्यातील सौंदर्य प्रतित होते,

''जीवनाची सुंदरता म्हणजे मैत्री
काळजातील असीम उदारता म्हणजे मैत्री
मैत्री : मानवतेचं लोभस रूप
मैत्री : निर्मल स्मृतीचा स्तूप
मैत्री : त्यागाचा सुगंधी धूप'' (डेमोफून-२३)

अर्थगर्भ अशी केतनची कविता असून तिच्यामध्ये असणारी समाजनिष्ठा पदोपदी

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जाणवते. कवितेतील सौंदर्यात्मकतेविषयी आपले विचार व्यक्त करतांना प्रा.रा.ग. जाधव म्हणतात, "अपूर्वता, उत्कटता व काव्यात्मता ही साहित्यातील सौंदर्याची लक्षणे ठरतात"(४)

'माय डिअर जिंदगी' या कवितेत कवी केतन पिंपळापुरे म्हणतात,

"इथे तर भाकरच ठरली आहे
आम्हा गरिबांसाठी उंबराचे फूल
आणि उदास प्राण्यांच्या कबरीवर
कुणी पांघरत नाही मायेची झूल" (हेमलॉक पृ. ६५)

आणिवेच्या कक्षा रूंदवणारे काव्यशिल्प केतन पिंपळापुरे यांच्यामुळे आंबेडकरी काव्य सृष्टीला लाभले आहे. केतन कवितेत पारंपारिक मिथ्थकांचा वापर करीत नाही तर जाणिवपूर्वक आंबेडकरी, बौद्ध, प्रतिके, प्रतिमा वापरतो. 'मार्शलरेस' मध्ये भीमा कोरेगावच्या शौर्यस्तंभाला सलामी देतांना 'अमृतनाम' 'सोमनाक' या अस्पृश्यांतील लढवय्यांची आठवण कवी करून देतो. लेखनातून तो आपल्या आंबेडकरी निष्ठेला तडा जाऊ देत नाही. तथागत बुद्ध, सम्राट अशोक, डॉ. बाबासाहेबांच्या भूमित कविला मानवतेच्या विचाराचा प्रसार करावयाचा आहे.

बुद्ध तत्वज्ञानावर आधारित जीवनाच नवं पंचशील मांडतांना, जीवन असावं गतिशील नवनिर्मिती करणाऱ्या हातासारखं, तर 'मैत्री' ही मानवतेचं लोभस रूप आहे असे केतन म्हणतो. कवितेतील आशयसघन वाक्यरचनेतून, नवं शब्दातून कवी त्या कवितेला सौंदर्य बहाल करतो. जसे 'दगडी पहाडावर हिरवळ फुलवणे', 'बेबंद दुनियेच बेहरम अरण्य', 'उदात्त जीवनमूल्यांचा शाश्वत दीप', 'ढगांच्या पाठीवर विजेचे प्रतोद', 'अग्नीच्या प्रपाताची विद्रोही कविता', 'मानवतेच्या तृषार्त ओठांवर करूणेचे तत्त्वथेंब', 'काळ सुतारपक्षासारखा माणसाचे काळीज पोखरतो'. अशा सौंदर्यपूर्ण विधानात्मक वाक्यातून तर 'साथी', 'शोषणशाहीचं ब्लडबँक', 'अग्निकमल', 'भावचिंब आसमंत' या शब्दातून कविता संवादी बनते. सौंदर्यपूर्ण शब्दकळेमुळे कवितेतील काव्यात्मक बाजही सांभाळला जातो.

केतन पिंपळापूरे हे अग्निफुलाची वाटपांघरून क्रांतीची पाहाट पाहणारे कवी आहेत. त्याच्या कवितेत वैचारिक एकसंघता जाणवते. कवितेमध्ये अभिव्यक्तीचा वेगळेपणा आहे. परिवर्तनवादी विचारकांचे व संघटनेचे सामर्थ्य वाढविणारी केतनची कविता आहे. या देशातील उपेक्षित वंचितांच्या सार्थ अपेक्षा प्रकट करणारी त्यांची कविता आहे. आंबेडकरी चळवळीला उर्जा बहाल करणारी केतन पिंपळापुरे यांची

कविता आहे. त्याच्या कवितेत समाजाभिमुख चिंतन आहे. त्याची कविता समष्टीची संवेदना व्यक्त करते. वंचितांचे दुःख दैन्य पाहून तो कवितेतून अस्वस्थता प्रकट करतो. बदलत्या वास्तवाचे प्रतिबिंब केतनच्या कवितेतून उमटते. सैरभैर शब्दाची मांडणी तो करत नसून प्रत्येक शब्दात, वाक्यात आशय ठासून भरलेला आहे. कवी आपल्या विचारांशी, आपल्या मातीशी, आपल्या माणसांशी प्रमाणिक असल्याची अनुभूती त्यांच्या कवितेतून होते.

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◆◆◆

। साभार पोच ।

आकाशवाणी चिंतने/डॉ. शे.मा. हराळे/मेघा प्रकाशन/अमरावती
आगाजा/विनोद कुमरे/लोकवाङ्मयगृह/मुंबई
ठसे बदललेल्या मुक्कामावरुन/विनायक येवले/काव्याग्रह प्रकाशन/वाशिम
दिशांतराच्या गोष्टी/उर्मिला राघवेंद्र चाकूरकर/पैठणी प्रकाशन, औरंगाबाद

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A PATH FOR HORIZING YOUR INNOVATIVE WORK

NANOCRYSTALLINE MIXED METAL OXIDE SEMICONDUCTOR SYNTHESIZED BY HYDROTHERMAL METHOD

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Abstract: This paper covers the synthesis of nanocrystalline mixed metal oxide by using hydrothermal method. Common themes related to the synthesis are outlined and their advantages over conventional reactions are described. Nanostructure ZnO-TiO_2 mixed metal oxide was synthesized by hydrothermal technique. Structural characteristics of synthesized material were studied by using X-ray powder diffraction (XRD), Fourier transform Infrared spectrometer (FTIR), scanning electron microscope (SEM), energy dispersive spectrometer (EDS) and transmission electron microscope (TEM). The average particle size of synthesized mixed metal oxide (ZnO-TiO_2) was found to be in the range of 56 nm. The transition from microparticles to nanoparticles can lead to a number of changes in physical properties. Nanoparticles are currently made out from wide variety of materials. The most common name prominently used in the generation of nanocystalline ceramics, is transition metal oxide such as ZnO-TiO_2. Because it can provides solutions to variety of engineering and scientific problems.

Keywords: ZnO: TiO2; Nano-material; Ceramic; Hydrothermal Techniques

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INTRODUCTION

Nano-meter sized particles of metal oxide semiconductors are important because of their novel electrical, optical, magnetic and chemical properties. It is important to mention here that physical and chemical properties of materials depend on synthesis routes, governed by the synthesizing conditions. The effect of particle size on the electronic and optical properties of the nanosized particles during the growth of crystallite from molecular level to the bulk material is important. In literature, several routes are described for synthesis of nanomaterials. These are chemical, mechanical, gas phase and molten salt synthesis [1]. Hydrothermal technique is the chemical synthesis method that allows fabrication of shape and size oriented materials without involving any melting steps [2]. The advantages of the hydrothermal technique are [3]: the duration of the experiments is reduced by two orders of magnitude compared to classical synthesis procedures, crystal size, morphology and controls the level of agglomeration for different ceramic oxides. It requires low cost instruments and less consumption of energy as compared to other synthesis routes. It is also an eco-friendly method [2]. Hence the hydrothermal technique is treated as the green technology which is useful for synthesis of nanocrystallile metal oxide semiconductors.

Because of significant optical and electrical properties of ZnO, this material has been studied extensively. Low cost of precursors, simplicity and high efficiency of its chemical synthesis method encourage scientists to investigate on nano-ZnO. Note to this facts, ZnO has different nano-morphologies at various synthesis conditions where by different properties can be obtained [4, 5].

Titanium dioxide has promising applications in covering materials, air purification, self-cleanliness, functional ceramics, cosmetics, catalysts, and waste water treatment [6, 7]. That is due to its numerous particular physicochemical properties, such as large specific area, high surface activity, good thermal diffusivity etc.

Nanocrystalline mixed metal oxides could be extended to the potential applications such as chemical sensors, optoelectronic devices, photocatalysis, antibacterial activity etc. [4, 5]. Beside this , the mixed metal oxide getting from transition metal oxides are started to use as humidity and gas sensor. Use of these nanocrystalline materials can provide solution to difficult engineering problems. ZnO-TiO_2 nano-composites have strong physical and chemical interaction with adsorbed species and thereby these nano-composites have a variety of applications as gas sensing materials, antistatic films, surface acoustic wave devices, catalysts and antireflection coatings in solar cells [8-10]. Although a large volume of literature is available on the synthesis of oxide nano-composite powders, very little attention has been given to the

hydrothermal synthesis of ZnO-TiO_2 mixed metal oxide semiconductor. It is interesting to know how the morphology and size distribution of obtained particles change by using this technique.

The objective of this work is to synthesize the nanocrystalline mixed transition metal oxide by hydrothermal technique for different engineering and scientific applications.

2. EXPERIMENTAL DETAILS

For obtaining nanocrystalline ZnO-TiO_2 with molar ratio 1:1, analytical grade ZnO and TiO_2 were dispersed in aqueous NaOH solution followed by hydrothermal treatment at 180 ^oC for 24 h in Teflon-lined autoclave. Then it was allowed to cool naturally and the obtained precipitate was isolated from the solution by centrifugation at 5,000 rpm for 30 min. and subsequently washed with distilled water and ethanol and then dried at 120^oC for 12 h. The synthesized material was examined by X-ray diffraction (XRD, XPERT-PRO), Fourier transform infrared spectrometer (FTIR, IR Affinity, SHIMADZU), scanning electron microscope (SEM, JSM6380, JEOL), energy dispersive spectrometer (EDS, Bruker) and transmission electron microscope (TEM, Techai G2 20). All the chemicals used in the present work were of AR grade without further purification.

3. RESULTS AND DISCCUSTION

3.1 X-ray diffraction pattern

Fig.1 shows XRD patterns of synthesized ZnO-TiO_2 powder sample. From XRD, it is seen that the material is polycrystalline in nature with mixed hexagonal and tetragonal phases. The characteristic peak in the XRD pattern matches the hexagonal ZnO (JCPDS card no. 00-036-1451) and tetragonal TiO_2 (JCPDS card no 01-071-1166). Also the peaks which appeared at 2θ = 29.95°, 36.83°, 56.74°, 62.18° and 70.41° correspond to Zn_2TiO_4 (JCPDS card no 01-073-0578). The extra peak appeared at 2θ = 44.8° is related to surface hydroxyl groups on the ZnO-TiO_2 surface [11].

The average crystallite size (D) was determined by using Debye-Scherrer formula [12]:

$D = 0.9 \lambda / \beta \cos \theta$ .....(2)

Where λ is the wavelength of incident beam (1.5406 Å), β is the full width at half maxima (FWHM) of the peak in radian and θ is the diffraction angle. The average crystallite size of sample was calculated from bordering of the diffraction line and found to be in the range of 56 nm.

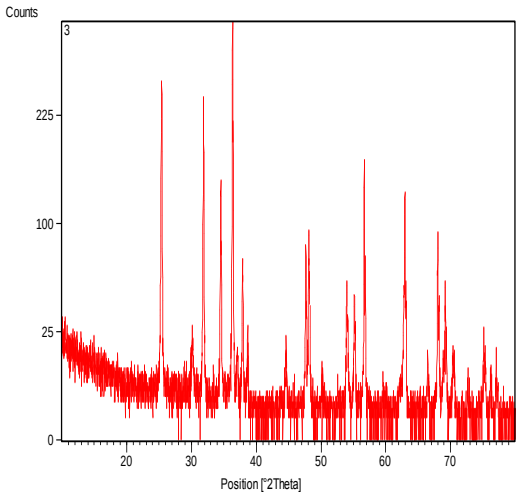


Fig.1. X-ray diffraction pattern of synthesized ZnO-TiO_2.

3.2 Scanning electron microscope (SEM)

The SEM image of Synthesized ZnO-TiO_2 nanoparticles is shown in fig.2. Surface morphology and structure were observed by SEM. From the image it is observed that the ZnO-TiO_2 particles are of aggregate star like structure.

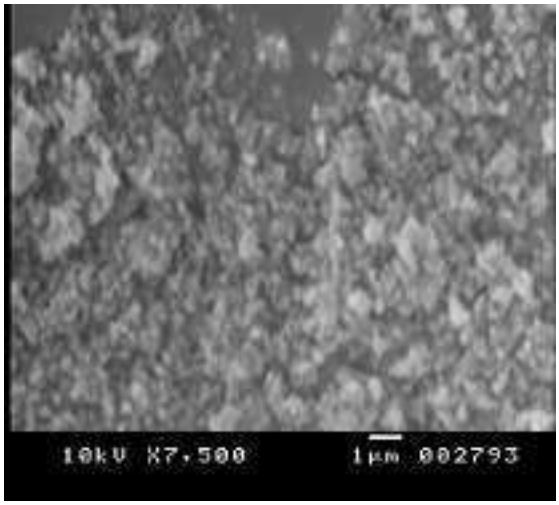


Fig.2. SEM image of synthesized ZnO-TiO_2.

3.3 Transmission electron microscopy (TEM)

Fig.3 illustrates TEM image of synthesized ZnO-TiO_2 powder sample. The small amount of agglomerations can be seen in the micrographs. TEM image indicates that the average crystallite size of synthesized material is in the range of nanometer.

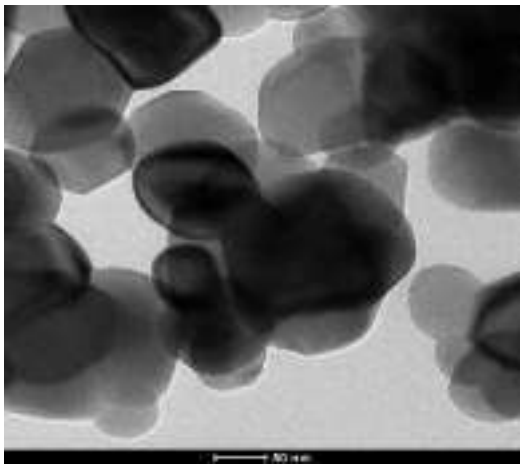


Fig.3. TEM image of synthesized ZnO-TiO_2.

3.4 Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of synthesized ZnO-TiO_2 material is recorded between 4000 – 400 cm^{-1} and presented in fig. 4. It is seen that the spectrum manifests several bands in the range of 1000 – 400 cm^{-1} related to the oxygen-metal linkage [13].

The band which had appeared at 406 cm^{-1} is due to the stretching vibrations of Zn-O [14]; 419 cm^{-1} corresponds to wurtzite zinc oxide [15] and band at 439 cm^{-1} appeared due to anatase TiO_2 [16]. The absorption bands in 3600 – 3200 cm^{-1} are connected to stretching vibration of hydroxyl group. This is assigned to the physical absorption of water [17]. The FTIR results are in good accordance with XRD data.

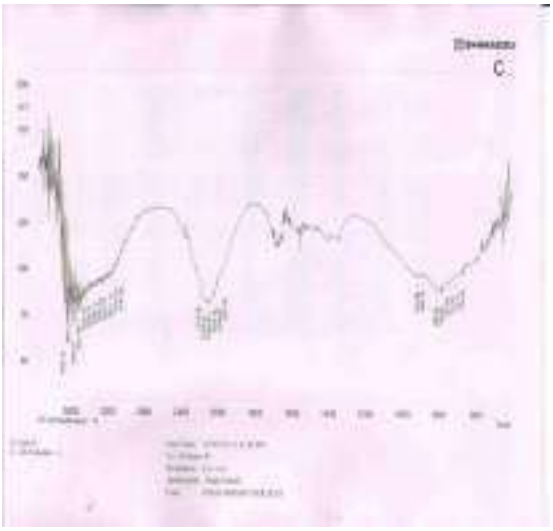


Fig. 4 FTIR spectrum of synthesized ZnO-TiO_2.

3.5 Energy dispersive spectrometery (EDS)

The elemental composition of synthesized nanocrystalline ZnO-TiO_2 (with molar ratio 1:1) was analyzed by using energy-dispersive spectrometer (EDS). Fig.5 shows EDS spectrum synthesized ZnO-TiO_2 (with molar ratio 1:1). From the spectrum, it can be seen that there are no elements other than O, Ti and Zn. The elemental composition of synthesized ZnO-TiO_2 (with molar ratio 1:1) is shown in table 1.

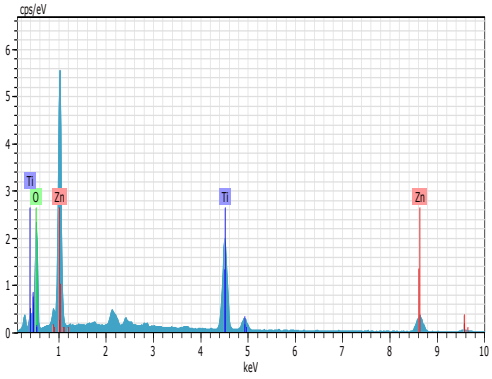


Fig.5: EDS spectrum of synthesized ZnO-TiO_2.

4. CONCLUSION

The nanocrystalline ZnO-TiO_2 mixed metal oxide semiconductor have been synthesized successfully by hydrothermal technique. The average size of synthesized material was

calculated by using XRD Scherrer formulae and it comes out to be in the range of 56 nm. The XRD, FTIR, SEM, EDS and TEM characterization of synthesized material confirm the formation of nanocrystalline ZnO-TiO_2.

Table 1. Composition of nanocrystalline ZnO-TiO_2.

Element	ZnO-TiO_2 (molar ratio 1:1)	
	Norm. wt.%	Atom. at.%
O	32.58	63.30
Zn	40.66	19.33
Ti	26.76	17.37

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SEASONAL DIVERSITY AND POPULATION DYNAMICS OF OPHIDIAN FAUNA IN BULDHANA DISTRICT MAHARASTRA INDIA

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ABSTRACT

The present paper provides the information about the seasonal diversity and population dynamics of ophidian fauna from Buldhana District Maharashtra, India. The study conducted during February 2012 to January 2014. During study the effective protocol was adopted. Study reveals the presence of thirty three varieties of snakes belonging to six families of which ten species were Abundant, four species were Common, eight species were Occasional, and six species Frequent while five were Rare. A general trend of increased population was reported in monsoon while decreased reported during winter to early monsoon.

KEYWORDS : Diversity, Population, Ophidian Fauna, Buldhana.

Snakes! the very word evoke feelings of horror and disgust in most of us. Snakes are also perceived as messenger of death. They fascinate us more than any other animals of the world. Snakes occupied deserts, forests, marshy, swampy places, lakes, streams and rivers of difficult terrains (Dhamankar 2006). The different anthropogenic activities and modifying environment are the biggest threats to the fauna and our current knowledge about behaviour, natural history and status of ophidian species is far from complete. So, one of the prime objectives of study was to build a reliable data-base about the seasonal diversity and population dynamics of these fascinating snakes from Buldhana District (M.S.) India.

Buldhana district is situated in Amravati division of Maharashtra state in Western India. It is situated at the westernmost border of Vidarbha region of Maharashtra and is 500 km from the state capital, Mumbai. It lies between 19°51' and 21°17' N. latitude and 75°57' and 76°59' E. longitude. It has a total area of 9745 square kilometers (3761 square miles). The climate of this district is characterized by a hot summer, well-distributed rainfall during the south-west monsoon season and generally dry weather during the rest of the year. The cold season is from December to February (Joshi, 2011, Joshi et al., 2014).

METHODOLOGY

The study conducted during February 2012 to January 2014 aims to examine monthly and seasonal diversity and population dynamics of ophidian fauna from Buldhana district, (M.S.) India. After detection, specimen was photographed and identified with the help of visible structural features. For identification and comparative studies of observed specimens, keys and methods suggested by Daniel (2002) Whitaker and Captain (2004), and Khaire (2010) were adopted. The Diversity data was quantified with the help of PAST Version 1.60 software (Hammer et al. 2001). The differences between the diversity and evenness indices of snakes among different seasons were statistically analyzed using Analysis of Variance.

RESULTS AND DISCUSSION

Buldhana district of Maharashtra (India) has healthy environment and climatic condition, with classical demography setup as mountainous terrain, rugged configuration and sudden fall in elevation is phenomenal. The thirty three varieties of snakes belonging to six families have been identified within two years of search in the Buldhana district. In these, the maximum species were non venomous representing the Colubridae family. Such community composition was also observed by Nande and Deshmukh (2007) in Amaravati and Melghat (M.S.) India. In the observations, characters were found almost same as per existing records (Whitaker and Captain, 2008., Khaire, 2010).

A fauna was observed to be most diversified during monsoons. A general trend of increased population was also reported in monsoon while decreased reported during winter to early monsoon. Such trends were shown by

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Table 1: Representing the Status of Ophidian Species in Buldhana District Maharastra India

Sr. No.	Scientific Name*	Common Name*	Type	Length Max. (inch)	Relative Domin -ance	Occurr -ence Status
Family: Typhlopidae						
1.	*Grypotyphlops acutus*	Beaked worm snake	NV	014	1.175	F
2.	*Ramphotyphlops braminus*	Common worm snake	NV	006	4.837	C
Family: Pythonidae						
3.	*Python molurus molurus*	Indian rock python	NV	124	0.361	O
Family: Boidae						
4.	*Gongylophis conicus*	Common sand boa	NV	038	3.165	F
5.	*Eryx johnii*	Red sand boa	NV	036	0.814	R
Family: Colubridae (NV)						
6.	*Amphiesma stolatum*	Striped keelback	NV	018	1.537	F
7.	*Argyrogena fasciolata*	Banded racer	NV	040	5.244	A
8.	*Coronella branchyura*	Indian smooth snake	NV	012	0.271	O
9.	*Coelognathus h. helena*	Common trinket snake	NV	048	5.289	A
10.	*Coelognathus h. monticollaris*	Montane trinket snake	NV	030	0.407	O
11.	*Dendrelaphis tristis*	Bronzback tree snake	NV	046	1.627	F
12.	*Lycodon aulicus*	Common wolf snake	NV	018	8.002	A
13.	*Lycodon flavomaculatus*	Yellow spotted wolf snake	NV	014	3.526	C
14.	*Lycodon striatus*	Barred wolf snake	NV	016	5.154	A
15.	*Macropisthodon plumbicolour*	Green keelback	NV	024	3.526	C
16.	*Oligodon arnesis*	Common kukri snake	NV	018	6.419	A
17.	*Oligodon taeniolatus*	Russell's kukri snake	NV	014	0.723	O
18.	*Ptyas mucosa*	Indian rat snake	NV	090	10.17	A
19.	*Sibynophis subpunctatus*	Black headed snake	NV	018	0.949	O
20.	*Xenochrophis piscator*	Checkered keelback	NV	048	10.26	A
Family: Colubridae (SV)						
21.	*Ahaetulla nasuta*	Common vine snake	SV	036	0.769	O
22.	*Boiga trigonata*	Indian cat snake	SV	030	6.103	A
23.	*Elachistodon westermanni*	Indian egg eater	SV	030	0.045	R
24.	*Psammophis condanarus*	Condanarus sand snake	SV	042	1.763	F
25.	*Psammophis leithii*	Leith's sand snake	SV	036	0.587	O
26.	*Psammophis longifrons*	Stout sand snake	SV	048	0.587	O
Family: Elapidae						
27.	*Bungarus fasciatus*	Banded krait	V	036	0.045	R
28.	*Bungarus caeruleus*	Common krait	V	060	4.611	C
29.	*Calliophis melanurus*	Slender coral snake	V	015	0.135	R
30.	*Naja naja*	India spectacled cobra	V	075	6.645	A
Family: Viperidae						
31.	*Daboia russelii*	Russell's viper	V	048	6.238	A
32.	*Echis carinatus*	Saw-scaled viper	V	024	1.356	F
33.	*Trimeresurus gramineus*	Green pit viper	V	016	0.090	R
Type: NV- Non Venomous; SV - Semi Venomous; V - Venomous						
Occurrence Status: A- Abundant; C- Common; F-Frequent; O- Occasional; R- Rare						

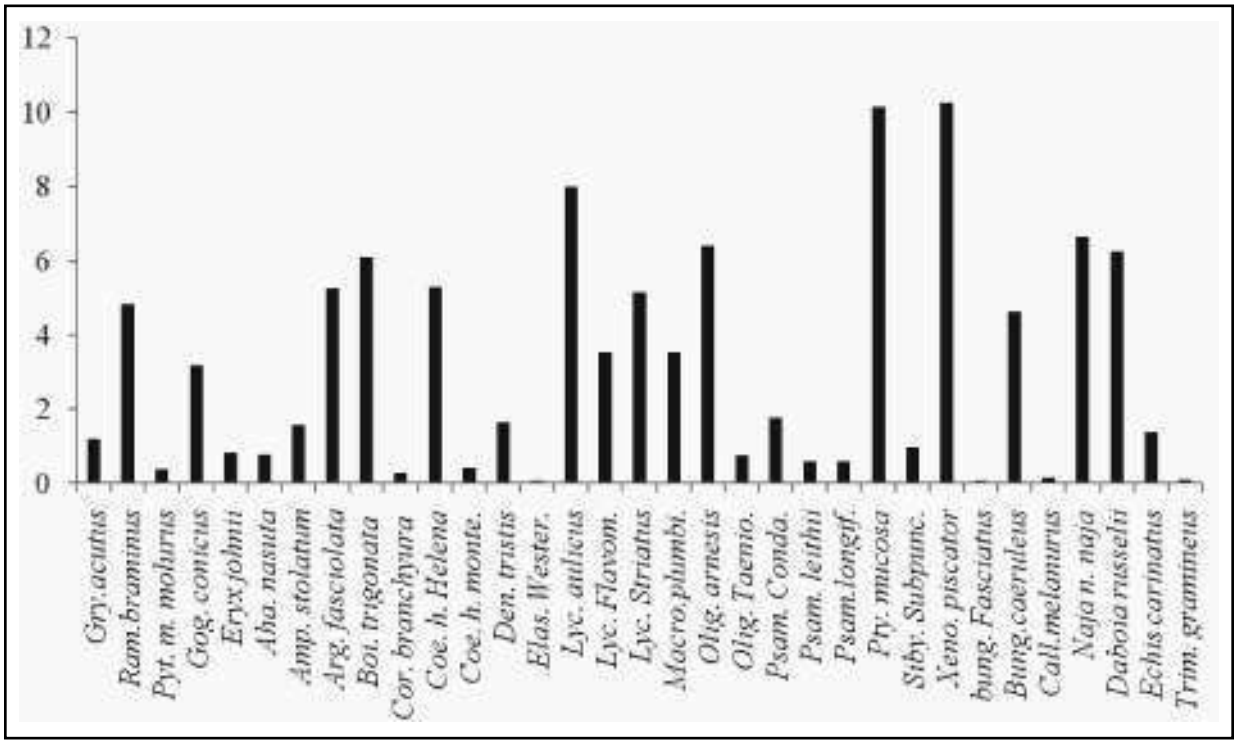


Figure 1: Representing Status of Ophidian Species in Buldhana District Maharastra, India

Table 2: Representing Status of Ophidian Families in Buldhana District Maharastra India

Sr. No.	Family	Percent occurrence	Relative occurrence	Occurrence Status
1.	**Typhlopidae**	6.060	6.009	F
2.	**Pythonidae**	3.030	0.366	R
3.	**Boidae**	6.060	3.977	O
4.	**Colubridae**	63.64	70.55	A
5.	**Elapidae**	12.12	11.42	C
6.	**Viperidae**	9.090	7.678	F
Occurrence Status: A- Abundant; C - Common; F -Frequent; O - Occasional; R- Rare				

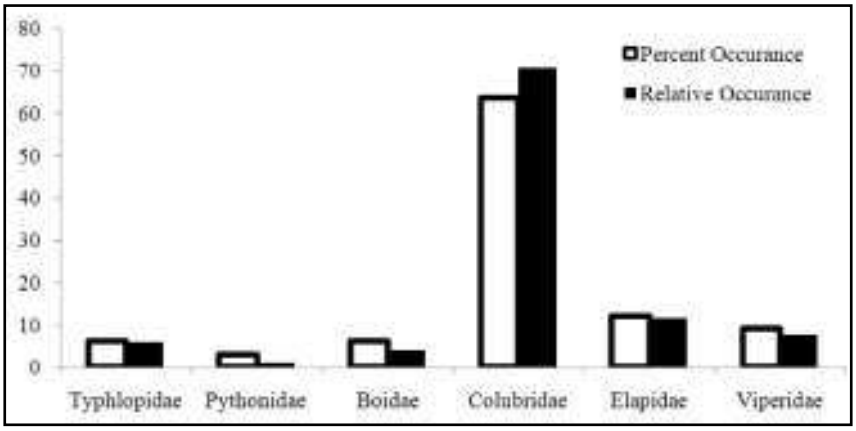


Figure 2 : Representing Status of Ophidian Families in Buldhana District Maharastra India

Table 3: Diversity of Ophidian Fauna During February 2012 to January 2014 in Buldhana District Maharastra India

Year / Month	No. of species	Mean % abundance[a]	Shannon diversity[b]	Equitability[c]	Species richness[d]
2012-13					
Summer	22	09.684	2.851	0.9224	4.667
Monsoon	28	27.994	2.981	0.8947	5.403
Winter	21	11.472	2.664	0.8750	4.289
2013-14					
Summer	19	09.324	2.671	0.9071	4.041
Monsoon	27	28.357	3.056	0.9274	5.117
Winter	25	13.169	2.964	0.9208	4.706

a = Mean percent abundance of snake populations was significantly different ($F=31.413$, $df=05$, $p<0.05$). b = Diversity values of snake populations was significantly different ($F=8.191$, $df=05$, $p<0.05$). c = Species equitability among different seasons was significantly different ($F=17.274$, $df=05$, $p<0.05$). d = Species richness among different seasons was significantly not different ($F=1.412$, $df=05$, $p>0.05$).

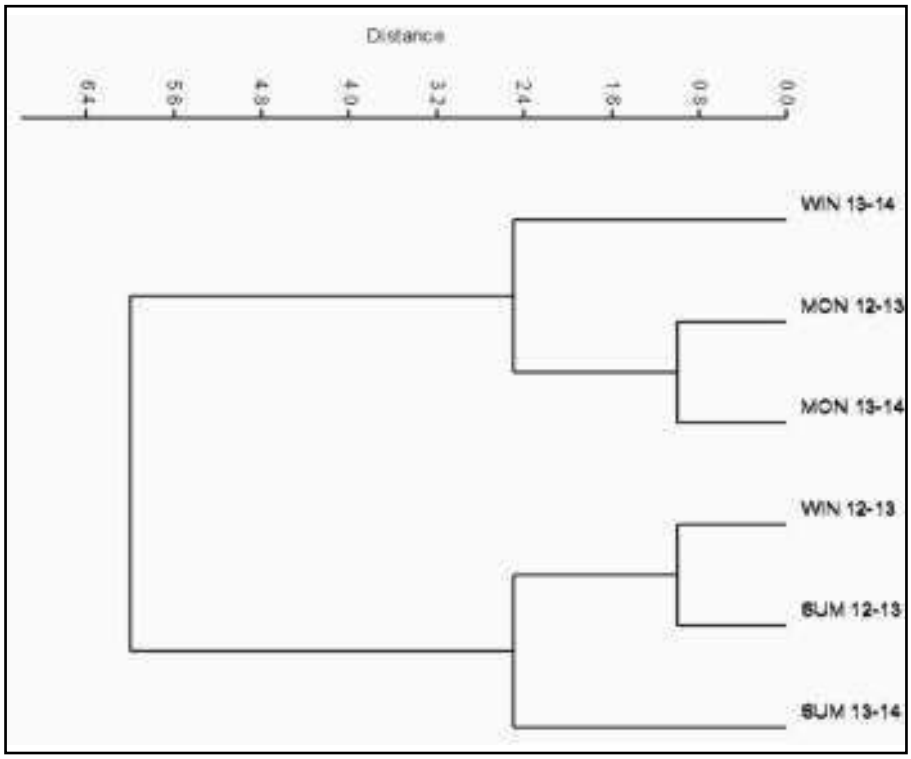


Figure 3.1 : Dendrogram Showing the Similarity of Ophidian Fauna in Different Seasons During February 2012 to January 2014 in Buldhana District Maharastra India

every species from all families of snakes. As the Snakes are cold-blooded animals accordingly during winter to early summer they hibernate in their burrows or resting places, which was the cause behind their minimum diversity in the winter to early summer season. Due to favourable environmental condition, monsoon is the breeding season for most of the snakes' which leads to their maximum population in rainy season (Joshi 2009, Pal et al. 2012).

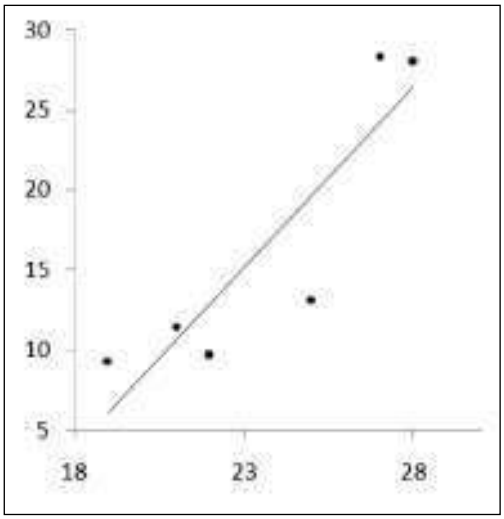
The following tables provide complete information about all the observed species.

The *Ptyas mucosa* and *Xenochrophis piscator* were showed the maximum while *Calliophis melanurus*, *Elachistodon westermanni* and *Trimeresurus gramineus* were observed with least relative dominance. (Figure 1)

The Colubridae family contributes maximum percent as well relative occurrence while least was showed by Pythonidae and Viperidae. (Figure 2)

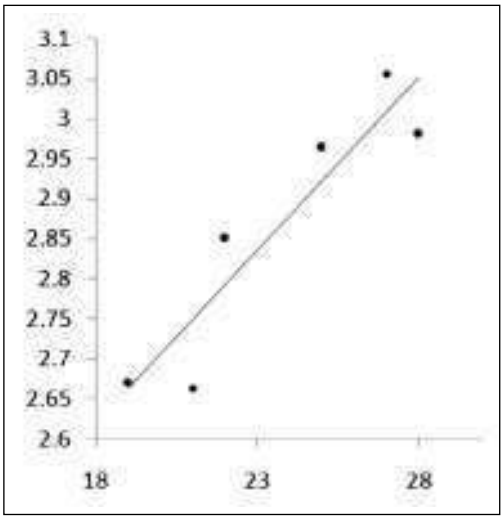
The similarity in species composition with number of species was observed maximum in Monsoon followed by winter and summer (Figure 3.1). The number of species in different seasons showed the significant relationship with different diversity indices (Figure 3.2).

R^2= 0.261 / P< 0.0001



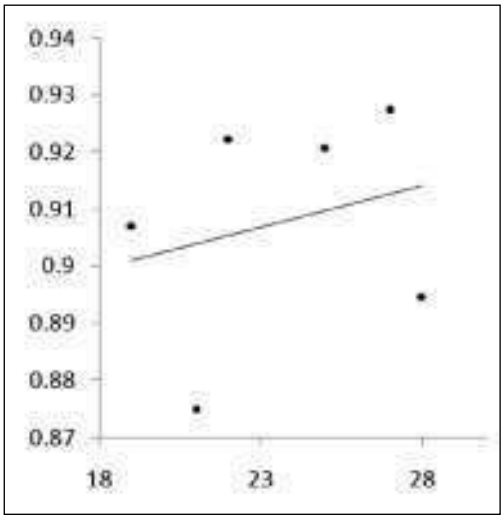
a. No. of Species Vs. Mean % Abundance

R^2= 0.356 / P< 0.0001



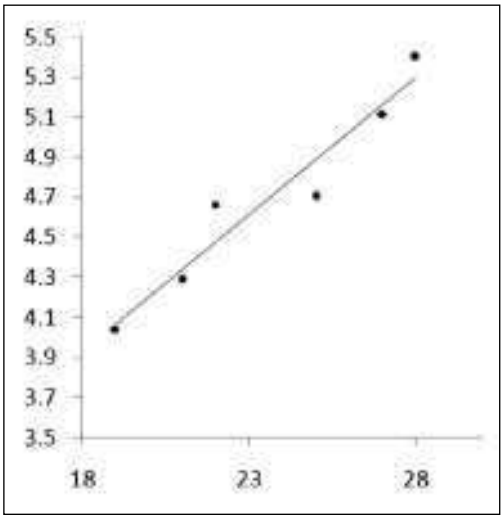
b. No. of Species Vs. Shannon Diversity

R^2= 0.195 / P< 0.0001



c. No. of Species Vs. Equitability

R^2= 0.205 / P< 0.0001



d. No. of species Vs. Species Richness

Figure 3.2. Relation Between No. of Ophidian Species And Different Diversity Indices

CONCLUSION

According to the observations, it has been concluded that the Buldhana district Maharastra India, has healthy environmental and demographic setup which accommodates rich ophidian diversity. The snakes are the Keystone species which plays an important role in ecosystem functioning but are threatened by anthropogenic activities as well as environmental alternation. The laws and legislation are not just sufficient for protection of these animals but it is necessary to raise the awareness levels by providing important information about snakes to different sections of people for conservation of ophidian biodiversity in Buldhana district Maharastra, as well as neighborhood. Because it is clear that disappearance of snakes will have tremendous social and ecological implications.

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Original article

Diversity of Saurian fauna in the Buldhana district, Maharashtra, India

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ABSTRACT

The present report provides knowledge about the diversity of Saurian fauna in the Buldhana district of the Indian state of Maharashtra as a model geographic area to promote conservation management. The presented study is based on the field work carried out in the study sites during February 2014 to January 2015. The study revealed the presence of 14 Saurian species belonging to 5 families dominated by Gekkonidae (43.05%), Scincidae (29.15%), Agamidae (21.35%), Varanidae (6.1%), and Chamaeleonidae (0.35%). The relative dominance of species varied with different months, apparently indicating that the Buldhana district has a healthy environmental and demographic setup that accommodates rich Saurian diversity.

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Introduction

The biological diversity of the earth and its origins has long been a source of amazement and curiosity (Tantarpale 2015). The study of biological diversity encompasses both the intrinsic and anthropocentric values associated with it. The values of the biological elements are recognized in correspondence to the perceived importance by the human being, which is realized in terms of the ecosystem services (Daily 1997; Baumgartner 2007). Biological diversity is the base for upholding the ecosystems and the functional aspects of the species that provide goods and services for human well-being. Monitoring of species diversity of a region enables estimation of the prospective functional roles of the species. In any ecosystems, monitoring species diversity can be used as a tool to reduce human mismanagement and pollution in urbanized, industrial, rural, and other managed areas (Wilson 1997). Extending this view, studies on species diversity in any ecosystems are necessary to understand the effect of anthropocentric development on the integrity and sustenance of an ecosystem.

The diversity of reptiles has been emphasized in many studies owing to their dominance in the terrestrial and aquatic ecosystems and provision of ecosystem services such as pest control and ecological maintenance (Joshi 2014). Among reptiles, saurian fauna is a diverse group that changes from the primitive to the specialized, phylogenetically, and their structural modifications exhibit greater variations than any other group of reptiles (Smith 1935). Lizards are members of the suborder Sauria which is one of the two suborders of the order Squamata (Class: Reptilia). They are poikilothermous, insectivorous, and oviparous to ovoviviparous (Matthew 2007). Presently, lizards are one of the most diversified groups of vertebrates that have ever lived on earth over the past 250 million years. Over 5,000 species of lizards have lived on earth, inhabiting a variety of habitats ranging from the highest mountainous peak to the low-lying terrestrial and aquatic habitats (Lalrinchhana et al 2015). South Asia, including the Indian subcontinent, is the home for herpetological diversities in the tropical region with India harboring 228 Saurian species in different biophysical zones (Venugopal 2010).

In this context, the conservation of lizards is necessary to sustain varied kinds of ecosystem services for human well-being. In view of the essential ecosystem services rendered by lizards and to promote conservation management, the present study was aimed at the estimation of the saurian diversity in the Buldhana District, Maharashtra, India. The results of the study are expected to supplement the necessary information on the conservation management and enhance the ecological roles of the saurian species in the Buldhana District and similar geographical regions.

Materials and methods

Study area

The Buldhana district (Figure 1) is one of the most diversified regions in Maharashtra State of India, with respect to biodiversity.

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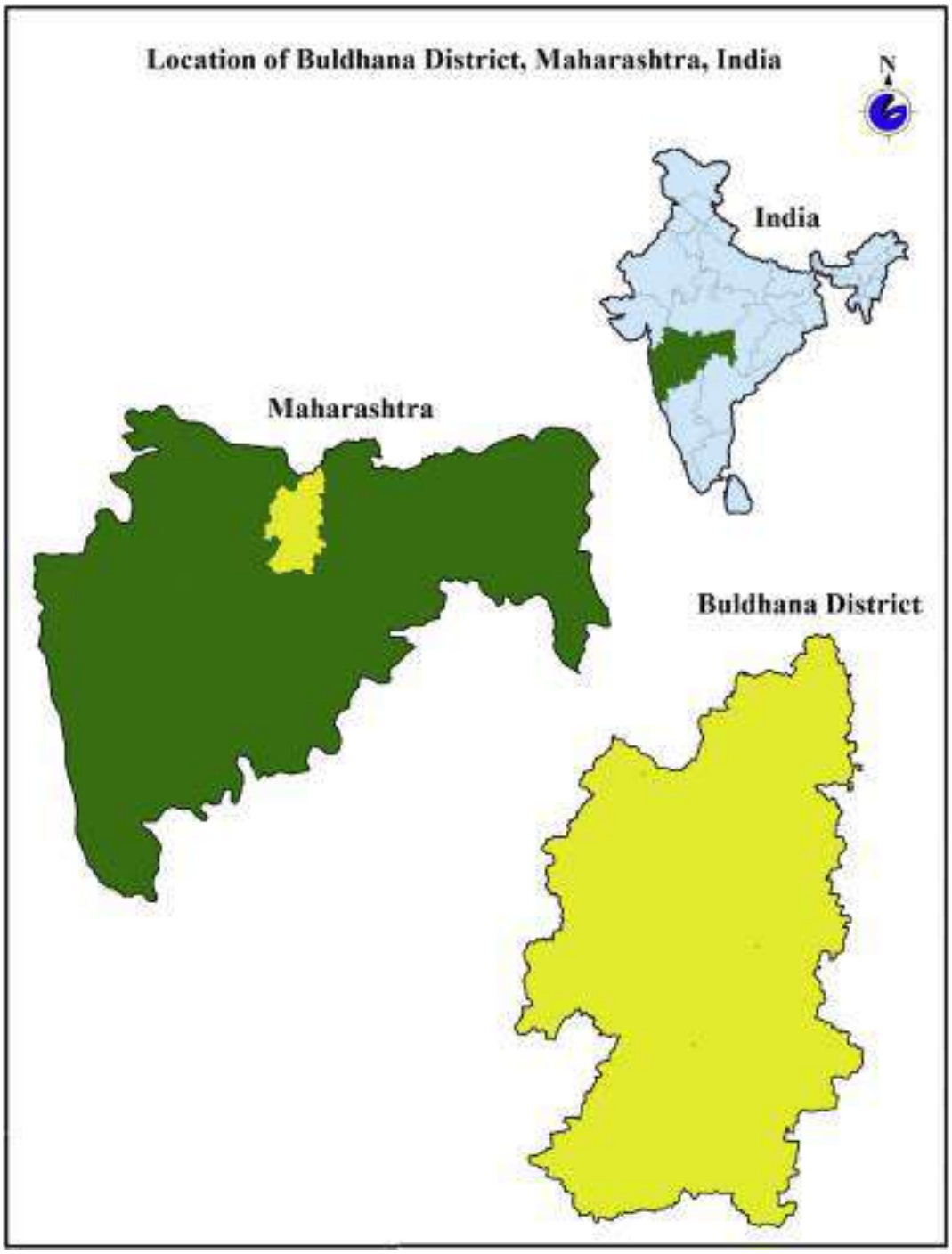


Figure 1. Buldhana District, Maharashtra, India.

Table 1. Diversity of Saurian fauna during February 2014 to January 2015 in the Buldhana district, Maharashtra, India.

Family	Scientific name	Common name	No. of individuals	IUCN national	Local status
Agamidae	*Calotes versicolor* (Daudin, 1803)	Indian garden lizard	42	NE	Abundant
	Calotes rouxii (Dumeril and Bibron, 1844)	Indian forest lizards	16	NT	Occasional
	Psammophilus blanfordanus (Stoliczka, 1871)	Blanford's rock agama	5	NE	Rare
Chamaeleonidae	*Chamaeleo zeylanicus* (Stoliczka, 1872)	Indian Chamaeleon	01	NE	Rare
Gekkonidae	*Hemidactylus brookii* (Gray, 1930)	Brook's house gecko	12	LC	Rare
	Hemidactylus flaviviridis (Murray, 1886)	Yellow-green House Gecko	35	LC	Common
	Hemidactylus frenatus (Dumeril and Bibron, 1844)	Asian house gecko	25	LC	Frequent
	Hemidactylus giganteus (Stoliczka, 1871)	Giant Indian gecko	03	NE	Occasional
	Hemidactylus leschenaultii (Dumeril and Bibron, 1844)	Common bark gecko	42	LC	Abundant
	Hemidactylus triedrus (Daudin, 1802)	Termite hill gecko	10	NT	Rare
Scincidae	*Eutropis carinata* (Schneider, 1799)	Keeled grass skink	34	NT	Common
	Eutropis macularia (Blyth, 1853)	Bronze grass skink	40	LC	Abundant
	Lygosoma punctatus (Gmelin, 1799)	Spotted supple skink	12	NT	Rare
Varanidae	*Varanus bengalensis* (Daudin, 1803)	Bengal monitor lizard	18	VU	Frequent

LC = least concern; NE = not evaluated; NT = nearly threatened; VU = vulnerable.

Its healthy climate, mountainous terrain, rugged configuration, and sudden fall in elevation are phenomenal (Joshi et al 2015). It is in the Amravati division of Maharashtra state in Western India. It is situated at the westernmost border of the Vidarbha region of Maharashtra, and is 500 km from the state capital, Mumbai. It lies between 19°51′ N and 21°17′ N latitude and 75°57′ E and 76°59′ E longitude. It has a total area of 9,745 km^2 (3,761 square miles). The climatic condition of this district is characterized by a hot summer, well-distributed rainfall during the south-west monsoon season, and generally dry weather during the rest of the year. The cold season is from December to February. The average annual rainfall in the district is 796.6 mm (31.37 inches). During summer, the mean daily maximum temperature was 42.3°C and the minimum was 27.4°C, and it decreased toward winter with a mean daily maximum temperature of 27.6°C and a minimum of 15.1°C (Buldhana Gazetteer 2015).

Survey methods

The present study is based on the field work carried out in the study sites during February 2014 to January 2015. During the survey, an efficient protocol was adopted. The survey was made using a "visual encounter survey" method (Doan 2003) as well as by employing randomized walking (Whitaker 2006). The selected area

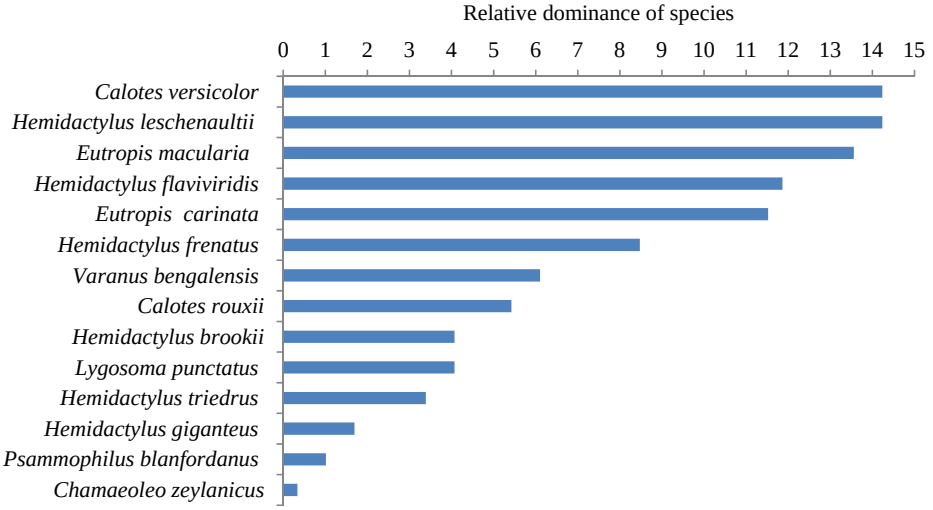


Figure 2. Relative abundance of saurian species in the Buldhana district, Maharashtra, India.

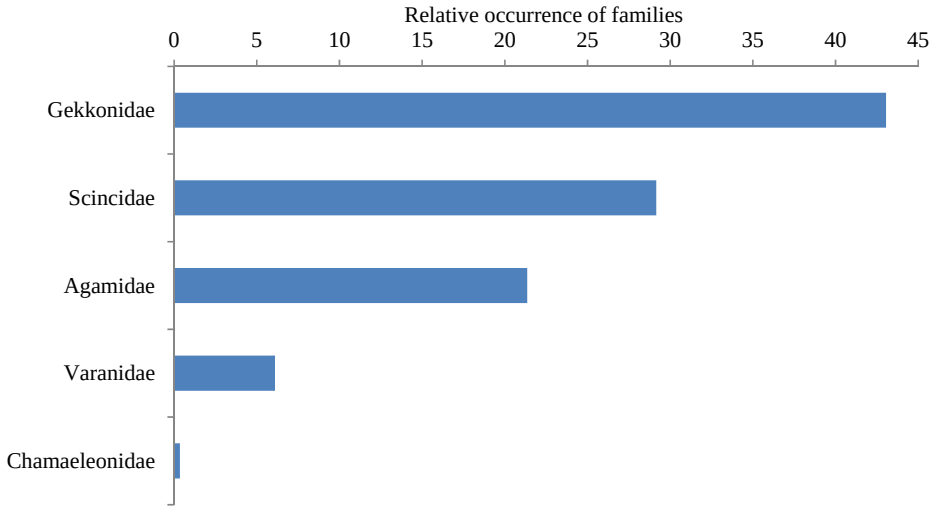


Figure 3. Relative dominance of saurian families in the Buldhana district, Maharashtra, India.

was randomly explored on the basis of habitat structure and the possibility of availability of species.

Species identification

After detection, a specimen was identified with the help of visible structural features. For identification and comparative studies of observed specimens, keys and methods suggested by Daniel (2002), Das (2002), and Ahmed et al (2009) were adopted. The International Union for Conservation of Nature (IUCN) status of each encountered species was categorized on the basis of Molur et al (1998), Kumbhar et al (2013), and Alexandar and Jayakumar (2014).

Data analysis

Species occurrence analysis was carried out by using the following formulas. Relative dominance (RD) of species was calculated as [RD = Ni × 100/Nt], where Ni is the number of individuals of species and Nt is the total number of individuals of all

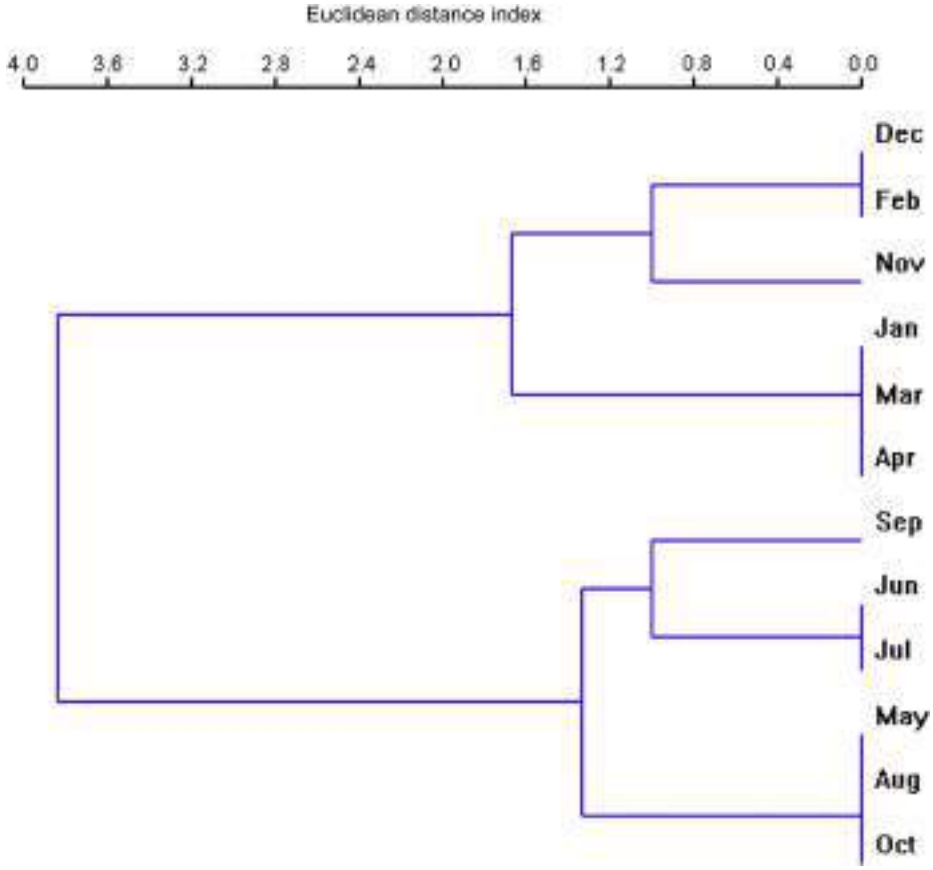


Figure 4. Dendrogram showing similarity in number of saurian species composition among the studied month during February 2014 to January 2015.

species (Basavarajappa 2006; Joshi 2014). Relative occurrence (RO) of the family was calculated as [RO = Ns × 100/Nt] where Ns is the number of species of each family and Nt is the total number of all species (Basavarajappa 2006; Joshi 2014). Mean percent occurrence (M%) for a month was calculated as [M% = Nm × 100/Nt] where Nm is the number of individuals in each month and Nt is the total number of individuals during the complete study tenure (Basavarajappa 2006; Joshi 2014). The mean values of the pooled species occurrence data were used to calculate the monthly diversity of and to categorize the local status of species.

The diversity assessment enabled highlighting the observed species richness pattern of the saurian species. The diversity indices were quantified with the help of PAST Version 1.60 software (Palaeontological Asso., Norway; Hammer et al 2001). The species diversity was calculated using the Shannon diversity index that calculated [$H' = -\sum_{i=1}^{R} Pi \log Pi$], where *Pi* is the proportion of the first species which is given by *Pi* = ni/N, where ni is number of individual in particular month and N is total number of species; species richness was obtained by using the Margalef equation [R = (S-1)/log N], where R is the index of species richness, S is total number of species and N is the total number of individuals (Magurran 1988); while species equitability was determined by the equation of Pielou [$J = N_1/N_0$] where N_1 is the number of abundant species in the sample and N_0 is the number of species in the sample (Hammer et al 2001). The similarity association matrix upon which the cluster was based was computed using the nearest neighbor pair linkage algorithm of Euclidean distance index for the presence and absence data (Hammer et al 2001).

The differences between the diversity and evenness indices among different study months were statistically analyzed using analysis of variance. The statistical analyses were performed following Zar (1999) using the SPSS version 10 (SPSS Inc., Chicago, IL, USA; Kinnear and Gray 2000).

Results

During the study, a total of 295 individuals of 14 saurian species belonging to 5 families were identified (Table 1). From the observed species, 3 were abundant, 2 were common, 2 were frequent, 2 were occasional, and 5 were rare. The maximum abundance was shown by *Calotes versicolor* followed by *Hemidactylus leschenaultii* and *Eutropis macularia*, while *Chamaeleo zeylanicus* was the most rarely observed with least abundance (Figure 2). During the study, the Gekkonidae family was observed to be more dominant over the Scincidae, Agamidae, Varanidae, and Chamaeleonidae families (Figure 3).

A monthly comparison of saurian species occurrence showed the highest number of species during June to September and the lowest during February to May. A dendrogram developed by Euclidean distance cluster analysis was observed to be multifaceted and showed variation in the level of similarity in the number of saurian species in 12 months. The months with the minimum to moderate number of species belong to one cluster, whereas the rest of the months with moderate to maximum number of species formed another cluster (Figure 4).

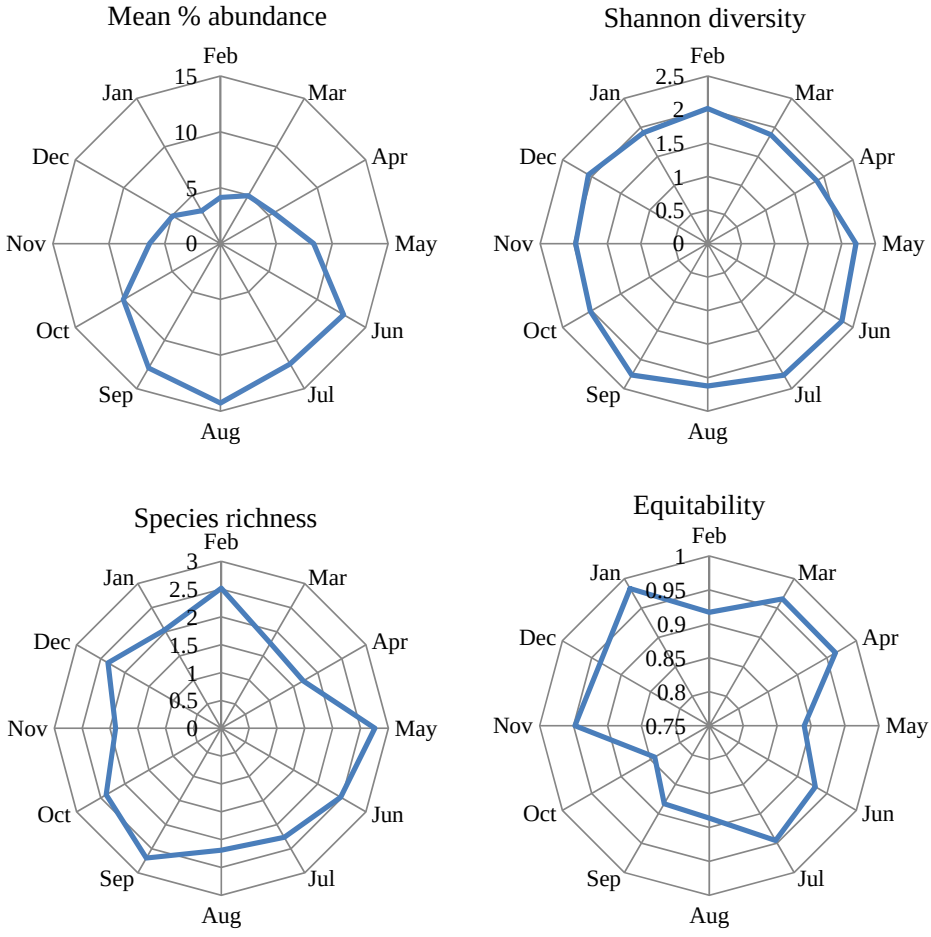


Figure 5. The values of the diversity indices in different months observed through the random sampling of the Saurian fauna in the Buldhana District, Maharashtra, India.

A monthly comparison of species diversity attributed to saurian fauna in the studied area revealed that faunal diversity was highest during June to September while lowest during February to May. Mean percent abundance of saurian fauna was significantly different ($F = 30.314$, $df = 11$, $p < 0.05$); Shannon diversity values of saurian fauna were significantly different ($F = 9.813$, $df = 11$, $p < 0.05$); species evenness among different months was significantly different ($F = 16.824$, $df = 11$, $p < 0.05$) while species richness among the study months was not significantly different ($F = 1.526$, $df = 11$, $p > 0.05$) showing a contradictory pattern. A trend in mean % abundance was noted to be nearly similar to that of Shannon diversity although species richness and species equitability showed contradictory patterns (Figure 5).

Discussion

The utility of saurian species as indicators of environmental conditions is a basis for studying seasonal saurian diversity. Observations on the saurian diversity provided information about the variations in the species richness and the abundance shaped by the seasons. The differences in the diversity can be attributed to the monthly changes in the climatic conditions. In the present context, a monthly comparison of saurian species occurrence showed the highest number of species during June to September and the lowest during February to May.

The possible cause behind their minimum diversity in the winter months to early summer months is the cold-blooded nature of reptiles. Lizards preferred to hibernate in their burrows or resting places during winter to early summer. Species were generally observed more during monsoon months. According to Pal et al (2012) and Joshi (2014), due to favorable environmental conditions, the monsoon season is the breeding season for most of the reptiles, which leads to their maximum abundance in rainy months. Earlier studies on the saurian diversity in various parts of Maharashtra show consistency with the present observations (Wadatkar 2003; Deshpande et al 2012; Kumbhar et al 2013; Pandharikar et al 2015).

As revealed through the present study, at least 14 saurian species belonging to 5 families were recorded during all the studied months. In the observations, characters of the studied species were found to be almost the same as per existing records of Daniel (2002) and Ahmed et al (2009). The maximum abundance was shown by *Calotes versicolor* followed by *Hemidactylus leschenaultia* and *Eutropis macularius*, while *Chamaeleo zeylanicus* was the most rarely observed with the least abundance. During the study, the Gekkonidae family was observed to be more dominant over Scincidae, Agamidae, Varanidae, and Chamaeleonidae.

In parity with the species diversity observed in the Buldhana district, it may be assumed that the saurian species carry out diverse functional roles for the sustenance of the ecosystems. The availability of the green space and the heterogeneity of the habitats in terms of the available vegetation and allied factors that render stability to the population and species assemblages in the landscapes are possibly important contributors to the observed variations in the saurian species observed in the present study. The present diversity study is confined to a limited area and selected habitats. There is, in the future, a chance of more species being reported because of few pockets and habitats in the studied area requiring more extensive exploration.

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The authors are thankful to Dr K.M. Kulkarni, Former Vice Chancellor (Swami Ramanand Tirtha Marathwada University, Nanded, India) and Former Director (Higher Education, Government of Maharashtra, Pune, India) for erudite guidance during conduct of this study.

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Topic:-DIVERSITY OF ANURAN FAUNA FROM JALGAON (JAMOD) TERRITORY, BULDHANA DISTRICT (M.S.), INDIA.

The Research paper is Original & Innovative it is Done Double Blind Peer Reviewed.

Authorised Signature

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BASKING ACTIVITY OF INDIAN MONITOR LIZARD (VARANUS BENGALENSIS)IN BULDHANA DISTRICT OF MAHARASHTRA (INDIA)

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ABSTRACT

The current report is on the basking activity of Indian monitor lizard that was noted during 18 to 24 October of 2014 from an agriculture field of Jalgaon (Jamod), District Buldhana of Maharashtra (India) (Table1). Indian Monitor Lizard Varanus bengalensis (Daudin, 1802) is diurnal and ectothermic animal that rely largely on external heat sources such as sunlight for thermoregulation. The species exhibited basking at morning to afternoon and some time showed twice a day that is in morning and afternoon both. After basking, species became more active, showed fast movement and quick capture of their prey.

Keywords: Varanus bengalensis, Basking activity, Buldhana, Maharashtra.

Introduction

The Indian monitor lizard Varanus bengalensis (Daudin, 1802) found widely distributed over the Indian Subcontinent (Daniel, 2002; Böhme, 2003; Venugopal, 2010). It has 'Least Concern' status in IUCN Red List of Threatened Species (Papenfuss et al., 2013). Indian monitors are usually solitary and mostly found on the ground, although the young are often seen on trees. It is ectothermic animal that rely largely on external heat sources such as sunlight to achieve their optimal body temperature for various bodily activities and thermoregulation. As species is diurnal, becoming active around 6 A.M. and bask in the morning sun (Auffenberg, 1994). Here this report provides the knowledge about basking activity of Varanus bengalensis from Buldhana District of Maharashtra (India).

Methodology

The basking activity of Varanus bengalensis were observed over 07 consecutive days during 18 to 24 October 2014 from Agriculture field of Jalgaon (Jamod), District Buldhana of Maharashtra (India). The habitat located between N 210 02' 31.2" and E 760 31' 56.64" at elevation of 291 m.

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During study period, climate was generally dry as no rain occurred. The observations were made by 'Visual encounter method' suggested by Campbell and Christman (1982) for reptiles. The continuous observations were made with the help of using binoculars as well with necked eyes from early morning to late evening. During studied hours, temperature was also noted to establish their correlation with basking tenure.

Figure 1.Google Earth Map of Study area from Agriculture field of Jalgaon (Jamod), District Buldhana (M.S.) India with location of habitat occupied by Varanus bengalensis



Observations and Results

The current report is on the basking activity of Indian monitor lizard Varanus bengalensis. The Habitat of species was structurally a long hollow crevice with an opening width of size near about 50-60 cm. The species exhibited basking at morning to afternoon and some time show twice a day that is in morning and afternoon both. Morning basking observed begins around 07.30 A.M. to 09.30 A.M. while afternoon basking begins near about 01.00 P.M. to 02.00 P.M., and continues until 03.00 P.M. Species showed out its head from crevice opening at early morning suggesting that animal is waiting for the maximum sun light. As the light radiate to the opening of habitat, species move very slowly, comes straight out from crevice to gain maximum sun light. During basking activity, species remain steady for about an hour. After then species moved slowly up its head in direction of stimulus, captured prey or turn back to its crevice. Nearly same observations were also noted at afternoon period but the duration of exposures was less than morning hours. These observations were clears that the duration of basking increases with decrease in temperature (Figure 3). After basking, species was observed to be more active.

Figure 2: The Indian monitor lizard Varanus bengalensis (Daudin, 1802)

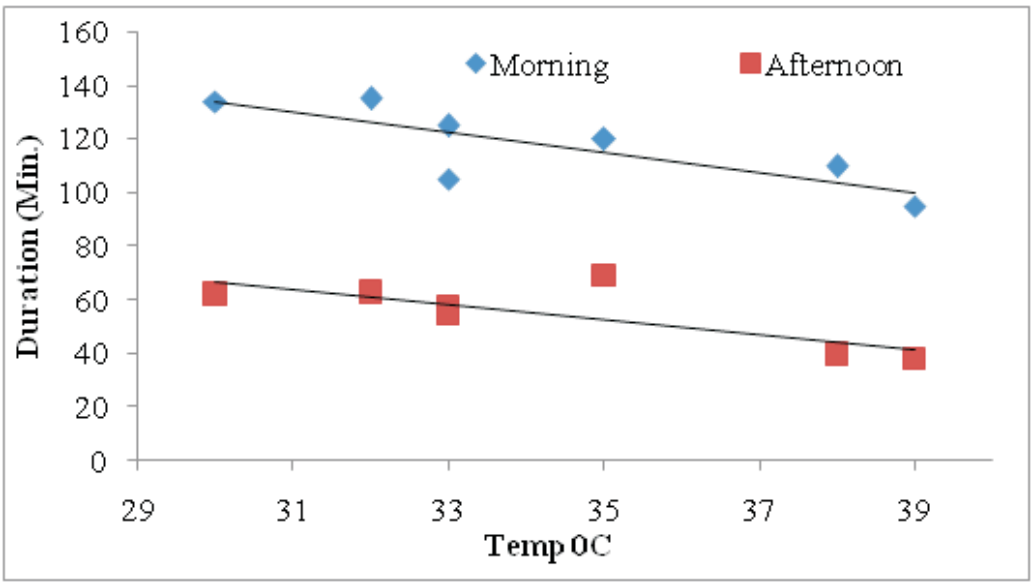


The observations on basking behaviour of Indian monitor lizard were as tabulated below.

Table 1. Observation on basking activity of Indian monitor lizard

Sr.	Date	Basking Duration (Min.)		Temperature (^{0}C)
		Morning	Afternoon	
01	18-10-2014	110	040	38
02	19-10-2014	095	038	39
03	20-10-2014	125	057	33
04	21-10-2014	135	063	32
05	22-10-2014	120	069	35
06	23-10-2014	134	062	30
07	24-10-2014	105	055	33

Figure 3: Relation between Temperature and Basking duration



Discussion

Study area has healthy environment and climatic condition, with classical demographic setup (Joshi et al., 2015). The available environment supports the life history of Varanus bengalensis. The monitor lizards basks by taking advantage of sun exposure (Pianka and King, 2004; Murthy, 2010; Islam and Saikia, 2013) that is evidence of their ectothermic nature which supports the thermoregulation mechanism of their body (Auffenberg 1994). With basking activity, monitor lizard increase its body temperature to the optimum level that physiological functions viz. heart rate and cardiovascular control can be well operated (Christian and Bedford, 1996; Seebacher and Grigg, 2001).

After basking, the Varanus bengalensis was observed to be more active, showed fast movement and quick capture of their prey. The present observations are in accordance with Traeholt (1997), in which the monitor followed sunlight to receive solar radiation and to increase its body temperature before commencing its daily activities (Rathnayake et al., 2003). This observation is also in agreement with the compiled knowledge that many reptiles regulate their body temperatures by basking in the sun until the temperature rises to the level requisite for their normal activity. Basking before returning to its refuge should be required in order to maintain physiological activity (Duengkae, 2008; Deungkae and Chuaynkern, 2009; Vitt and Caldwell, 2009).

The monitor lizard does not make its refuge. As found in previous research (Pattanavibool, 1993; Poonswad, 1997); it prefers to inhabit the refuge like long hollows crevice rather than burrows. Hence, the available refuge like long hollows crevice are an essential factor that supports the occurrence of Varanus bengalensis in the studied area from Buldhana District of Maharashtra (India) and should be considered as an important factor for the management and conservation of this incredible species or its congener.

Conclusion

In conclusion, the Varanus bengalensis is usually solitary and mostly found on the ground. It is diurnal ectothermic animal that rely largely on external heat sources such as sunlight to achieve their optimal body temperature for various bodily activities and thermoregulation. The species exhibits basking at morning to afternoon and some time show twice a day that is in morning and afternoon. After basking, species became more active, showed fast movement and quick capture of their prey.

Acknowledgement

Authors are thankful to Dr. K. M. Kulkarni, Former Vice Chancellor (S. R. T. M. University, Nanded) and Former Director (Higher Education, Government of Maharashtra, Pune) for their guidance during conduct of this study.

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EFFECTS OF DIETARY GARLIC ON GROWTH PERFORMANCE IN THE FRESH WATER FISH *CLARIAS BATRACHUS* (LINN.)

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Abstract:
The aim of this study was to assess the effect of garlic (*Allium sativum*) on growth performance in the fresh water fish *Clarias batrachus* (Linn.) A total number of 80 fish (average weight 20.86±0.27 g) was used. Fish were divided into four groups fed on diets containing garlic in different levels and the control group diet was without garlic. The experiment extended for two months. The results showed that, significant weight gain and growth performance increased in all groups fed on garlic. The results of this study show that addition of garlic *Allium sativum* to fish diet can promote growth of fish.
Keywords: garlic (*Allium sativum*), growth factors, fresh water fish (*Clarias batrachus*).

Introduction

Feed and feeding are among the most important factors influencing growth, feed utilization and tissue composition of the fish in intensive culture (Okumus and Mazlum, 2002). Garlic is an important vegetable extensively cultivated in many countries. It is used as food for humans as well as some animals and as remedy for several diseases, as reported in folk medicine (Shalaby *et al.,* 2006). It is probably one of the earliest known medicinal plants. In recent years, the concern about bacterial resistance to antibiotics in livestock industry has led to legislation minimizing/eliminating the use of such compounds. Garlic contains sulfur containing compounds. Alliin, is converted to the antimicrobial active allicin, when the bulb is cut or bruised. The fresh bulb contains Alliin, Allicin and volatile oils. Allicin gives garlic its characteristic pungent smell. Also, it contains vitamins and minerals and trace elements (selenium and germanium) (Skidmore-Roth, 2003). Allicin (diallythiosulfinate) is the most abundant compound representing about 70% of all thiosulfinates present, or formed in crushed garlic (Block, 1992; Han *et al.,* 1995). Using of garlic in fish farming has become popular for as a growth promoter (Diab *et al.,* 2002; Metwally, 2009) also it increased body gain, feed intake and feed efficiency ratio (Abd-El Allatif and Ebraheem, 1996; Metwally, 2009).

This work was carried out to study the effect of different values of garlic on growth factors in *Clarias batrachus.*

Material and Methods

1. **Experimental fish**: The *Clarias batrachus* (20.88±0.25 g) were obtained from a commercial farm and were transferred to the place of experiment and acclimated for 2 weeks. During the acclimation, fish were fed the experimental diet to satiation twice a day at 09:00 and 15:00 hours. After acclimation, fish were fasted for one day; batch weighted and randomly distributed among density of 20 fish per tank.
2. **Experimental diet and feeding regime:** The basal experimental diets were formulated with the commonly available ingredients. The formula and analyzed proximate composition of the basal diet are shown in Table 1. The ingredients were grinded, milled, weighed, mixed and pelleted with meat mincer through a 2 mm die. After pelleting, the feeds were air dried and put in an air-tight container. During the experiment, fish were fed the experimental diet to satiation third a day at 08:00, 12:00 and 16:00 hours.
3. **Measurements and sample analysis:** It was carried out each 20 days. Water temperature was 15°C, O2 7-8 mgl-1, pH 7-8 and light: dark cycle of 12:12 h was maintained during the feeding trial. Proximate composition of diets and tissues were carried out using the Association of Analytical Chemists (AOAC, 2000) methods.
4. **Calculations and statistical analysis:** The following variables were calculated:

a) Body weight increase (BWI) = Wt – W0 (Tacon, 1990)

b) Specific growth rate (SGR) = (ln Wt – ln W0) × 100 t^{-1} (Hevroy *et al.,* 2005)

Where, Wt and W0 = Final and initial fish weights (g), respectively,

(t) = the experimental period in da

c) Feed conversion ratio (FCR)=$\frac{\text{Total dry feed consumed (g)}}{\text{total weight gained (g)}}$ (Shalaby *et al.,* 2006)

d) The data obtained from the trial is expressed as mean (±SD).

Results and Discussion:

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Growth performances of the fishes after 60 days of feeding are summarized in Table 2. Third fish group had higher final weight, weight gain, and SGR than fish fed on other levels of garlic and control. The highest amounts of dry feed intake (g/fish/day) were seen in the same third fish groups. Results also show that FCR decreased significantly to 1.39±0.01 in the third group.

It is clear that garlic is a main vegetable extensively cultivated in many countries. It is used as food for humans as well as some animals and as remedy for several diseases, as reported in folk medicine (Shalaby *et al.,* 2006). In this study the highest growth performance was observed in fish fed diets containing garlic, especially on 30 g garlic. It agrees with studies results of Diab *et al.,* (2002), Abou-Zeid, (2002), Shalaby *et al.,* (2006). Feed intake increased with increasing *Allium sativum* levels. Feed conversion ratio decreased with increasing *Allium sativum* levels. These results are also in agreement with those obtained by Gomes *et al.,* (1993), Degani *et al.,* (1997), Khattab *et al.,* (2004) and Farahi *et al.,* (2010).

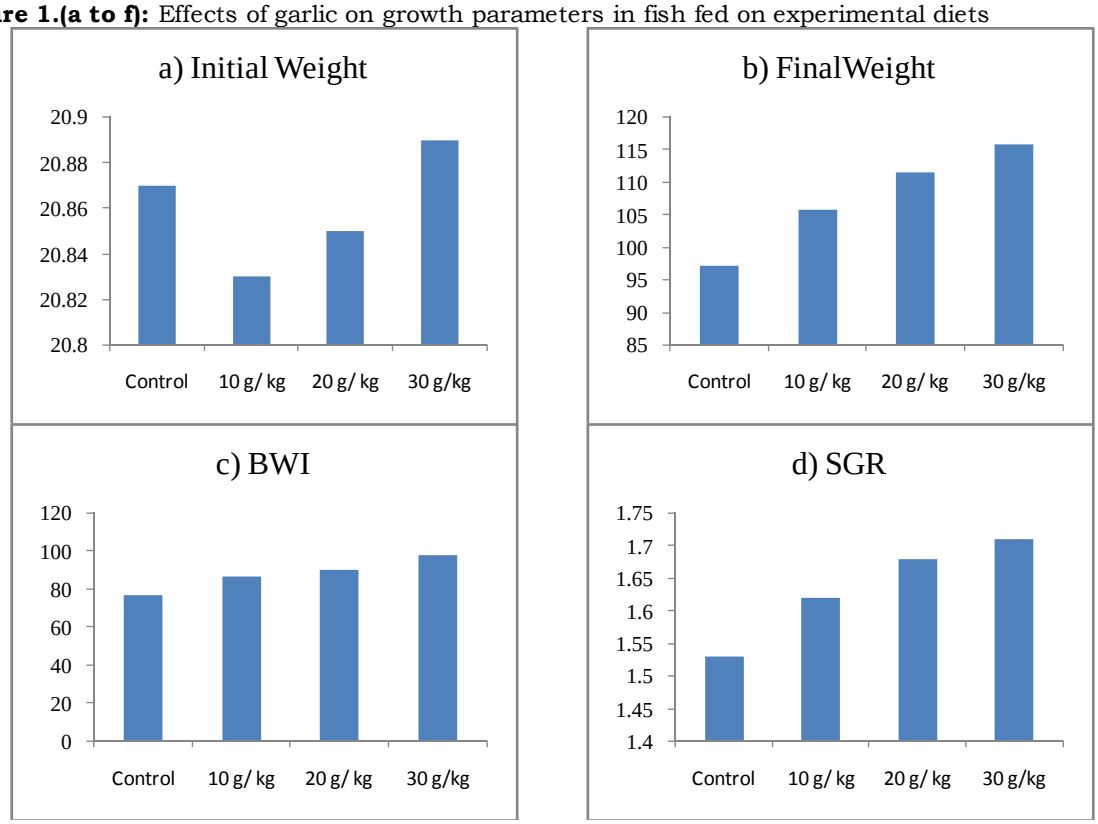
Table 1. Formulation and proximate composition of the basal fish diets

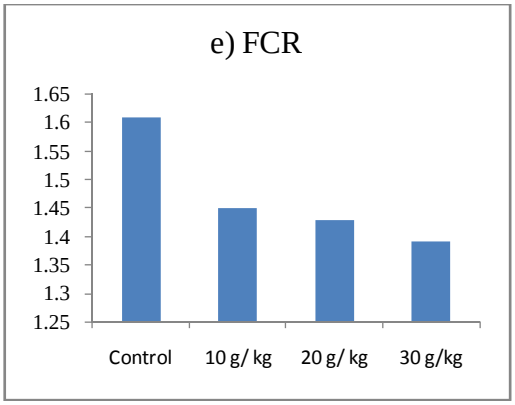
Ingredients	**Control**	***Allium sativum* diets Ingredients (g /100g diet)**		
Meat	25	25	25	25
Wheat	50	47	44	41
Soybean	20	20	20	20
Soybean oil	05	05	05	05
Garlic	00	03	06	09

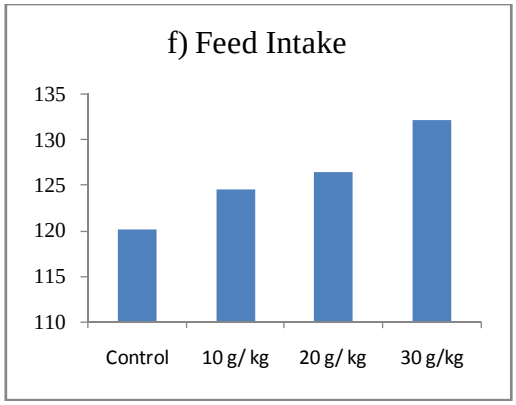
Table 2: Effects of garlic on growth parameters in fish fed on experimental diets(g/100g)

Parameters	**Control**	**I**	**II**	**III**
Initial weight(g)	20.87±0.30	20.83±0.09	20.85±0.34	20.89±0.33
Final weight (g)	97.05±3.10	105.76±4.12	111.51±4.23	115.88±2.51
BWI (g)	76.81±3.39	86.81±4.13	90.03±4.56	98.02±3.42
SGR	1.53±0.06	1.62±0.05	1.68±0.04	1.71±0.03
FCR	1.61±0.05	1.45±0.04	1.43±0.05	1.39±0.01
Feed intake (g)	119.12±1.29	123.35±2.31	127.24±1.33	133.02±2.12

Figure 1.(a to f): Effects of garlic on growth parameters in fish fed on experimental diets







Conclusions

From obtained results, it could be recommended that garlic (*Allium sativum*) can be used as a growth promoter in *Clarias batrachus* so garlic should be added to the diets of fish.

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RECORD OF LEUCISM IN GREEN KEELBACK *MACROPISTHODON PLUMBICOLOR* (CANTOR, 1839) IN AMRAVATI DISTRICT, MAHARASHTRA, INDIA

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ABSTRACT

The present paper provides the information about a record of leucism in *Macropisthodon plumbicolor* (Cantor, 1839).Leucistic wild individuals are less common in nature. A specimen with a length of approximately 21 inch was observed on 23 July 2015 from a field near MIDC old bye pass road of Amravati district (M.S.) India. It was observed, photographed and identified with the help of visible morphological characters.

KEY WORDS: *Macropisthodon plumbicolor*, Leukism, Amravati, India.

INTRODUCTION :

Unusual coloration in vertebrates does not occur frequently in nature, yet it is recorded in a large variety of species (Bried *et al.*, 2005, Franz and Fleck, 2009). In general, colour and pattern in reptiles is produced by a combination of pigments and structural compounds (Bechtel, 1995). There are multiple varieties of chromatophores, the failure to produce a normal amount of pigment in one cell type does not generally alter the ability of the other chromatophores. Thus, various aberrant colours and patterns in reptiles are expressed and the most striking colour pigment anomaly is albinism and leucism (Gamble *et al.*, 2006).

Albinism and Leucism have already been recorded in fish (Veena *et al.*, 2011), amphibians (Mitchell and Church, 2002), reptiles (Krecsak, 2008), birds (Nogueira and Alves, 2011) and mammals (Reisinger *et al.*, 2009). Albinism, derived from a Latin word 'albus' which means 'White', is a form of

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hypopigmentary congenital disorder, characterized by lack of melanin pigment and an animal with such a condition could have either pure or partial albinism (Cyril, 2009). Albinism is caused by the absence of the tyrosinase enzyme, which is necessary for the synthesis of melanin, resulting in the absence of pigment in the skin, the iris and the choroid. Further, it is due to a genetically inherited condition in which a recessive gene affects enzymes involved in the metabolism of various chromatophore pigments (Spadola and Toro 2007). Leucistic snakes have a diminished number of iridophores and probably very low number or no melanophores and xanthophores (Bechtel, 1991). Leucism is a form of partial albinism characterized by the normal pigmentation of eyes, legs and beak, while skin or feathers present lowered or absent coloration (Sage, 1962; Forrest and Naveen, 2000).

Many researchers consider leucism as partial albinism (McCardle, 2012; Costa de Noronha *et al.*, 2013). Albinism is caused by several different genes (Summers, 2009), while leucism is controlled by a single recessive allele (Owen and Shimmings, 1992). Inherited color defects, such as albinism and leucism, are well known in several animal species including snakes (Bechtel, 1991). Wild albino and leucistic animals are rare (Walter, 1938), mainly due to their low survival rates. Albinotic and leucistic individuals are less common in nature, but are popular and intentionally selected by herpetoculturists, who breed color variants of several species of Pythononiae and Colubridae (Bechtel, 1995).

Methodology

Healthy climatic and ecological condition of Amravati district (M.S.) India is well known for its rich biodiversity. On 23 July 2015, a white color snake was observed in a field near MIDC old bye pass road Amravati district (M.S.) India. Area lies between 20°55'33"N and 77°45'53" E. Specimen was observed, photographed and identified by observing morphological characters. For identification of the observed snake, keys and methods suggested by Daniel (2002), Whitaker and Captain (2008), and Khaire (2010) were used.

Observation and Discussion

Observed snake specimen was identified as adult *Macropisthodon plumbicolor* (Cantor, 1839) with leucism. Body of specimen was stout with approximate length of 21 inch. Dorsally, the snake was white in colour with light brown small bands from anterior to posterior part of body. An inverted V shaped light brownish coloured mark was present on the head. The dorsal scales were strongly keeled. Ventrally the belly was whitish to light cream in colour without any spots or markings. Eyes were large and green with round pupil as found in normal specimen. Tongue was pinkish in color. Tail was short (fig. 1 and 2).

Generally, the normal specimens have bright or dull green body, sometimes with faint irregular black bands. Body structure is rounded. Eye fairly large and the rostral scale are just visible from above. The dorsal scales are strongly keeled, in 23 to 27 rows. Young snakes have a bright yellow or orange inverted V shaped mark on neck, bordered on both sides by a dark blue-black area and also have a black stripe from eye to angle of mouth (Whitaker and Captain, 2004). Naturally feeds on toads, lizards and frogs.

A perusal of literature revealed that there are a number of instances of complete, incomplete and partial albinism in Indian reptiles in general and snakes in particular (Lahiri, 1955; Whitaker, 1971; Basu and Srivastava, 2003, Cyril, 2009; Vyas 2012, 2013; Vyas et al., 2012; Sayyed, 2012; Hoshing et al., 2013). Cases of albinism and leucism among viperinae have been also reported from Europe (Krecsák, 2008). Few cases of total albinos have been reported in *Macropisthodon plumbicolor* with yellowish

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body (Sayyed 2012) and whitish-pinkish body (Hoshing et al., 2013). A case of leucism has also reported in Pseudoboa nigra in southern Amazon, Brazil (Costa de Noronha et al., 2013).

Albinism can be defined in several different ways, but there are a few distinctive types of albinism depending on certain defining characteristics. True or complete albinism is the total absence of integumentary and retinal pigmentation (Sandoval et al., 2006). Partial albinism occurs when pigment is reduced or absent from the skin, feathers, or eyes (Berdeen and Otis, 2011). Leucism or leukism is a form of partial albinism characterized by retention of color in the eyes, bill, and legs but the skin or plumage contains no color pigment (Forrest and Naveen, 2000).

Vyas (2013) has pointed out that the further research is needed on histopathology and biopsies of skin tissue and 'dopa test' to enrich the knowledge on colour anomaly in reptilian species. Further, a substantial quantitative data is required to analyze the pattern of occurrence of leucism in snakes.



Image.1 Leucistic *Macropisthodon plumbicolor*



Image .2 Leucistic *Macropisthodon plumbicolor*

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3D-QSAR and docking studies on adenosine A_{2A} receptor antagonists by the CoMFA method

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3D-QSAR and docking studies on adenosine A_{2A} receptor antagonists by the CoMFA method

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Parkinson's disease affects millions of people around the world. Recently, adenosine A_{2A} receptor antagonists have been identified as a drug target for the treatment of Parkinson's disease. Consequently, there is an immediate need to develop new classes of A_{2A} receptor antagonists. In the present analysis, three-dimensional quantitative structure–activity relationship (3D-QSAR) studies were performed on a series of pyrimidines, using comparative molecular field analysis (CoMFA). The best prediction was obtained with a CoMFA standard model (q^2 = 0.475, r^2 = 0.977) and a CoMFA region focusing model (q^2 = 0.637, r^2 = 0.976) combined with steric and electrostatic fields. The structural insights derived from the contour maps helped to better interpret the structure–activity relationships. Also, to understand the structure–activity correlation of A_{2A} receptor antagonists, we have carried out molecular docking analysis. Based on the results obtained from the present 3D-QSAR and docking studies, we have identified some key features for increasing the activity of compounds, which have been used to design new A_{2A} receptor antagonists. The newly designed molecules showed high activity with the obtained models.

Keywords: 3D-QSAR; docking; CoMFA; A_{2A} receptor antagonists; drug design

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting up to 10 million people worldwide [1]. A disease that typically affects individuals of an advanced age, PD is often difficult to diagnose before the appearance of the typical signs and symptoms of advancing disease; the lack of an early diagnosis contributes to increased overall morbidity and decreased quality of life [2]. It is characterized by a motor impairment caused by the degeneration of dopaminergic neurons located in the substantia nigra pars compacta and by the reduction of dopamine levels in the striatum [3]. This reduction is responsible for the major symptoms of the disease, such as bradykinesia, muscular rigidity and tremor [4]. Adenosine is a neuro-modulator that coordinates responses to dopamine and other neurotransmitters that play important roles for motor function, mood, and memory [5–8]. Adenosine is known to act via four major receptor subtypes, A_1, A_{2A}, A_{2B} and A_3, which have been

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characterized according to their primary sequences [9]. At present, it is believed that A_{2A} receptor antagonists can be used in combination with the dopamine precursor L-DOPA to minimize the motor symptoms of patients with PD [10]. Selective A_{2A} antagonists have been a much sought-after target for the symptomatic relief of dopamine [11–13], with some reports suggesting that they may also slow disease progression because of their neuroprotective potential [14]. The potential of these antagonists has been deduced from considerable investigation of the functional interactions between dopamine and adenosine receptors in the basal ganglia [10]. These interactions can activate the dopamine receptor, or alternatively block the adenosine A_2 receptor as a means to improving the symptoms of PD. Recently, a novel series of benzyl substituted thieno[2,3-d] pyrimidines was identified as potent A_{2A} receptor antagonists by Shook et al. [15].

Computational chemistry has recently developed extensively and provided the rational drug design approach. Quantitative structure–activity relationship (QSAR) modelling results in a quantitative correlation between chemical structure and biological activity [16–21]. Typically, a 3D-QSAR analysis allows the identification of some key features around special substituents in a molecular graph for increasing the activity of compounds, and provides guidelines for the design of next-generation compounds with enhanced bioactivity or selectivity. A successful 3D-QSAR model not only helps in better understanding of the structure–activity relationships of any class of compounds, but also provides researchers an insight at the molecular level about lead compounds for further development [22]. The first applicable 3D-QSAR method was proposed by Cramer et al. in 1988 [23]. Among the current 3D-QSAR methods, comparative molecular field analysis (CoMFA) is widely used in drug design, because it allows rapid prediction of the biological activities of newly designed molecules [24–30]. In CoMFA, the biological activity of molecules is correlated with their steric and electrostatic interaction fields. However, the combination effects of fields around a molecule should be studied carefully for successful interpretation and designing of novel compounds, which is sometimes difficult due to insufficient experimental information. Another major problem with CoMFA modelling is its reduced sensitivity regarding the conformation of compounds but higher dependency on the alignment process. Therefore, to compensate for these deficiencies molecular docking analysis can be run to detect all interaction information, leading to better drugs. Coupling this information with that obtained by 3D-QSAR could result in a better understanding of regional effects with regard to biological activities.

In the present work, CoMFA and CoMFA region focusing studies were carried out on some pyrimidines such as adenosine A_{2A} receptor antagonists to understand the influence of different physico-chemical and structural parameters on these compounds. Molecular docking studies were also performed to detect the interactions leading to potent inhibitors, and based on the derived results some novel potent A_{2A} receptor antagonists have been designed.

2. Material and methods

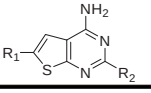
2.1 *Data set*

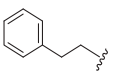
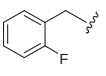
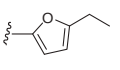
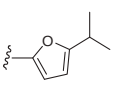
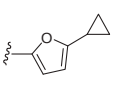
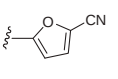
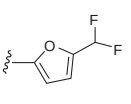
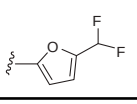
All pyrimidines and their biological activities (K_i) were taken from the literature [15]. A set of 46 compounds was divided into the training set (80% of compounds), and test set (20% of compounds) comprising 37 and nine molecules, respectively, by using the hierarchical clustering technique (Figure S1, available via the Supplementary Material section online). For smoother partial least-squares (PLS) analysis for the CoMFA model, all the reported affinity values of the pyrimidines were converted to $pK_i = -\log K_i$ (M). These molecules have wide

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range of affinity values (K_i). The test set compounds represent both the distribution of biological data and structural diversity. Molecular structures and their pK_i values are presented in Table 1. It can be seen that except for the highest and lowest activity, compounds were

Table 1. A_{2A} receptor antagonists and their observed and predicted activities.

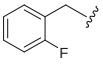
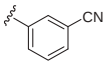


				Pred.			
No.	*R_1*	*R_2*	*Exp.(pIC_{50})*	*CoMFA-1*	*Res.*	*CoMFA-2*	*Res.*
1	H		6.96	7.03	–0.07	7.07	–0.11
2	Ph		7.17	7.17	0.00	7.23	–0.06
3	Bn		7.95	7.82	0.13	7.73	0.22
4			6.69	6.82	–0.13	6.86	–0.17
5[a]			7.96	8.34	–0.38	8.37	–0.41
6			8.54	8.38	0.16	8.36	0.18
7			8.43	8.33	0.10	8.29	0.15
8			7.40	7.54	–0.14	7.48	–0.07
9[a]	Bn		7.31	7.43	–0.12	7.60	–0.29
10	Bn		6.77	6.72	0.05	6.82	–0.05
11	Bn		6.58	6.59	–0.01	6.56	0.02
12	Bn		6.52	6.60	–0.08	6.50	0.02
13	Bn		7.60	7.70	–0.10	7.58	0.02
14			7.88	7.87	0.01	7.77	0.11

(*Continued*)

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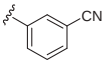
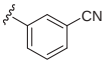
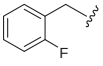
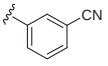
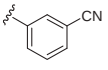
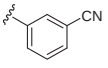
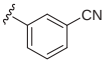
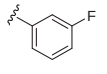
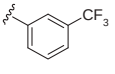
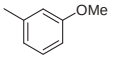
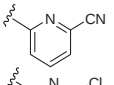
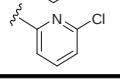
Table 1. (*Continued*).

No.	R_1	R_2	*Exp.*(pIC_{50})	*Pred.*			
				CoMFA-1	*Res.*	*CoMFA-2*	*Res.*
15	Bn		6.17	6.14	0.03	6.10	0.07
16[a]	Bn		8.33	8.53	–0.20	8.51	–0.18
17	Bn		8.05	8.34	–0.29	8.32	–0.27
18	Bn		7.79	7.59	0.20	7.54	0.25
19			7.88	7.95	–0.07	8.03	–0.15
20			8.16	8.32	–0.16	8.28	–0.12
21			8.01	8.06	–0.05	8.09	–0.08
22			7.00	6.99	0.01	7.11	–0.11
23			7.51	7.49	0.02	7.51	0.00
24			6.97	6.91	0.06	6.92	0.05
25	Bn		7.24	7.30	–0.06	7.20	0.04
26	Bn		6.27	6.20	0.07	6.23	0.04
27	Bn		6.30	6.43	–0.13	6.39	–0.09
28	Bn		6.68	6.60	0.08	6.58	0.10
29	Bn		7.53	7.38	0.15	7.40	0.13
30	Bn		7.94	7.92	0.02	7.94	0.00

(*Continued*)

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Table 1. (*Continued*).

				Pred.			
No.	R_1	R_2	*Exp.*(pIC_{50})	*CoMFA-1*	*Res.*	*CoMFA-2*	*Res.*
31			8.21	8.44	–0.23	8.42	–0.20
32			8.85	8.67	0.18	8.72	0.13
33[a]			8.14	8.35	–0.21	8.50	–0.35
34[a]			6.47	7.71	–1.24	7.77	–1.30
35[a]			7.20	7.85	–0.65	7.98	–0.78
36			6.65	6.61	0.04	6.66	–0.01
37	Bn		7.38	7.30	0.08	7.36	0.02
38	Bn		5.99	6.01	–0.02	5.94	0.05
39	Bn		6.93	6.83	0.10	6.99	–0.06
40[a]	Bn		6.23	7.15	–0.92	7.20	–0.97
41[a]	Bn		6.67	6.16	0.51	6.30	0.38
42	Bn		7.17	7.19	–0.02	7.23	–0.06
43	Bn		8.62	8.46	0.16	8.51	0.11
44	Bn		7.77	7.77	0.00	7.83	–0.06
45[a]	Bn		7.59	7.67	–0.08	7.83	–0.24
46	Bn		6.76	6.83	–0.07	6.79	–0.03

[a]Compounds used as test set.

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included in the training set, and the test set compounds have a range of biological activity values similar to that of the training set.

2.2 *Molecular modelling and alignment*

All molecular modelling and calculation studies were performed using the SYBYL X.1.1.1 [31] software package. The position of each atom is important to CoMFA because the descriptors are calculated based on the 3D space grid [32]. Energy minimization was performed using the Tripos force field with a distance-dependent dielectric and the Powell conjugate gradient algorithm with a convergence criterion of 0.01 kcal/mol Å. Partial atomic charges were calculated using the Gasteiger–Hückel method [33]. A good alignment of the complete data set is another essential element for successful CoMFA analysis. The quality and the predictive ability of the models are directly dependent on the alignment rules [34]. The lowest energy conformation of compound **32** was used as a template because it had the highest activity, and all other compounds were aligned on the basis of the common substructure. The structure of compound **32** with bold common substructure and aligned compounds are displayed in Figures 1 and 2.

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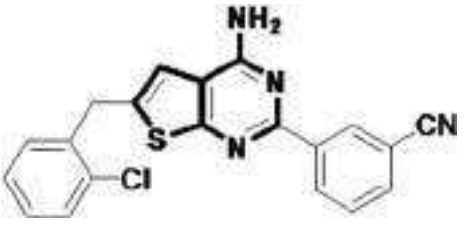


Figure 1. Structure of template compound (molecule **32**), common substructure is in bold.

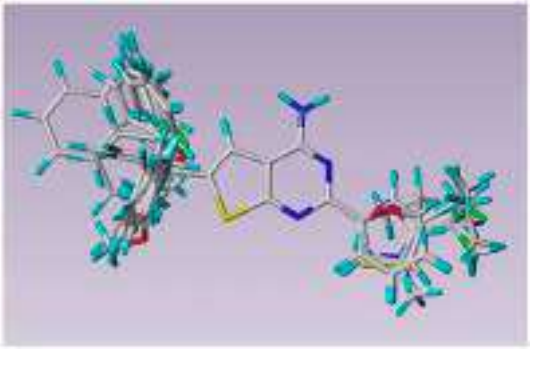


Figure 2. Alignment of training and test compounds on compound **32**.

2.3 *CoMFA setup*

CoMFA is a powerful and well-established tool for building 3D-QSAR models that can be applied to drug design [35,36]. The steric and electrostatic field energies for CoMFA were calculated at each lattice intersection of a regularly spaced grid of 2 Å. The lattice was defined automatically and is extended at least 4 Å beyond the van der Waals volume of all aligned molecules in X, Y and Z directions. The steric field represented by Lennard-Jones potential and the electrostatic field represented by coulombic potential were calculated using the Tripos force field and distance-dependent dielectric solvation treatment. A sp^3 carbon atom with a van der Waals radius of 1.52 Å and 1.0+ charge served as the probe atom to calculate these fields. The steric and electrostatic contributions were confined to the default 30 kcal/mol [27]. CoMFA region focusing is a method of application of weights to the lattice points in a CoMFA region to enhance or attenuate the contribution of these points to subsequent analysis. Here, 'StDev*-Coefficients' values and different weighing factors were applied in addition to grid spacing to achieve a better model [37].

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2.4 *Partial least-squares analysis*

Finding the best predictive model is the major objective of CoMFA analysis. PLS methodology was performed to quantify the relationships between the CoMFA descriptors and the biological activity. Column filtering was set to 1.0 kcal/mol to speed up the analysis and reduce the noise. The CoMFA descriptors were used as independent variables, and pK_i values as dependent variables in PLS regression analysis to derive 3D-QSAR models using the standard implementation in the SYBYL package [31]. The predictive ability of the models was evaluated by leave-one-out (LOO) cross-validation. This results in the cross-validation correlation coefficient (q^2) and the optimum number of components N. The final model was developed with an optimum number of components yielding the highest q^2 [16]. Then, the PLS analysis was performed without cross-validation, applying no column filtering. After this, the coefficient of determination (r^2) values, standard error of predictions and F values are calculated. The bootstrapping [38] and the leave-group-out cross-validation (10 groups out) techniques were carried out and confirmed by the average value for 10 runs from each cross-validation.

2.5 *Molecular docking*

The most active compound in the data set was docked into the active site of the A_{2A} receptor to provide the interactions between the ligand and receptor. The docking study was carried out using AutoDock 4.2 [39]. This program starts with a ligand molecule in an arbitrary conformation, orientation and position, and finds favourable dockings in a protein-binding site using both simulated annealing and genetic algorithms. Among crystallized complexes, PDB ID: 4EIY [40] was selected based on the resolution and the size of the co-crystal ligand which is similar to the experiment set. Initially, the protein was prepared by removing all water molecules, and polar hydrogen atoms and Kollman charges were introduced into the protein [41]. The grid box size and the grid spacing were set as 70, 70, 70 A˚ and 0.375 A˚, respectively. The number of docking runs was set to 50. The best docking result can be considered to be the conformation with the lowest energy. Pharmacophore studies were performed using the LigandScout 3.03 program [42].

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3. Results and discussion

3.1 *CoMFA analysis*

The 3D-QSAR model was established by CoMFA analysis, and its statistical parameters are listed in Table 2. The best results were obtained at a column filtering of 1.0 kcal/mol for both steric and electrostatic fields. The cross-validation [23,43] analysis was performed using the LOO method in which one compound is removed from the data set, and its activity is predicted using the model derived from the rest of the data set. This resulted in the cross-validation correlation coefficient (q^2) of 0.475 with an optimum number of components of six. Next, non-cross-validated PLS regression was performed using the six previously obtained factors, which resulted in the regression coefficients r^2 of 0.977, F = 210.564 and a standard error of estimate (S) of 0.155. The steric field descriptors explained 48.7% of the variance, while the electrostatic descriptors explained 51.3%.

The predicted activities for both training and test sets and also their residuals are listed in Table 1. Figure 3(a) depicts the correlation between the predicted activities and the experimental activities of the CoMFA model. From Figure 3(a), it can be seen that almost all points are rather uniformly distributed around the regression line, indicating no existence of systematic errors in the model, which further proves the satisfactory predictive ability of the derived model. The outlier status is due to the higher residual between the observed and predicted biological activity [44]. As can be seen, by inclusion of compound **34**, the model shows poor predictive ability with an r^2 of 0.578 for the test set. Omission of compound number **34** results in an increased r^2_{test} value to 0.715. Therefore, compound number **34** in the optimum CoMFA model is treated as an outlier. After excluding the outlier, the activities predicted by the constructed CoMFA model are in good agreement with the experimental data, suggesting that a reliable CoMFA model was successfully constructed.

Region focusing was considered as an additional strategy to improve q^2. As an iterative procedure, it involves giving additional weight to the lattice points in a given CoMFA region to enhance or attenuate the contribution of those points in a further analysis [34]. A new model (CoMFA-2) was generated with increased predictive power (q^2), enhanced resolution, tighter grid spacing and greater stability at the same number of components [37]. It can be seen from the CoMFA-2 model in Table 2 that the application of region focusing resulted in

Table 2. Statistical results of CoMFA models.

	CoMFA-1	*CoMFA-2(after region focusing)*
PLS statistics		
LOO cross q^2 /SEP[a]	0.475/0.592	0.637/0.492
Group cross q^2 /SEP	0.481/0.589	0.612/0.509
Non-validated r^2 /SEE[b]	0.977/0.155	0.976/0.128
CCC_{tr}/CCC_{ext}	0.988/0.669	0.988/0.632
F	210.564	199.982
$r^2_{bootstrap}$	0.984 ± 0.005	0.973 ± 0.011
$S_{bootstrap}$	0.105 ± 0.062	0.168 ± 0.081
Optimal compounds	6	6
r^2_{test}	0.715	0.728
Field distribution %		
Steric	48.7	46.8
Electrostatic	51.3	53.2

[a]SEP: standard error of prediction.
[b]SEE: standard errors of estimate.

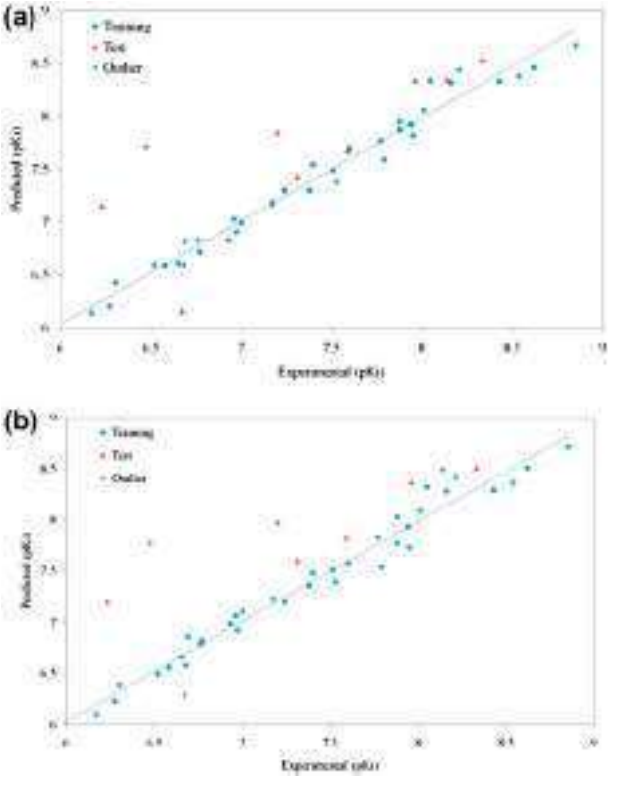


Figure 3. Plot of the calculated vs. observed pK_i values using CoMFA (a) and CoMFA region focusing (b) analysis.

a significant increase for the internal validity (q^2) from 0.475 to 0.637. The steric and electrostatic field contributions to the final CoMFA-2 model were 46.8% and 53.2%, respectively. A graph of observed versus predicted activities of the CoMFA region focusing model was plotted, as shown in Figure 3(b). For the CoMFA region focusing model, molecule **34** is also regarded as an outlier since its residual between the experimental value and the predicted value is high. By inclusion of this compound, the model shows poor predictive ability with r^2_{test} of 0.602, and omission of compound **34** results in an increased r^2_{test} value to 0.728. This analysis revealed that the proposed CoMFA model could also adequately predict all the compounds in the test set. This suggests that the CoMFA model is reliable for predicting structural requirements to improve potency of the target chemicals. Y-randomization analysis was also performed over CoMFA results (Figure S2, available on the article's online page), and after 15 randomly iterations of Y-response, the results indicated that the derived CoMFA model could be accepted and the difference between q^2 and r^2 values will not generate a significant problem.

3.2 *Contour maps*

To visualize the information content of the derived 3D-QSAR models, CoMFA contour maps were generated. Such contour maps provide some information (such as steric and electrostatic) on factors affecting the activity of the studied compounds. This is particularly

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important when increasing or reducing the activity of a compound by changing its molecular structure [45]. The CoMFA contour maps of steric and electrostatic fields for CoMFA and CoMFA region focusing are shown in Figures 4 and 5, respectively. As can be seen, the contour maps of CoMFA are well correlated with the CoMFA region focusing contour maps.

The contour maps using region focusing are of better quality because the region focusing resulted in a sort of image enhancement. The CoMFA green contours (contribution level of 80%) indicate the area in which steric bulk might have a positive effect on activity, while the yellow regions (contribution level of 20%) are favourable for small groups. Similarly, the blue contours indicate regions where the addition of electropositive substituent increases activity (contribution level of 80%); red indicates regions where the addition of an electronegative substituent increases activity (contribution level of 20%).

The steric contour map of CoMFA-2 region focusing (Figure 5(a)) shows the large green contours around the R_1 substituent. This indicates that bulky groups around the R_1 substituent are beneficial to activity. This conclusion is in agreement with the experimental results by Shook et al. [15]. According to molecules1 and 2 in the data set (see Table 1), the two molecules have the same structure except in the R_1 position, while the R_1 substituent is H and Ph for compounds 1 and 2, respectively. As can be seen, by increasing the size of R_1 from H to Ph, the pK_i values will increase from 6.96 to 7.17. Several small yellow regions near the R_2

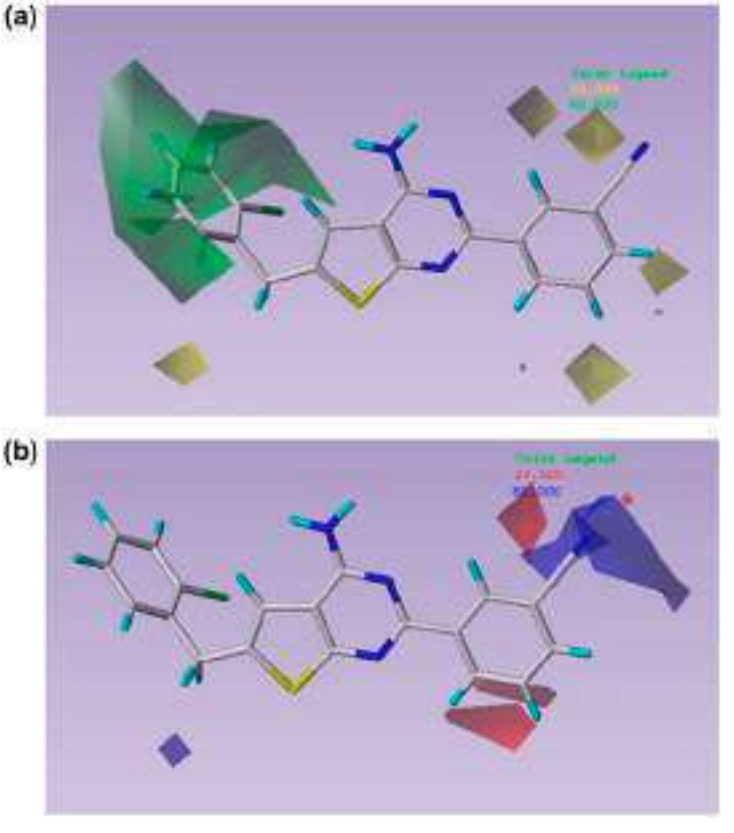


Figure 4. Contour maps of CoMFA: steric (a) and electrostatic (b) based on compound **32**.

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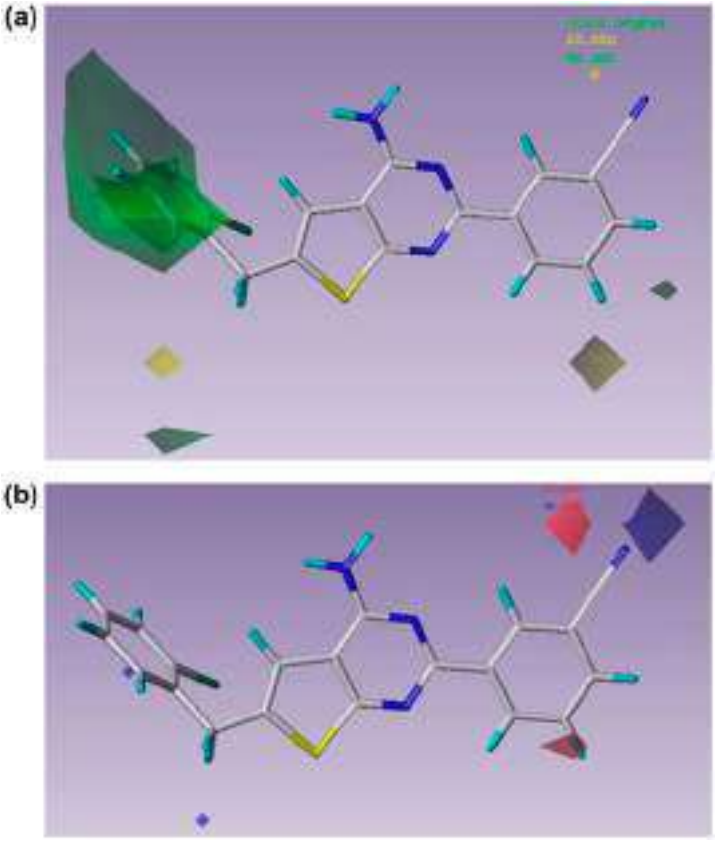


Figure 5. Contour maps of CoMFA region focusing: steric (a) and electrostatic (b) based on compound **32**.

position indicate that the less bulky substituents are preferred for higher activity. This may be the reason why compounds with small substituents in this area, for example compounds 3 and 9, have higher biological activity than molecules with bulky substituents, such as compounds 11 and 10.

The electrostatic contour map is displayed in Figure 5(b) for the CoMFA-2 model. Two regions of red beside the R_2 substituent (between positions 1 and 2 and also at position 4 of the benzene ring) show that presence of the electronegative substituents such as CN and F is very important for increasing biological activity (pK_i), in such a way that compounds 13 and 30 are more potent than compounds 10 and 29. A blue region near R_2 (at position 2 of the benzene ring) means that electropositive substituents at this region would increase the biological activity (pK_i). This information will be used for the design of new A_{2A} receptor antagonists.

3.3 *Docking result of the most potent molecule*

We selected the most potent inhibitor **32** in the experiment to perform the docking study. Figure 6 represents the interaction model of that with A_{2A} receptor, in which the inhibitor is

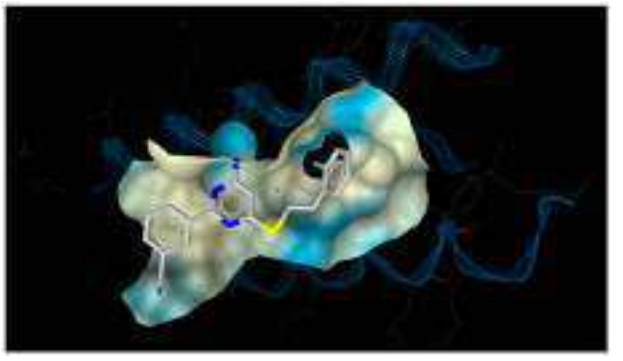


Figure 6. Docking conformation of the most potent inhibitor 32 with corresponding binding pocket of A_{2A} receptor.

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suitably situated at the binding site. As can be seen, there are various interactions between the inhibitor and the binding region of the enzyme. The two-dimensional representation for the interaction mode between compound **32** and the A_{2A} receptor generated by the LigandScout 3.03 program is shown in Figure 7. The phenyl and methyl groups showed hydrophobic interactions with Leu 194, Leu 190, Alu 243, Val 239 and Leu 194, Alu 236, Tyr 197 and Val 239 residues, respectively. Also, one hydrophobic interaction is formed between the benzonitrile ring of compound **32** and the Phe 201 residue. Therefore, according to structural analyses and study of existing interactions, we can conclude that these residues play an important role in compound affinity potency with the A_{2A} receptor. As a result, the docking mode of compound **32** provided some important information for the development of novel A_{2A} receptor antagonists. For more details about molecular docking results, the Discovery studio program

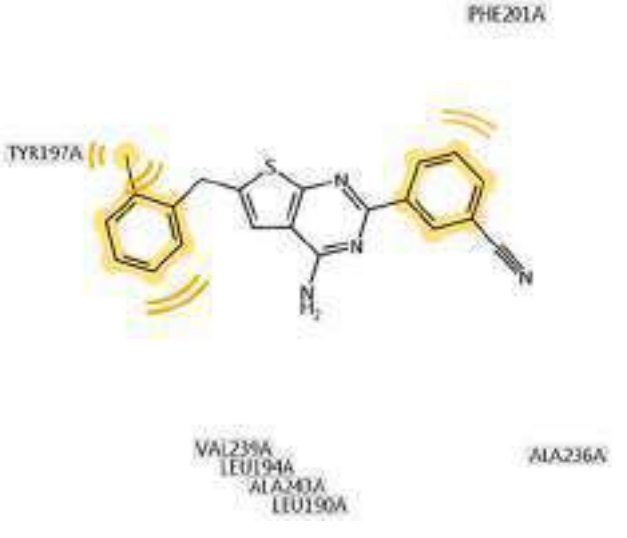
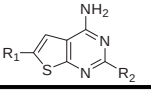
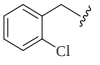
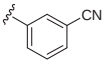
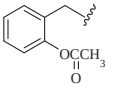
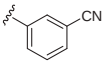
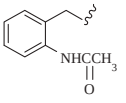
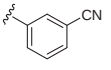
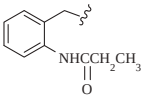
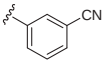
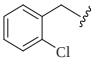
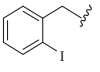
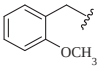
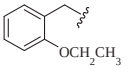
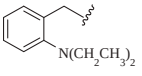
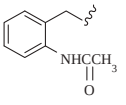
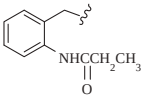
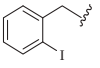


Figure 7. 2D structure of interaction sketched by LigandScout program.

Table 3. Structure and predicted pIC_{50} values of newly designed compounds.



No.	Substituents		Predicted pIC_{50}	
	R_1	R_2	CoMFA-1	CoMFA-2
32			**8.67**	**8.72**
N1			8.65	8.61
N2			8.50	8.38
N3			8.61	8.54
N4			8.95	9.08
N5			8.92	9.06
N6			8.81	8.98
N7			8.61	8.80
N8			8.62	8.76
N9			8.96	8.93
N10			9.00	8.99
N11			8.61	8.91

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was also used, and the results can be found in the supplementary information (available online). Meanwhile, docking analysis was also employed for the main ligand (4-{2-[(7-amino-2-furan-2-yl [1,2,4] triazolo [1,5-a] [1,3,5] triazin-5-yl) amino] ethyl} phenol) of receptor (4EIY) to compare with residuals derived for compounds **32** and N4. The results were amended in SIF and showed some similar residuals responsible for increasing the biological activities of these inhibitors.

3.4 *Design of new A_{2A} receptor antagonists*

Based on the structure–activity relationship obtained these 3D-QSAR models, a series of new A_{2A} receptor antagonists was designed and predicted by the obtained models (Table 3). The most potent molecule (compound **32**) was used as a reference structure to design new molecules. These new proposed compounds were generated by combining some bulky and electron-donating groups, such as a substituents containing -NHCOR, $-N(CH_2CH_3)_2$, $-OCOCH_3$, -OR, NH_2, Cl and I groups at the R_1 position, and some electron-withdrawing groups such as CN and electron-donating group such as  at R_2 position, and some new compounds were designed. Most of them greatly enhanced A_{2A} receptor activity in comparison with the reference molecule; in particular, compound N4 showed the strongest activity with its predicted $pK_i = 9.08$. Other compounds as well as compound **32** also exhibited predicted activity well. Such results further suggest that these CoMFA models have strong predictive ability and can be prospectively used in molecular design or structural modification. Docking analyses were also performed for the most potent designed compound (N4) and amended to SIF. The results of docking showed that the designed compound has a large number of interactions with its receptor and indicated higher biological activity.

4. Conclusion

The 3D-QSAR models of 46 pyrimidines as adenosine A_{2A} receptor antagonists were developed using the CoMFA technique. The CoMFA region focusing model provided the most significant correlation of steric and electrostatic fields with biological activity. The developed model had high internal validity (q^2 above 0.5) and high predictive ability (test set r^2 above 0.5). The CoMFA region focusing contour maps emphasized important regions in 3D space where modifications of steric and electrostatic properties would be strongly associated with concomitant changes in observed activity. The docking results showed that hydrophobic interactions were highly correlated with the activities of A_{2A} receptor antagonists. Some potent compounds were designed based on analysis of contour maps. The proposed models are being used to predict the A_{2A} receptor antagonist activity of newly designed compounds. These models could provide useful information for the design of new potent A_{2A} receptor antagonists.

Supplementary material

The supplementary material for this paper is available online at http://dx.doi.org/10.1080/1062936X.2015.1049666.

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Optimization of antiproliferative activity of substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates: QSAR and CoMFA analyses

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ABSTRACT

Multiple separate quantitative structure–activity relationships (QSARs) models were built for the antiproliferative activity of substituted Phenyl 4-(2-Oxoimidazolidin-1-yl)-benzenesulfonates (PIB-SOs). A variety of descriptors were considered for PIB-SOs through QSAR model building. Genetic algorithm (GA), available in QSARINS, was employed to select optimum number and set of descriptors to build the multi-linear regression equations for a dataset of PIB-SOs. The best three parametric models were subjected to thorough internal and external validation along with *Y*-randomization using QSARINS, according to the OECD principles for QSAR model validation. The models were found to be statistically robust with high external predictivity. The best three parametric model, based on steric, 3D- and finger print descriptors, was found to have $R^2 = 0.91$, $R^2_{ex} = 0.89$, and $CCC_{ex} = 0.94$. The CoMFA model, which is based on a combination of steric and electrostatic effects and graphically inferred using contour plots, gave $F = 229.34$, $R^2_{CV} = 0.71$ and $R^2 = 0.94$. Steric repulsion, frequency of occurrence of carbon and nitrogen at topological distance of seven, and internal electronic environment of the molecule were found to have correlation with the anti-tumor activity of PIB-SOs.

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1. Introduction

Recent reports from WHO and other organizations clearly highlights cancer as a leading cause of mortality, and economic problems for millions of peoples (WHO, 2012, 2013). Chemotherapy is a preferred method of treatment, although, various therapies like radiation, different types of surgeries etc. are available Chemotherapy for cancer treatment usually involves three or four anti-cancer drugs in combination (Aziz et al., 2013; Natarajan and Senapati, 2012; Temirak et al., 2012). Few examples of anticancer drugs are presented in Fig. 1. Despite high treatment success in many cases, severe side effects and emergence of resistance for marketed anti-cancer drugs are serious concerns for modern chemotherapy (Fortin et al., 2011; Krishnegowda et al., 2011; Temirak et al., 2012). Therefore, extensive search for a drug with high activity against cancer and good ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile is a challenge for modern medicinal chemistry.

Modern medicinal chemists employ different strategies to optimize the pharmacological activity, the ADMET profile and a viable synthesis route for an available lead candidate (i.e. lead optimization). In modern drug designing process, computer-aided drug design (CADD) is helpful in identifying new potent compounds and saves drug development time, and money. It provides a useful alternative to animal testing, as well. CADD is a method of choice in drug designing process due to its faster, economical, and result oriented high success rate (Mahajan et al., 2012, 2013; Masand et al., 2012a,b, 2013a,b). QSAR, molecular docking, pharmacophore modeling, etc. are some of the successful brushwood of CADD that have led to the introduction of many drugs in the market (Jawarkar

Abbreviations: CoMFA, comparative molecular field analysis; PIB-SOs, Phenyl 4-(2-Oxoimidazolidin-1-yl)-benzenesulfonates; GA, genetic algorithm; MLR, multiple linear regression; QSAR, quantitative structure–activity relationship; ADMET, Absorption, Distribution, Metabolism, Excretion and Toxicity; CADD, computer aided drug designing; OLS, ordinary least square; QSARINS, QSAR insubria.

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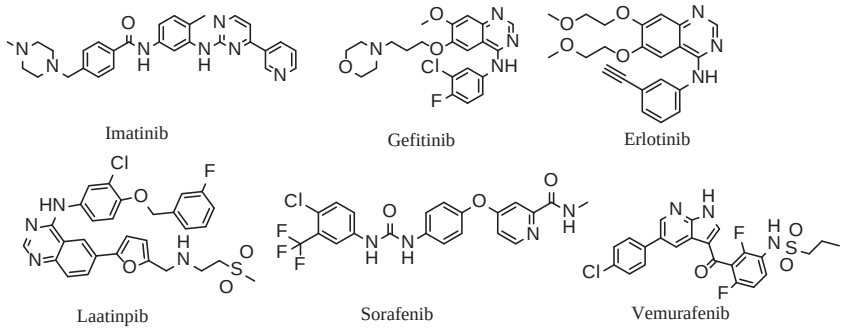


Fig. 1. Few examples of approved anti-cancer drugs.

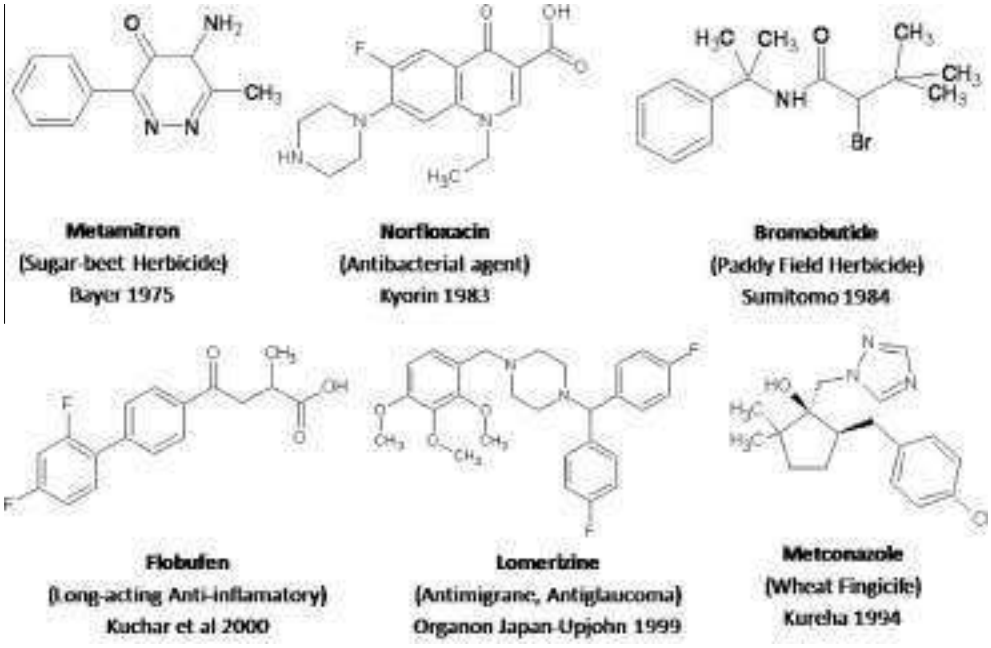


Fig. 2. Some of the commercial drugs developed using QSAR.

et al., 2010; Mahajan et al., 2010, 2012, 2013; Masand et al., 2011, 2012a,b, 2010a,b, 201s3a,b) (see Fig. 2).

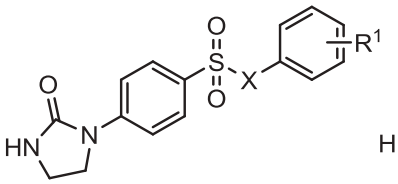
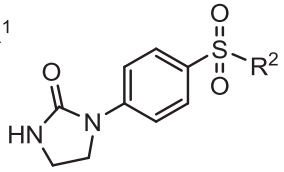
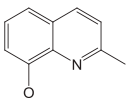
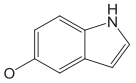
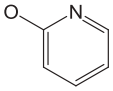
Molecular docking can be effectively used for optimization of drug when the 3D structure of the protein/enzyme with which the drug interacts is known (Mahajan et al., 2012). According to one school of thought, in absence of information about the target protein/receptor, QSAR and pharmacophore modeling are preferable techniques for lead optimization (Mahajan et al., 2012). Since the exact mechanism of action and the receptors with which PIB-SOs interact are unknown (Fortin et al., 2011; Turcotte et al., 2012), we have performed extensive QSAR, and CoMFA (ligand based drug design) analyses on PIB-SOs to determine the structural features that control their anti-proliferative activity. This will provide understanding of drug mechanism for PIB-SOs class and will help in developing potentially active and better drug candidates against cancer.

The selected dataset (Fortin et al., 2011; Turcotte et al., 2012) consists of ninety seven PIB-SOs having diverse substituents like $-NH_2$, $-OH$, $-OCH_3$ and $-Cl$. The compounds were assayed against skin melanoma M-21 cell lines according to the NCI/NIH Developmental Therapeutics Program (Fortin et al., 2011; Turcotte et al., 2012). The activity expressed as the concentration of drug inhibiting cell growth by 50% (IC_{50}) was converted to pIC_{50} ($-\log_{10}$ IC_{50}) for QSAR analysis (Jawarkar et al., 2010; Mahajan et al., 2010, 2012; Masand et al., 2013a). The substituents, experimental IC_{50} and pIC_{50} have been listed in Table 1.

The standard procedure as specified in SYBYL was followed to build a database of ninety-seven PIB-SOs. For thriving CoMFA analysis, proper alignment of 3D structures of the molecules is very important (Mahajan et al., 2012; Masand et al., 2012a, 2010a). To enhance the fruitfulness of CoMFA analysis, Gasteiger–Marsili partial charges were assigned to all the molecules before carrying out descriptor calculation and alignment. The lowest energy conformer of most active compound **92** was used as a template structure for aligning the compete set of molecules. The molecules in their respective lowest conformations were superimposed on the template using the atom based alignment option in SYBYL. It was followed by partial least square (PLS) analysis and 3D contour generation with optimum number of components set to 5. Default settings and procedure as implemented in SYBYL were used throughout the work.

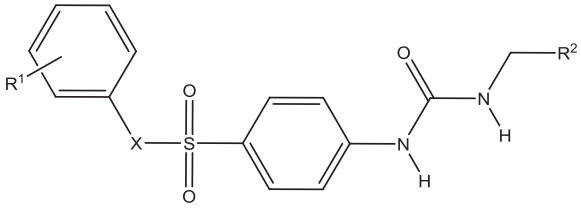
The central idea of the present work is to use conventional QSAR to obtain extensive information about the structural features that govern the activity. Therefore, a new strategy was employed, in which, multiple models were built using 50% training set and validating them on remaining set (50% prediction set) using random splitting. In next step, the training and the prediction sets were interchanged for model building and validation. Thus, new

Table 1
Experimental data showing IC_{50} and pIC_{50} for substituted *N*-phenyl ureidobenzenesulfonate derivatives.

S. no.	X	R^1 or R^2	IC_{50} (μM) (M-21)	pIC_{50} (M) (M-21)
				
1.	O	2-Me	26	7.585
2.	O	3-Me	54	7.268
3.	O	4-Me	93	7.032
4.	O	4-OMe	98	7.009
5.	O	4-NMe_2	350	6.456
6.	O	2-Et	52	7.284
7.	O	2-Prop	61	7.215
8.	O	2-OMe	130	6.886
9.	O	2-OEt	24	7.62
10.	O	2-Cl	45	7.347
11.	O	2-F	34	7.469
12.	O	2-I	40	7.398
13.	O	2-NO_2	150	6.824
14.	O	2-Me,3-Me	17	7.77
15.	O	2-Me,4-Me	39	7.409
16.	O	2-Me,5-Me	8.5	8.071
17.	O	2-Me,4-Me, 5-Me	41	7.387
18.	O	2-Cl,4-Cl, 5-Cl	31	7.509
19.	O	2-Cl,4-Cl, 6-Cl	120	6.921
20.	O	2-F,4-F	35	7.456
21.	O	2-F,6-F	15	7.824
22.	O	2-F,3-F,4-F,5-F, 6-F	220	6.658
23.	O	3-Prop	27	7.569
24.	O	3-OMe	24	7.62
25.	O	3-OEt	12	7.921
26.	O	3-Cl	9.2	8.036
27.	O	3-F	31	7.509
28.	O	3-I	10	8
29.	O	3-NO_2	48	7.319
30.	O	3-NH_2	170	6.77
31.	O	3-Me,5-Me	16	7.796
32.	O	3-Me,4-Me,5-Me	15	7.824
33.	O	3-OMe,4-OMe	45	7.347
34.	O	3-OMe,5-OMe	4.3	8.367
35.	O	3-OMe,4-OMe,5-OMe	4	8.398
36.	O	2-Cl,5-Cl	8.2	8.086
37.	O	3-F,4-F	47	7.328
38.	O	3-F,5-F	15	7.824
39.	O	3-F,4-F,5-F	43	7.367
40.	O	3-Me,4-NO_2	100	7
41.	O	3-Me,4-NH_2	360	6.444
42.	O	4-Et	120	6.921
43.	O	4-Prop	59	7.229
44.	O	4-secBut	830	6.081
45.	O	4-OEt	39	7.409
46.	O	4-OProp	96	7.018
47.	O	4-OBut	530	6.276
48.	O	4-Cl	58	7.237
49.	O	4-F	89	7.051
50.	O	4-I	110	6.959
51.	O	4-NO_2	570	6.244
52.	O	4-NH_2	920	6.036
53.	O		130	6.886
54.	O		65	7.187
55.	O		290	6.538
56.	O	3-OMe,4-OMe,5-OMe	240	6.62

(*continued on next page*)

Table 1 (*continued*)

S. no.	X	R^1	R^2	IC_{50} (μM) (M-21)	pIC_{50} (M) (M-21)
					
57.	O	4-OH	4-CEU	2.8	5.553
58.	O	2-Me	3-CEU	7.2	5.143
59.	O	2-CH_2-CH_3	3-CEU	21	4.678
60.	O	2-$(CH_2)_2$-CH_3	3-CEU	18	4.745
61.	O	4-OH	3-CEU	43	4.367
62.	O	2-CH_2-CH_3	4-CEU	1.2	5.921
63.	O	2-$(CH_2)_2$-CH_3	4-CEU	40	4.398
64.	NH	2-Me	3-CEU	4.8	5.319
65.	NH	2-CH_2-CH_3	3-CEU	17	4.77
66.	NH	2-$(CH_2)_2$-CH_3	3-CEU	73	4.137
67.	NH	2-Me	4-CEU	13	4.886
68.	NH	2-CH_2-CH_3	4-CEU	2.1	5.678
69.	NH	2-$(CH_2)_2$-CH_3	4-CEU	91	4.041
70.	O	2-Me	3-CPU	65	4.187
71.	O	2-CH_2-CH_3	3-CPU	17	4.77
72.	O	2-$(CH_2)_2$-CH_3	3-CPU	63	4.201
73.	O	4-OH	3-CPU	68	4.167
74.	O	2-Me	4-CPU	29	4.538
75.	O	2-CH_2-CH_3	4-CPU	29	4.538
76.	O	2-$(CH_2)_2$-CH_3	4-CPU	24	4.62
77.	O	4-OH	4-CPU	15	4.824
78.	NH	2-Me	3-CPU	49	4.31
79.	NH	2-CH_2-CH_3	3-CPU	25	4.602
80.	NH	2-$(CH_2)_2$-CH_3	3-CPU	15	4.824
81.	NH	2-Me	4-CPU	13	4.886
82.	NH	2-$(CH_2)_2$-CH_3	4-CPU	47	4.328
83.	O	2-Me	4-CEU	60	4.222
84.	O	2-CH_2-CH_3	3-EU	23	4.638
85.	O	4-OH	3-EU	38	4.42
86.	O	2-Me	4-EU	51	4.292
87.	O	2-CH_2-CH_3	4-EU	30	4.523
88.	O	2-$(CH_2)_2$-CH_3	4-EU	25	4.602
89.	O	4-OH	4-EU	42	4.377
90.	O	3-Me	4-CEU	3.1	5.509
91.	NH	2-Me	3-EU	2.5	5.602
92.	NH	2-CH_2-CH_3	3-EU	0.8	6.097
93.	NH	2-$(CH_2)_2$-CH_3	3-EU	4.3	5.367
94.	NH	2-CH_2-CH_3	4-EU	131	3.883
95.	O	4-Me	4-CEU	60	4.222
96.	O	4-OMe	4-CEU	90	4.046
97.	O	4-$N(Me)_2$	4-CEU	41	4.387

CEU: 2-chloroethylurea; PIB-SO: Phenyl 4-(2-oxoimidazolidin-1-yl)benzenesulfonate; PUB-SO: *N*-phenyl ureidobenzenesulfonate; PUB-SA: *N*-phenyl ureidobenzenesulfonamide; CPU: 3-chloropropylurea; EU: ethylurea;

multiple models were built and validated on prediction set (which was initially the training set). This ensures that all the relevant information about the structural features that governs the anti-tumor activity of these molecules is expressed in the developed QSAR models. Additionally, multiple QSAR models were built using whole dataset (no splitting) to verify the capturing of all the relevant structural and activity information (see Fig. 3).

Modeling subjective feature selection using genetic algorithm (GA) in QSARINS was employed for selecting optimum number and set of descriptors for ordinary least square (OLS) model development. The heuristic search was limited to three variables per model in order to develop easy and informative GA-MLR QSAR models. The selected descriptors were used to build the statistically robust OLS QSAR models followed by thorough statistical validation according to the OECD principles for QSAR model validation. QSARINS was used to build tri-parametric OLS models with default settings, except for Lack of Fit (LOF) which was set to a value of 0.5. The selected fitness function used to maximize in GA was Q^2, this avoids naive Q^2 also. All the models having low internal and external predictivity were rejected. The descriptors that were selected in model-1 to 12 are provided in supplementary information.

All the models were subjected to thorough internal as well as external validation along with *Y*-scrambling using QSARINS to eliminate over-fitting and spurious models. Various parameters for internal validation include: determination coefficient R^2, leave-one-out (LOO) cross-validation Q^2, leave-many-out (LMO) cross validation Q^2_{LMO}, coefficient of determination for *Y*-scrambling R^2_{Yscr}, and root mean squared error (*RMSE*). The LMO were repeated 500 times with 30% of the objects left out randomly from the training set each time; the mean value of Q^2_{LMO} has been reported. The external validation parameters are $RMSE_{ex}$, MAE_{ex}, R^2_{ex}, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, and CCC_{ex}.

Model validation was carried out also by checking the model applicability domain (AD), which was verified by the Williams plots. AD is a theoretical region defined by the physico-chemical,



Fig. 3. Flowchart diagram for the methodology used in the present study.

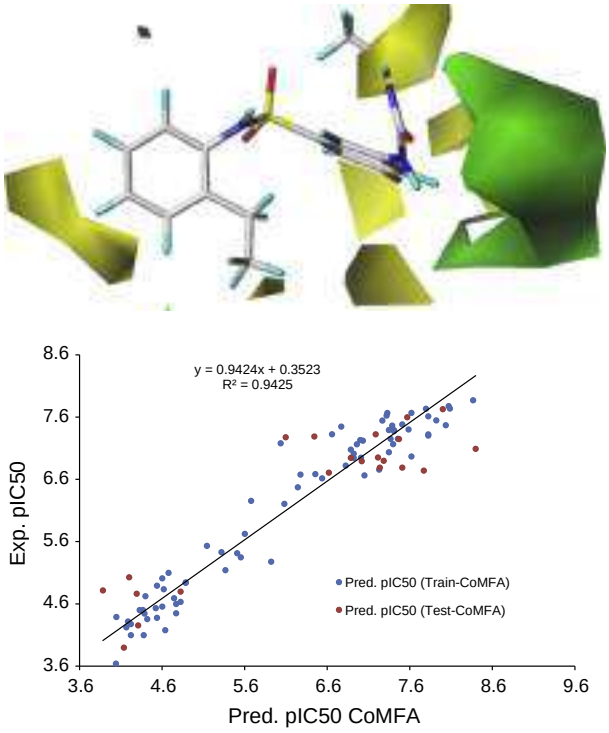


Fig. 4. CoMFA contour maps for PIB-Sos with compound **92** as representative along graph correlation between experimental and predicted pIC_{50} (CoMFA model).

structural or biological space on which the model has been developed using the training set, it's applicable to make predictions for new compounds. Thus, AD is related to interpolation rather than extrapolation. A widely accepted method for AD determination is based on leverage calculation from the diagonal values of the hat matrix using modeling modelecular descriptors. It is evaluated by leverage (or hat) analysis using the formula: $h_i = x_i\ (X^T\ X)^{-1}\ x_i^T$ where ($i = 1, \ldots, m$), x_i is the descriptor row-vector of the query compound i, m is the number of query compounds and X is the $n \times p$ matrix of the training set (p is the number of descriptors in the model and n is the number of compounds in the training set). The limit of the model domain is quantitatively defined by the leverage cut-off h^* and is set as $3(p + 1)/n$. A leverage bigger than h^* for the training set means that the compound is very dominant in determining the model. For the prediction set (X outlier), it means that the prediction is the substantial extrapolation of the model and could be unreliable. Also, a compound with a

Table 2
Multiple separate GA-MLR QSAR models for antiproliferative activity of PIB-SOs.

S. no.	Variable	Coefficient	Std. Coeff.	C. I. 95%
Model-1	*Intercept*	49.77		4.17
	X3A	−177.39	−0.71	24.74
	BEHp6	−3.35	−0.28	1.26
	F07[C-N]	−0.67	−0.29	0.22
Model-2	*Intercept*	58.21		6.58
	MAXDP	−1.95	−0.22	0.87
	X3A	−215.22	−0.86	22.85
	F07[C-N]	−0.73	−0.31	0.22
Model-3	*Intercept*	44.15		4.51
	X3A	−188.50	−0.75	24.92
	RDF020u	−0.22	−0.22	0.10
	F07[C-N]	−0.84	−0.36	0.21
Model-4	*Intercept*	42.53		4.78
	X3A	−197.012	−0.79	23.69
	R4e+	35.29	0.21	16.08
	F07[C-N]	−0.79	−0.34	0.22
Model-5	*Intercept*	42.94		4.73
	X3A	−181.94	−0.73	26.48
	R7u	−1.98	−0.23	0.91
	F07[C-N]	−0.85	−0.37	0.21
Model-6	*Intercept*	41.51		5.08
	X3A	−170.69	−0.68	29.75
	R8e	−3.42	−0.27	1.61
	F07[C-N]	−0.71	−0.31	0.23
Model-7	*Intercept*	16.53		4.88
	Xt	−120.44	−0.52	21.12
	VEA2	113.18	0.80	13.35
	F07[C-N]	−0.54	−0.21	0.23
Model-8	*Intercept*	13.95		5.45
	Xt	−115.31	−0.50	23.73
	VEA2	113.71	0.80	14.31
	RDF110v	0.16	0.20	0.08
Model-9	*Intercept*	15.90		5.37
	Xt	−121.54	−0.53	23.40
	VEA2	116.92	0.83	14.26
	F06[C-N]	−0.39	−0.17	0.23
Model-10	*Intercept*	13.90		5.73
	Xt	−96.15	−0.42	32.64
	VEA2	94.73	0.67	22.92
	nHDon	−0.49	−0.28	0.30
Model-11	*Intercept*	17.18		5.40
	Xt	−127.03	−0.55	22.97
	VEA2	114.81	0.81	15.23
	B01[N-S]	−0.64	−0.16	0.43
Model-12	*Intercept*	19.43		5.63
	Xt	−133.04	−0.58	22.56
	VEA2	122.21	0.87	13.95
	R4v	−4.63	−0.13	3.27

C. I. – Confidence interval and Std. coeff. – Standardized Coefficient.

Table 3
Statistical parameters for multiple separate GA-MLR QSAR models 1–12 for antiproliferative activity of PIB-SOs.

S. no.	Statistical parameter	Model-1	Model-2	Model-3	Model-4	Model-5	Model-6
1.	N_{tr}	49	49	49	49	49	49
2.	N_{ex}	48	48	48	48	48	48
Fitting parameters							
3.	R^2_{tr}	0.92	0.91	0.91	0.91	0.90	0.90
4.	$R^2_{adj.}$	0.91	0.90	0.90	0.90	0.90	0.90
5.	*LOF*	0.17	0.20	0.20	0.20	0.20	0.20
6.	$RMSE_{tr}$	0.38	0.40	0.40	0.40	0.41	0.41
7.	MAE_{tr}	0.30	0.31	0.32	0.31	0.28	0.30
8.	CCC_{tr}	0.96	0.95	0.95	0.95	0.95	0.95
9.	*s*	0.40	0.42	0.42	0.42	0.43	0.43
10.	*F*	167.87	147.15	145.54	145.05	143.65	141.82
Internal validation parameters							
11.	R^2_{cv} (Q^2)	0.89	0.88	0.88	0.88	0.88	0.88
12.	$RMSE_{cv}$	0.43	0.46	0.45	0.46	0.46	0.46
13.	MAE_{cv}	0.33	0.35	0.35	0.34	0.31	0.33
14.	CCC_{cv}	0.94	0.94	0.94	0.94	0.94	0.93
15.	Q^2_{LMO}	0.90	0.89	0.89	0.89	0.89	0.89
16.	R^2_{Yscr}	0.06	0.06	0.06	0.06	0.06	0.06
External validation parameters							
17.	$RMSE_{ex}$	0.55	0.48	0.55	0.59	0.49	0.54
18.	MAE_{ex}	0.43	0.38	0.40	0.45	0.39	0.42
19.	R^2_{ex}	0.85	0.89	0.85	0.83	0.88	0.86
20.	Q^2_{F1}	0.85	0.89	0.85	0.83	0.88	0.86
21.	Q^2_{F2}	0.85	0.89	0.85	0.83	0.88	0.86
22.	Q^2_{F3}	0.83	0.87	0.83	0.80	0.86	0.83
23.	CCC_{ex}	0.92	0.94	0.92	0.91	0.94	0.92

S. no.	Statistical parameter	Model-7	Model-8	Model-9	Model-10	Model-11	Model-12
1.	N_{tr}	48	48	48	48	48	48
2.	N_{ex}	49	49	49	49	49	49
Fitting parameters							
3.	R^2_{tr}	0.92	0.91	0.91	0.91	0.90	0.90
4.	$R^2_{adj.}$	0.92	0.91	0.90	0.90	0.90	0.89
5.	*LOF*	0.19	0.22	0.23	0.23	0.24	0.24
6.	$RMSE_{tr}$	0.40	0.42	0.44	0.44	0.44	0.45
7.	MAE_{tr}	0.31	0.34	0.34	0.34	0.35	0.35
8.	CCC_{tr}	0.96	0.95	0.95	0.95	0.95	0.95
9.	*s*	0.42	0.44	0.45	0.46	0.46	0.47
10.	*F*	171.77	152.31	142.73	141.37	136.90	134.20
Internal validation parameters							
11.	R^2_{cv} (Q^2)	0.91	0.90	0.89	0.89	0.89	0.89
12.	$RMSE_{cv}$	0.44	0.46	0.47	0.48	0.48	0.48
13.	MAE_{cv}	0.34	0.37	0.37	0.37	0.38	0.38
14.	CCC_{cv}	0.95	0.95	0.94	0.94	0.94	0.94
15.	Q^2_{LMO}	0.91	0.90	0.89	0.89	0.89	0.89
16.	R^2_{Yscr}	0.07	0.07	0.07	0.06	0.06	0.06
External validation parameters							
17.	$RMSE_{ex}$	0.53	0.73	0.63	0.58	0.67	0.70
18.	MAE_{ex}	0.40	0.52	0.45	0.42	0.46	0.49
19.	R^2_{ex}	0.86	0.76	0.81	0.83	0.80	0.78
20.	Q^2_{F1}	0.84	0.70	0.77	0.81	0.75	0.72
21.	Q^2_{F2}	0.84	0.70	0.77	0.80	0.74	0.72
22.	Q^2_{F3}	0.86	0.74	0.80	0.83	0.78	0.76
23.	CCC_{ex}	0.92	0.86	0.90	0.91	0.88	0.87

R^2 – correlation coefficient, Q^2 – leave-one-out 'cross validated $R^{2'}$, R^2_{adj} – adjusted R^2, SEE – standard error of estimates, *RMSE* – root mean squared error, *MAE* – mean absolute error, *CCC* – concordance correlation coefficient, for the training (tr), and test (ex) sets; *LOF* – lack of fit, *F* – Fischer's value; R^2_{LMO} and Q^2_{LMO} – leave many-out correlation coefficient and cross-validation coefficients; R^2_{Ycr} and Q^2_{Ycr} – *Y*-scramble correlation and cross-validation coefficients;

standardized residual greater than 3σ ($3 \times$ standard deviation units) is recognized as a *Y* outlier.

Though Fortin et al. performed CoMFA analysis for a dataset of PIB-SOs, the developed CoMFA model was based on a relatively small dataset of thirty seven molecules with moderate statistical performance ($R^2_{CV} = 0.552$). The present CoMFA model, based on a larger dataset of ninety-seven PIB-SOs, is statistically robust with $CCC_{ex} = 0.892$, $R^2_{ex} = 0.91$ for $N_{ex} = 21$. For $N_{train} = 76$, $CCC_{tr} = 0.970$. A higher value of CCC_{ex} along with R^2_{ex} confirms the good external predictivity of the CoMFA model. The leave-one-out (LOO) correlation coefficient (R^2cv) and R^2 were found to be 0.712 and 0.942, respectively. Further, standard error of estimate was found to be 0.338 with an optimized component of **5**. This implies that the model is not only trustworthy in capturing the essence of structural features that govern the anti-cancer activity but it is very good at predicting the anti-cancer activity of PIB-SOs also. The pIC_{50}values predicted by CoMFA model have been depicted in Fig. 4.

From Fig. 4, it is evident that the biological activity is predominantly governed by steric factors.

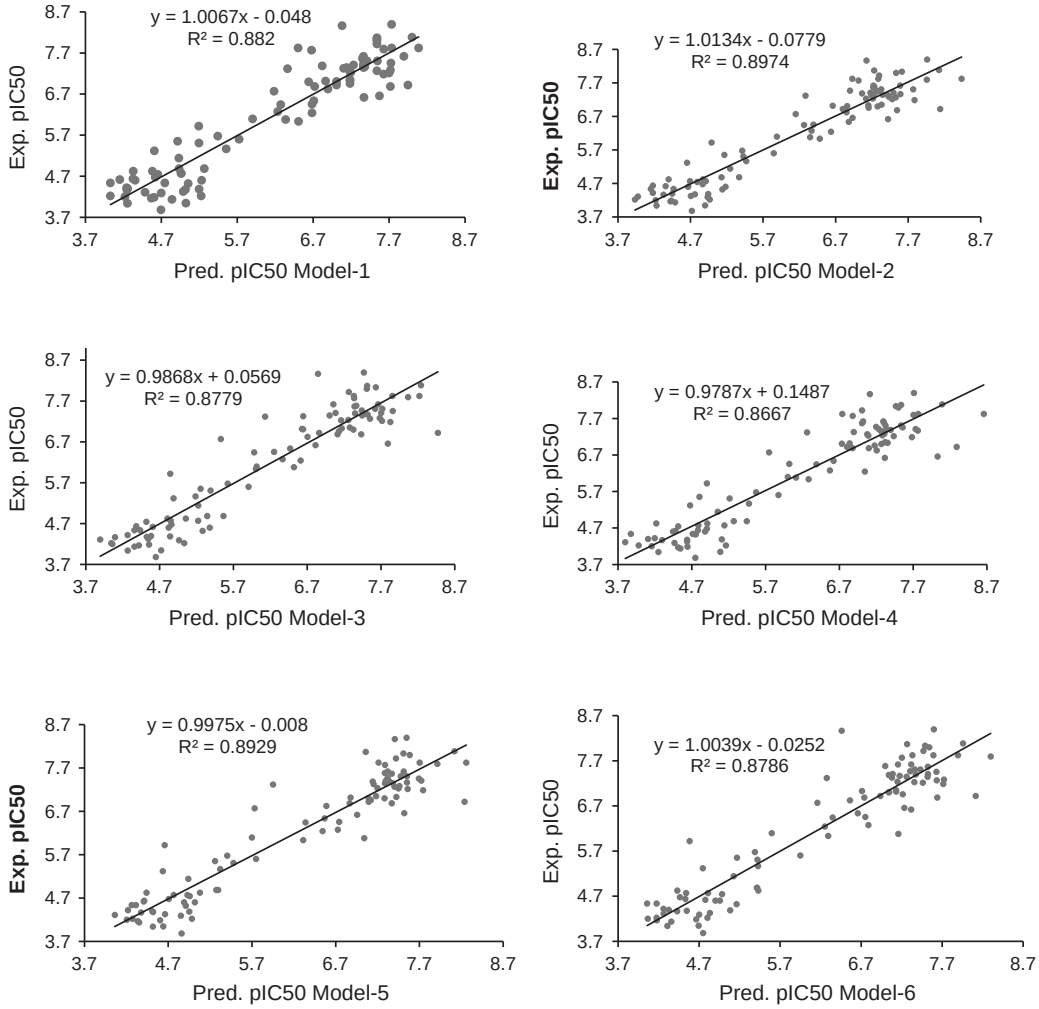


Fig. 5. Graph between experimental and predicted pIC_{50} (on *Y*-axis) vs. molecule number (on x-axis).

The presence of a green colored contour near the ring A indicates that bulky groups are favoured in this region. This could be a possible reason for the differences in the activity of compounds: **84** with **59** and **71**, **86** with **74**, **89** with **57** and **77**. A yellow contour near to ring A suggests that presence of bulkier groups in this region is unfavourable for the anti-cancer activity. Another yellow contour present in the close vicinity of nitrogen at substituted urea moiety indicates that bulkier groups need to be avoided as substituent on this nitrogen. In a nut shell, steric factors play crucial role in deciding the anti-cancer activity of PIB-SOs.

The GA-MLR analysis resulted in many statistically acceptable QSAR models, listed in Table 2. The analysis was able to shed light on the structural features that steer the anti-cancer activity.

The different parameters for model 1–12, depicted in Table 3, indicate that all the models satisfy many statistical parameters like R^2_{tr}, Q^2_{Fn}, R^2_{ex} and CCC_{ex}. These parameters are necessary to establish the internal and external predictive ability of a model. The predicted pIC_{50} values by different models have been depicted in Fig. 5 (predicted pIC_{50} values are available in Tables S3 and S4 provided as supplementary information).

From Table 3, it is clear that *X3A* (Average connectivity Index that a represents of the steric character of the molecule) and *F07[C-N]* (frequency of occurrence of carbon and nitrogen at topological distance of seven) are continually present in model 1–6. Similarly *Xt* (Total structure connectivity index, a representative of the steric character of the molecule) and *VEA2* (average eigenvector coefficient sum from adjacency matrix) are present in model 7–12. For *X3A*, a connectivity index, the coefficient (−194.319 in model-1) and standard coefficient (std. coeff. = −0.743 in model-1) are negative, which indicate its negative correlation with the activity. Same is applicable to *F07[C-N]*, a 2D frequency fingerprint descriptor, and *BEHp6* (highest eigenvalue *n*. 6 of Burden matrix/weighted by atomic polarizabilities), both have negative std. coeff. and coefficients in model 1. This observation is more clarified and vindicated by the CoMFA analysis. That is, CoMFA and QSAR analyses are complementary and supporting to each other. For better activity, the values of *X3A*, *BEHp6* and *F07[C-N]* should be as low as possible. *X3A* accounts for the multiplicity of the bond and for the presence of hetero atoms in the molecule, especially the hydrogen bond donor/acceptor atoms. For better anticancer activity of PIB-SOs, heteroatoms capable of forming H-bonding must be placed as far as possible.

From model 2–6, it is clear that *MAXDP* (maximal electrotopological positive variation), *RDF020u* (Radial Distribution Function – 2.0/unweighted), *R7u* (R autocorrelation of lag 7/unweighted) and *R8e* (R autocorrelation of lag 8/weighted by atomic Sanderson electronegativities) have negative correlation with the activity. The only descriptor that was found to have positive correlation (see model 4) with activity is *R4e+*(R maximal autocorrelation of lag 4/weighted by atomic Sanderson electronegativities).

Further a model based on undivided dataset was developed using the same parameters as for model 1–12 to understand the inclusion of new molecules in dataset for descriptor selection i.e. effect of augmentation of dataset size.

Model-13: $p\mathrm{IC}_{50} = 8.559\ (\pm 4.043) - 55.8097\ (\pm 23.1356)\ Xt + 71.0572\ (\pm 18.4287)\ VEA2 - 0.7420\ (\pm 0.2572)\ nHDon.$

$N_{tr} = 97,\ Q^2 = 0.85,\ R^2_{tr} = 0.87,\ R^2_{adj} = 0.86,\ LOF = 0.27,\ K_{xx} = 0.44,\ \Delta K = 0.15,\ RMSE_{tr} = 0.50,\ RMSE_{cv} = 0.52,\ S = 0.51,\ F = 205.12,\ CCC_{tr} = 0.93,\ CCC_{cv} = 0.92,\ MAE_{tr} = 0.38,\ MAE_{cv} = 0.40,\ R^2_{LMO} = 0.87,\ Q^2_{LMO} = 0.86,\ R^2_{Yscr} = 0.03.$

The model 13 is found to be similar to model 10 (see above table) apropos of selected descriptors only. The statistical parameters for model 13 clarifies that inclusion of more molecules in the dataset has acceptable influence on the statistical performance. Thus, the developed models are able to capture all the essential features that influence the anti-cancer profile of PIB-SOs. The training set of the models 7–12 has a distribution of data more similar to the full set, this could be a plausible reason for similarity between model 10 and 13.

In conclusion, various QSAR models and CoMFA model are developed and they are found to be statistically acceptable with good internal and external predictive ability. Both analyses reveal that steric repulsion has important correlation with the activity. The anti-cancer activity (against M 21 cell lines) of PIB-SOs is found to be largely influenced by the steric factors. The developed QSAR and CoMFA model insinuate constructive hints for optimization of PIB-SOs with improved activity profile. The models could be used to design new ligands with better activity, prior to their actual synthesis.

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Appendix A. Supplementary material

The experimental methodology for QSAR and CoMFA analyses, correlation matrix for descriptors, values of descriptors, etc. are available in supplementary file. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejps.2015.06.001.

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has participated and presented the paper entitled Teaching Employee Involvement in corporate Governance at multinational Level

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TEACHING EMPLOYEE INVOLVEMENT IN CORPORATE GOVERNANCE AT THE MULTINATIONAL LEVEL

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A. Different Forms of Employee Involvement in Corporate Governance:

As the transactions of companies overrun the borders of countries, the roles of corporate Constituencies increasingly gain cross-border nature. Employees as one of the corporate Constituencies have been playing an increasingly important role at the transnational level. Nevertheless, employees' roles in the corporate governance differ among states since regulations of companies are quite different from one country to another even though the increasing number of companies now has activities beyond the national borders. For example, in cross-border mergers and acquisitions, as the form of growth and internationalization, the relations between the management and workers in the companies involved, may be subject to laws and regulations of more than one country, where there is great diversity. At one extreme, employee participation which provides participation for employees in corporate decision making, together with the two-tier board structure, is regulated. At other extreme, employees are only provided with information and consultation in major corporate decisions. The diversity between the employees' role in the governance of companies is one of impediments to major corporate transactions in the globalized world, which adversely affects the economic relations between countries and creates an obstacle to the development of the world economy.

There are efforts to approximate differences of employees' role in companies. For example, in the European Union (EU) it seems that major steps have been taken to harmonize different systems of employee involvement in the corporate governance. In 1994 the EU adopted European Works Council Directive[1] which requires member states to set up a general framework for employees' information and consultation rights in multinational companies. Under the Directive, consultation is defined as a two-way communication process; the exchange of views and establishment of dialogue between employees and management.[2] The Directive imposes on member states the establishment of a Works Council in Community scale undertakings or groups of undertakings which have at least 1,000 or in companies which have at least 150 employees in each of two or more member states and where employees or their representatives request this.[3] Put simply, the Directive provides a collective voice through a central information and consultation forum.

The National Works Council Directive[4] also imposes on national companies of member states to set up minimum requirements for employees' information and consultation rights to complement the European Works Council Directive. Under the Directive employees are to be informed and consulted on a regular basis on major corporate decisions concerning employees' interests. Information and consultation are achieved through works councils, or in rare cases, through direct contact between management and employees or their representatives. Further, employee involvement in Societies European (SE) is regulated by the Directive[5] supplementing the Regulation for a European company (European Company Statute)[6] which introduced a new legal entity under EU law. The purpose of the Regulation for a European company is to offer a company with a European dimension free from the obstacles arising from the disparity and the limited territorial application of national company law.[7] The European company, which is primarily governed by the same rules, can therefore move freely from one country to another without legal restrictions imposed on national entities. The European company will permit cross-border mergers and the cross-border transfer of a company's registered office without the need for liquidation and for the formation of a new company.

The Directive supplementing the Regulation for a European company then provides employee involvement in companies moving from one country to another to be subject same provisions. The Directive[8] supplementing the Regulation for a European company, drawing on experiences and laws

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of member states, governs three forms of employee involvement in the corporate decision making: participation, consultation and information[9]. Employee participation should be clearly distinguished from other forms of employee involvement. This is because; of the three forms of employee involvement under the Directive only participation affects the structure of the company.

Nevertheless, there are still major divergences between the laws of member states concerning employee involvement in corporate governance. This stems from the fact that the employees' role in corporate governance is related to not only laws and regulations of corporate governance of countries, but also the underlying philosophy of corporate governance. The shareholder primacy prevails in the Anglo-American countries where the company is considered a profit making organization. This philosophy encourages corporate directors to maximize corporate profit. The directors are elected by the shareholder, which ensures the responsibility of the directors only to shareholders.[10] The directors act, as agents of shareholders, in the best interests of shareholders. The shareholders are the owners of the company carry the risk of investment. They, in turn, should be the one who decides in the company.[11] The Anglo-American corporate governance system has therefore mainly drawn on contractual theory. This leads to the relationship between corporate constituencies and the companies to be treated as contract.12 Therefore, employees as one of corporate constituencies are regarded as outsiders. Their contractual rights are supplemented by certain statutory protections for the individual worker, and by collective rights of bargaining and consultation.[13]

The stake holding approach, on the other hand, prevails on the Continent. The company is regarded as the institution in which the interests of different corporate constituencies, such as employees, suppliers, certain long-term customers, environment and society are reconciled. Employees, as one of corporate constituencies, or of stakeholders are protected within the company through mainly two tier board structure. The members of supervisory board are elected by shareholders and employees, and those of the management board are elected by the supervisory board. This structure of the company makes it possible for employees to participate in the decision making of companies[14]. Therefore, employee voice is related to corporate culture, historical, political and sociological development of countries that shape legal rules of employee involvement in the decision-making of companies.

B. Teaching Employee Involvement in Corporate Governance from a Comparative Perspective:

The laws and regulations relating to employee involvement in corporate governance which have evolved in different cultural, sociological, historical and economic development of countries can be thought from a comparative perspective. Different roles of employees can be illustrated by explaining laws of UK, Germany and the Netherlands concerning employee involvement in corporate governance. Examining law of the UK about shareholder primacy together with employee involvement will show that employees can only have information and consultation rights in major corporate decisions. On the other hand, an explanation of laws of Germany and the Netherlands relating to employee participation can make a fuller understanding how the corporate structure enables the interest of company to include the interests of shareholders, creditors, employees and society.

Information and consultation rights in UK law stem from the implementation of Directives[15] which impose on member states to regulate, at least, the lowest level of employee involvement. Employees' information and consultation rights are not likely to provide influence upon decisions on corporate policies whereas participation must at least have the capacity to influence decisions and policies. Information and consultation, on the other hand, can be deemed as the essential step in the process of participation[16] Two-tier board system, as the corporate structure, comprising the supervisory board and the management board is the major characteristics of laws of Germany and Netherlands providing for employee participation. However, while employee involvement in these two countries can be referred to as employee participation, there are differences in these two countries' laws concerning employee involvement. Explanation of the laws of Germany and the Netherlands about employees' role, in a comparative way, will help the students to understand

different types of employee participation, which is also reflected in the Directive[17] supplementing the Regulation for a European Company.

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INVESTIGATION OF ALOE-VERA TOOTH GEL CONTAINING ACTIVE SALT AND ALUM BY TIME KILL TEST

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ABSTRACT

The aim of the present study was to investigate efficacy and performance of Aloevera tooth gel against selected bacteria and fungi This test method measures the changes of a population of Aerobic microorganism with in a specified time period, when tested against Staphyllacoccus aureus, Streptococcus mutans, Candida albicans, Escherichia coli and Pseudomonas aeruginos a which were selected as a test micro-organism against which Aloe-vera tooth gel was tested. It included the evaluation of dentifrices by antimicrobial testing.

This investigation showed that newly formulated tooth gel has shown 99.99% reduction of test bacteria viz Staphyllacoccus aureus, Streptococcus mutans, Escherichia coli, Pseudomonas aeruginosa and Candida albicans in 30 sec, 60 cec and 2 minutes, Bright Tooth Paste has shown >99.99% reduction of test bacteria Staphylococcus aureus, Streptococcus mutans, Escherichia coli in 30 sec, 60 sec and 2 minutes, Bright Tooth Paste has shown no reduction of Pseudomonas aeruginosa in 30 sec, 60 sec and 2 minutes, when analysed as per ASTM E 2315 – 03 (Re. 2008) Method.

Key words : Aloe gel dentifrice, Staphylococcus aureus, Streptococcus mutans, Candida albicans, Escherichia Coli, Pseudomonas aeruginosa.

Introduction :-

Dental Caries, Cavities and other oral diseases are the most common diseases world-wide including both developed and developing countries affecting peoples of all ages and sex. These diseases are Caused by a mixture of micro-organism and food debris. Specific types of acid producing bacterias like Streptococcus mutans colonize the dental surface structure in the prcsence of fermentable Carbohydrates, for example sucrose, fructose and glucose. Also other microflora are also associated with it. Teeth provides a unique environment for bacterial colonization, Since unlike other parts of the mouth they are non-shedding inorganic structure retentative areas.

Aloe-vera is a stemless or very short succulent, Cacturs like plant that actually is part of lily family, growing to 60-100 cm (24-39 inches) tall, spreading by off sets. There are more than 300 varieties of the Aloe plant but the Aloe-barbadensis variety exhibits the best medicinal properties. It has been suggested for a wide variety of ailments but its use in dentistry is limited.

Literature survey showed that though Aloe-vera gel were studies and can be used for minor burns, skin abrasions and moisturizing properties but comparatively less works has been reported on its use in dentistry. In the view of this, the present study the Aloe tooth

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gel was prepared by incorporating Aloe-vera along with active salt and Alum in it and then the formulation was screened for time kill test.

Time Kill Test is a basic microbiology method of assessment of Antimicrobial activity of an Anti-Microbial test material or Disinfectant. The kill time test is carried out to evaluate the microbial reduction by a disinfectant against selected bacteria or fungi. Various organism are studied depending upon the type of analysis and test materials. However most common organism tested include : Staphylococcus aureus, Pseudomonas aeruginosa, E-coli etc.

The test product or a dilution of the test product is brought into contact with a known population on of micro-organisms approximately 10^6 CFU/ml specified period of time at a specified temperature. At selected time points including zero time aliquots are removed and placed into a neutralizer blank. Dilutions of the neutralizer are made and selected dilutions plated onto agar. Colonies are enumerated.

The percentage or log reduction or both form either on initial microbial population, or test blank is calculated. The amount of sample required is 100 ml per lot per organism.

Materials and Methods :

For this purpose following materials were requested to different companies for samples are ;

1. Aloe-vera extract – kingvish Company, Mumbai
2. Precipitated silica (ABSIL – Madhu silica Pvt. Ltd.Gujrat)
3. Hydrated Silica (M-Fil – Madhu Silica Pvt. Ltd Gujrat)
4. Carraeingn gum (VTP-Sarin industries FMC Biopolymer Navi-Mumbai.)
5. Clolours – Neelikon food Dyes and chemicals Ltd. Mumbai.

All the reagents used were of analytical grade. After collecting all the Samples, Aloe-vera tooth gel were formulated by incorporating Aloe-vera, active salt and alum as are active ingredients, to checkout the effectiveness against different micro-organisms with in a specified period of time.

EXPERIMENTAL WORK :

Finalized base formulation for gel tooth paste with aloe – vera extract , salt and alum as an active ingredients with other common ingredients of gel dentifrice.

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Table 1: Formulation of Aloe-Vera Gel containing dentifrice

S. N.	Ingredients	% (w/w)
1	Sorbitol	65.00
2	VTP Gum (Carrageenan gum)	0.55
3	F - Sil 100 (Abbrasive Silica)	13.5
4	M - Fil 100 (Hydrated Silica)	6.5
5	Poly ethylene glycol 400	0.5
6	Sodium Saccharin	0.3
7	Sodium fluoride	0.22
8	Sodium lauryl sulphate	2.5
9	Methyl Paraben	0.1
10	Propyl Paraben	0.01
11	Colour	0.1
12	Flavour	0.5
13	Water	0.92
14	Aloe – vera gel	9.0
15	Sodium salt	0.2
16	Alum	0.1

Preparation of Aloe Tooth gel :

In order to optimize the concentration of gelling agent to achieve proper consistency of the gel formulations were prepared with different gel formers, Carboxy methylcellulose sodium, Carbomer 934, HPMC and different concentration of viscosity enhancer vis. 1.0, 2.0, 3.0 and 4.0 % were tried and finally gel that showed good spreadability and consistency was selected.

Weigh all the ingredients. Take sufficient quantity of water , Add sodium saccharin, Sodium fluoride , preservatives , colour, Sodium salt, alum in it . Mix it properly. Then warm the water up to 45 – 50°c . Then at this temperature add VTP gum. Then add sorbitol, Poly-ethylene glycol. Then add both silica powder i.e. abrasive silica & hydrated silica to it. Mix it 15 minutes. The add Aloe – vera gel & flavour to it and mix it 10 -15 minutes properly. Lastly add sodium lauryl sulphate to the formulation by making a slurry. Slight amount of foam will generate. Remove air by vacuum.

Finalized base formulation for gel tooth paste with aloe – vera extract , salt and alum as an active ingredients with other common ingredients of gel dentifrice.

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Antimicrobial Analysis of Aloe Tooth Gel by Time Kill Test :

Name of Test : Time Kill Test

Test Standard ; ASTM E 2315 – 03 (Re 2008)

Test Inoculum :

1. Staphylococcus aureus ATCC 6538
2. Streptococcus mutans ATCC 25175
3. Escherichia coli ATCC 10535
4. Psedomonas aeruginosa ATCC 9027
5. Candida albicans ATCC 10231

Test Conditions :

Test Product	:	1:2 dilution
Diluent / Neutraliser	:	DE broth
Contact Time	:	30 seconds, 60 seconds and 2 minutes
Contact Temperature	:	Room Temperature
Media and Reagent	:	Soyabean-casein digest agar, plates incubated at 37°C; Sabourauds Dextrose agar, incubated at 28°C

Procedure :

1:2 dilution product was inoculated with test organisms bacteria / fungi indivudually (approximately 106 CFU /ml). After the specified exposure time of 30 seconds, 60 seconds and 2 minutes, surviging microorganisms were recovered by drawing an alliquot, neutralizing it and performing Standard Pour Plate Technique, Culture count was ascertained by dilution Blank. Adequate Validation of Neutralizing agent was also carried. Test was carried out in duplicate and average count was taken as CFU/ml.

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Sample Measurement Tube Vortex Shaker



Remove Sample with Micropipette



Mixing Sample in



Preparation of Plates



Inoculation of Microbial Plate



Spiral Plater

Neutralizer Validation :

Validation Test		
Test Organism	**Viable count in Saline (CFU/ml)**	**Viable Count in Neutraliser**
Staphylococcus aureus	78	80
Streptococcus mutans	45	46
Escherichia	53	52
Psedomonas aeruginosa	80	78
Candida albicans	32	30

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Results :

Sample Identification	Test Organism	Exposure Time	Count of Test Organism			Antimicrobial Activity	
			Initial Count	After Exposure		Log Reduction	Percentage Reduction
				CFU/ml	Log		
Aloevera Gel Tooth Paste	Staph. Aureus	30 Sec	$1.45x10^5$	<10	<1	>4.16	>99.99
		60 Sec	CFU/ml	<10	<1	>4.16	>99.99
		2 Min	L = 5.16	<10	<1	>4.16	>99.99
Bright Tooth Paste		30 Sec	$1.41x10^5$	<10	<1	>4.14	>99.99
		60 Sec	CFU/ml	<10	<1	>4.14	>99.99
		2 Min	L = 5.14	<10	<1	>4.14	>99.99
Aloevera Gel Tooth Paste	Streptococcus Mutans	30 Sec	$1.35x10^5$	$9.50x10^4$	4.97	0.16	29.62
		60 Sec	CFU/ml	$1.00x10^4$	4.0	1.13	92.59
		2 Min	L = 5.13	<10	<1	>4.13	>99.99
Bright Tooth Paste		30 Sec	$3.50x10^5$	<10	<1	>4.54	>99.99
		60 Sec	CFU/ml	<10	<1	>4.54	>99.99
		2 Min	L = 5.54	<10	<1	>4.54	>99.99
Aloevera Gel Tooth Paste	Escherichia Coli	30 Sec	$1.08x10^5$	<10	<1	>4.16	29.62
		60 Sec	CFU/ml	<10	<1	>4.16	92.59
		2 Min	L = 5.03	<10	<1	>4.16	>99.99
Bright Tooth Paste		30 Sec	$1.10x10^5$	<10	<1	>4.16	>99.99
		60 Sec	CFU/ml	<10	<1	>4.16	>99.99
		2 Min	L = 5.04	<10	<1	>4.16	>99.99
Aloevera Gel Tooth Paste	Pseudomonas aeruginosa	30 Sec	$1.09x10^5$	<10	<1	>4.16	>99.99
		60 Sec	CFU/ml	<10	<1	>4.16	>99.99
		2 Min	L = 5.03	<10	<1	>4.16	>99.99
Bright Tooth Paste		30 Sec	$1.15x10^6$	$>1.00x10^6$	>6.0	< 1	0.00
		60 Sec	CFU/ml	$>1.00x10^6$	>6.0	< 1	0.00
		2 Min	L = 5.06	$>1.00x10^6$	>6.0	< 1	0.00
Aloevera Gel Tooth Paste	Candida albicans	30 Sec	$4.60x10^5$	<10	<1	>4.66	>99.99
		60 Sec	CFU/ml	<10	<1	>4.66	>99.99
		2 Min	L = 5.66	<10	<1	>4.66	>99.99
Bright Tooth Paste		30 Sec	$2.60x10^5$	<10	<1	>4.41	>99.99
		60 Sec	CFU/ml	<10	<1	>4.41	>99.99
		2 Min	L = 5.41	<10	<1	>4.41	>99.99

Percentage Reduction of Microorganism = 100 (Initial – After Exposure)/ Initial
Log Reduction = Log Initial – Log after Exposure

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Candida_Aloe_2_mins



Candida_Bright_L_control and_right_2_min



S_mutans_Aloe_L_control_ and_right_2_mi



S_mutans_Bright_L_control_ and_right 2_min

Conclusion :

Test Product named as Alovera Tooth Gel has shown >99.99% reduction of test bacteria viz Staphyllacoccus aureus, Streptococcus mutans, Escherichia coli, Pseudomonas aeruginosa and Candida albicans in 30 sec, 60 cec and 2 minutes, Bright Tooth Paste has shown >99.99% reduction of test bacteria viz Staphylococcus aureus, Streptococcus mutans, Escherichia coli in 30 sec, 60 sec and 2 minutes, and Bright Tooth Paste has shown no reduction of Pseudomonas aeruginosa in 30 sec, 60 sec and 2 minutes when analysed as per ASTM E 2315 – 03 (Re. 2008) Method.

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Original article

Diversity of Saurian fauna in the Buldhana district, Maharashtra, India

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ABSTRACT

The present report provides knowledge about the diversity of Saurian fauna in the Buldhana district of the Indian state of Maharashtra as a model geographic area to promote conservation management. The presented study is based on the field work carried out in the study sites during February 2014 to January 2015. The study revealed the presence of 14 Saurian species belonging to 5 families dominated by Gekkonidae (43.05%), Scincidae (29.15%), Agamidae (21.35%), Varanidae (6.1%), and Chamaeleonidae (0.35%). The relative dominance of species varied with different months, apparently indicating that the Buldhana district has a healthy environmental and demographic setup that accommodates rich Saurian diversity.

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Introduction

The biological diversity of the earth and its origins has long been a source of amazement and curiosity (Tantarpale 2015). The study of biological diversity encompasses both the intrinsic and anthropocentric values associated with it. The values of the biological elements are recognized in correspondence to the perceived importance by the human being, which is realized in terms of the ecosystem services (Daily 1997; Baumgärtner 2007). Biological diversity is the base for upholding the ecosystems and the functional aspects of the species that provide goods and services for human well-being. Monitoring of species diversity of a region enables estimation of the prospective functional roles of the species. In any ecosystems, monitoring species diversity can be used as a tool to reduce human mismanagement and pollution in urbanized, industrial, rural, and other managed areas (Wilson 1997). Extending this view, studies on species diversity in any ecosystems are necessary to understand the effect of anthropocentric development on the integrity and sustenance of an ecosystem.

The diversity of reptiles has been emphasized in many studies owing to their dominance in the terrestrial and aquatic ecosystems and provision of ecosystem services such as pest control and ecological maintenance (Joshi 2014). Among reptiles, saurian fauna is a diverse group that changes from the primitive to the specialized, phylogenetically, and their structural modifications exhibit greater variations than any other group of reptiles (Daniels 1992). Lizards are members of the suborder Sauria which is one of the two suborders of the order Squamata (Class: Reptilia). They are poikilothermous, insectivorous, and oviparous to ovoviviparous (Matthew 2007). Presently, lizards are one of the most diversified groups of vertebrates that have ever lived on earth over the past 250 million years. Over 5,000 species of lizards have lived on earth, inhabiting a variety of habitats ranging from the highest mountainous peak to the low-lying terrestrial and aquatic habitats (Tahmasbi et al. 2015). South Asia, including the Indian subcontinent, is the home for herpetological diversities in the tropical region with India harboring 228 Saurian species in different biophysical zones (Tantarpale 2015).

In this context, the conservation of lizards is necessary to sustain varied kinds of ecosystem services for human well-being. In view of the essential ecosystem services rendered by lizards and to promote conservation management, the present study was aimed at the estimation of the saurian diversity in the Buldhana District, Maharashtra, India. The results of the study are expected to supplement the necessary information on the conservation management and enhance the ecological roles of the saurian species in the Buldhana District and similar geographical regions.

Materials and methods

Study area

The Buldhana district (20°32′N 76°11′E) is one of the most diversified regions in Maharashtra State of India, with respect to biodiversity.

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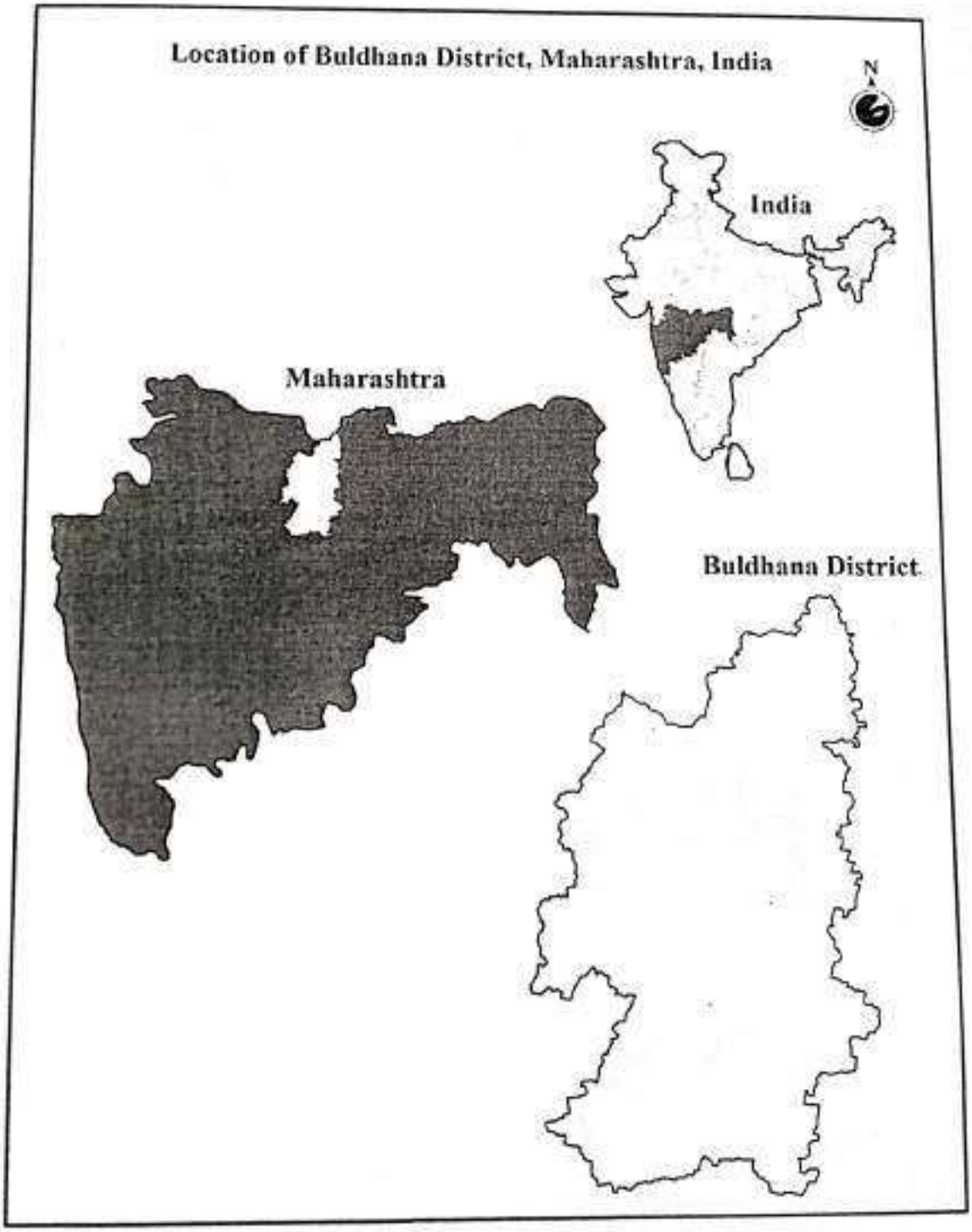


Figure 1. Buldhana District, Maharashtra, India.

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Table 1. Diversity of Saurian fauna during February 2014 to January 2015 in the Buldhana district, Maharashtra, India.

Family	Scientific name	Common name	No. of individuals	IUCN national	Local status
Agamidae	*Calotes versicolor* (Daudin, 1803)	Indian garden lizard	42	NE	Abundant
	Calotes rouxii (Dumeril and Bibron, 1844)	Indian forest lizards	16	NT	Occasional
	Psammophilus blanfordanus (Stoliczka, 1871)	Blanford's rock agama	5	NE	Rare
Chamaeleonidae	*Chamaeleo zeylanicus* (Stoliczka, 1872)	Indian Chamaeleon	01	NE	Rare
Gekkonidae	*Hemidactylus brookii* (Gray, 1930)	Brook's house gecko	12	LC	Rare
	Hemidactylus flaviviridis (Murray, 1886)	Yellow-green House Gecko	35	LC	Common
	Hemidactylus frenatus (Dumeril and Bibron, 1844)	Asian house gecko	25	LC	Frequent
	Hemidactylus giganteus (Stoliczka, 1871)	Giant Indian gecko	03	NE	Occasional
	Hemidactylus leschenaultii (Dumeril and Bibron, 1844)	Common bark gecko	42	LC	Abundant
	Hemidactylus triedrus (Daudin, 1802)	Termite hill gecko	10	NT	Rare
Scincidae	*Eutropis carinata* (Schneider, 1799)	Keeled grass skink	34	NT	Common
	Eutropis macularia (Blyth, 1853)	Bronze grass skink	40	LC	Abundant
	Lygosoma punctatus (Gmelin, 1799)	Spotted supple skink	12	NT	Rare
Varanidae	*Varanus bengalensis* (Daudin, 1803)	Bengal monitor lizard	18	VU	Frequent

LC = least concern; NE = not evaluated; NT = nearly threatened; VU = vulnerable.

Its healthy climate, mountainous terrain, rugged configuration, and sudden fall in elevation are phenomenal (Joshi et al 2015). It is in the Amravati division of Maharashtra state in Western India. It is situated at the westernmost border of the Vidarbha region of Maharashtra, and is 500 km from the state capital, Mumbai. It lies between 19°51′ N and 21°17′ N latitude and 75°57′ E and 76°59′ E longitude. It has a total area of 9,745 km^2 (3,761 square miles). The climatic condition of this district is characterized by a hot summer, well-distributed rainfall during the south-west monsoon season, and generally dry weather during the rest of the year. The cold season is from December to February. The average annual rainfall in the district is 796.6 mm (31.37 inches). During summer, the mean daily maximum temperature was 42.3°C and the minimum was 27.4°C, and it decreased toward winter with a mean daily maximum temperature of 27.6°C and a minimum of 15.1°C (Buldhana Gazetteer 2015).

Survey methods

The present study is based on the field work carried out in the study sites during February 2014 to January 2015. During the survey, an efficient protocol was adopted. The survey was made using a "visual encounter survey" method (Doan 2003) as well as by employing randomized walking (Whitaker 2006). The selected area

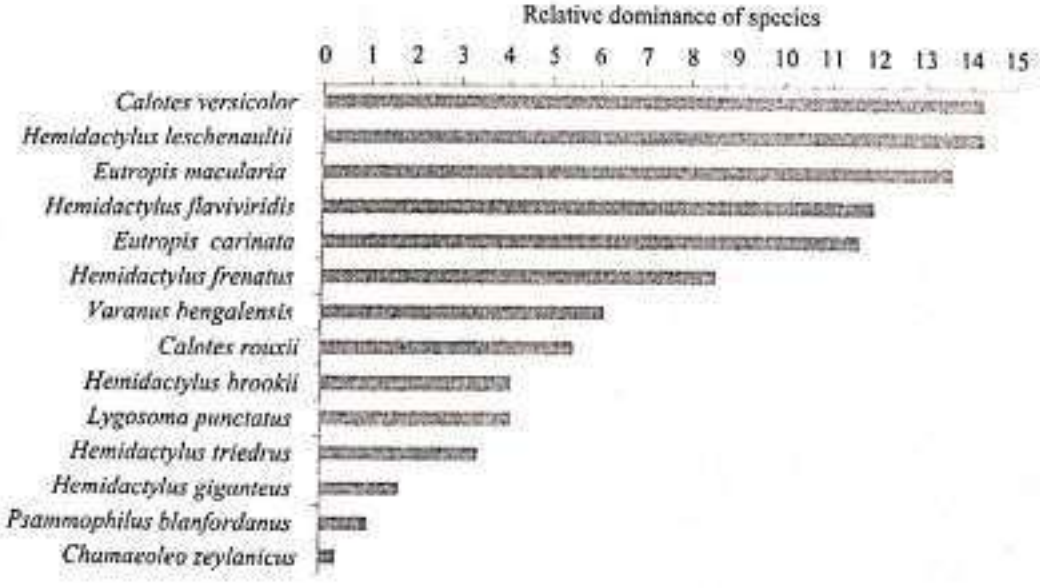


Figure 2. Relative abundance of saurian species in the Buldhana district, Maharashtra, India.

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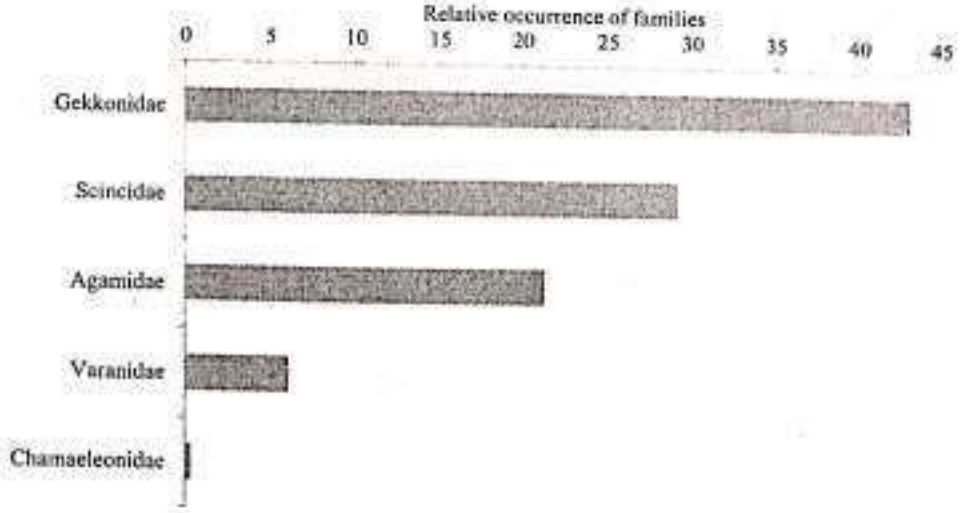


Figure 3. Relative dominance of saurian families in the Buldhana district, Maharashtra, India.

was randomly explored on the basis of habitat structure and the possibility of availability of species.

Species identification

After detection, a specimen was identified with the help of visible structural features. For identification and comparative studies of observed specimens, keys and methods suggested by Daniel (2002), Das (2002), and Ahmed et al (2009) were adopted. The International Union for Conservation of Nature (IUCN) status of each encountered species was categorized on the basis of Molur et al (1998), Kumbhar et al (2013), and Alexander and Jayakumar (2014).

Data analysis

Species occurrence analysis was carried out by using the following formulas. Relative dominance (RD) of species was calculated as [RD = Ni × 100/Nt], where Ni is the number of individuals of species and Nt is the total number of individuals of all

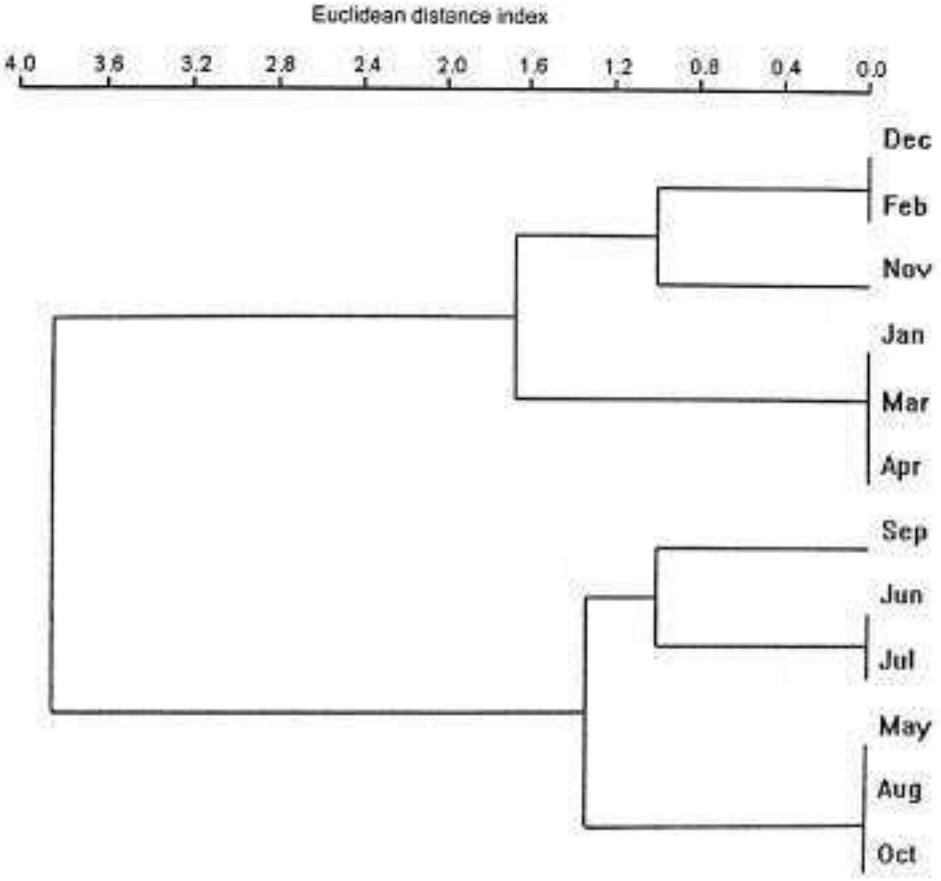


Figure 4. Dendrogram showing similarity in number of saurian species composition among the studied month during February 2014 to January 2015.

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species (Basavarajappa 2006; Joshi 2014). Relative occurrence (RO) of the family was calculated as [RO = Ns × 100/Nt] where Ns is the number of species of each family and Nt is the total number of all species (Basavarajappa 2006; Joshi 2014). Mean percent occurrence (M%) for a month was calculated as [M% = Nm × 100/Nt] where Nm is the number of individuals in each month and Nt is the total number of individuals during the complete study tenure (Basavarajappa 2006; Joshi 2014). The mean values of the pooled species occurrence data were used to calculate the monthly diversity of and to categorize the local status of species.

The diversity assessment enabled highlighting the observed species richness pattern of the saurian species. The diversity indices were quantified with the help of PAST Version 1.60 software (Palaeontological Asso., Norway; Hammer et al 2001). The species diversity was calculated using the Shannon diversity index that calculated [$H' = -\sum_{i=1}^{S} Pi \log Pi$], where Pi is the proportion of the first species which is given by $Pi = ni/N$, where ni is number of individual in particular month and N is total number of species; species richness was obtained by using the Margalef equation [$R = (S-1)/\log N$], where R is the index of species richness, S is total number of species and N is the total number of individuals (Magurran 1988); while species equitability was determined by the equation of Pielou [$J = N_1/N_0$] where N_1 is the number of abundant species in the sample and N_0 is the number of species in the sample (Hammer et al 2001). The similarity association matrix upon which the cluster was based was computed using the nearest neighbor pair linkage algorithm of Euclidean distance index for the presence and absence data (Hammer et al 2001).

The differences between the diversity and evenness indices among different study months were statistically analyzed using analysis of variance. The statistical analyses were performed following Zar (1999) using the SPSS version 10 (SPSS Inc., Chicago, IL, USA; Kumar and Gour 2008).

Results

During the study, a total of 295 individuals of 14 saurian species belonging to 5 families were identified (Table 1). From the observed species, 3 were abundant, 2 were common, 2 were frequent, 2 were occasional, and 5 were rare. The maximum abundance was shown by *Calotes versicolor* followed by *Hemidactylus leschenaultii* and *Eutropis macularia*, while *Chamaeleo zeylanicus* was the most rarely observed with least abundance (Figure 2). During the study, the Gekkonidae family was observed to be more dominant over the Scincidae, Agamidae, Varanidae, and Chamaeleonidae families (Figure 3).

A monthly comparison of saurian species occurrence showed the highest number of species during June to September and the lowest during February to May. A dendrogram developed by Euclidean distance cluster analysis was observed to be multifaceted and showed variation in the level of similarity in the number of saurian species in 12 months. The months with the minimum to moderate number of species belong to one cluster, whereas the rest of the months with moderate to maximum number of species formed another cluster (Figure 4).

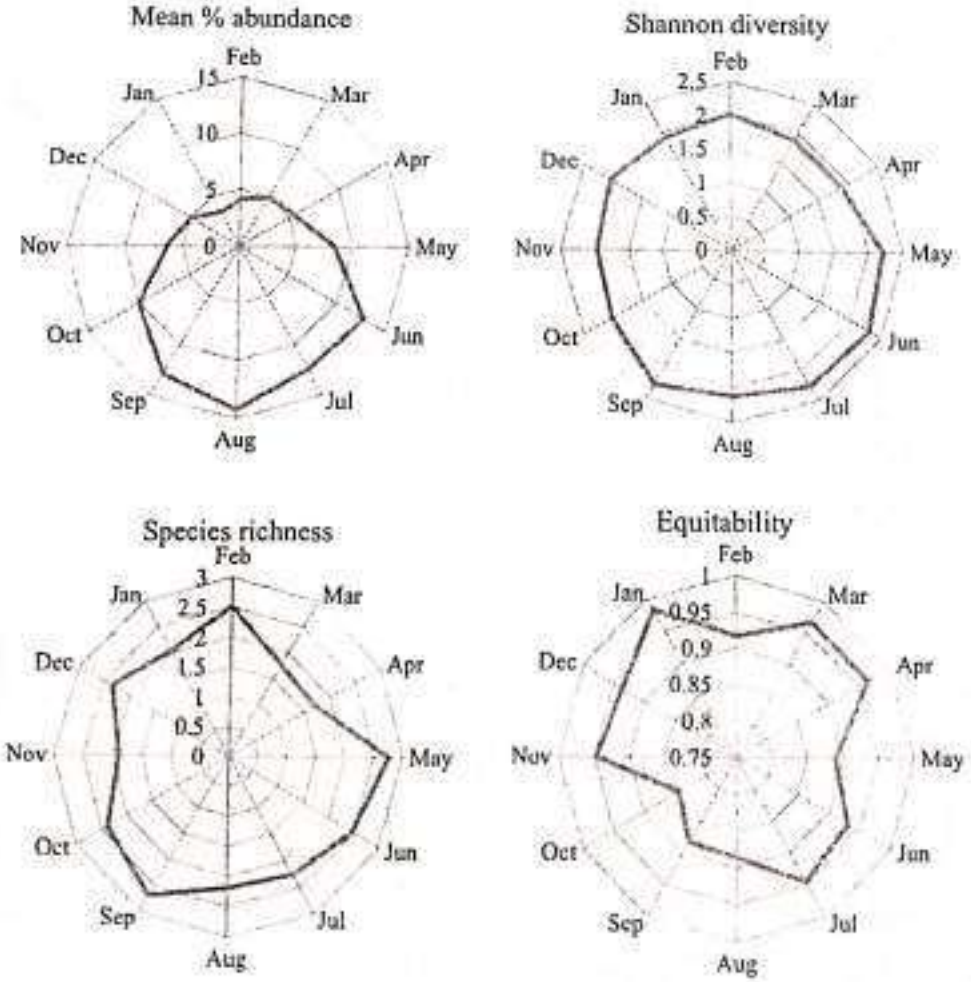


Figure 5. The values of the diversity indices in different months observed through the random sampling of the Saurian fauna in the Buldhana District, Maharashtra, India.

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A monthly comparison of species diversity attributed to saurian fauna in the studied area revealed that faunal diversity was highest during June to September while lowest during February to May. Mean percent abundance of saurian fauna was significantly different ($F = 30.314$, $df = 11$, $p < 0.05$); Shannon diversity values of saurian fauna were significantly different ($F = 3.811$, $df = 11$, $p < 0.05$); species evenness among different months was significantly different ($F = 15.824$, $df = 11$, $p < 0.05$) while species richness among the study months was not significantly different ($F = 1.328$, $df = 11$, $p > 0.05$) showing a contradictory pattern. A trend in mean % abundance was noted to be nearly similar to that of Shannon diversity although species richness and species equitability showed contradictory patterns (Figure 1).

Discussion

The utility of saurian species as indicators of environmental conditions is a basis for studying seasonal saurian diversity. Observations on the saurian diversity provided information about the variations in the species richness and the abundance shaped by the seasons. The differences in the diversity can be attributed to the monthly changes in the climatic conditions. In the present context, a monthly comparison of saurian species occurrence showed the highest number of species during June to September and the lowest during February to May.

The possible cause behind their minimum diversity in the winter months to early summer months is the cold-blooded nature of reptiles. Lizards preferred to hibernate in their burrows or resting places during winter to early summer. Species were generally observed more during monsoon months. According to Pal et al. (2012) and Joshi (2014), due to favorable environmental conditions, the monsoon season is the breeding season for most of the reptiles, which leads to their maximum abundance in rainy months. Earlier studies on the saurian diversity in various parts of Maharashtra show consistency with the present observations (Wadekar 2003; Deshpande et al. 2012; Kumbhar et al. 2013; Pandhalkar et al. 2013).

As revealed through the present study, at least 14 saurian species belonging to 5 families were recorded during all the studied months. In the observations, characters of the studied species were found to be almost the same as per existing records of Daniel (2002) and Ahmed et al. (2005). The maximum abundance was shown by *Calotes versicolor* followed by *Hemidactylus leschenaultia* and *Eutropis macularius*, while *Chamaeles zeylanicus* was the most rarely observed with the least abundance. During the study, the Gekkonidae family was observed to be more dominant over Scincidae, Agamidae, Varanidae, and Chamaeleonidae.

In parity with the species diversity observed in the Buldhana district, it may be assumed that the saurian species carry out diverse functional roles for the sustenance of the ecosystems. The availability of the green space and the heterogeneity of the habitats in terms of the available vegetation and allied factors that render stability to the population and species assemblages in the landscapes are possibly important contributors to the observed variations in the saurian species observed in the present study. The present diversity study is confined to a limited area and selected habitats. There is, in the future, a chance of more species being reported because of few pockets and habitats in the studied area requiring more extensive exploration.

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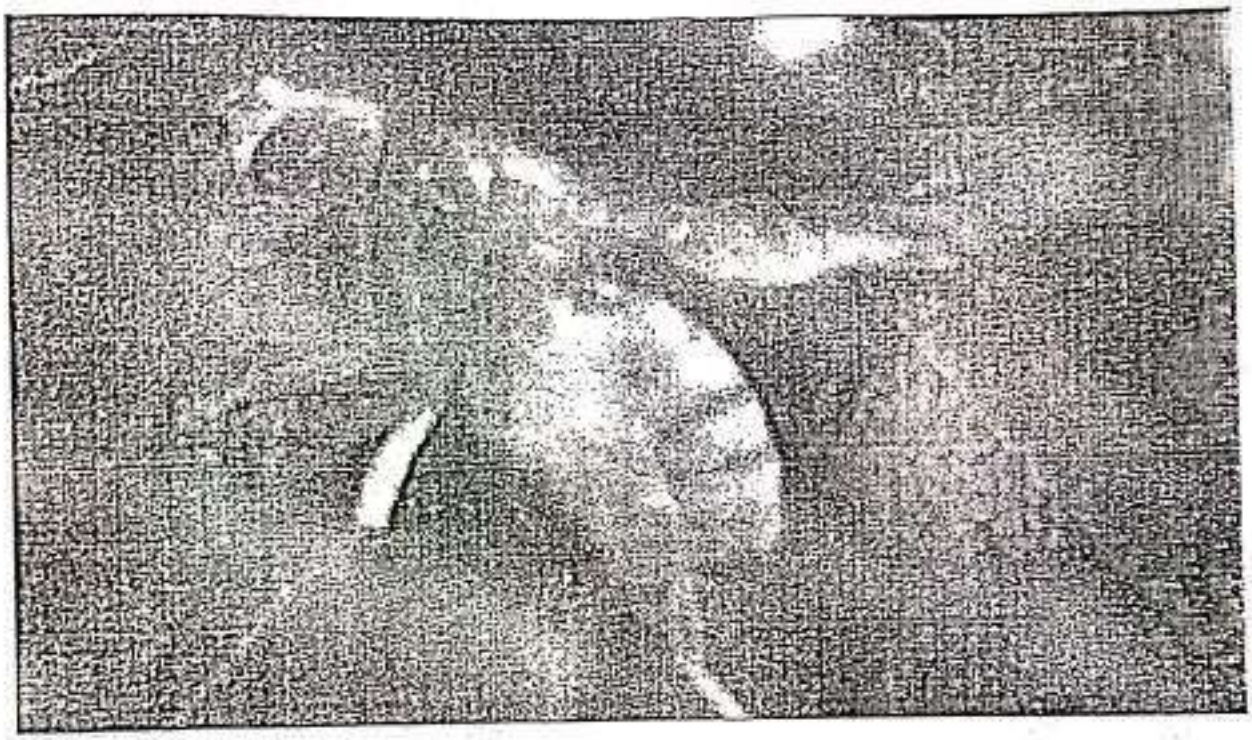
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EFFECT OF AZADIRACHTIN ON THE PHENOTYPE OF DIFFERENT DEVELOPMENTAL STAGES OF *DROSOPHILA MELANOGASTER*



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ABSTRACT:

In the present study we have studied the effect of azadirachtin on insect model *Drosophila melanogaster. Drosophila melanogaster* is a small, common fly and exhibit complete metamorphism. *Drosophila melanogaster* captured from rotten food, ripped banana and kitchen. They were cultured in controlled culture media and also kept separate normal culture one. After the development of each stages various parameter have been taken place and statically compared the controlled and normal flies, andeventually we have observed decrease in the size of flies which were fed on controlled culture media.

KEY WORDS: *Drosophila melanogaster*, Azadirachtin.

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INTRODUCTION:

A drug includes all chemicals other than food that affect living processes. If this effect helps the body than drug is acting as a medicine but if a drug causes a harmful effect on the body the drug is acting as a poison. To investigate about the drug effect on the human body the drug is not directly applied to the human body but various tests is done on various other organism, so far several studies have mainly been done on rat or mouse animal model and rarely with other animals like monkey, cat, dog, rabbit etc.

Regarding the various reason like more proliferation and low price scientist have focused on insect models. *Drosophila melanogaster* is a small, common fly found near unripe and rotted fruit. Drosophila is very valuable in terms of four pairs of chromosomes for genetic researchers, due to its small size, ease of culture and short generation time. There are several reason to be taken *Drosophila* as an experimental animal because they can be easily handled, anesthetized and manipulated individuals with very unsophisticated equipment. *Drosophila* are sexually dimorphic (males and females are different), making it is quite easy to differentiate the sexes. It is easy to obtain virgin males and females, as virgins are physically distinctive from mature adults. Flies have a short generation time (10-12 days) and do well at room temperature. The care and culture requires little equipment, is low in cost and uses little space even for large cultures.

Drosophila melanogaster exhibits complete metamorphism, meaning the life cycle includes an egg, larval (worm-like) form, pupa and finally emergence (enclosure) as a flying adult. This is the same as the well-known metamorphosis of butterflies and many other insects. The larval stage has three instars, or molts. After the third instars, larvae will begin to migrate up the culture vial in order to pupate.

Azadirachtin, a botanical pesticide derived from the neem tree, *Azadirachta indica* is one of the most promising natural compounds (Winkaler *et al.*, 2007), where it is less harmful to the environment than the synthetic pesticides (Sundaram, 1996).

Azadirachtin is structurally similar to that of insect hormone known as ecdysones. The insect hormone ecdysone plays an important role during growth of insect when passing from larva to adult. As Azadirachtin is similar to ecdysone it controls the process of metamorphosis by affecting on corpus cardiacum (an organ which secrete hormone in insects) means controls the secretion of hormone.

MATERIALS & METHODS

Collection of *Drosophila* flies: - Fruit fly has cosmopolitan distribution, and flies were easily collected on ripe banana or fruit. Ripe banana was put in a Petridis in one place then, the fruit flies were attracted and feed on ripe banana and the flies were transferred to a conical flask in the lab, we cover to the opening of the flask with a Maslin cloth the flies were easily collected with a brush.

Preparation of *Drosophila* culture media

Material required

Potato, sugar, Propionic acid, yeast.

Potato	-	100g
Agar	-	1.09 g
Water	-	100 ml
Dextrose	-	1 gm
Propionic acid	-	0.8 ml
Yeast	-	0.5 gm

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Boil the potato and clean it then weight up to 100 g, then add 1.09 g agar, 100 ml of H_2O added in it and I gm dextrose. Homogenize the mixture and make a fine paste. After formation of paste autoclave it at 15 IP for 10-15 min.

Cool the media up to 60°C. Then add 0.8 ml propionic acid put the culture media up to 40°C add 0.59 gm yeast in it by dissolving it in distilled water then sterilize it in autoclave at 15 IP.

Preparation of culture vials: - After sterilization of culture vials, transferred the culture, medium in ordered manner. First label the four cultured vials as A,B,C,D and then the vials with culture media. Arrange the vials at different azadirachtin concentrations.

Vials	A	-	75 µl
	B	-	35 µl
	C	-	18 µl
	D	-	Control

Transfer of *Drosophila* flies into culture vials:-

Drosophila flies were collected in collection bottle, the transfer 10-15 fruit flies into culture vials (half male and half female) and close the mouth of vials. Different concentration of drug was added to the culture as mentioned in the experimental set-up. These flies laid eggs in culture, hatch and completed their life cycle within 10-15 days. After completion of life cycle, various stages of the flies were collected and proceed for the measurement. The life cycle of Drosophila melanogaster were studied in these culture vials.

Observation of various stages: - Male and female copulate after 2-3 hours of copulation, female lay fertilized eggs. After 24 hrs of fertilization eggs hatches into first instars larva. First instar larvae change into second instars larvae, after 3-days. After the fifth day second instar larvae changes into third instar larvae and in sixth day third instars larvae changes into pupa. The sizes of larvae changes in all stages were found to be shrinkage than in normal condition in case of azadirachtin fed larvae.

Collection of adult flies: - The pupa changes in adult fly. After the development of adults, flies were collected for the observation and measurement of various parameters. First etherized them and collected in Petridis.

Measurement of various parameters: - The measurement of different developmental stages of the flies was done in under the microscope. These observations made under 10 x magnifications by using occulometer having scale given in micrometer (um).

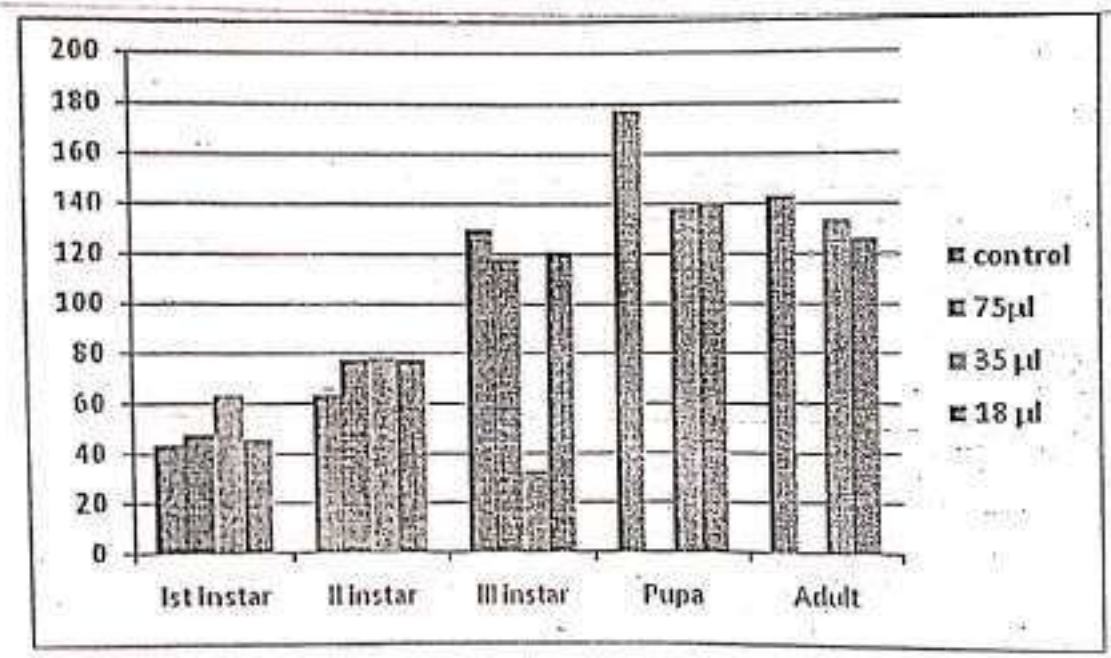
OBSERVATIONS AND RESULT

In our present work we observed the effect of azadirachtin on the molting of the flies and we found the inhibition of the molting with the increased dosages of azadirachtin, at higher doses (1ml, 0.5ml, 0.01ml) we observed the total mortality which shows the highly toxicity of azadirachtin. But at (18µl, 35µl, 75µl) respectively we noticed the development of 3rd instar larvae into pupa and adult incase of azadirachtin (18µl and 35µl) but at (75µl) no 3rd instar larvae developed into pupa thus the pupae development was inhibited or we may say the moulting was inhibited.

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Sr. No.	Devpt.-stage / Concentration	Ist Instar (µm)	IInd Instar (µm)	IIIst Instar (µm)	Pupa (µm)	Adult (µm)
1	Control	42.83±5.15	63.5±6.80	130.16±15.38	177.83±4.99	143.16±9.6
2	75µl	48±4.73^{NS} (10.77)	77.66±4.45** (18.23)	118.5±3.44^{NS} (9.83)		
3	35µl	63.83±4.30** (32.89)	78.5±15.01* (19.10)	32.5±4.27^{NS} (1.76)	138.5±13.18** (28.39)	134.16±10.12* (13.16)
4	18µl	46±7.48^{NS} (6.89)	77.66±5.31** (6.20)	120.83±6.64^{NS} (7.72)	140.5±6.09** (26.56)	126.5±6.44* (7.90)

Values are mean ± SD of six observations, * p<0.05>, ** p<0.01 & NS- Not Significant. Values are in paranthesis indicate the percent change in size over the control.



Graph- Effect of azadirachtin on the size of different developmental stages *of Drosophila melenogaster.*

DISCUSSION AND CONCLUSION

Paul B. Tanzubil and Alan R. M. Caffery (1990) studied the treatment of larvae of the African armyworm (*Spodoptera exempta*) with azadirachtin and aqueous neem seed extracts produced a range of adverse effects that were dose dependent. High doses of up to 10 µg per larva of azadirachtin resulted in 100% larval mortality, but this effect was delayed and prolonged. At lower doses of azadirachtin, however, inhibition and disruption of molting was observed and larval-pupal intermediates or abnormal pupae were commonly found. Similar results were obtained with the aquebus extracts of neem seeds. The few pupae obtained from larvae treated with lower doses of the extracts (0.01 and 0.1 µg per larva) either failed to develop further or developed into adults that died during eclosion, or had frizzled, curled wings.

Low doses of azadirachtin merely prolonged the inter-moult stage, apparently due to a delayed

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ecdysteroid peak. Medium and high doses suppressed adult ecdysis, and the larvae became permanent larvae, the longevity of which increased with rising doses. Although medium doses prevent ecdysis, apolysis and secretion of adult cuticle were taking place. The ecdysteroid peak was further delayed in these larvae and was somewhat lower than in controls. Permanent larvae induced by high azadirachtin doses showed neither ecdysis nor apolysis. Larvae also showed an ecdysteroid peak, which was considerably delayed and distinctly lower than in the controls. Thus, treatment with different azadirachtin doses allowed some dissection of the molting cycle into different steps, in which the hormonal regulation could be studied independently.

Menakshi Bhat et al (2011) in their study using invivo diabetic murine model, *AZadiracta indica* and *Bougainvillea spectabilis* chloroform, methanolic and aqueous extracts were investigated for the biochemical parameters important for controlling diabetes. It was found that *A. indica* chloroform extract and *B. spectabilis* aqueous, methanolic extracts showed a good oral glucose tolerance and significantly reduced the intestinal glucosidase activity. Interestingly, *A. indica* chloroform and B. spectabilis aqueous extracts showed significant increase in glucose-6-phosphate dehydrogenase activity and hepatic, skeletal muscle glycogen content after 21 days of treatment. In immunohistochemical analysis, they observed a regeneration of insulin-producing cells and corresponding increase in the plasma insulin and c-peptide levels with the treatment of *A. indica* chloroform and *B. spectabilis* aqueous, methanolic extracts.

A. J. Mordue et al (2008) studied the biological effect of azadirachtin on fifth instars nymphs of *Locusta migratoria migratorioides*. Azadirachtin injection at the beginning of the instar resulted in a dose-dependent range of developmental aberrations. Low concentrations (c. 1.7/µg/g body weight) resulted in adults with curled wing tips and reduced longevity; higher concentrations (c. 2.9µg/g) resulted in death during the imaginal molt; doses of c. 6.5µg/g cause death immediately prior to the molt; and doses of c. 7.3µg/g induce a greatly extended instar. Such doses were related to a proportionately slower growth rate of the insect and a significantly reduced food intake, as assessed by wet weight and faeces production. Doses of 80µg/g resulted in death within 24 h. Experiments *in vivo* and *in vitro* demonstrate a significant reduction with azadirachtin treatment in the rate of passage of food through the gut, and in gut motility. The significance of that direct effect on gut motility was discussed in relation to the mode of action of azadirachtin on growth and molting.

In our study *Drosophila melanogasters* were fed on culture containing different concentration of azadirachtin as at (0.01ml, 0.5ml, 0.01ml) we found the total death of the feeding drosophila that is the total mortality was observed the mortality hence may be attributed to the pesticidal effect of azadiractin and also concluded that azadirachtin responsible for decreasing the size of *Drosophila melanogaster.*

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Molecular structure investigation and biological evaluation of Michael adducts derived from dimedone

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Abstract Trimolecular salt Michael adducts **2a–c** were synthesized in excellent yields up to 92 % via one-pot multicomponent reactions in an aqueous medium. The chemical structures of compounds **2a–c** were characterized by X-ray single-crystal diffraction techniques. Calculations of the density functional theory for the synthesized compound were performed. The stability of the products was deduced by TGA analysis. Compounds **2a–c** were screened in vitro for different bio-assays such as thymidine phosphorylase inhibition assay, urease inhibition assay, β-glucuronidase inhibition assays and cytotoxicity against PC-3 and HeLa cell lines.

Keywords Michael adduct · Dimedone · Thymidine phosphorylase assay · Urease inhibition assay · β-Glucuronidase inhibition assay

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Introduction

5,5-Dimethylcyclohexane-1,3-dione, commonly known as dimedone, belongs to the family of cyclic 1,3-diketones –class of organic compounds. A wide range of applications of dimedones includes its use as reagent for various analytical techniques [1, 2], as well as a versatile synthon for synthesis of several *spiro* and heterocyclic compounds [3], such as xanthene derivatives, which have emerged as an important class of compound because of their industrial importance [4] and other synthetic applications [5].

The versatile chemistry [6–10] and ready availability of cyclohexane-1,3-diones [11–13] and its derivatives make them suitable precursors for the preparation of divergent organic compounds, for example chromene derivatives, which possess anticancer, antioxidant, spasmolytic, anti-anaphylactic, anti-HIV and anti-bacterial activities [14, 15], oxozolidinones with antibacterial activity [16–19], substituted xanthene derivatives with several uses in dyes [20, 21], laser technology [22], fluorescent compounds [23], and more importantly, have been reported to show a variety of biological activity [24–26]. Additionally, acridine and its derivatives display antimalarial, anticancer, antibacterial, and mutagenic properties, while phenylbutazones exhibit unique pharmacological uses for pain treatment associated with Tietze's syndrome and rheumatoid arthritis [27].

On the other hand, with the increasing environmental concerns, green chemistry has attracted major scientific and commercial interest in recent years. Multicomponent one-pot reactions are an efficient and economical procedure, with wide uses in the preparation of heterocycles molecules [28–30]. On the other hand, organic transformation takes place in aqueous media gives a clean, environmentally safe, and cost-effective approach. Recently, Barakat and coworkers reported examples for MCR (one-pot fission) for example reaction of substituted cyclohexanedione with alkanal mediated by diethylamine in water [31–36].

In the current study, the structure of salt Michael adducts **2a–c** were elucidated by X-ray single-crystal diffraction and TGA study. In addition, density functional theory (DFT) using B3LYP/6-311G(d,p) method were used to study different structural aspects of the compounds. Also, the synthesized compounds **2a–c** were evaluated for a set of in vitro biochemical assays.

Experimental

General

Chemical reagents were purchased from Fluka, Sigma-Aldrich, Aldrich, etc., and were used without further purification, unless otherwise stated. The crystal data were collected on a Bruker APEX-II CCD area diffractometer, crystallographic data for the compounds, **2a**, **2b** and **2c** are deposited with the CCDC-993141, 993142, and 993140 respectively.

*Diethylammonium 2-((4-bromophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-5,5-dimethyl-3-oxocyclohex-1-enolate (**2a**)*

Compound **2a** was synthesized from dimedone and *p*-bromobenzaldehyde **1a** as a white crystal. The structure of **2a** was unambiguously deduced by X-ray diffraction analysis. A suitable colorless cubic crystal of **2a** was grown in $CHCl_3/Et_2O$ at rt after 48 h.

*Diethylammonium 2-((3-bromophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-5,5-dimethyl-3-oxocyclohex-1-enolate (**2b**)*

Compound **2b** was synthesized from dimedone and *m*-bromobenzaldehyde **1b** as a crystalline compound. Colorless cubic crystals of compound **2**, found suitable for X-ray analysis, were grown in CH_2Cl_2/pet. ether at rt after standing for 24 h.

*Diethylammonium 2-((2,4-dichlorophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-5,5-dimethyl-3-oxocyclohex-1-enolate (**2c**)*

Compound **2c** was synthesized from dimedone and 2,4-dichlorobenzaldehyde (**1c**) as a colorless cubical crystals in CH_2Cl_2/pet. ether at rt. The crystals suitable for X-ray analysis were obtained after 3 days.

DFT calculations

In the present work, DFT calculations using the B3LYP method, together with local or non-local functionals, were performed that unites the Becke's three-parameter exchange functional (B3) with the Lee, Yang, and Parr correlation functional (LYP). The density functional theory (DFT) calculations were carried out utilizing GAMESS program. The input geometry of the synthesized compounds were optimized using at B3LYP/6-311G(d,p) basis set for C, O, N, and H atoms without imposing any external constraint on the potential energy surfaces.

Biological assay

The *p*-nitrophenyl-*β*-D-glucuronide (N-1627) and *β*-glucuronidase (E.C. 3.2.1.31, from bovine liver, G-0251) were purchased from Sigma Chemical Co. (U.S.A.). Na_2CO_3 anhydrous and all other reagents of standard grade were getting from E. Merck. The anhydrous EtOH and $CHCl_3$were used in experiment and these were dried by using the standard methods. All other solvents and reagents were of standard grade like the benzoyl chloride.

β-D-glucuronidase assay

β-D-glucuronidase inhibition assay was performed as described by Khan et al. [37].

Urease assay and inhibition

The assay was performed as described by Khan et al. [38] and Weatherburn et al. [39].

Thymidine phosphorylase assay protocol

The assay was performed as described by Krenitsky et al. [40].

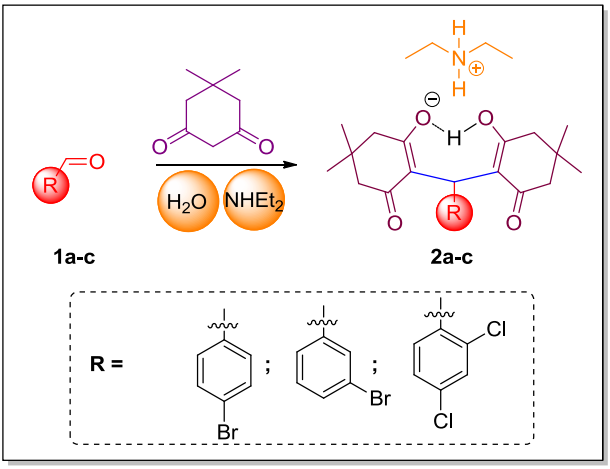
Cytotoxic activity

The assay was performed as described by Mosmann et al. [41].

Results and discussion

Synthesis of the salt of Michael adduct

Recently, there has been a lot of interest in the development of highly efficient transformations for the synthesis of biologically active organic molecules, with potential utilities in agrochemical or pharmaceutical industries. There is also interest in discovering new, strategically important protocols, which are efficient and environmentally benign, and lead to the complex structural variations with simple work-up procedures in high yields [32–35]. During the current study, diethylamine in aqueous medium mediated the one-pot two-component Aldol-Michael addition of 5,5-dimethylcyclohexane-1,3-dione (dimedone), with different arylaldehyde **2a–c** in 2:1 molar ratio to provide trimolecular Michael adducts **2a–c** in excellent yields up to 92 % (Scheme 1) [31].



Scheme 1 Synthetic protocol used in the present work

X-ray crystal structures

The chemical structures of the final adduct **2a–c** were unambiguously deduced by single-crystal X-ray diffraction technique (Fig. 1a–c). Tables 1, 2, 3 and 4 display the crystal data and main geometrical parameters of the compounds.

Slow evaporation of compounds **2a** ($CHCl_3/Et_2O$, 3 days), **2b** (DCM/pet. ether, 24 h), and **2c** (DCM/pet. ether, 2 days), at room temperature yielded pure crystals of **2a–c**. Crystals of dimensions 0.38 × 0.37 × 0.24 (**2a**), 0.47 × 0.42 × 0.14 (**2b**) and 0.31 × 0.21 × 0.20 (**2c**) mm were selected for X-ray diffraction analysis on a

Table 1 The crystal data of **2a–c**

	2a	**2b**	**2c**
Empirical formula	$C_{27}H_{37}BrNO_4$	$C_{27}H_{37}BrNO_4$	$C_{27}H_{36}Cl_2NO_4$
Formula weight	519.49	519.41	509.47
Temperature	273 (2)	273 (2)	273 K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/n$
A	10.2861 (11) Å	12.6829 (13) Å	10.3400 (10) Å
B	18.1701 (19) Å	12.2729 (13) A	18.2984 (18) Å
C	15.6171 (16) Å	18.5831 (19) Å	15.0374 (15) Å
α	90°	90°	90°
β	106.5 (2)°	108.283 (3)°	98.257 (2)°
γ	90°	90°	90°
Volume	2798.5 (5) A^3	2746.5 (5) A^3	2815.7 (5) A^3
Z	4	4	4
Calculated density	1.233 mgm^{-3}	1.256 mgm^{-3}	1.202 mgm^{-3}
Absorption coefficient	1.498 mm^{-1}	1.527 mm^{-1}	0.261 mm^{-1}
F(000)	1092	1092	1084
Crystal size	0.38 × 0.37 × 0.24 mm	0.47 × 0.42 × 0.14 mm	0.31 × 0.21 × 0.20 mm
θ range	1.76–25.50°	1.69–25.50°	1.76–28.37°
Reflections collected	16,291	15,992	20,357
Reflections unique	5202	5050	7014
(R_{int})	0.0384	0.0597	0.0442
R_1 with $I > 2\sigma(I)$	0.0553	0.0518	0.0605
R_2 with $I > 2\sigma(I)$	0.1273	0.1142	0.1358
R_1 for all data	0.1068	0.1192	0.1092
R_2 for all data	0.1528	0.1438	0.1609
Goodness of fit	1.081	0.972	1.017
Max/min ρ e^{-3}Å	0.567 and −0.730	0.326 and −0.258	0.474 and −0.225
CCDC	993,141	993,142	993,140

Table 2 Geometric parameters (Å, °) of **2a** (selected)

Bond	Experimental	Calculated
Br1–C3	1.902 (4)	1.8905
O2–C13	1.286 (4)	1.2595
O4–C19	1.334 (4)	1.3831
N1–C26	1.481 (6)	1.4785
N1–C25	1.492 (6)	1.4786
C8–C13	1.388 (4)	1.3831
C14–C19	1.353 (4)	1.3558
Bond angle	Experimental	Calculated
C26—N1—C25	114.5 (4)	117.6644
O2—C13—C8	122.2 (3)	122.5294
O2—C13—C12	115.4 (3)	111.9032
O4—C19—C14	124.3 (3)	127.8520
CO4—C19—C18	110.9 (3)	113.9985
N1—C26—C27	110.3 (4)	109.9599
C24—C25—N1	111.7 (5)	111.5620

Table 3 Geometric parameters (Å, °) of **2b** (selected)

Bond	Experimental	Calculated
Br1–C2	1.897 (4)	1.8930
O1–C9	1.329 (4)	1.2650
O3–C17	1.290 (3)	1.2301
N1–C25	1.467 (4)	1.4768 s
N1–C26	1.501 (5)	1.4770
C8–C9	1.358 (4)	1.3560
C16–C17	1.386 (4)	1.3646
Bond angle	Experimental	Calculated
C25—N1—C26	112.2 (3)	117.6644
O1—C9—C8	124.6 (3)	121.5499
O1—C9—C10	111.4 (3)	119.5021
O3—C17—C16	122.6 (3)	121.3063
O3— C17— C18	116.2 (3)	111.9032
C24— C25— N1	112.8 (3)	111.5620
C27—C26—N1	111.9 (4)	109.9599

Bruker Smart Apex II diffractometer, equipped with CCD detector and graphite monochromatic MoKα radiations ($\lambda = 0.71073$ Å) at 293 (2) K. Cell refinement and data reduction were carried out by Bruker SAINT [14]. The chemical structure

Table 4 Geometric parameters (Å, °) of **2c** (selected)

Bond	Experimental	Calculated
Cl1–C9	1.741(2)	1.7354
C12–C11	1.736(3)	1.7207
O2–C5	1.299(2)	1.2307
O4–C19	1.329(3)	1.2639
N1–C26	1.472(4)	1.4774
N1–C25	1.482(4)	1.4775
C4–C5	1.508(3)	1.5113
C14–C19	1.360(3)	1.3646
Bond angle	Experimental	Calculated
O2–C5–C6	121.97(19)	121.9985
O2–C5–C4	115.08(18)	118.2618
O4–C19–C14	125.1(2)	120.7989
O4–C19–C18	110.92(19)	119.0782
C8–C9–Cl1	120.03(19)	119.9182
C11–C10–C9	118.8(2)	119.8890
C12–C11–C10	120.0(2)	120.1922
C12–C11–Cl2	120.1(2)	119.9325
N1–C26–C27	110.9(3)	110.2876
C24–C25–N1	112.1(3)	110.1151

was solved by using SHELXS-97 [15, 16]. The listed crystallographic parameters in Table 1 indicate that compounds **2a**, **2b**, and **2c** were crystallized in monoclinic crystal system with space group $P2_1/n$ for **2a** and **2c** and $P2_1/c$ for **2b**. The crystal structures **2a**, **2b**, and **2c** (Fig. 1a) were finally refined with R factor of 5.5, 5.1, and 6.0 %, respectively. The molecule of diethyl amine solvate played an important role to stabilize the structures in crystal lattice through intermolecular hydrogen bondings (Fig. S7–S9; Table S1–S3; see supplementary material).



Fig. 1 The structure of **2a–c** (ORTEP diagrams)

DFT calculations

Optimized molecular geometry

From our XRD data, it is clear that compounds **2a, 2b**, and **2c** possess monoclinic crystal structures. The cell dimensions and other data are presented in Table 1. Selected values of calculated DFT and experimental geometric parameters for the synthesized molecules were found to be in good agreement, and are listed in Tables 2, 3 and 4. Figures 2 and 3 depict the optimized structures and HOMO–LUMO for compounds **2a, 2b**, and **2c**.

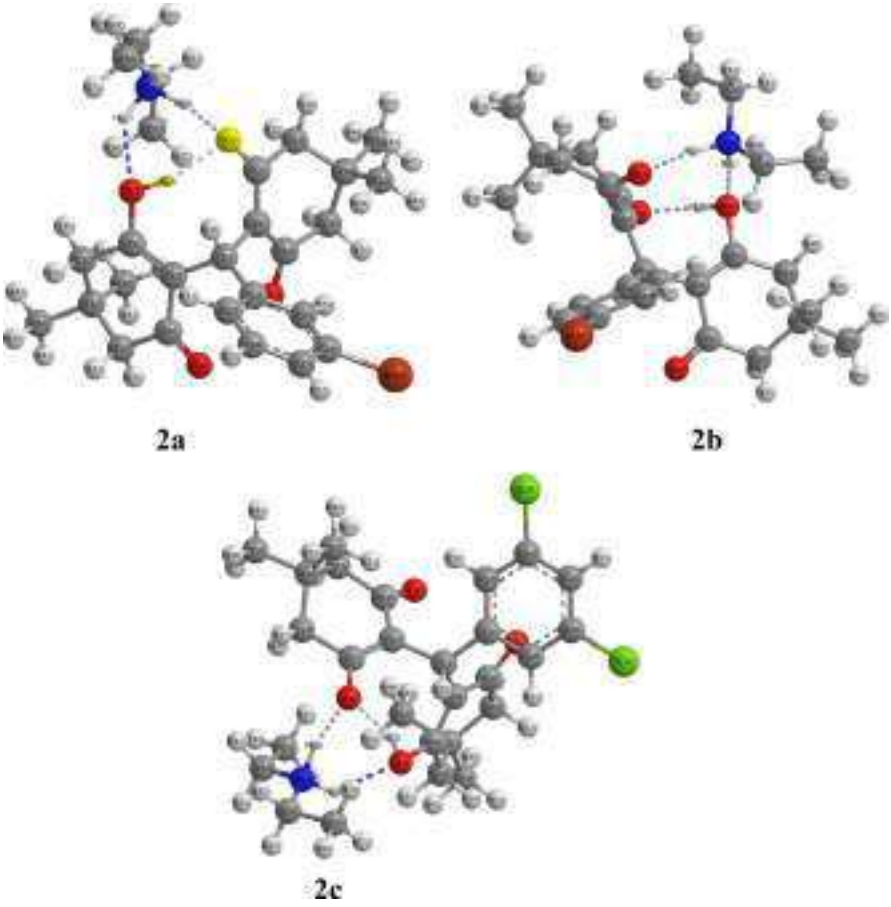


Fig. 2 Optimized molecular structures of compounds **2a, 2b**, and **2c**

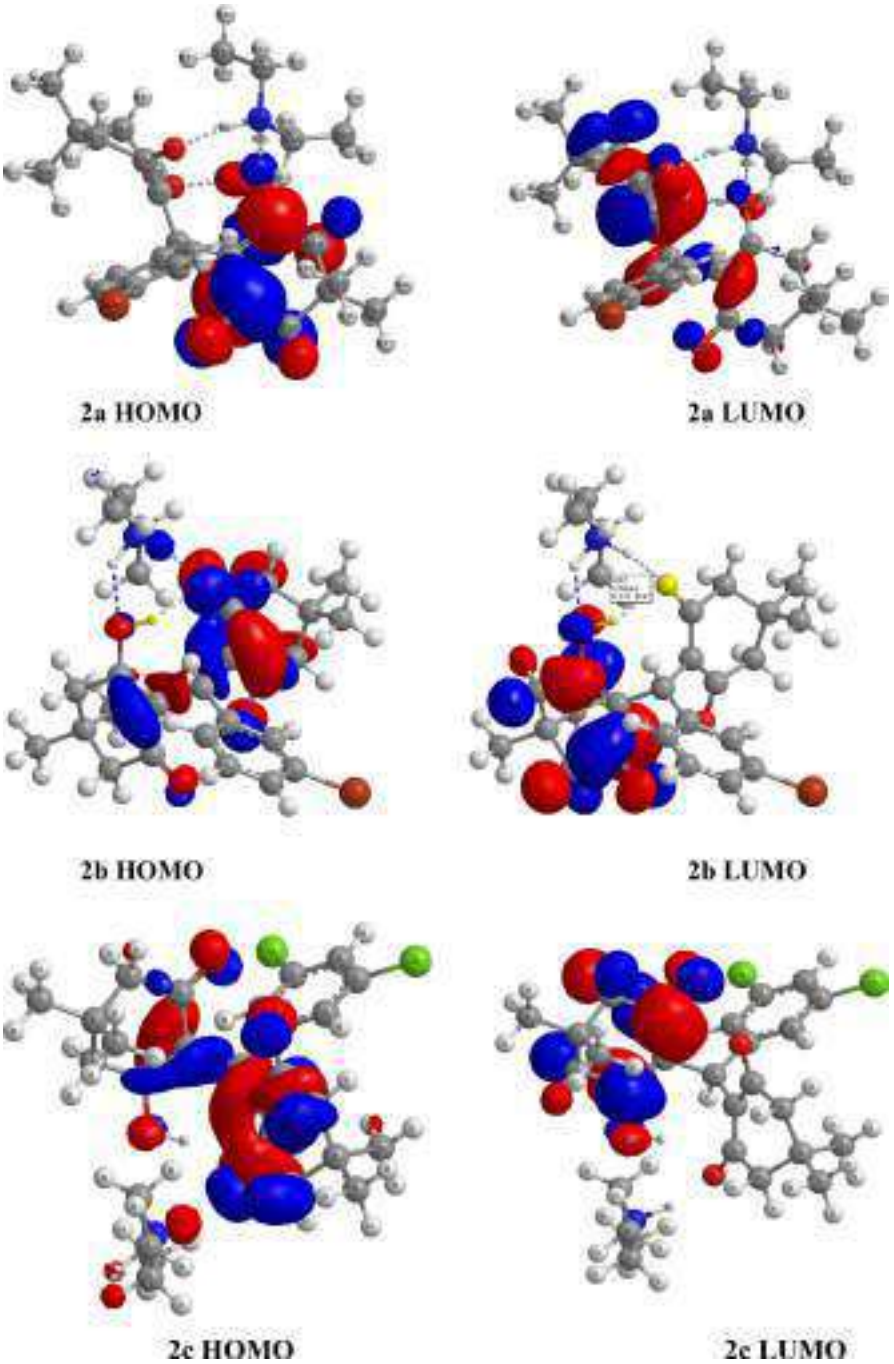


Fig. 3 HOMO and LUMO for compounds **2a, 2b**, and **2c**

Thermal gravimetric analysis (TGA)

Thermal stability of the synthesized compounds was investigated by thermogravimetric analysis (TGA). All the samples were made under nitrogen atmosphere in the temperature ranges between 0 and 800 °C with a heating ramp rate of 10 °C per min (Table 5). It has shown that all the synthesized compounds demonstrated thermal stability up to 200 °C, with a percentage weight loss of 31.45, 22.42, and 16.12 for the compounds **2a**, **2b**, and **2c**, respectively. When the temperature was further raised to 300 °C, dramatic percentage weight loss of up to 98.9, 97.3, and 97.7 for the compounds **2a**, **2b**, and **2c** respectively. Hence, it can be said that the synthetic compounds are thermally stable up to 200 °C, and from there on a rapid degradation occur (Fig. 4).

Biological activity evaluation

Compounds **2a–c** were screened in vitro for different bio-assays such as thymidine phosphorylase, urease, and β-glucuronidase inhibition assays. These compounds

Table 5 Weight loss of synthesized molecules with temperature

Temperature	Weight loss (%)		
	2a	**2b**	**2c**
100	0.07	0.24	0
200	31.45	22.42	16.12
300	98.907	97.301	97.794
400	99.5205	98.977	98.17
500	99.8727	99.318	98.212
600	99.6842	99.621	98.045
700	99.6564	99.4393	97.682
800	99.8236	99.088	97.215

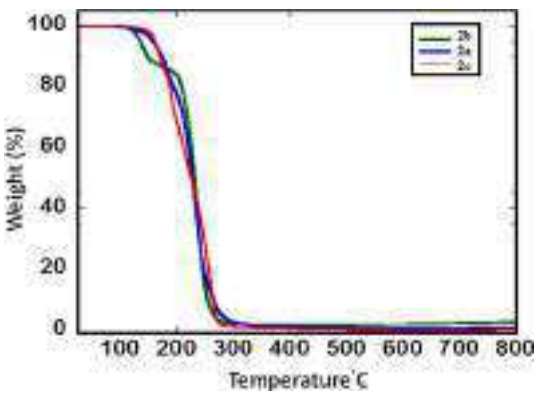


Fig. 4 The TGA curve of the studied compounds **2a**, **2b** and **2c**

Table 6 Results of biological activity of the synthesized compounds **2a–c**

Compounds	Cytotoxicity (PC-3 cell line)	Cytotoxicity (HeLa cell line)	Thymidine phosphorylase inhibition $IC_{50} \pm SEM$ (μM)	Urease inhibition $IC_{50} \pm SEM$ (μM)	β-glucuronidase inhibition $IC_{50} \pm SEM$ (μM)
2a	NA	NA	NA	154.8 ± 1.33	351.6 ± 4.12
2b	>30	>30	283.3 ± 0.7	75.4 ± 1.46	NA
2c	>30	>30	243.3 ± 1.5	108.2 ± 1.3	NA
Std.	Doxorubicin 0.912 ± 0.12	Doxorubicin 0.506 ± 0.15	7-Deazaxanthine 41 ± 1.64	Thiourea 21.2 ± 1.3	D-Saccharic acid 1-4 lactone 45.75 ± 2.16

were also evaluated for their cytotoxic effect against PC-3 and HeLa cell lines. Results are summarized in Table 6.

Compounds **2b, c** showed a varying degree of thymidine phosphorylase inhibition with IC_{50} values 283.3 ± 0.7 and 243.3 ± 1.5 μM, respectively, against the tested standard drug 7-deazaxanthine ($IC_{50} = 41 \pm 1.64$ μM). Compound **2a** found to be inactive (Table 6).

The tested compound **2a–c** ($IC_{50} = 154.8 \pm 1.33$, 75.4 ± 1.46, and 108.2 ± 1.3 μM) showed weak urease inhibition activity against the standard compound thiourea ($IC_{50} = 21.2 \pm 1.3$ μM). Michael adducts **2a–c** were also evaluated for their in vitro β -glucuronidase inhibitory potential and compound **2a** ($IC_{50} = 351.6 \pm 4.12$ μM) showed weak inhibition of β-glucuronidase enzyme in comparison to the standard drug D-saccharic acid 1-4 lactone ($IC_{50} = 45.75 \pm 2.16$ μM). Michael adducts **2b** and **2c** found to be inactive.

Michael adducts **2b–c** were found to be non cytotoxic against of PC-3 normal and HeLa cancer cell lines, and showed >30 % inhibition while compound **2a** was found to be inactive against PC-3 normal and HeLa cancer cell lines (Table 6).

Conclusions

In the present study, three Michael adducts were synthesized by using a simple, high-yielding, and economical synthetic scheme. The structures were established with the help of physico-chemical properties and single-crystal X-ray diffraction technique. Single-crystal X-ray analysis and DFT calculations revealed that H-bonding plays a crucial role in stability of the molecules. It was observed that all the synthesized compounds demonstrated a thermal stability up to 200 °C. Compounds **2a–c** were also evaluated for their biological activities in various in vitro biological assays.

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A PARADIGM SHIFT IN SERVICE SECTOR IN INDIAN ECCONOMY – A REVIEW

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Abstract
The rising India has a very strong service base that contributes more than 50% to national Gross Domestic Product (GDP). It resulted out of paradigm shift that has taken place with the major structural changes in Indian economy since 1991. This was the watershed year in Indian economic history when major economic changes in terms of liberalization, privatization and globalization (LPG) were brought in Indian economic regulations by the 'the then finance minister' (**Dr. Manmohan Singh**). The revolution brought new technologies, new companies, new concepts and new customers to Indian market. India's unilateral liberalization and deregulation and shift in economic paradigm towards integration with the world economy have contributed to a favorable environment for the boom in service sector. It is now equipped with better technologies, better reach to overseas market and improved methods and processes. The study advocates the paradigm shifts in the service sector with new perspectives. The general objective of this paper is to provide an overview of the Indian Services sector. However, to be specific this paper provides an overview of the growth of Services sector and its components in India, focusing on its contribution to Gross Domestic Product (GDP)

Introduction:

Services sector is the lifeline for the socio-economic growth of a country. It is today the largest and fastest growing sector globally contributing more to the global output and employing more people than any other sector. In alignment with global trend, the Indian Services sector has witnessed a major boom and is one of the major contributors to both employment and national income in recent time. Services sector in India today accounts for more than half of India's GDP. Since independence, there has been a marked acceleration in Services sector growth in India.

In India, growth in services sector has been linked to the liberalization and reforms of the 1990s. In the first three decades (1950s to 1970s) after India's independence in 1947, GDP grew at an average decadal growth rate of less than four per cent. India was largely an agrarian economy. The share of services sector was small and a large number of services were government monopolies. Services sector started to grow in the mid-1980s but growth accelerated in the 1990s when India initiated a series of economic reforms after the country faced a severe balance of payment crisis. Reforms in the services sector were a part of the overall reform process, which led to privatization, removal of FDI restrictions and streamlining of the approval procedures, among others.

Existing studies show that liberalisation and reforms is one of the important factors contributing to the growth of services sector in India. With economic growth and rise in per capita income, there is a change in demand pattern from necessary to discretionary consumptions like education and personal and health care services. High income elasticity of demand for services has contributed to the high growth of this sector. Technological progress and availability of high skilled manpower has led to growth of services like information technology (IT) and IT enabled services. Developed countries outsource its services to developing countries like India leading to a rise in demand for services from the developing market. High government expenditure on certain services like community, social and personal services has also led to high growth of services.

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Reasons For Growth in Service Sector

India's service sector is the 12th largest in the world by nominal GDP and 4th largest when purchasing power is taken into account. The service sector provides employment to 27% of the population. Let us look into the factors that have led to the growth of the service sector in India:

Economic Affluence

The Indian society is characterized by an increasing middle class. In addition the liberalization of the Indian economy has had a positive impact on the Indian households. Their income and expenditure has been pushed up fostering the demand for goods and services;

Changing Role of Women

Earlier women were a neglected lot, who only had to carry out household chores. But with time there has been a change in the way of thinking. Women are educated and allowed to work. They are employed in several erstwhile male dominated services such as defense services, police services, postal services, software services, health services etc. An increase in the number of working women has led to the creation of a market for a number of products and services.

Changing Culture

The traditionally common joint family system is slowly disintegrating and making way for a nuclear family way of living. This has been accompanied by an increased demand for a number of services like education, health care, entertainment, tourism etc. There has also been a marked change in a person's way of thinking with respect to investment, recreation and time perception leading to increased demand for services.

Growth of IT Sector

In India information technology and business outsourcing are amongst the fastest growing sectors having a cumulative growth rate of revenue.

The growth of IT sector can be attributed to several factors such as increased specialization and availability of a large pool of low cost, highly skilled educated and fluent English speaking workers. This supply is matched by increased demand from foreign customers who are interested in India's service exports or those looking to outsource their operation.

Development of Markets

Both the urban and the rural areas have witnessed wide spread retailing and whole selling. In fact retailing has even extended to remote rural areas.

Health Care Consciousness

The present generations are becoming more and more diet and health conscious. They are resorting to services of gymnasiums and fitness clubs to maintain their physical and mental health.

Economic Liberalization

The opening up of the Indian economy in 1991 was followed by a policy of disinvestment. This facilitated the entry of multinational Corporations leading to its accompanying increase in demands. This acted as a spurt for the development of the service sector.

Migration from Rural to Urban Areas

With rapid industrialization and other developments in this era of globalization, there takes place large scale migration from the rural to the urban areas. This changes the life-style and enhances the demand for services.

Export Potential

The services offered by India to various parts of the world include banking, insurance, transportation, company data services, education, software services, tourism etc. In fact tourism and software services are among the major foreign exchange earners of the country.

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Service Tax

The coverage of this tax has been extended. The tax net covers hotels and restaurants, transport, storage and commercialization, financial services, real estate, business services and social/personal services.

India has the second fastest growing services sector with its compound annual growth rate at nine per cent, just below China's 10.9 per cent, during the last 11-year period from 2001 to 2012, the Economic Survey for 2013-14 said. Russia at 5.4 per cent is a distant third. Among the world's top 15 countries in terms of GDP, India ranked 10th in terms of overall GDP and 12th in terms of services GDP in 2012, it said, adding that services share in world GDP was 65.9 per cent but its share in employment was only 44 per cent in 2012. As per the survey, in India, the growth of services-sector GDP has been higher than that of overall GDP between the period FY 2001- FY 2014. Services constitute a major portion of India's GDP with a 57 per cent share in GDP at factor cost (at current prices) in 2013-14, an increase of 6 percentage points over 2000-01.



(Source: The Hindu- Business-budget-New Delhi July 9, 2014)

In fact the growth rate of 6.8 per cent for the sector is marginally lower than in 2012-13. "This is due to deceleration in the growth rate of the combined category of trade, hotels, and restaurants and transport, storage, and communications to 3 per cent from 5.1 per cent in 2012-13," the survey said. On the other hand, robust growth was seen in financing, insurance, real estate, and business services at 12.9 per cent. FDI inflows to the services sector (top five sectors including construction) declined sharply by 37.6 per cent to USD 6.4 billion compared to an overall growth in FDI inflows at 6.1 per cent. India's share in world services exports, which increased from 0.6 per cent in 1990 to 1.1 per cent in 2000 and further to 3.3 per cent in 2013, has been increasing faster than its share in world merchandise exports, according to the survey. While exports of software services, accounting for 46 per cent of India's total services exports, decelerated to 5.4 per cent in 2013-14 from 5.9 per cent in 2012-13, travel, accounting for a nearly 12 per cent share, witnessed negative growth of 0.4 per cent. However, moving in tandem with global exports of financial services, India's exports of financial services registered a high growth of 34.4 per cent in 2013-14.

Sector-wise contribution of GDP of India

Indian economy is classified in three sectors — Agriculture and allied, Industry and Services. Agriculture sector includes Agriculture (Agriculture proper & Livestock), Forestry & Logging, Fishing and related activities. Industry includes Manufacturing (Registered & Unregistered), Electricity, Gas, Water supply, and Construction. Services sector includes Trade, repair, hotels and restaurants, Transport, storage, communication & services related to broadcasting, Financial, real estate & professional services, Community, social & personal services.

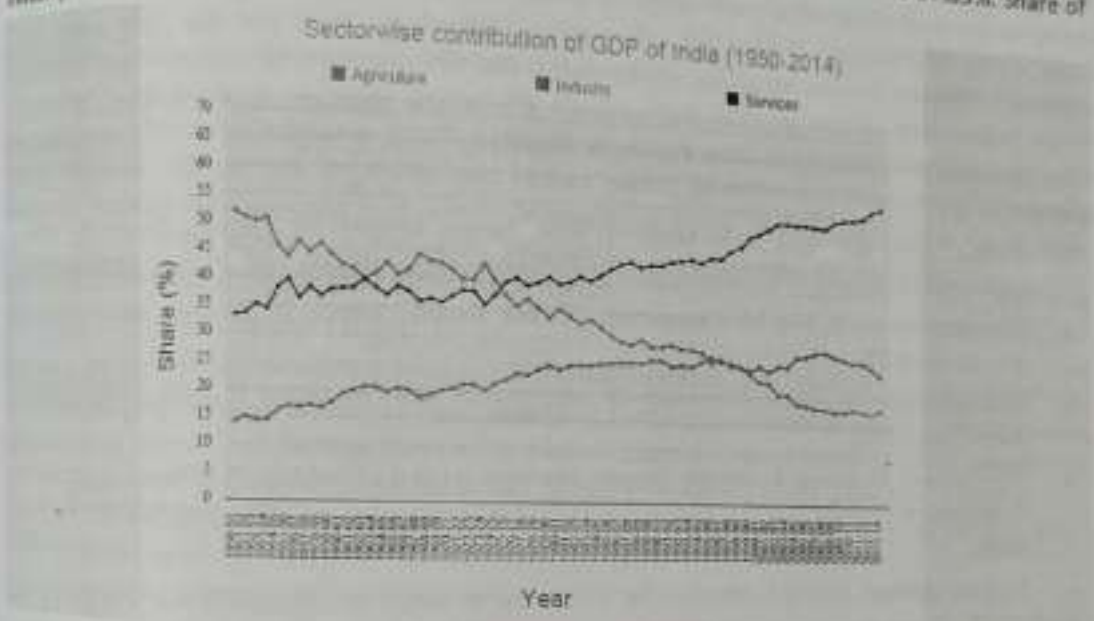
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Services sector is the largest sector of India. Gross Value Added (GVA) at current prices for Services sector is estimated at 61.18 lakh crore INR in 2014-15. Services sector accounts for 52.97% of total India's GVA of 115.50 lakh crore Indian rupees. With GVA of Rs. 34.67 lakh crore, Industry sector contributes 30.02%. While, Agriculture and allied sector shares 17.01% and GVA is around of 19.65 lakh crore INR.

At 2011-12 prices, composition of Agriculture & allied, Industry, and Services sector are 16.11%, 31.37%, and 52.52%, respectively.

According to CIA Fackbook sector wise Indian GDP composition in 2014 are as follows : Agriculture (17.9%), Industry (24.2%) and Services (57.9%). Total production of agriculture sector is $366.92 billion. India is 2nd larger producer of agriculture product. India accounts for 7.68 percent of total global agricultural output. GDP of Industry sector is $495.62 billion and world rank is 12. In Services sector, India world rank is 11 and GDP is $1185.79 billion. Contribution of Agriculture sector in Indian economy is much higher than world's average (6.1%). Contribution of Industry and Services sector is lower than world's average 30.5% for Industry sector and 63.5% for Services sector.

At previous methodology, composition of Agriculture & allied, Industry, and Services sector was 51.81%, 14.16%, and 33.25%, respectively at current prices in 1950-51. Share of Agriculture & allied sector has declined at 18.20% in 2013-14. Share of Services sector has improved to 57.03%. Share of industry sector has also increased to 24.77%



(Source : Planning Commission, Government of India)

Future Prospects

Indian economy which was growing at an accelerated rate from 1998 to 2010 had a setback of sorts in 2012. The economy however is gradually picking up and moving in the right path. This will lead undoubtedly to increase the Per Capita Income of the high and middle income groups, while simultaneously striving to reduce the number of people below the poverty line.

The entire process would have stimulating effect with an increase in the literacy level. India has to her credit one of the youngest populations in the world. The cumulative effects of all this will be an increase in the demand for services like education, health, hotels, restaurants etc.

According to the Planning Commission India's service sector is expected to grow at the rate of 10% per annum in the period between 2012 and 2017.

India also ranks high in international trade accounting for 3.34% of exports and 3.31% of imports of services. It is in addition among the top 10 rankers of WTO members as regards export and import of services.

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Conclusions

As we have discussed the service sector is the fastest growing sector in India, contributing significantly to the GDP and is projected to rise even further. However, the increase in employment is not in keeping with the share of the sector in the GDP and even among those employed the big question is how many of these work in the organized service sector?

India has a number of problems which are socio economic in nature. Poverty and accelerated population growth are major constraints, thereby depriving several people of access to basic health and education.

A number of obstacles hamper the progress of this sector and its contribution to inclusive growth. Bureaucratic inertia, multiple government bodies having their own sets of rules and regulations, rampant corruption and absence of a uniform concrete policy have an adverse effect on the system. Slow reform process, restrictions on foreign direct investment, poor infrastructural facilities, absence of uniformity in the quality and standard of education, in spite of having renowned Brain Power and the existence of unemployable educated youth are all limiting factors.

India, however, has vast potential for promotion of service economy. This is attributed to factors such as emergence of a new middle class with increasing aspirations, opening of the economy leading to the availability of a wide range of goods and services, growing retail and improving domestic and international market for Information Technology. With just the right policy mix, propelled further by the revival of the US economy and the potential for India's IT and Business Process outsourcing sectors in different parts of the world together with increased domestic demand will no doubt take our country to greater heights.

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IMPACT OF SOCIAL NETWORKING SITES ON THE ACADEMIC PERFORMANCE OF SENIOR COMMERCE COLLEGE STUDENTS.

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Abstract:

There is no doubt that Social media has gained wider acceptability and usability and is also becoming probably the most important communication tools among students especially at the higher level of educational pursuit. As much as social media is viewed as having bridged the gap in communication that existed. Within the social media Facebook, Twitter, Watsapp and others are now gaining more and more patronage.

This study attempts to obtain students' perceptions on how social networking sites impact their academic performance. In this paper a survey was conducted by distributing 200 questionnaires to selected students from the Faculty of Commerce in Amravati city. The purpose was to obtain respondents' opinion on the use of social networking sites and its influence on their academic performance. The study confirmed that most of the students are engage in the use of SNSs mainly for socializing activities rather than for academic purpose. However, most of the students do feel that the SNSs have more positive impact on their academic performance through collaborative learning.

Introduction

The world has been changed rapidly by the evolution of technology; this has resulted into the use of technology as the best medium to explore the wide area of knowledge. The evolution of internet technology has led to its use as the best medium for communication. Whereby, two-third of the world's internet population visits social networking or blogging sites, thus serving as a communication and connection tool. The use of Internet has increased drastically between the year 2000 and 2007. According to Markey and Well during the year 2000 the number of people with access globally was estimated to be around 400 million. This number grew to 600 million in 2002. Internet is a tool that is used for different things by different people. It is used by employees of various organizations to search for information and to also exchange information with other people. At home the internet is used as means to chat to other people and to get news that affect the world in general. Some people make use of it to do business transactions through e-banking facility. The benefit that often come with the use of the internet such as obtaining useful information, chatting with friends, discussing and gaining knowledge on all sort of topics etc, have persuaded the college students. And access of social networking sites on internet has become a major attraction to these students.

The social media has become one of the most important communication means in recent times. However, social networking exist so as to provide communication among people regardless of the distance, making it open to people easily share information, files and pictures and videos, create blogs and send messages, and conduct real-time conversations. These systems are referred to as social, simply because they allow communication with buddies and co-workers so easily and effectively. It also strengthens the ties between people of those systems. The favorite in the realm of internet sites are Facebook, Twitter and others. These websites and social forums are way of communication directly with other people socially and in media. They are playing a large and influential role decision-making in the occasions from the global world economically, politically, socially and educationally. The driving factors for adoption of social media are the progressively ubiquitous access, convenience, functionality, and flexibility of social technologies. It has been

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contended that, poor greater education, social technologies supports social constructivist techniques to learning they potentially have to improve students' construction of understanding and promote student interaction. An additional benefit of social technologies provided on the internet is that they are frequently free or require marginal investment, eliminating a potential barrier to adoption. There has been various overview and opinions which recognized four major advantages of social media use in higher education. These include, enhancing relationship, improving learning motivation, offering personalized course material, and developing collaborative abilities. This means that social networking activities have the possibility of enhancing student contact and is used to improve their participation in class, particularly where introverted students are involved. Students can function in online group learning, with less or no anxiety of needing to raise questions before peers at school.

Review of Literature

Different researchers have conducted research to ascertain the influence of social media on users; for example, Moon (2011) in a study on "impact of facebook on undergraduate academic performance", averred that social media have negative impact on students. According to the result, the more students use facebook, the more it affects their academic performance. Similarly, Oye (2012) notes that most of the younger students use social networking sites mainly for socialising activities, rather than for academic purpose. Oye (2012) further observed that most of the students do feel that social networking sites have more positive impact on their academic performance. In another study conducted by Shana (2012), it was revealed that students use social network mainly for making friends and chatting. The result showed that only 26 percent of the students (respondents) indicated that they use social media for academic purpose. Seo (2004) corroborates Jeong's assertion when he opined that the negative influence of internet is only on excessive users and not on all users.

Statement of Problem

The expansion in technology has also affected internet software, thus leading to chatting sites known by the name "social media". However the study will evaluate the impact of social networking on academic performance of college students.

Need & Purpose of the study

It is a common scene to see a youth chatting in sensitive and highly organized places like church, mosque and lecture venues. Some are so carried away that even as they are walking along the highway, they keep chatting and put their lives in danger. The manufacturing and distribution of equally sophisticated cellular phones has complicated the situation, as youths no longer need to visit a cybercafé before they send and receive messages. Attention has been shifted from visible to invisible friends, while important ventures like studying and writing are affected in the process. This phenomenon has become a source of worry to many who believe in knowledge and skill acquisition.

The emergence of social media as a result of advancement in technology and expansion in internet software has raised eye brows among academics on its (social media) impacts on studies. Students at all levels of learning now have divided attention to studies, as a result of available opportunities to be harnessed from social media. Whether these opportunities promote studies is a question that needs to be answered. Thus, the study investigated the "Impact of social networking on the academic performance of senior college students."

Objectives of the study.

- To analyse the time spent by the students on internet daily.
- To evaluate the students perception towards usage of social networking sites.
- To study the daily pattern of college attendance, tuitions and study time spent by students.
- To analyse the length of time since the student is using internet on mobile.
- To study whether the student is aspired to check social networking sites during studies.
- To evaluate how the use of internet have improved the learning pattern of students.

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- To analyse whether it has been assumed that the use of social networking sites has become a status symbol among students.

Hypothesis:

Ho: There is no relationship between the use of social networking site and the academic performance of senior college students.

Data collection:

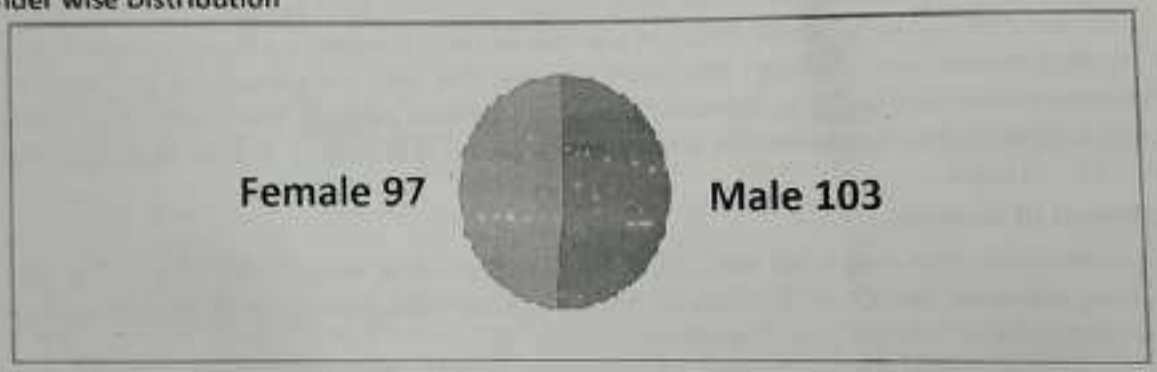
- Primary data was collected through questionnaire mailed through electronic media.
- Secondary data was collected from magazines, books and internet.

Sampling:

- Universe: Area was selected from Amravati city with the help of cluster sampling, the traditional senior colleges of commerce in the cluster.
- Size: 200 respondents.
- Sampling method: Disproportionate stratified random sampling method.

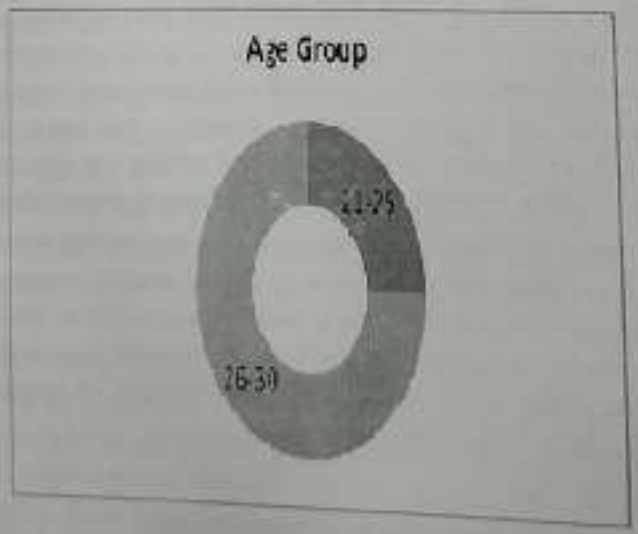
Analysis and Interpretation

ender wise Distribution



Interpretation: In the sample there were 97 Females and 103 Male.

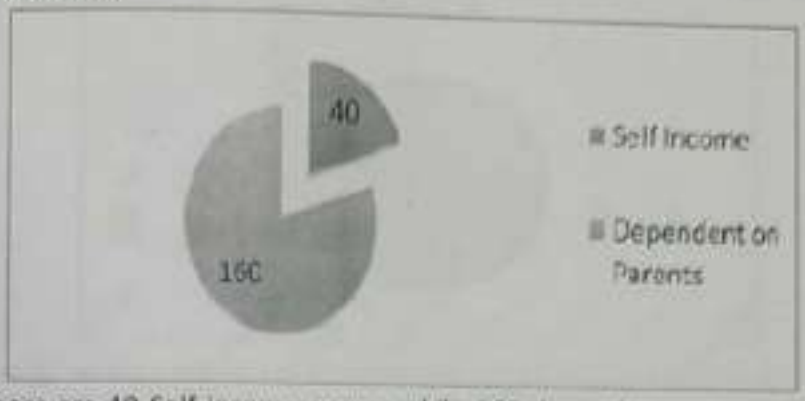
Age wise Distribution



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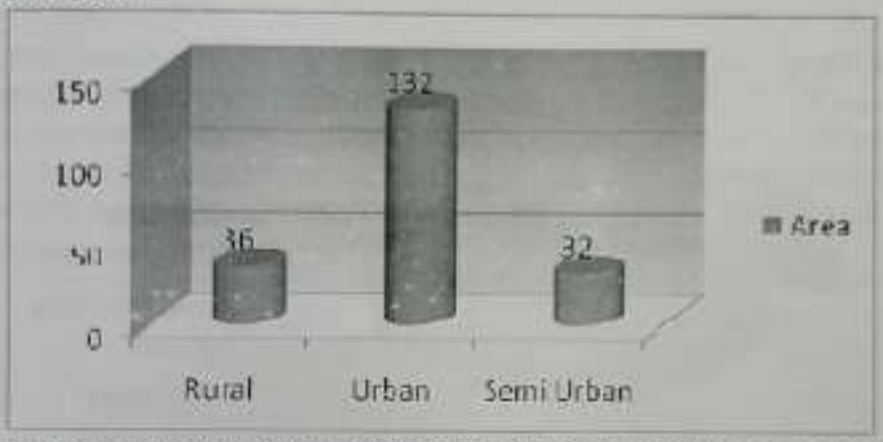
Interpretation: There are 150 respondents who are of the age group of 26-30 and 50 respondents are of 21-25 age group.

Income wise Distribution



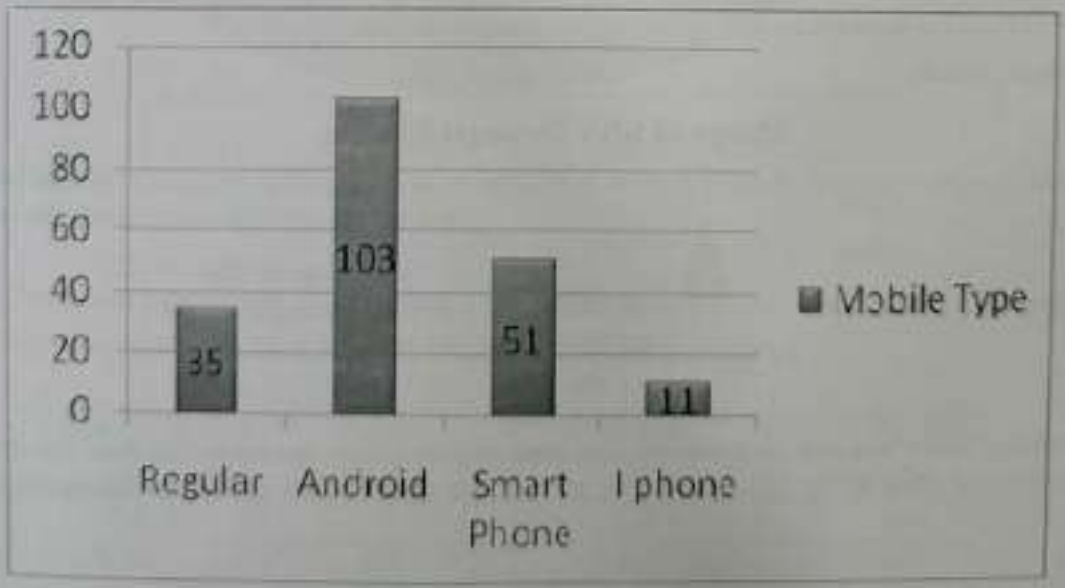
Interpretation: There are 40 Self income earner while 160 dependent on parents for their income source.

Area Wise Distribution



Interpretation: There are 36 respondents from Rural area, 132 from Urban area and 32 from Semi Urban area.

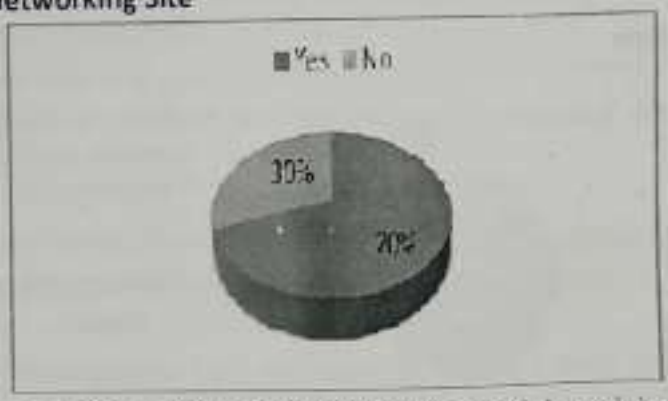
Type of Mobile



Interpretation: There are 35 respondents who have Regular Mobile, 103 who have Android Mobile, 51 who have Smart Phones and 11 who have I phones.

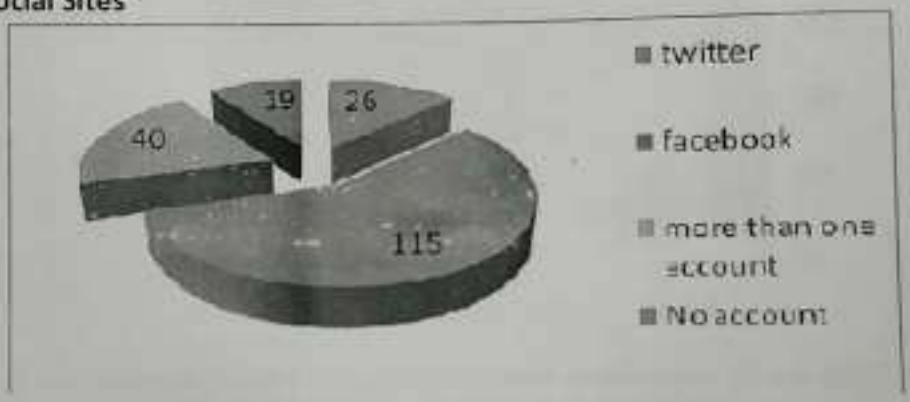
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Necessity of Social Networking Site



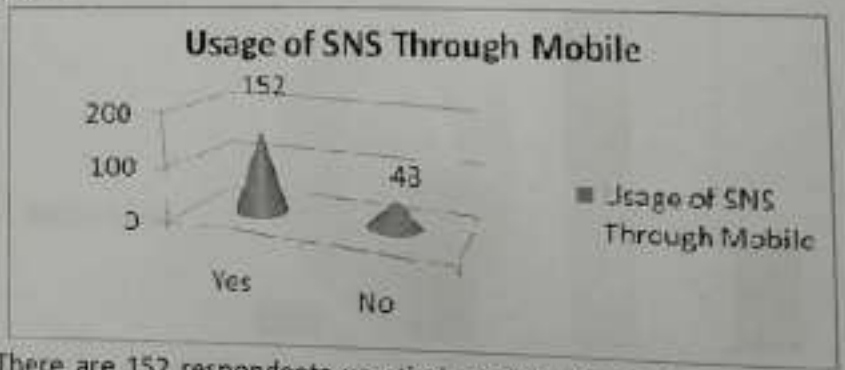
Interpretation: There are140 i.e. 70% of the respondents are of the opinion of having an account on SNSs while 60 i.e. 30% of the respondents feel that there is no need of opening or having an account on these sites. Therefore it may be said that having an account on these sites have become necessary among students for collaborative learning as well as have become status symbol among students.

Preferred Social Sites



Interpretation: There are 26 respondents out of 200 who prefer twitter account, 115 respondents have facebook account, 40 respondents prefer more than one account on these sites while 19 respondents have no account on any of the social networking sites.

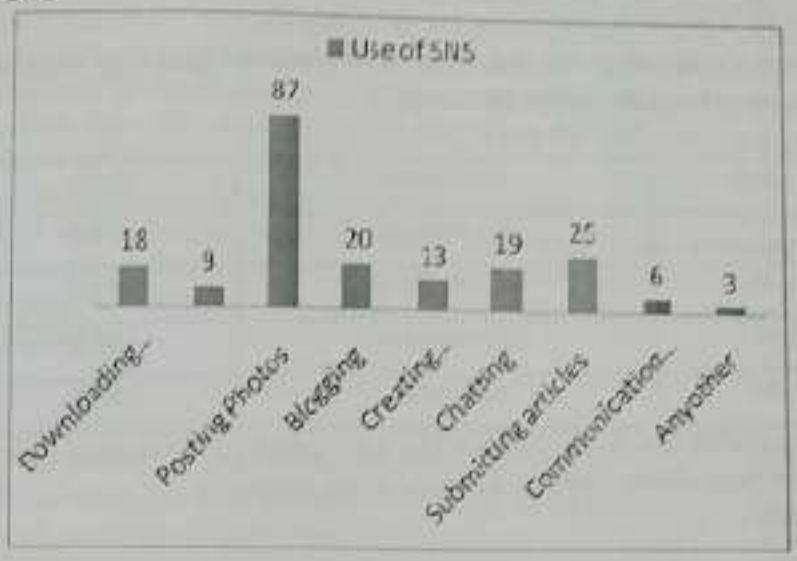
SNS through mobile



Interpretation: There are 152 respondents use their mobile phone for accessing their account on social networking sites while 48 respondents do not use their mobile phone for operating these sites.

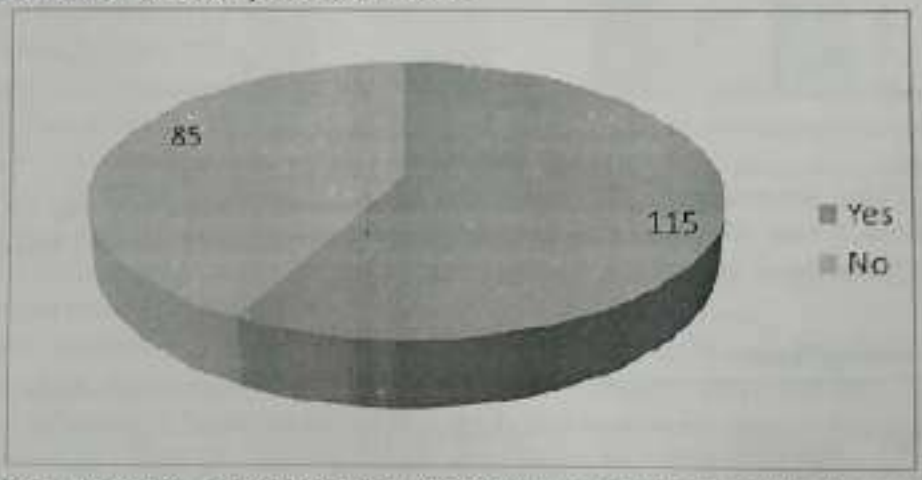
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Primary use of SNS



Interpretation: The primary use of SNS is for posting photos responded by 87 respondents, 25 respondents use it for submitting articles, 20 respondents use it for blogging, 19 respondents use it for chatting, 18 respondents use it for downloading music/videos, 13 respondents use it for creating polls/quizzes or surveys, 9 respondents use it for uploading music/videos, 6 respondents use it for communication with teachers/class fellow, 3 respondents use it for any other purpose.

Friends on SNS are more compared to real life



Interpretation: There are 115 respondents who have more friends in real life than real life and 85 respondents don't agree with this statement.

Testing of Hypothesis through Chi Square for proving SNS to be an effective tool for E-learning

Hypothesis for testing: SNS is NOT an effective tool for E-learning

E-learning	Friends	Teachers	Total
Yes	128	72	200
No	72	128	200
Total	200	200	400

Conclusion:

The calculated value is 31.36 which is greater than the table value 3.841. Hence, our hypothesis that SNS is not an effective tool for e-learning is proved wrong.

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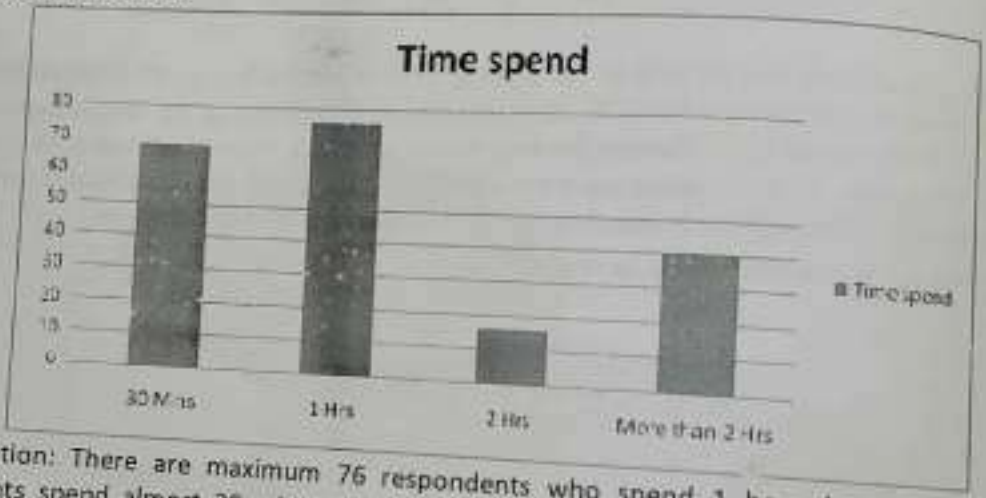
Therefore, we can say that SNS is an effective tool for e-learning

Weighted Average Distribution on the basis of Preference given by respondents on the choice of community they join/subscribe on SNS.

Rank	Particulars	Score
I	Educational	59.6
II	Informational	52.4
III	Entertainment	50.8
IV	Any other	32.4

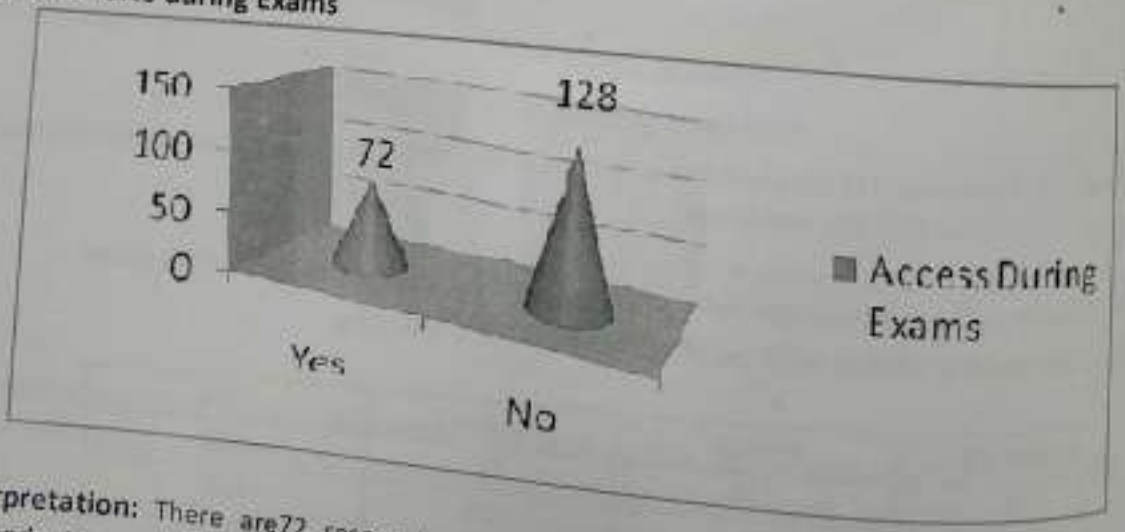
NOTE: Respondents stating any other communities were asked as to reasoned that they subscribe communities for marriage, sports, hobbies, astrological etc. purposes.

Time spend on SNS's



Interpretation: There are maximum 76 respondents who spend 1 hour in a day on SNS, 38 respondents spend almost 30 minutes on SNS whereas, 16 respondents spend 2 hours and 40 respondents for more than 2 hours a day.

Access of SNS during Exams



Interpretation: There are72 respondents accesss their SNS account during exams while 128 respondents are matured enough and don't access their account during exams.

Findings:

Positive perceptions obtained from users of social networking sites i.e. effective learning which has resulted in an easy learning climate among students. Through the study it has been explored that

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how social networking sites encourage friendliness through the use of Facebook, Twitter and watsapp. The study concluded that numerous approaches can be used to encourage amiability among students which leads to a positive effect from SNSs user's point of view. It has been found that Facebook networking site is used by students more frequently and also faculty members. Recent data obtained from net, showed that approximately 297,000 users are university faculty members, although there are pros and cons in each case.

It has been found that internet is advantageous to both students and teachers if used as a tool of knowledge creation and dissemination. In the study conducted, it was observed that maximum students spent almost 1 hour daily on these sites as well as there are maximum of 128 out of 200 respondents who don't access these sites during exam which on the other hand don't affect their academic performance.

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Liberalization of Indian Banking and Regulation

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Banking is an ancient business in India with some of oldest references in the writings of Manu. Bankers played an important role during the Mogul period. During the early part of the East India Company era, agency houses were involved in banking. Modern banking (i.e. in the form of joint-stock companies) may be said to have had its beginnings in India as far back as in 1786, with the establishment of the General Bank of India. Three Presidency Banks were established in Bengal, Bombay and Madras in the early 19th century. These banks functioned independently for about a century before they were merged into the newly formed Imperial Bank of India in 1921. The Imperial Bank was the forerunner of the present State Bank of India. The latter was established under the State Bank of India Act of 1955 and took over the Imperial Bank.

The Swadeshi movement witnessed the birth of several indigenous banks including the Punjab National Bank, Bank of Baroda and Canara Bank. In 1935,the Reserve Bank of India was established under the Reserve Bank of India Act as the central bank of India. In spite of all these developments, independent India inherited a rather weak banking and financial system marked by a multitude of small and unstable private banks whose failures frequently robbed their middle-class depositors of their life's savings. After independence, the Reserve Bank of India was nationalized in 1949 and given wide powers in the area of bank supervision through the Banking Companies Act (later renamed Banking Regulations Act). The nationalization of the Imperial bank through the formation of the State Bank of India and the subsequent acquisition of the state owned banks in eight princely states by the State Bank of India in 1959 made the government the dominant player in the banking industry. In keeping with the increasingly socialistic leanings of the Indian government, 14 major private banks, each with deposits exceeding Rs. 50 crores, were nationalized in 1969. This raised the proportion of scheduled bank branches in government control from 31% to about 84%. In 1980, six more private banks each with deposits exceeding Rs 200 crores , were privatized further raising the proportion of government controlled bank branches to about 90%. As in other areas of economic policy-making, the emphasis on government control began to weaken and even reverse in the mid-80s and liberalization set in firmly in the early 90's. The poor performance of the public sector banks, which accounted for about 90% of all commercial banking, was rapidly becoming an area of concern. The continuous escalation in non-performing assets (NPAs) in the portfolio of banks posed a significant threat to the very stability of the financial system. Banking reforms, therefore, became an integral part of the liberalization agenda.

The first Narasimham Committee set the stage for financial and bank reforms in India. Interest rates, previously fixed by the Reserve Bank of India, were liberalized in the 90's and directed lending through the use of instruments of the Statutory Liquidity Ratio was reduced. While several committees have looked into the ailments of commercial banking in India, but major work has been done according to the Narsimham committee reports.- the Narasimham committee I (1992) and II (1998)

Liberalization

Liberalization (or liberalization) refers to a relaxation of previous government restrictions, usually in areas of social or economic policy. In some contexts this process or concept is often, but not always, referred to as deregulation. In the arena of social policy it may refer to a relaxation of laws restricting. Most often, the term is used to refer to economic liberalization, especially trade liberalization or capital market liberalization.

Liberalization in Indian Banking Sector-

Liberalization in Indian banking sector was begun since 1992, following the Narsimham Committee Report (December 1991). The 1991 report of the Narasimhan Committee served as the basis for the initial banking sector reforms .In the following years, reforms covered the areas of interest rate deregulation, directed credit rules, statutory pre-emptions and entry deregulation for both domestic and foreign banks. The objective of banking sector reforms was in line with the overall goals of the 1991 economic reforms of opening the economy, giving a greater role to markets in setting prices and allocating resources, and increasing the role of the private sector. The Narsimhan Committee was first set up in 1991 under the chairmanship of Mr. M. Narasimham who was 13th governor of RBI. Only a few of its recommendations became banking reforms of India and other were not at all considered. Because of this a second committee was again set up in 1998.As far as recommendations regarding bank restructuring, management freedom, strengthening the regulation are concerned, the RBI has to play a major role. If the major recommendations of this committee are accepted, it will prove to be fruitful in making Indian banks more profitable and efficient.

Problems Identified By The Narasimham Committee

1. **Directed Investment Program** : The committee objected to the system of maintaining high liquid assets by commercial banks in the form of cash, gold and unencumbered government securities. It is also known as the Statutory Liquidity Ratio (SLR). In the old days, in India, the SLR was as high as 38.5 percent. According to the M. Narasimham Committee it was one of the reasons for the poor profitability of banks. Similarly, the Cash Reserve Ratio- (CRR) was as high as 15 percent. Taken together, banks needed to maintain 53.5 percent of their resources idle with the RBI.

2. **Directed Credit Program** : Since nationalization the government has encouraged lending to agriculture and small-scale industries at a confessional rate of interest. known as the directed credit programme. The committee opined that these sectors

matured and thus do not need such financial support. This directed credit programme was successful from the government's point of view but it affected commercial banks in a bad manner. Basically it deteriorated the quality of loan, resulted in a shift from the security oriented loan to purpose oriented. Banks were given a huge target of priority sector lending, etc. ultimately leading to profit erosion of banks.

3. **Interest Rate Structure**: The committee found that the interest rate structure and rate of interest in India are highly regulated and controlled by the government. They also found that government used bank funds at a cheap rate under the SLR. At the same time the government advocated the philosophy of subsidized lending to certain sectors. The committee felt that there was no need for interest subsidy. It made banks handicapped in terms of building main strength and expanding credit supply.

4. **Additional Suggestions:** Committee also suggested that the determination of interest rate should be on grounds of market forces. It further suggested minimizing the slabs of interest.

Along with these major problem areas M. Narasimham's Committee also found various inconsistencies regarding the banking system in India.

Narasimham Committee Report I – 1991

The Narsimham Committee was set up in order to study the problems of the Indian financial system and to suggest some recommendations for improvement in the efficiency and productivity of the financial institution.

The committee has given the following major recommendations:-

1. **Reduction in the SLR (Statutory Liquidity Ratio) and CRR(Cash Reserve Ratio)** : The committee recommended the reduction of the higher proportion of the Statutory Liquidity Ratio (SLR) and the Cash Reserve Ratio (CRR). Both of these ratios were very high at that time. The SLR then was 38.5% and CRR was 15%. This high amount of SLR and CRR meant locking the bank resources for government uses. It was hindrance in the productivity of the bank thus the committee recommended their gradual reduction. SLR was recommended to reduce from 38.5% to 25% and CRR from 15% to 3 to 5%.

2. **Phasing** out **Directed Credit Programme** : In India, since nationalization, directed credit programmes were adopted by the government. The committee recommended phasing out of this programme. This programme compelled banks to earmark then financial resources for the needy and poor sectors at confessional rates of interest. It was reducing the profitability of banks and thus the committee recommended the stopping of this programme.

3. **Interest Rate Determination** : The committee felt that the interest rates in India are regulated and controlled by the authorities. The determination of the interest rate should be on the grounds of market forces such as the demand for and the supply of fund. Hence the committee recommended eliminating government controls on interest rate and phasing out the concessional interest rates for the priority sector.

4. Structural Reorganizations of the Banking sector : The committee recommended that the actual numbers of public sector banks need to be reduced. Three to four big banks including SBI should be developed as International banks. Eight to Ten Banks having nationwide presence should concentrate on the national and universal banking services. Local banks should concentrate on region specific banking. Regarding the RRBs (Regional Rural Banks), it recommended that they should focus on agriculture and rural financing. They recommended that the government should assure that henceforth there won't be any nationalization and private and foreign banks should be allowed liberal entry in India.

5. **Establishment of the ARF Tribunal** : The proportion of bad debts and Non-performing asset (NPA) of the public sector Banks and Development Financial Institute was very alarming in those days. The committee recommended the establishment of an Asset Reconstruction Fund (ARF). This fund will take over the proportion of the bad and doubtful debts from the banks and financial institutes. It would help banks to get rid of bad debts.

6. **Removal of Dual control** : Those days banks were under the dual control of the Reserve Bank of India (RBI) and the Banking Division of the Ministry of Finance (Government of India). The committee recommended the stepping of this system. It considered and recommended that the RBI should be the only main agency to regulate banking in India.

7. **Banking Autonomy** : The committee recommended that the public sector banks should be free and autonomous. In order to pursue competitiveness and efficiency, banks must enjoy autonomy so that they can reform the work culture and banking technology upgradation will thus be easy.

Some of these recommendations were later accepted by the Government of India and became banking reforms.

Narasimham Committee Report II – 1998

In 1998 the government appointed yet another committee under the chairmanship of Mr Narsimham. It is better known as the Banking Sector Committee. It was told to review the banking reform progress and design a programme for further strengthening the financial system of India. The committee focused on various areas such as capital adequacy, bank mergers, bank legislation, etc.

It submitted its report to the Government in April 1998 with the following recommendations.

1. **Strengthening Banks in India:** The committee considered the stronger banking system in the context of the Current Account Convertibility (CAC). It thought that Indian banks must be capable of handling problems regarding domestic liquidity and exchange rate management in the light of CAC. Thus, it recommended the merger of strong banks which will have 'multiplier effect' on the industry.

2. Narrow Banking: Those days many public sector banks were facing a problem of the Non-performing assets (NPAs). Some of them had NPAs were as high as 20 percent of

their assets. Thus for successful rehabilitation of these banks it recommended 'Narrow Banking Concept' where weak banks will be allowed to place their funds only in short term and risk free assets.

3. **Capital Adequacy Ratio:** In order to improve the inherent strength of the Indian banking system the committee recommended that the Government should raise the prescribed capital adequacy norms. This will further improve their absorption capacity also. Currently the capital adequacy ration for Indian banks is at 9 percent.

4. **Bank ownership:** As it had earlier mentioned the freedom for banks in its working and bank autonomy, it felt that the government control over the banks in the form of management and ownership and bank autonomy does not go hand in hand and thus it recommended a review of functions of boards and enabled them to adopt professional corporate strategy.

5. **Review of banking laws:** The committee considered that there was an urgent need for reviewing and amending main laws governing Indian Banking Industry like RBI Act, Banking Regulation Act, State Bank of India Act, Bank Nationalisation Act, etc. This upgradation will bring them in line with the present needs of the banking sector in India.

Apart from these major recommendations, the committee has also recommended faster computerization, technology upgradation, training of staff, depoliticizing of banks, professionalism in banking, reviewing bank recruitment, etc.

Changes due to the recommendations made by the Narsimham committee are-

1. Statutory pre-emptions: The degree of financial repression in the Indian banking sector was significantly reduced with the lowering of the CRR and SLR, which were regarded as one of the main causes of the low profitability and high interest rate spreads in the banking system. During the 1960s and 1970s the CRR was around 5%, but until 1991 it increased to its maximum legal limit of 15%.The reduction of the CRR and SLR resulted in increase flexibility for banks in determining both the volume and terms of lending.

2. Priority sector lending: Besides the high level of statutory pre-emptions, the priority sector advances were identified as one of the major reasons for the below average profitability of Indian banks. The Narasimham Committee therefore recommended a reduction from 40% to 10%. However, this recommendation has not been implemented and the targets of 40% of net bank credit for domestic banks and 32% for foreign banks have remained the same.

3. Interest rate liberalization: Prior to the reforms, interest rates were a tool of cross-subsidization between different sectors of the economy. To achieve this objective, the interest rate structure had grown increasingly complex with both lending and deposit rates set by the RBI. The deregulation of interest rates was a major component of the banking sector reforms that aimed at promoting financial savings and growth of the organized financial system. The lending rate for loans in excess of Rs200,000 that account for over90% of total advances was abolished in October 1994. Banks were at the same

time required to announce a prime lending rate (PLR) which according to RBI guidelines had to take the cost of funds and transaction costs into account.

4. Entry barriers: Before the start of the 1991 reforms, there was little effective competition in the Indian banking system for at least two reasons. First, the detailed prescriptions of the RBI concerning for example the setting of interest rates left the banks with limited degrees of freedom to differentiate themselves in the marketplace. Second, India had strict entry restrictions for new banks, which effectively shielded the incumbents from competition. Through the lowering of entry barriers, competition has significantly increased since the beginning of the1990s. Seven new private banks entered the market between 1994 and 2000. In addition, over 20 foreign banks started operations in India since 1994. By March 2004, the new private sector banks and the foreign banks had a combined share of almost 20% of total assets. Deregulating entry requirements and setting up new bank operations has benefited the Indian banking system from improved technology, specialized skills, better risk management practices and greater portfolio diversification.

5. Prudential norms: The report of the Narasimham Committee was the basis for the strengthening of prudential norms and the supervisory framework. Starting with the guidelines on income recognition, asset classification, provisioning and capital adequacy the RBI issued in 1992/93, there have been continuous efforts to enhance the transparency and accountability of the banking sector. The improvements of the prudential and supervisory framework were accompanied by a paradigm shift from micro-regulation of the banking sector to a strategy of macro-management.

6. Public Sector Banks : At the end of the 1980s, operational and allocative inefficiencies caused by the distorted market mechanism led to a deterioration of Public Sector Banks' profitability. Enhancing the profitability of PSBs became necessary to ensure the stability of the financial system. The restructuring measures for PSBs were threefold and included recapitalization, debt recovery and partial privatization.

Despite the suggestion of the Narasimham Committee to rationalize PSBs, the Government of India decided against liquidation, which would have involved significant losses accruing to either the government or depositors. It opted instead to maintain and improve operations to allow banks to create a good starting basis before a possible privatization.

Conclusion

Nevertheless, more than a decade since the beginning of economic reforms, the banking sector is still struggling under the burden of considerable NPAs and the poor performance of public sector banks continues to be a major issue. Liberalization has, however, had a predictable effect in the distribution of scheduled commercial banking in India. The reform era growth in banking have focused on the more profitable urban and metro areas of the country. Between 1969 and 1991 for instance, the share of the rural branches increased from about 22% to over 58%. In 2004, the corresponding figure stood at a much lower

46%. The number of rural bank branches actually declined from the 1991 figure of over 35,000 branches by about 3000 branches. Between 1969 and 1991 the share of urban and metro branches fell from over 37% to less than 23%. In the years since it has crawled back up to over 31%.

Since India has decided to move toward a more market-based system, it is now important for policy makers to create the conditions for the well-functioning of a market based banking system. Among the necessary tasks are the building and strengthening of the necessary institutions like oversight bodies, accounting standards and regulations as well as the further restructuring and privatization of PSBs. If India continues on its current path of banking sector liberalization, it should be in a position to further strengthen its banking system, which will be vital to support its economic growth in the years to come. Thus Liberalisation has proved to be a great boon to the banking system as the structural changes which have been implemented due to the liberalisation has transformed the Indian banking system and moreover the recommendations of various committees has led to further strengthening banking system. Thus liberalisation has made banking from class banking to mass banking.

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Current account convertibility refers to freedom in respect of Payments and transfers for current international transactions.

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TOTAL QUALITY MANAGEMENT IN Dr. PANJABRAO DESHMUKH AGRICULTURAL UNIVERSITY LIBRARY, AKOLA, MAHARASHTRA: A USERS' STUDY

Vishal R. Shekawat* and Vaishali P. Godadhe**

ABSTRACT

Since formation the State of Maharashtra has undoubtedly provided leadership at the national level in matters of economic growth and development. Moreover it has tried to retain the participation of agriculture and provided much needed research and development facilities by not only creating agricultural universities which are spread across the state in a balanced manner but taken them above record keeping and paper work to actually empower them to serve the purpose of transformation of conventional farming and agro practices into modern globalised one.

This research paper aims to bring about the use of total quality management techniques in managing the most essential support systems to any educational institutions, the libraries which pool up and arrange knowledge materials so as to be able to be used whenever needed. Naturally it becomes easy for all those who require using the services and smoothly continuing with their work whereas the library stays away from limelight playing a silent role.

*India walks a new path to glory and being the only third world developing country which still relies on agriculture as its major source of national income a lot has to be done. But, not only at the top level but also at every juncture right from educating the next generation agro community members but also doing it in such a way that they are able to cope with the changes in the international environment. The paper reflects use of the following six attributes, which are: **Reliability, Responsiveness, Assurance, Access, Communication, and Tangibility.** The paper aims to put forth the benefits of use of Total Quality Management methods in getting better results making the path easy for overall development.*

INTRODUCTION

Since the ancient times, it has been assured that libraries are the sources of knowledge and also the treasures of gentle culture. Their terminology is supposed to be the heart of a university and also in the form of soul and brain. There was also the occurrence of books by the Sardars' during the Mughal period. They used to keep their private libraries for learning. The then Sultans and Mughal monarchs were also book lovers. With this, are comes to know that libraries were in vogue during the Mughal period. Total Quality Management is not just a concept, rather an attitude that deals and touches every function, eliminating non-conformances with required objectives, identifying more suitable ways of handling and controlling operations so as to achieve desired results.

OBJECTIVES OF THE STUDY

The objectives of the research study were as following:

1. To understand the essentials of Total Quality Management (TQM) in Agricultural university libraries in Maharashtra.
2. To study the essence of TQM for library and information services.
3. To study quality techniques in Dr. Panjabrao Deshmukh Agricultural university library for sustainable library management.

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4. To identify internet resources and their quality for libraries.
5. To measure the users satisfaction using the different attributes of TQM.

SCOPE AND LIMITATION

The present research work was limited to the users of Dr. Panjabrao Deshmukh Agricultural University Library.

SAMPLE POPULATION

In order to satisfy the qualitative and quantitative information required for this research paper, the researcher selected 150 respondents i.e. the users of the Dr. Panjabrao Deshmukh Agricultural University library.

A standard structured questionnaire was designed to collect the required information where five point Likert type scale was used.

DESCRIPTION OF THE QUESTIONNAIRE USED

The questionnaire is essentially a skillful translation of objective into a set of questions intended to be answered in writing. It is a written list of questions requiring answers in writing.

USERS STUDY

Questionnaire was prepared to incur the data relating to the "Users" & to observe and record the actual reactions of the "Users" of Dr. Panjabrao Deshmukh Agricultural University library.

Dr. PANJABRAO DESHMUKH AGRICULTURAL UNIVERSITY LIBRARY

To study the performance of Dr. Panjabrao Deshmukh Agricultural University library on different attributes with regard to total quality management, the data was obtained on the following six attributes namely reliability, responsiveness, assurance, access, Communication, Tangibles and the respondents were asked to give their opinions on each attributes in the manner of 5 points scale.

Data was collected from 150 respondents from the University. These respondents were consisting of 100 students & 50 teachers. The score obtained for each point of the attributes was tabulated as under:

Note: The scoring pattern adopted by the researcher is as follows:

Option:	a	b	c	d	e
Score:	5	4	3	2	1

Note: 's' denotes Students, and 't' denotes Teachers

Reliability:

Table 1: Indicating Scores of Reliability

R12	s1	t1	s2	t2	s3	t3	s4	t4	s5	t5	total
1	55	15	36	19	15	7	13	5	11	4	150
2	43	32	25	8	13	4	9	3	10	3	150
3	49	24	25	11	7	3	10	5	9	3	150
4	52	23	22	11	12	8	10	4	4	4	150
5	45	23	27	14	13	3	9	4	7	4	150
6	47	20	26	14	10	7	8	4	9	5	150
7	44	15	27	14	9	5	9	8	11	8	150
8	47	24	21	12	12	6	10	4	10	3	150
9	46	13	36	18	17	9	11	5	10	5	150
10	52	20	23	12	15	9	16	8	14	5	150
11	32	14	20	14	21	11	9	3	12	4	150
12	32	16	31	16	12	9	15	5	12	1	150
Total	474	239	325	169	155	83	127	56	119	53	1800

From the Table no. 1, it was observed that, to study whether there is any similarity or discrepancy between the opinions of teachers & students with respect to scoring we calculated correlation co-efficient for each opinion. This co-relation between the opinion of teachers & students for each score is as follows:

Table 2: Correlation of Student & Teacher

Score	5	4	3	2	1
Correl	0.67444	0.66299	0.78846	0.58647	0.25763

From the Table no. 2, it was observed that for the score 5, 4, 3 & 2 there is consistency (positive co-relation between the opinions of teachers & students). As for as score 1 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small (0.25763).

With respect to the total Scores for the reliability, we calculated total Scores for teachers & students separately & also calculated the means of score. The total score is calculated with the help of following formula:

Total score for the teachers = 5 x total number of teachers giving score 5 + 4 x total number of teachers giving score 4 + 3 x total number of teachers giving score 3 + 2 x total number of teachers giving score 2 + 1 x total number of teachers giving score 1, i.e.

Total score for teacher = 5 x 239 + 4 x 169 + 3 x 83 + 2 x 56 + 1 x 53 = 2285

The total score for the student is also obtained in the same manner.

Total score for student = 5 x 474+ 4 x 325 + 3 x155 + 2 x 127 + 1 x119 = 4508

Then the mean of scores for teachers is obtained as:

Mean score for teachers = total score for teachers/ total number of teachers & the same formula is used for calculating mean score for students. The total and means scores for teachers & students were given below:

Table 3: Means Score of Student & Teacher

Respondents	Total Score	Mean Score
Teachers	2285	45.7
Students	4508	45.8

From the Table no. 3, it was observed that, there was no significant difference between the mean score of teachers & students. The scores were so matching that no need of statistical tests for the same is needed.

Responsiveness

Table 4: Scores of Responsiveness

RI2	s1	t1	s2	t2	s3	t3	s4	t4	s5	t5	Total
1	39	22	19	15	10	5	7	6	5	4	150
2	31	27	22	15	11	4	9	4	7	3	150
3	34	25	18	10	11	7	9	4	8	4	150
4	32	23	26	18	7	3	6	5	9	1	150
5	33	24	13	12	16	4	14	5	4	5	150
6	31	24	18	10	12	5	11	7	8	4	150
7	41	31	27	10	12	2	9	4	11	3	150
8	36	22	28	11	14	5	12	7	9	5	150
9	34	32	27	18	10	4	11	3	8	3	150
10	44	23	22	12	9	3	15	6	10	6	150
11	37	31	22	11	23	4	9	2	9	2	150
12	47	19	21	13	15	6	9	6	8	6	150
Total	569	293	263	150	159	62	122	59	96	46	1800

From the Table no.4, it was observed that, to study whether there is any similarity or discrepancy between the opinions of teachers & students with respect to scoring we calculated correlation co-efficient for each opinion. This co-relation between the opinion of teachers & students for each score is as follows:

Table 5: Correlation of Student & Teacher

Score	5	4	3	2	1
correl	-0.3271	0.36523	0.14325	0.28083	-0.182743471

From the Table no. 5, it was observed that for the score 4, 3, 2 & 1. As for as score is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small (0.36523), (0.14325), (0.28083) & (0.182743). For score 5, there is a negative co-efficient of co-relation (-03271), which indicates that, there is a difference between the opinions of teachers & students.

With respect to the total Scores for the responsiveness, we calculated total Scores for teachers & students separately & also calculated the means of scores. The total score is calculated with the help of following formula:

Total score for the teachers = 5 x total number of teachers giving score 5 + 4 x total number of teachers giving score 4 + 3 x total number of teachers giving score 3 + 2 x total number of teachers giving score 2 + 1 x total number of teachers giving score 1, i.e.

Total score for teacher = 5 x 293+ 4 x 150 + 3 x52 + 2 x 59 + 1 x 46 = 2335

The total score for the student is also obtained in the same manner.

Total score for student = 5 x 569+ 4 x 263 + 3 x150 + 2 x122 + 1 x 96 = 4687

Then the mean of scores for teachers is obtained as:

Mean score for teachers = total score for teachers total number of teachers & the same formula is used for calculating mean score for students. The total and means scores for teachers & studepts were given below:

Table 6: Means Score of Student & Teacher

Respondents	Total Score	Mean Score
Teachers	2385	47.7
Students	4687	46.86

From the Table no. 6, it was observed that, there is no significant difference between the mean score of teachers & students. The scores were so matching that no need of statistical tests for the same is needed.

Assurance

Table 7: Scores of Assurance

A6	s1	t1	s2	t2	S3	t3	s4	t4	s5	t5	Total
1	58	28	13	10	13	7	8	3	8	2	150
2	62	33	15	7	8	3	9	3	6	4	150
3	61	28	14	7	12	5	7	5	6	5	150
4	59	23	16	8	13	8	7	3	1	8	150
5	52	26	25	12	10	4	7	5	6	3	150
6	52	31	24	12	13	1	7	3	6	3	150
Total	344	169	107	56	69	28	45	22	35	25	900

The Table no. 10 shows that, to study whether there is any similarity or discrepancy between the opinions of teachers & students with respect to scoring calculated correlation co-efficient for each opinion. This co-relation between the opinion of teachers & students for each score is as follows:

Table 11: Correlation of Student & Teacher

Score	5	4	3	2	1
correl	0.86491	0.46879	0.69908	0.32124	-0.5653

From the Table no. 11, it was observed that for the score 5 & 3 there is consistency (positive co-relation between the opinions of teachers & students). For score1, there is a negative co-efficient of co-relation (– 0.5653), which indicates that, there is a difference between the opinions of teachers & students. As for as score 4 & 2 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small (0.46879) & (0.32124)

With respect to the total Scores for the access, we calculated total Scores for teachers & students separately & also calculated the means of score. The total score is calculated with the help of following formula:

Total score for the teachers = 5 x total number of teachers giving score 5 + 4 x total number of teachers giving score 4 + 3 x total number of teachers giving score 3 + 2 x total number of teachers giving score 2 + 1 x total number of teachers giving score 1, i.e.

Total score for teacher = 5 x 137 + 4 x 47 + 3 x23 + 2 x 21 + 1 x 22 = 1006

The total score for the student is also obtained in the same manner.

Total score for student = 5 x 239+ 4 x 100 + 3 x62 + 2 x 56 + 1 x 42 = 1936

Then the mean of scores for teachers is obtained as:

Mean score for teachers = total score for teachers/ total number of teachers & the same formula is used for calculating mean score for students. The total and means scores for teachers & students were given below:

Table 12: Means Score of Student & Teacher

Respondents	Total Score	Mean Score
Teachers	1006	20.12
Students	1936	19.36

From the Table no. 12, it was observed that, there is no significant difference between the mean score of teachers & students. The scores were so matching that no need of statistical tests for the same is needed.

Communication

Table 13: Scores of Communication

C&	s1	t1	s2	t2	s3	t3	s4	t4	s5	t5	Total
1	35	32	36	11	8	3	9	3	12	1	150
2	44	27	19	12	11	3	12	4	14	4	150
3	52	23	26	8	9	5	7	6	6	6	150
4	32	17	35	14	10	5	13	7	10	7	150
5	49	25	12	9	15	9	13	4	11	3	150
6	46	20	17	9	14	7	12	6	11	5	150
Total	258	149	145	63	67	32	66	30	64	26	900

From the Table no. 13, it was observed that, to study whether there is any similarity or discrepancy between the opinions of teachers & students with respect to scoring we calculated correlation co-efficient for each opinion. This co-relation between the opinion of teachers & students for each score is as follows:

Table 14: Correlation of Student & Teacher

Score	5	4	3	2	1
correl	0.14421	0.54299	0.8492	0.10541	-0.534

From the Table no. 14, it was observed that for the score 4 & 3 there is consistency (positive co-relation between the opinions of teachers & students). For score 1, there is a negative co-efficient of co-relation (– 0.534), which indicates that, there is a difference between the opinions of teachers & students. As for as score 5 & 2 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small (0.14421) & (0.10541)

With respect to the total Scores for the communication, we calculated total Scores for teachers & students separately & also calculated the means of score. The total score is calculated with the help of following formula:

Total score for the teachers = 5 x total number of teachers giving score 5 + 4 x total number of teachers giving score 4 + 3 x total number of teachers giving score 3 + 2 x total number of teachers giving score 2 + 1 x total number of teachers giving score 1, i.e.

Total score for teacher = 5 x 149 + 4 x 63 + 3 x32 + 2 x 30 + 1 x 26 = 1179

The total score for the student is also obtained in the same manner.

Total score for student = 5 x 258 + 4 x 145 + 3 x67 + 2 x 66 + 1 x 64 = 2267

Then the mean of scores for teachers is obtained as:

Mean score for teachers = total score for teachers/total number of teachers & the same formula is used for calculating mean score for students. The total and means scores for teachers & students were given below:

Table 15: Mean Score of Student & Teacher

Respondents	Total Score	Mean Score
Teachers	1179	23.58
Students	2267	22.67

From the Table no.15, it was observed that, there is no significant difference between the mean score of teachers & students. The scores were so matching that no need of statistical tests for the same is needed.

Tangibles

Table 16: Scores of Tangibles

T15	s1	t1	s2	t2	s3	t3	s4	t4	s5	t5	Total
1	32	26	19	17	20	5	14	2	15	0	150
2	43	22	26	21	8	3	12	2	11	2	150
3	54	26	19	9	5	5	7	5	12	5	150
4	48	22	21	13	11	6	11	4	9	5	150
5	48	23	17	9	12	5	14	6	9	7	150
6	35	19	30	13	14	8	10	5	11	5	150
7	39	22	24	17	16	9	12	1	9	1	150
8	37	23	24	12	14	7	14	2	11	6	150

Table 16 Contd...

T15	s1	t1	s2	t2	s3	t3	s4	t4	s5	t5	Total
9	38	21	20	11	17	6	12	8	13	4	150
10	38	19	20	12	15	9	15	4	12	6	150
11	38	17	25	9	14	8	11	7	12	9	150
12	41	22	22	12	10	6	14	7	13	3	150
13	50	24	11	5	13	8	12	5	14	8	150
14	39	22	17	10	27	9	6	5	11	4	150
15	31	15	17	9	21	10	18	9	13	7	150
Total	**611**	**323**	**312**	**179**	**220**	**104**	**182**	**72**	**175**	**72**	**2250**

From the Table no. 16, it was observed that, to study whether there is any similarity or discrepancy between the opinions of teachers & students with respect to scoring we calculated correlation co-efficient for each opinion. This co-relation between the opinion of teachers & students for each score is as follows:

Table 17: Correlation of Student & Teacher

Score:	5	4	3	2	1
Correl	0.53395	0.60406	0.5995	0.1439	-0.0312

From the Table no. 17, it was observed that for the score 5, 4 & 3 there is consistency (positive co-relation between the opinions of teachers & students). For score 1, there is a negative co-efficient of co-relation (-0.0312), which indicates that, there is a difference between the opinions of teachers & students. As for as score 2 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small (0.1439).

With respect to the total Scores for the tangibles, we calculated total Scores for teachers & students separately & also calculated the means of score. The total score is calculated with the help of following formula:

Total score for the teachers = 5 x total number of teachers giving score 5 + 4 x total number of teachers giving score 4 + 3 x total number of teachers giving score 3 + 2 x total number of teachers giving score 2 + 1 x total number of teachers giving score 1, i.e.

Total score for teacher = 5 x 323 + 4 x 179 + 3 x104 + 2 x 72 + 1 x 72 = 2859

The total score for the student is also obtained in the same manner.

Total score for student = 5 x 611 + 4 x 312 + 3 x220 + 2 x 182 + 1 x 175 = 5502

Then the mean of scores for teachers is obtained as:

Mean score for teachers = total score for teachers/total number of teachers & the same formula is used for calculating mean score for students. The total and means scores for teachers & students were given below:

Table 18: Mean Score of Student & Teacher

Respondents	Total Score	Mean Score
Teachers	2859	57.18
Students	5502	55.02

From the Table no. 18, it was observed that, there is no significant difference between the mean score of teachers & students. The scores are so matching that no need of statistical tests for the same is needed.

Table 19: Means Score of Student & Teacher according to Attributes

Student	teacher
45.8	45.7
46.86	47.7
24.8	24.44
19.36	20.12
22.67	23.58
55.02	57.18

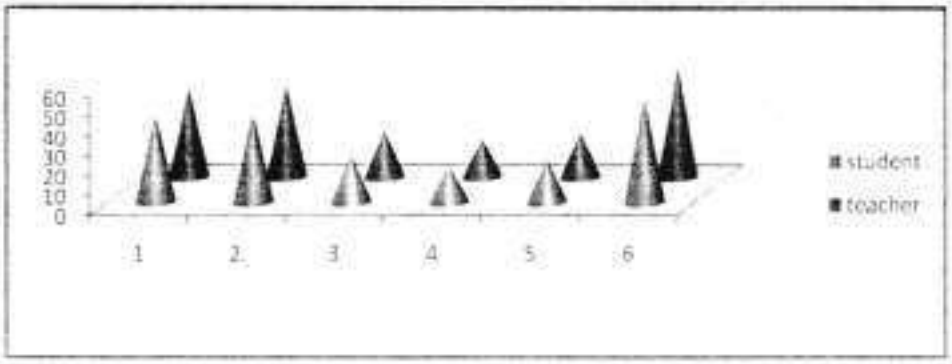


Fig. 1: Means Score of Student & Teacher

CONCLUSION

The study concluded the following facts with reference to the first attribute i.e. "Reliability". These facts are as under:

The researcher concluded that, majority of the respondents i.e. "The Users of the Library", are able to find the reliable information to most of their queries in the reference of their collection and had not the experience of giving up a search due to finding difficulties in getting the relevant information. According to majority of the respondents, their university library is very consistent in making "Cataloging and Classifications" of their library materials, at the same time, the OPAC i.e. Online Public Access Catalogue in giving their required information is very reliable.

Majority of the respondents responded "Strongly Agree" on the "Accuracy" of the "Overdue and Fines" sent to them by their concerning library staff. Whenever they requested for any special service from their library, they got it "Very Consistently".

- Majority of the respondents are completely satisfied about the reliability in the references of "Inter – Library Loan Service", "CD-ROM/Database/Online Database Services", "Indexing and Abstracting Service", "Photo Copying Services" "Library Orientation Services" and "Information Literacy Programme"
- After applying the statistical tools i.e. Co-efficient of Co –relation, the researcher concluded that, there is positive co-relation between the opinions of teachers and students. At the same time, there is no significant difference between the mean score of teachers and students.

With reference to the second attribute i.e. "Responsiveness", the researcher concluded the following facts:

- Majority of the respondents got the latest and current published books in their subject area "very promptly i.e. within 3 minutes". Majority of them expected that, the books should be re-shelved within "Half – Day", as the inter library system in satisfying the information required by the users is

"Very effective". Majority of them are fully satisfied about the behaviour of the library staff while providing them OPAC service at the same time, they are highly satisfied about the availability of current newspapers and periodicals on the periodicals display shelves.

- Majority of the respondents are "Very Satisfied" about "Registration of User", "Duration of Books", "Compilation of reading list for users", "Prompt Bindery Services", "SDI Selection" and the "Answering user queries" provided to them by their library.
- After applying the statistical tools i.e. Co-efficient of Co- relation, in order to study, any similarity or discrepancy between the opinions of teachers and students with respect to scoring, the researcher concluded that, as for as score is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small. At the same time, there is no significant difference between the mean score of teachers and students.

With reference of the third attribute i.e. "Assurance", the researcher concluded the following facts

- The behaviour of the concerning library staff is very calm and co-operative while providing the relevant information from the collections, to the users. The library staff always take personal interest whenever any user approaches them for any requirement. Thus, majority of the respondents are very satisfied about the "quality based services" by their library at the same time, they are familiar with the CD ROM Database/Online Database system.
- After making applications of statistical tools, in order to study, any similarity or discrepancy between the opinions of teachers and students with respect to scoring, the researcher observed it that, for score 1 and 2 there is a negative co-efficient of co-relation and for the score 3 and 4 there is consistency (positive co-relation between the opinions of teachers and students). At the same time, there is no significant difference between the mean score of teachers and students.

In the reference of the fourth attribute i.e. "Access", the researcher concluded the following facts:

- The concerning library staff is "Always" available at the reference desk, photocopier machines available in sufficient quantity. The researcher further observed it that, majority of the respondents are not required to wait for using the computer terminal for accessing OPAC, Online Database, E-books, E- Journals, etc. at any time. Working hours of the library are convenient to the majority of the respondents, and they are not required to wait in the long queues at circulations counter.
- After making applications of statistical tools, in order to study, any similarity or discrepancy between the opinions of teachers and students with respect to scoring, the researcher observed it that, for score 1 there is a negative co efficient of co-relation (-0.5653), which indicates that, there is a difference between the opinions of teachers and students. For score 2 and 4 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small and for the score 3 and 5 there is consistency (positive co-relation between the opinions of teachers and students). The researcher further observed it that, there is no significant difference between the mean score of teachers and students.

In the reference of the fifth attribute i.e. "Communication", the researcher concluded the following facts:

- Majority of the respondents are aware of the facilities and services available in the library and they learnt about its uses from the "Orientation of the Library". The researcher further observed that majority of the respondents got "OPAC user manuals", and "CD-ROM Database/ Online Database user manual" very easily and regularly. "E-learning modules available" are helpful to them to use library resources effectively and efficiently.
- After making applications of statistical tools, in order to study, any similarity or discrepancy between the opinions of teachers and students with respect to scoring, For score 1, there is a negative co-efficient of co-relation, i.e. there is a difference between the opinions of teachers and students. As for as score 2 and 5 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small. For the score 3 and 4 there is consistency (positive co-relation between the opinions of teachers and students). The researcher further observed it that, there is no significant difference between the mean score of teachers and students.

In the reference of the sixth attribute i.e. "Tangible"; the researcher concluded the following facts:

- Majority of the respondents are "Very Satisfied" about the "Sitting Arrangements", "Maintenance of Lighting and Temperature in the Library", at the same time, all the staff members as well as the users have the cognizance to keep and maintain "Sufficient Silence" within the campus particularly in the library hall. The researcher further observed that majority of the respondents was satisfied towards the "Adequate and Comfortable Reading Rooms". At the same time, majority of them are satisfied about the various tangible facilities provided to them by their library. Thus, majority of them felt comfortable while using these facilities and services provided to them as per their requirements by their library.
- After making applications of statistical tools, in order to study, any similarity or discrepancy between the opinions of teachers and students with respect to scoring. For score 1, there is a negative co-efficient of co-relation, for score 2 is concerned, no such conclusions can be drawn as the corresponding co-efficient of co-relation is very small and for the score 3, 4 and 5 there is consistency (positive co-relation between the opinions of teachers and students). There is no significant difference between the mean score of teachers and students.

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Synthesis and Characterization of Photoconductive CdS thin Semiconductor Film by Sillar Method

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ABSTRACT : Glass substrate modified with ultrasonic cleaning were used to deposit CdS thin films in the process of successive ionic layer absorption and reaction [SILAR]. The films were characterized by X –ray diffraction, u. v. absorption ,and atomic force microscopy [AFM]. AFM showed that after ultrasonic cleaning substrate were in favor of the growth of films by comparison with the commercial glass slide. The deposition rate of the films was faster after the ultrasonification of glass substrate.

Key words : CdS ,thin films ,SILAR deposition

Introduction

CdS under thin film form is well known as an optoelectronic material for solar cell, photo detector and other optoelectronic devices [1-5]. Various chemical method have been used to grow CdS films, including electro deposition [6], chemical bath deposition [7,8] and SILAR deposing [9,10]. In comparison with other method, SILAR deposition has some advantages such as easy control, simple and less expensive. In the successive ionic layer absorption and reaction process the substrate are impressed into separated cationic and anionic precursor solution and rinsed with purified water after each immersion [11] many kinds of thin films have been prepared by SILAR technique [12]. However, because of weak interaction between ions and glass substrate, it is difficult to prepare the thin film on bare glass substrate. It is reported that the adhesion of the copper thin film to glass substrate was poor [13].

In this paper, we described how to improve interaction between ions and glass substrate. The glass substrate were modified with ultrasonification to anchor the cd^{2+} and s^{2-} ions to substrate. This work aimed to explore a way to improve the adhesion of the film to substrate. The structural and optical properties of CdS film were characterized.

Experimental:

The glass substrate were cleaned in boiling chromic acid for 1h, rinsed with double distilled water and dried in air .the glass substrate placed under the source of ultrasonic source of Radiology center. The treated glass substrate was first immersed into a 0.15 mol cadmium sulphate solution (pH-8) for 40s. The substrate was sufficiently rinsed with doubled distilled water for 25s. to remove superfluous cd^{2+} ions that interacted rather weakly with substrate. The substrate was then immersed into a 0.15 mol Thiourea solution (Ph -8) for 40s and rinsed with double distilled water for 25s. The temperature maintain at 75 0c with NH_3 complexing agent. The above deposition cycle were repeated to get desired film thickness.

The structural characterization of the film was carried out using XPERT-PRO X-ray diffractormeter with CuKα radiation (α = 1.5406 A^0) in 2θ range from 0 to 100^0. The surface morphological study of CdS film was carried out by scanning electron microscopy using model JSM-7600F resolution 1 nm (15 KV). The optical absorption spectra of the film was recorded LAMBDA-25 (USA) spectrophotometer in the wavelength range 200 nm to 1100 nm. The grain morphology of thin

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films was investigated using Atomic Force Microscopy (solver pro companies, model NT –MDT). It was operated in contact mode with the NS-01 cantilever.

RESULT AND DISCUSION

Utilizing ultrasonificated cleaned glass substrate cadmium ions were easily anchored to substrate. The pretreatment of the substrate accelerated the growth of CdS film. The substrate after formation of CdS film look like a yellow mirror. It can be concluded that average growth rates of CdS film were 0.30 nm/cycle on the modified substrate and 0.030 nm/cycle on the unmodified substrate as compare with growth rate reported for CdS film is 0.098 nm/cycle.[10]

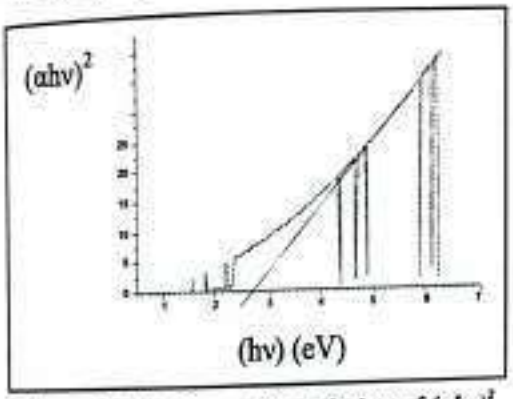
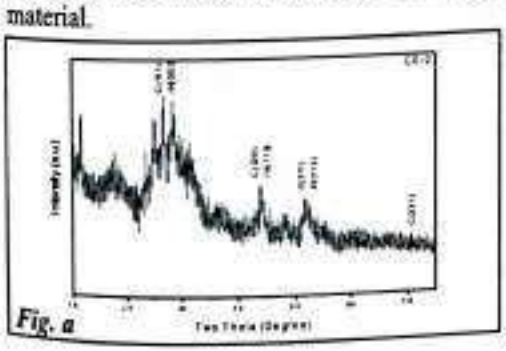


Figure 1: Plot shows the variation of $(\alpha hv)^2$ verses (hv) of as deposited CdS thin film.

Figure 1 shows the spectra of the film were typical for those reported by many workers for polycrystalline CdS thin film. The band gap of the film were found to be 2.37 eV as compare with 2.4 eV.[8] The linear dependence of αhv^2 verses hv was indicative of direct band gap material.



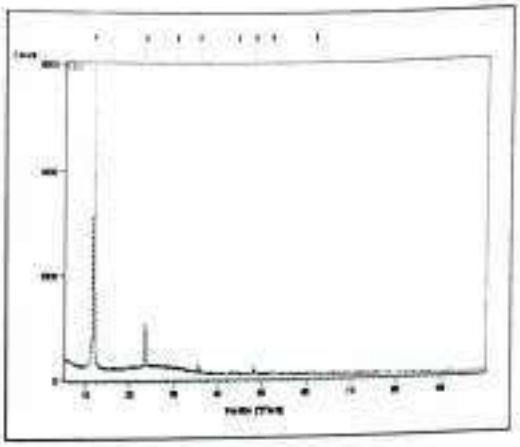


Fig. b

Figure 2 : X-ray diffraction pattern of CdS thin film with 27 cycles
a. Ultrasonified glass substrate
b. An un ultrasonified glass substrate

Figure 2 shows the x-ray diffraction pattern of CdS thin film. It was known that the CdS film on substrate without ultrasonification was amorphous while the film on the ultrasonified glass substrate was of both cubic an hexagonal crystal structure. The major peaks found for these two sets indicate the presence of both cubic and hexagonal phases. The peak of maximum broadening centered at 26.7 degree is suggestive of combination of many peaks including the dominant c(1 1 1)/h(0 0 2) at 26.6 degree.[14] Presence of CdO phase here is most likely in nano-CdS as it is very prone to oxidation when exposed to air. Also there are two characteristic peaks at 44.0 degree and 52.1degree. A sharper peak at 44.0 degree also indicates either c(2 2 0)/h(1 1 0). Another peak of relatively large broadening at 51.8 degree can be associated with c(3 1 1) or h(1 1 2). However, a small intensity peak at 70.6 degree bears the signature of c(3 3 1)which is characteristic of cubic phase. The grain size is found to be 36 nm. JCPDF (80-0006 and 75-0581).

Figure 3 and Figure 4 shows the AFM images of CdS thin film on glass substrate. It can be seen from figure 3 that only some particles of microsize of CdS sparsely spread on the un

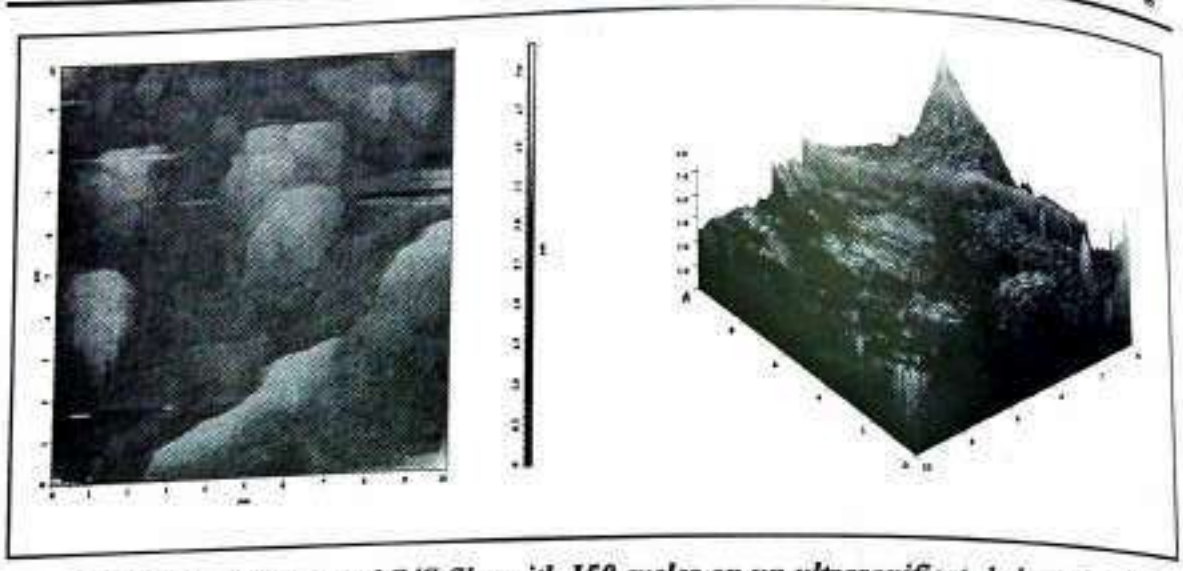


Figure 3: AFM image of CdS film with 150 cycles on un ultrasonificated glass substrate

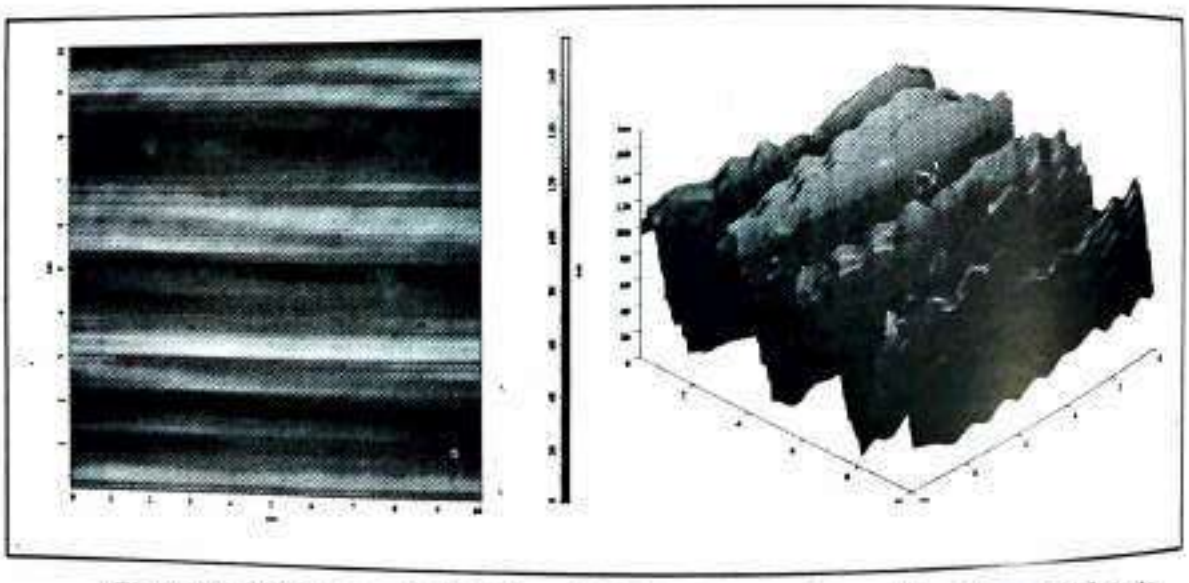


Figure 4 : AFM image of CdS film with 150 cycles on ultrasonificated glass substrate

ultrsonificated substrate however the dense of nanoparticle size film of CdS grew on the ultrasonificated substrate as shown in figure 4.

Conclusion :

The CdS film were successfully deposited on glass substrate treated with altrasonification. Such type of substrate was beneficial to the growth of nanostructure films during SILAR process. The experimental result confirms that the ultrasonification of the glass substrate was necessary for the growth of uniform and dense film of wide band gap II –VI semiconductors.

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Synthesis and ammonia sensing properties of Bi_2O_3 nanoparticles

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Abstract : Bismuth oxide (Bi_2O_3) nanoparticles were prepared by ethylene glycol mediated citrate sol-gel method followed by calcination at 600 °C for 4 h. The structure and crystal phase of the powders were characterized by X-ray diffraction (XRD) and microstructure by transmission electron microscopy (TEM). The responses of Bi_2O_3 thick film to various reducing gases (hydrogen, hydrogen sulfide, ammonia and liquefied petroleum gas) were measured as function of operating temperature. The sensor element based on Bi_2O_3 nanoparticles exhibited good response to 500 ppm NH_3 as compared with other tested reducing gases.

Keywords: Nanoparticles; Bi_2O_3; Reducing gases; Doping

1. Introduction

Gas sensors play vital role in detecting, monitoring and controlling the presence of hazardous and poisonous gases in the environment at very low concentrations. It is well known that the gas adsorption onto the semiconductor surface can influence its electrical conductivity. Actually, conductivity of semiconductor gas sensor changes by few orders of magnitude with regard to initial value in the presence of gas concentrations up to few ppm in air at ambient pressure. Metal oxides such as ZnO, SnO_2, In_2O_3, and WO_3 are extensively used as sensing materials in industry, such as environmental monitoring, security systems, biomedical instruments, and healthcare systems [1-5] The general sensing mechanism of these sensors is based on the change in the resistance of the functional sensing elements when they are expose to different environments such as different gases, humidity, and light.

Bismuth oxide (Bi_2O_3) has been extensively studied due to its useful features, such as noteworthy energy band gap (2.85 and 2.58 eV for the monoclinic α- Bi_2O_3 and tetragonal β- Bi_2O_3 phases, respectively), high refractive index and high dielectric permittivity, as well as marked photoconductivity [6-8]. Consequently, it has a feasibility of practical applications, including optical coatings [9], microelectronics [10], ceramic glass manufacturing [11], and gas sensor technology [12–18]. In combination with other typically used metal oxide Bi_2O_3 was useful as sensitive materials for detecting CO, H_2, and NO gas, respectively [7-9]. In the present investigation, structural and gas sensing properties of Bi_2O_3 nanoparticles prepared by ethylene glycol mediated citrate sol-gel method were investigated.

2. Experimental

2.1. Synthesis of Bi_2O_3 nanoparticles

Appropriate quantity of bismuth nitrate [$Bi(NO_3)_3 \cdot H_2O$] was grounded for 30 min. in an agate mortar pestle and then were dissolved in distilled water and then adding them to the warm solution of citric acid

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monohydrate [$C_6H_8O_7.H_2O$] / Ethylene glycol. The resultant solution was stirred magnetically at 80 °C for 2 h to get homogeneous mixture. Then, this solution was subsequently transferred to Teflon lined stainless steel autoclave. The temperature of the autoclave was raised slowly to 125 °C and maintained for 12 hours to get gel precursor. Thereafter, the autoclave was allowed to cool naturally to room temperature and the resulting product further heated for 3 hours at 350 °C and subsequently calcined for 4 h at 600 °C to improve the crystallinity of the prepared materials.

2.2. Material characterization and gas sensing measurements

The phase constitution of as-prepared In_2O_3 powder was analyzed by X-ray diffractometer (Model: Philips X'pert) with a Cu Kα radiation (λ = 1.5406Å). The single phase was confirmed by comparison with JCPDS database. The average crystallite size (D) was calculated according to the Debye-Scherrer equation. The morphologies of the synthesized powder were observed through a transmission electron microscopy (TEM) (Model: Philips CM 200).

The sensing performance of the fabricated sensor elements was tested using a 'static gas-sensing system'. The description of the sensor element fabrication, schematic sensor assembly and the circuitry for the sensor characteristics measurement was reported in our earlier publication [30]. Sensor response (S) is defined as the ratio of change in conductance of the sensor on exposure to the target gas to the original conductance in air medium. The relation for S is as: $S=[G_g-G_a]/G_a$

where G_a and G_g are the conductance of a sensor in air and in gaseous medium, respectively.

3. Results and discussion

The X-ray diffraction pattern of Bi_2O_3 powder sample is illustrated in Fig. 1. The XRD pattern of as-prepared sample readily indexed Bi_2O_3 with monoclinic structure. The average crystallite size of the prepared Bi_2O_3 nanoparticles determined to be 35 nm from the XRD patterns. The average crystallite size estimated from XRD data corroborates with the TEM investigations. The TEM image of Bi_2O_3 powder calcinated at 600 °C is provided in Fig. 2. The significant amount of agglomeration was observed in the micrographs.

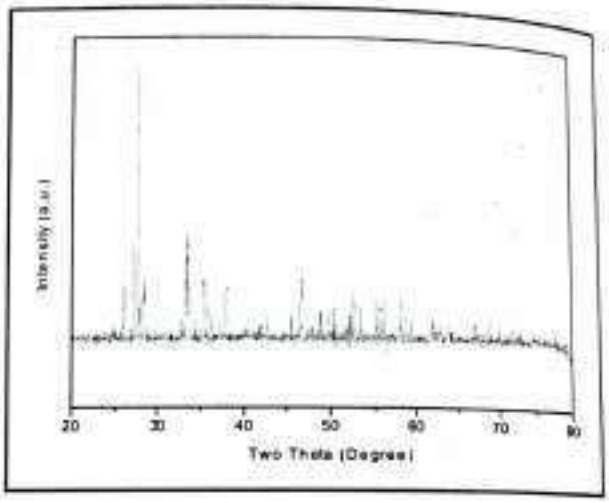


Fig. 1: X-ray diffraction pattern of Bi_2O_3 powder calcinated at 600 °C.



Fig. 2: TEM image of Bi_2O_3 calcinated at 600 °C.

The response of Bi_2O_3 towards various gases like hydrogen (H_2), hydrogen sulfide (H_2S), ammonia (NH_3) and liquefied petroleum gas (LPG) as a function of operating temperature is presented in Fig. 3. From the

figure it can be seen that the sensor element exhibited the superior response to 500 ppm NH_3 at 340 °C as compared to other tested reducing gases. The response of a semiconductor metal oxide based gas sensor to a particular gas depends on the speed of the chemical reaction on the surface of the grains and the speed of diffusion of the gas molecules into the surface. The conductance of the sample Bi_2O_3 in ammonia was obviously lower than that in air, indicating the p-type semiconducting properties of the samples. The result also demonstrates that Bi_2O_3 exhibited good selectivity towards 500 ppm NH_3. The stability of the sensor elements was also measured by repeating the tests up to the period of 90 days, at an interval of 10 days, from first measurement. During the tests, no considerable variations were observed indicating the good stability of the sensor.

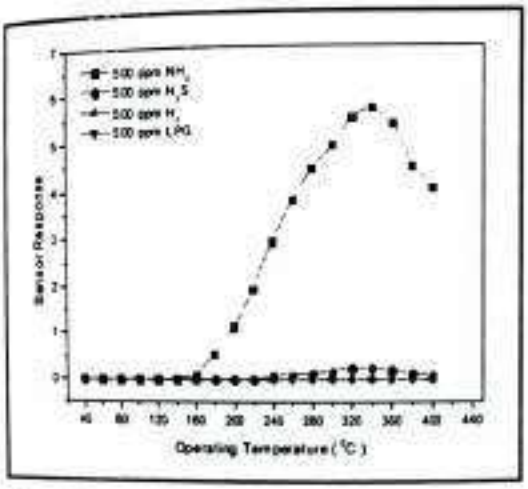


Fig. 3. Sensor response of pure Bi_2O_3 towards different reducing gases as a function of operating temperature

4. Conclusions

Bismuth oxide (Bi_2O_3) nanoparticles were successfully prepared by ethylene glycol mediated citrate sol-gel method followed by calcination at 600 °C for 4 h. The sensors based on Bi_2O_3 nanoparticles exhibited fair response to 500 ppm NH_3 gas as compared with other tested gases.

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Preparation techniques and applications of spinel ferrite nanoparticle: An overview

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Abstract : Nanostructured spinel ferrites are of *great interest for a wide variety of applications* like high density magnetic information storage, magnetic resonance imaging, targeted drug delivery, high density recording media etc. Spinel *ferrite nanomaterials are gaining importance due to its broad applications.* In order to meet the demands one must try to novel materials processing methods. This paper deals with the survey of the concept of ferrite nanoparticles, processing methods and application explored in gas sensing. Spinel ferrite powders can be fabricated by various methods such as hydrothermal method, sol-gel method, chemical co-precipitation method, citrate precursor method, combustion method, solid state high temperature reactions etc. In this article, various synthesis routes for the preparation of spinel ferrite nanomaterials and recent applications of nanostructured spinel ferrite have been discussed.

Key words: Spinel, Ferrites, Processing Methods, Nanoparticle

1. Introduction

Ferrites are one of the most significant materials giving useful magnetic, electrical, chemical, mechanical and structural properties [1-5]. These ferrites are classified as hard and soft on the basis of magnetic properties. Hard ferrites have properties such as high coercivity and high remanence after magnetization. eg. Permanent ferrite magnet and soft ferrites having properties like low coercivity. For this reason the magnetisation of the materials can reverse the direction easily without dissipating much energy. eg. Transformer, electromagnetic cores. Under soft ferrite there is a type of material called spinel ferrite which crystallizes in spinel structure, which is named after the mineral spinel, $MgAl_2O_4$ The unit cell of spinel corresponds to the space group O_h^7 (F3dm). The spinel crystaliline structure is determined firstly by the oxygen ion lattice and this oxygen anions are packed in a face centered cubic lattice Metallic cations, magnetic and nonmagnetic; reside on the interstices of the close-packed oxygen lattice. Moreover, in the spinel structure these cations have four- or six-fold coordination and form tetrahedra (A) and octahedra (B) sub-lattices and then they are arranged in a close-packed arrangement.

Spinel ferrites in general have the chemical formulae MFe_2O_4 (molecular precursors, concentration, temperature and growth rate, types of surfactant and solvent. Spinel ferrite is again classified into two types such as normal spinel and inverse spinel. In normal spinel ferrite, M^{2+}cations occupy tetrahedral sites and Fe^{3+}cations occupy octahedral sites. eg. $ZnFe_2O_4$ & $CdFe_2O_4$. In *inverse* spinel ferrite, half cations occupy sites as Fe^{3+}in tetrahedral sites and remaining $Fe^{3+}$and all of M^{2+} cations occupy octahedral sites. eg.

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$NiFe_2O_4$ and $CoFe_2O_4$.

The spinel ferrites are modified for its various applications by changing their physical and chemical properties. Spinel ferrites in general have the chemical formulae MFe_2O_4 (M = Mn, Fe, Co, Ni, Cu, Mg, Zn, etc.). The size and shape of spinel ferrite nanomaterial can be controlled by manipulating reaction variables such as properties is manipulated by changing the synthesis method, processing temperature and also substitution [6-8]. Nanoparticles of spinel ferrites are of growing interest for a wide range of applications like high density magnetic information storage, magnetic resonance imaging, targeted drug delivery etc. They also offer immense possibilities of tailoring its various properties for applications [9,10]. The review gives some general processing method and applications on spinel ferrite nanomaterial which is found to be useful due to their electronic, optical, electrical, magnetic and catalytic properties.

2. Preparation method of Ferrites

Ferrites are fabricated by using various methods. Some few methods such as sol-gel method [11,12], chemical co-precipitation [13], propagating high temperature synthesis (SHS) technique [14], citrate precursor method [15] etc. have been discussed.

2.1 Sol-Gel Method

The sol-gel process involves the transition of a solution of metal compounds from a liquid sol into a solid gel. In liquid, sol is a diffusion of the solid particles where only the Brownian motions suspend the particles and this sol is heated and then to form a homogenous gel which can achieved by the addition of base or acidic solutions. A gel is intermediate where both liquid and solid are dispersed in each other, which presents a solid network containing liquid components. Usually inorganic metal salts or metal organic compounds such as metal alkoxides are used as starting precursors in the preparation of the sol. The purpose of this precursor is to a series of hydrolysis and polymerization reactions to form a colloidal suspension, or a sol. By elimination of water, the hydroxide molecules get condensed and then formation of a metal hydroxide. When all metal hydroxides species are linked to one another in a network, and formation of dense porous gel is obtained. Further heating at higher temperature and then drying of the gel, the gel is converted into ultrafine powders of metal oxides.

2.2. Chemical Co-Precipitation

In the chemical co-precipitation method, an aqueous solution of suitable salts of iron, lithium, manganese and other desired, suitable materials is mixed under a fine control of pH by using a precipitating agent like NaOH or NH_4OH solutions which causes the precipitation of the other metals present in the solution. The precipitate represents a significantly uniform mixture of organic compounds of the ferrite metals on an atomic scale. In case of ferrite, it is important to prevent agglomeration; Ostwald ripening etc. Filtrated the precipitate and then dried. Then dried precipitate is heated at an high temperature to dehydrate the precipitate and to burn out carbonaceous matter leaving a residue of the oxides of the respective metals. After this, particles are sintered. The reaction and transport rates can be affected by the concentration of reactants, temperature, pH, the order in which the reagents are added to the solution and mixing. The particle structure and crystallinity can be influenced by reaction rates and impurities. This method doesn't work very well in cases where two reactants have very different solubilities in water and the reactants do not precipitate at the same rate. This method offers distinct advantages like simple, rapid preparation, easy control of particle size and composition.

2.3. Self Propagating High Temperature Synthesis Technique

In this method, organic acid is taken as precursur in aqueous solution. This solution containing all necessary cations and combustible anions in the desired product. After dehydration, the precursor becomes dry gel and this dry gel is amorphous in nature. Moreover, when calcinating this dry gel directly yields the required materials in presence of air/oxygen. In case of this process, the starting

materials are mixed in the atomic scale. The phase formation occurs at lower calcination temperature as compared to ceramic route and giving ultrafine powder. The overall process completes within 5 minutes.

2.4. Citrate Precursor Method

In this method, the starting materials such as nitrates are complexed in an aqueous solution with α–carboxylic acids such as citric acid. By adding ammonium hydroxide to the solution, the pH is controlled at 7. The solution is refluxed with continuous stirring using magnetic bar agitator and then dried. By the evaporation of the solution, a highly viscous mass is formed and resulting from metal nitrates and citric acid making a redox reaction to occur and then this metal nitrates react with water. The chelating agent citric acid is used for deprotonating with ammonium hydroxide and the metal hydroxide by removing protons. Then the formation of metal ions having a positive valency and carboxylic ions with negative valency together with water molecules. This co-ordinate bonds are used to form the metal and acid complex which is the ash-synthesized powder obtained. At last point auto-combustion process takes place. The powder is pressed into pellets and then given final sintering for densification.

3. Applications

There are various forms of application depending on the type like biomedical applications, permanent magnets, magnetic fluids, magnetic drug delivery, and high density recording media etc. Ferrites are primarily used for practical applications like sensor, power applications, EMI suppression, magnetic components, phase shifters, microwave devices etc. The application of ferrites like power are dominated by the power supplies for a large variety of devices such as TV, computers and video systems, and all types of small and medium instruments. A recent approach to increase efficiency of the ferrite cores is based on the decrease of eddy currents, by increasing resistivity and these ferrite cores are used for flyback transformers in television sets. This is to a great extent increase the energy received by a receiving antenna. Since ferrites have high permeability, also make them suitable for filter inductor applications. Ferrites are mostly used in cores for magnetic memories [16,17]. Since there is increasing interest in the amount of electronic equipment such as high-speed digital interfaces in notebooks and computers, digital cameras, scanners, and so forth, in small areas, has seriously enhanced the possibility of disturbing each other by electromagnetic interference (EMI). Hexaferrites can also be replaced by cubic ferrites as EMI suppressor components; they possess higher resonance frequencies, relatively high permeabilities (at microwave frequencies), and high electrical resistivities. The broad range of applications of nanostructured ferrite includes high density information storage, ferrofluid technology, magnetic resonance imaging enhancement, magnetically guided drug delivery and magnetocaloric refrigeration [18-21]. By using the combination of ferrite nanoparticles as contrast enhancement agents, harmless radio waves and computer technology, magnetic resonance imaging creates detailed images of the soft tissue morphology. Nanopowdered ferrites can also used for the design of magnetic storage and recording devices. Ferrofluids which is more stable colloidal suspensions composed of magnetic nanoparticles in organic or inorganic liquid carriers. The biocompatible ferrofluids which is based on ferrites are most promising for biomedical applications like cell separation and purification and magneto hyperthermia of tumour cells. Large number of biocompatible fluids are based on magnetitic and maghemite. Zinc ferrite nanoparticles gives enomorous potential applications in gas sensor and semiconductor photocatalysis [22, 23].

4. Conclusions

There is renewed interest in nanostructured spinel ferrite materials since many of the exhibit remarkable electrical and magnetic properties of these materials can be modified suitably and promising technological applications in different fields of life. There are various synthesis routes to prepare nanoparticles spinel ferrite. There are various

processing methods have been summarized for important ferrite systems along with some applications. The structural, magnetic, electrical and mechanical properties of spinel ferrites are found to be sensitive to their composition and microstructure, which in turn are dependent on the processing conditions.

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Miscibility studies of PVC/PMMA blends by FTIR analysis and measurements of AC electrical conductivity of PVC/PMMA blends.

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Abstract : The polymer electrolytes composing of the blend of polyvinyl chloride–polymethyl methacrylate (PVC/PMMA) with oxalic acid as a dopant were prepared by isothermal evaporation technique. FTIR studies confirm the complexation between PVC/PMMA blends. The miscibility between PVC & PMMA is due to a specific interaction of hydrogen bonding type between carbonyl groups (C =O) of PMMA and hydrogen from (CHCl) groups of PVC, as evidenced by FTIR spectroscopy. AC electrical conductivity of PVC/PMMA blends was measured in the temperature range 303-363K. It is found that ac conductivity of thin film decreases with increase in temperature for all values of frequencies and it increases with increase in frequencies at constant temperature.
Keywords: PVC, PMMA, FTIR, Miscibility, AC conductivity

1. Introduction:

In recent years, studies on the electrical and optical properties of polymers have attracted much attention in view of their applications in electronic and optical devices [1, 2]. Blending of two or more polymers may generate new materials with a combination of properties not found in the pure polymers.

Blending is often a faster and more cost effective way of achieving the required properties than synthesizing new polymers. A blend of two components is classified [3] miscible, thermodynamically, if the Gibbs free energy of mixing is less than zero and the second derivative of the Gibbs free energy of mixing is zero or positive. Among the polymer electrolytes, PMMA-based electrolyte has special significance in view of its well-known chemistry and cheaper method of processing as laminates. To get PMMA amenable, choice of blending with PVC has been suggested [4]. Although there are many ,those containing PVC are among the most important from both scientific and commercial point of views [5, 6]. A relatively small number of studies have been reported on the development of PVC/PMMA-based polymer electrolyte systems [7–9].

Electrical and optical properties of the polymers can be suitably modified by the addition of dopant depending on their reactivity with the host matrix. It has been shown that carrier mobility can be greatly affected by impregnating the polymers with suitable dopants. The charge storage property of polymers can be considerably modified with the help of suitable dopants.

The present work aims to calculate the electrical conductivity of pure PVC, PMMA, blends & oxalic acid doped samples. The

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charge transfer complex of PVC-PMMA with Oxalic Acid prepared in different weight ratios.

2. Experimental details:

The polymers PMMA (Otto Chemical, Mumbai) and PVC (Commercial Grade) in weight ratio were dissolved in 20ml solvent cyclohexanone (SD Fine Chemicals, Mumbai). For complete dissolution solution was kept in a stand for 3 days. After 3 days, the solution mixture was poured on perfectly plane and optically clean glass plate kept floating freely in a pool of mercury for perfect leveling. It was, thereafter, allowed to evaporate in air at room temperature. Further, it was dried for 48 hrs to remove any traces of solvent. The dry film was removed from the plate and cut into pieces (samples) of desired size, which were then coated on both sides with silver paint (Eltecks Corporation, Bangalore). The films of PVC-PMMA doped with 5%, 10% Oxalic acid were prepared by the same method given above. The thickness of the film was measured by DIGMATIC micrometer (Mitutoyo Corporation, Japan).

2.1. AC Electrical Conductivity :

The film was kept between the electrodes of a specially designed sample holder. The AC frequencies were applied (in the range 1 KHz –1 MHz) across the sample by using the 4284 A precision LCR meter (20 Hz –1 MHz) (Agilent Technologies, Singapore). The Corresponding dielectric constants were measured and AC conductivity of the samples was calculated by using the following relation given by equation 2.1 [10-12].

$$\sigma_{ac} = \frac{f \times \epsilon^{1} \times \tan\delta}{1.8 \times 10^{10}} \qquad (1)$$

Where, f = Frequency applied in Hz
ϵ^{1} = Dielectric Constant at frequency f
$\tan\delta$ = Dielectric loss tangent.

2.2. Fourier Transform Infrared Spectroscopy (FTIR) :

The freshly prepared samples are subjected to Fourier Transform Infrared Spectroscopy (FTIR) in the wave region between 4000-500cm^{-1}. The resolution of the spectra obtained at room temperature was 4 cm^{-1}. The FTIR data obtained were recorded in the transmission mode.

3.Results and Discussion:

3.1.Effect of Frequency on AC Conductivity:

The observed variation of AC electrical conductivity of pure PVC, pure PMMA and PVC–PMMA blend samples & PVC–PMMA doped samples, with frequency in the temperature range 313-363K is illustrated in figure (3.1.a,b,c.d,e). In all the samples it is found that A.C. conductivity increase with the frequency. The increasing of AC electrical conductivity in high frequency region can be related to the electronic polarization as well as to the hopping of charge carrier over a small barrier height [14]. The increasing of A.C electrical conductivity with angular frequency in the low frequency region can be attributed to the interfacial polarization [15].

At higher frequency, the mobility of charge carriers is higher and eventually contributes to higher electronic conductivity with respect to frequency [16]. It is due to the tremendous increase of the mobility of charge carriers in the composite film i.e. at higher frequencies blends of molecules starts vibrating with large amplitude within the polymeric chains hence the effect of increase in conductivity of blends[17].

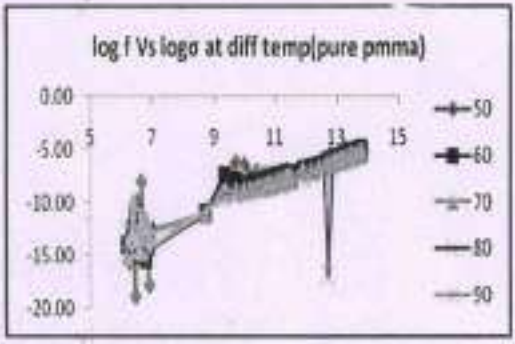


Fig.3.1. a

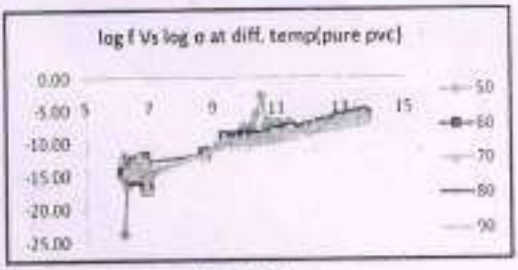


Fig.3.1. b

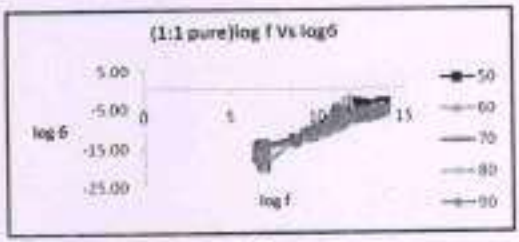


Fig.3.1. c

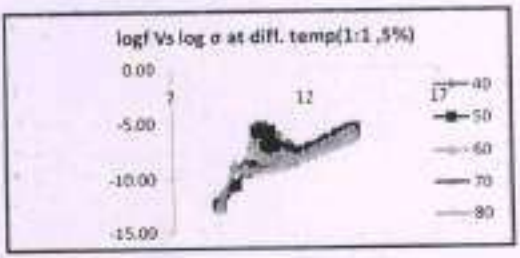


Fig.3.1. d

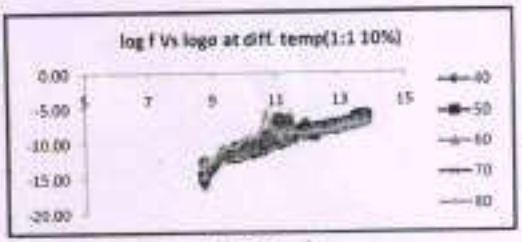


Fig.3.1. e

3.2. Effect of Temprature on A.C. Conductivity:

The following fig(.3.2a,b,c,d,e) shows the variation of electrical conductivity in the polymer blend (PVC-PMMA) with temprature in the frequncy range 5000Hz - 1MHz.

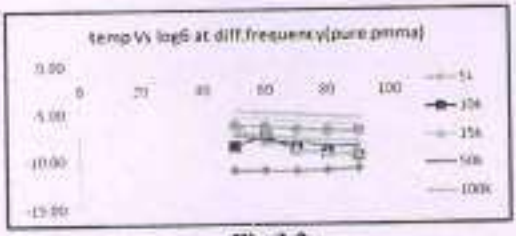


Fig.3.2 a

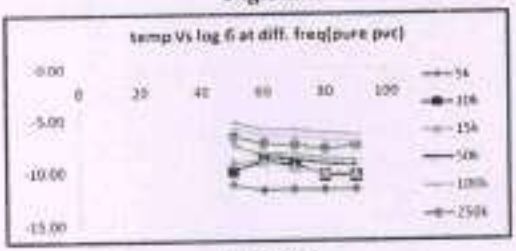


Fig.3.2 b

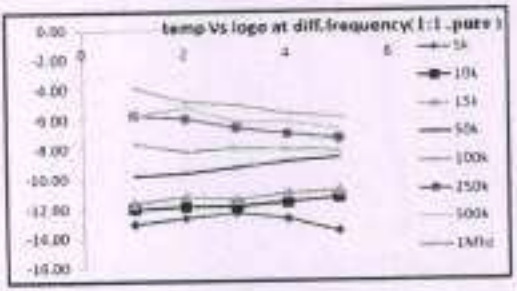


Fig.3.2 c

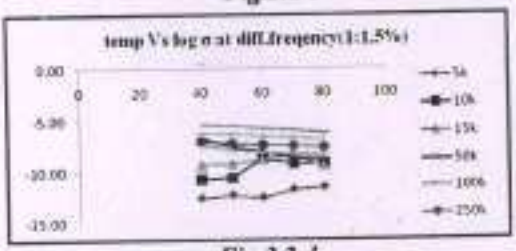


Fig.3.2 d

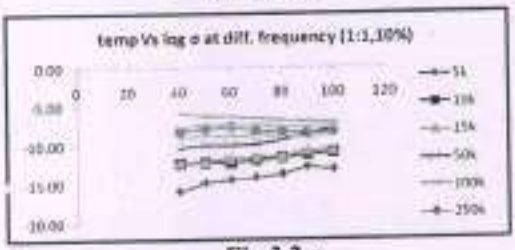


Fig.3.2 e

A decrease of conductivity was observed with increasing temperature. These phenomena can be explained by the fact that, thermal lattice vibration perturbs the quasi-free movement of electrons, thus scattering between electrons and phonon may occur & so conductivity decreases [18].

From above fig. 3.2.a,b,c,d,e it can also be seen that the value of conductivity gets decreases with increase in percentage of doping as compared to undoped samples. We can explained this decrement of conductivity due to the addition of Oxalic Acid. This Oxalic Acid contribute to the over crowed of the ionic dopants thus reduces the number of charge carriers further gives limitation on the mobility of ions & so conductivity decreases [29].

3.3. Fourier Transform Infrared Spectroscopy (FTIR) Studies :

Infrared (IR) radiation refers broadly to the part of the electromagnetic spectrum between the visible and microwave regions.

FTIR spectroscopy is an important tool in the investigation of polymer structure. The IR spectra of these material vary according to their composition & may be able to show the occurrence of complection & interaction between the various constituents.

FTIR spectra were recorded in the transmittance mode. The FTIR spectra of pure PVC, pure PMMA and PVC–PMMA blend samples & PVC–PMMA doped with 10% oxalic acid are shown in Figs. 3.3a,b,c,d respectively. The band assignments for PVC and PMMA have already been reported in the literature [19–21] and are listed in Tables 1 and 2, respectively.

Table 1: Vibrational modes and wavenumbers exhibited by PVC

Description of vibrations	Wavenumbers (cm^{-1})	References
C H stretching	2890–2958	[20]
CH_2 deformation	1339	[20,27]
CH rocking	1240–1257	[20,27]
trans CH wagging	961	[20]
C Cl stretching	844	[28]
cis CH wagging	600	[27]

Table 2: Vibrational modes and wavenumbers exhibited by PMMA

Description of vibrations	Wavenumbers (cm^{-1})	References
C H stretching	2927–2986	[27,28]
C O stretching	1700–1744	[27,28]
CH_3 stretching	1439	[28]
OCH_3 stretching	1195	[28]

These bands can also be observed in Fig. 3.3 a (for PVC) and in fig. 3.3 b (for PMMA).



Fig.3.3 a.FTIR spectra of pure PVC

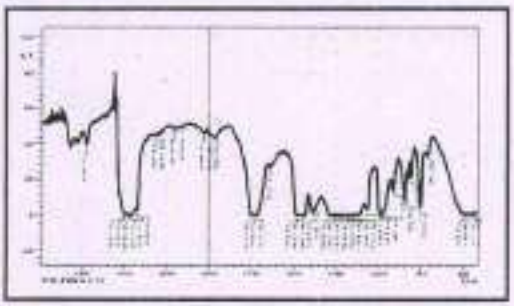


Fig.3.3 b FTIR spectra of pure PMMA

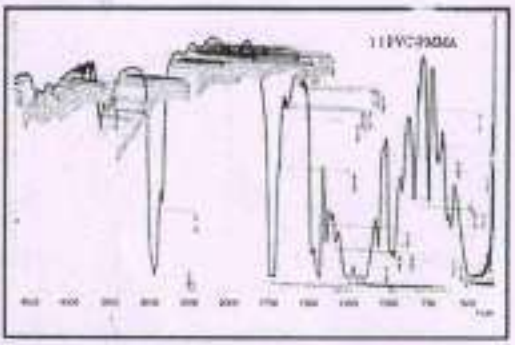


Fig.3.3 c FTIR spectra of pure PVC-PMMA blend

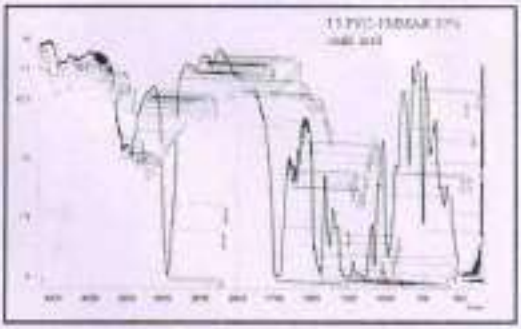


Fig.3.3 d FTIR spectra of pure PVC-PMMA blend with 10% doping

From fig.3.3 a, Vibrational bands of PVC are obtained at 2974 cm-1 (vC–H of CHCl), 2912.9 cm-1 (vas, C–H of CH2), 1435.9 cm-1 (w,CH2), 1334.1cm-1 (δ,C–H of CHCl), 1257.6 cm-1 (δ,C–H of CHCl), 1068 cm-1 (v(C–C)),966 cm-1 (r,CH2), 698 cm-1 (v,C–Cl), 638 cm-1 (v(C–Cl)) and 616 cm-1 (v ,C–Cl).

Figure 3.3 b which is FTIR spectrum of pure PMMA, it is observed from the spectrum reported by Saikia and Kumar [22] is similar to our spectrum. Peak at 749 cm-1 corresponds to out of plane C–H bending. Broader and stronger bands in the region 1300-1000 cm-1 correspond to C–O stretching vibrations, which usually consists of two asymmetric coupled vibrations. i.e.C–C (=O)–O and O–C–C. At approximate 1025 cm-1 ether lone pair peak is also present. The bands at 1387.2 and 1456.2 cm-1 correspond to symmetrical bending vibration (vsCH3) and asymmetrical bending vibration (vasCH3) of methyl group, respectively. Strong peak appearing in the region 1730.14cm-1 corresponds to C-O stretching vibrations. Two distinct bands appeared at 2978.4 and 2877.8 cm-1, the first band arises from the asymmetrical (as) stretching mode in which two C–H bonds of the methyl group are extending, while the third one is contracting (vasCH3) and the second band arises from symmetrical (s) stretching (vsCH3) in which all three of the C=H bonds extend and contract in phase.

Complexation may shift the polymer cage peak frequencies. FTIR would be sensitive both in situations where complexation has occurred in crystalline or amorphous phase [20].

Figure 3.3, c which is FTIR analysis of the 1:1 (PVC+PMMA) blends shows small shifting of the carbonyl bond of PMMA to lower wave numbers. The shift of the peak is about 4–6 cm^{-1} within the domain of miscibility of the two polymers.

The miscibility of PVC/PMMA blends is due to a specific interaction of hydrogen bonding type between carbonyl (C=O) of PMMA and hydrogen from (CHCl) groups of PVC [23], [24], [25] and [26].

4. Conclusions:

AC electrical conductivity have been measured at different temperatures and at the different frequencies. It is found that,

i. AC conductivity of thin film decreases with increase in temperature for all values of frequencies

ii. AC conductivity of thin film increases with increase in frequencies at constant temperature.

iii. AC conductivity of thin film decreases with increasing doping percentage.

iv. The increasing AC electrical conductivity with frequency can be attributed to the interfacial polorisation.The polorisation effect is dependent on the frequency of applied A.C. electrical field.[30]

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DC Conductivity of 2:1 (PVC:PMMA) Polyblends: Temperature Dependent

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Abstract: We have prepared the thin films of 2:1 (PVC: PMMA) Polyblends by using isothermal evaporation technique. The DC conductivity of 2:1 (PVC:PMMA) Polyblends thin films measured at different electric field (50V -650V) with respect to different constant temperatures (50°C to 125°C) were studied. It has been revealed that the electrical current increases with applied electric field at all the temperatures ,the conductivity of sample increases with temperature and the values of activation energy (E_a) have been found higher in high temperature region than those in low temperature region. The DC electrical conductivity of the sample has been found to increase with the increase in thickness of films.
Keywords: Polyblends thin films, 2:1 (PVC:PMMA), isothermal evaporation technique.

1. Introduction:

The polyblends are produced by the addition of small amount of a rubbery polymer to a polymeric glass. The impact strength of the glass is thus substantially increased .The rubbery polymer is not truly compatible and exist as a finely dispersed separate phase. Interpenetrating polymer networks, in which two different networks are intertwined constitutes on interesting special case of polyblends . Even though a large number of new polymers are synthesized it is still customary to use a mixture of two or more polymers in industry as a raw material for preparing various articles. The production of such mixture also helps in improving certain properties of individual polymer, like increase the strength of rubber by adding stronger plastic to them or improving the elastic properties of plastic by adding rubber to them. The enormous growth of synthetic polymers is due to the fact that they are lightweight materials, act as insulators for electricity and heat, cover a wide range of properties from soft packaging materials to fibers stronger than steel, and allow for relatively easy processing. The polymers are mainly divided into thermoplastics and thermosets. The major thermoplastics include high-density polyethylene (HDPE), low-density polyethylene (LDPE), polyethylene terephthalate (PET), polypropylene (PP), polystyrene (PS and EPS), poly(vinyl chloride) (PVC), polyamide (PA), poly(methyl methacrylate) (PMMA) and styrene copolymers (ABS, SAN). Poly (vinyl chloride) (PVC) is an important commercial thermoplastic, which is widely used in industrial fields due to its good properties and low cost. However, its brittleness, low thermal stability and poor process ability limit its application. Poly (methyl methacrylate) (PMMA) is amorphous in nature due to presence of bulky side groups in molecules. It is colorless transparent plastic with an excellent outdoor life period, good strength and higher impact strength than glass.

The polyblends are certain to show the properties different from basic polymers. PVC, PMMA among the most extensively studied polymers having a great range of applications. The addition of methyl methacrylate and its polymer (PMMA) to improve the thermal and mechanical properties of PMMA and for

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Deogaonkar [3] reported on the theory of electrical conduction and experimental findings have appeared in a number of such blends. The conductivity studies on PVC/PMMA polymer blend electrolytes have shown that the polymer component would render stability and they have many applications of blending [4].

2. Experimental:

In this work we have selected Polymethyl methacrylate (PMMA) as a base polymers which is in granule form obtained from Otto Kernl, Mumbai and PVC is prepared by the polymerization of vinyl chloride. The major role of Tetrahydrofuran (THF-E-Merck India Ltd., Mumbai) being as a solvent for polyblending process, which is a colorless, water-miscible organic liquid with low viscosity at standard temperature and pressure. The thin films of 2:1 (PVC: PMMA) Polyblends by weight ratio was prepared using isothermal evaporation technique [5]. The thin film was then sandwiched between two brass electrodes of the sample holder .The metal –insulator – metal system so formed was placed inside the furnace. The DC conductivity of Polyblends thin films measured by using two probe method at different electric field (50V - 650V) with respect to different constant temperatures (50°C to 125°C) were recorded. The same procedure was repeated for all the thin films of different thicknesses. In this present study, thickness of thin film is found to be in the range 20 to 50μm.

3. Results and Discussion:

The polymer films consist of both crystalline and amorphous regions [6,7]. Such polymers can exist in two states depending on temperature. At low temperature, they are glassy materials, while at high temperature (called their glass transition temperature T_g) they undergo transition from glassy to rubber like state. At this temperature gross molecular motion of polymer chains accompanies the transition from glassy to rubbery state .The motion of the molecular chains enhance the freeing of charge carriers and thus there is an increase in conductivity. As a result of this, the conductivity–temperature plot shows that conductivity increases in accordance to the temperature as shown in fig. 1.

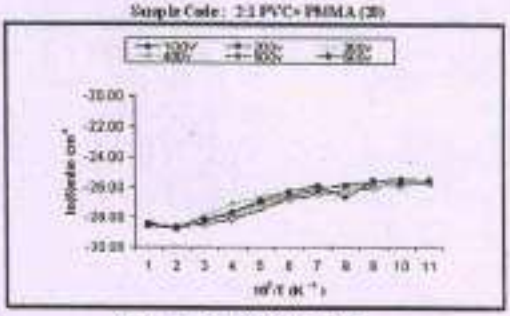
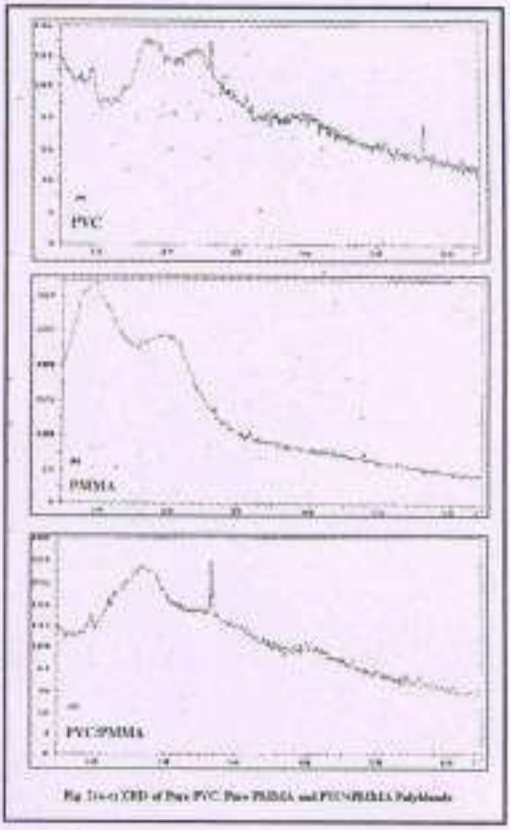


Fig. 1. Arrehnius Plot



Figures 2 (a), (b) and (c) illustrate the XRD diffractograms of pure PVC, pure PMMA and (PVC+PMMA) Polyblends respectively. From Figure 2(b), a broad characteristic peak of PMMA was obtained at angles of 2θ= 11.4° with a shoulder at 2θ= 21.5° which reveals the amorphous phase of PMMA. The intensity of these characteristic peaks is decreased after the impregnation of PVC. This implies that the addition of PVC disrupted the arrangement in the polymer backbone of PMMA [8]. The presence of interactions between PMMA and PVC, such as cross-linking, is attributed to complexation of PMMA and PVC. Apart from the peak intensity of these characteristic peaks, another evidence of complexation is observed by shifting of peaks. The blending of PMMA with PVC shifts the peaks at 2θ= 18.5° and 2θ= 28.1° revealing the change in crystallographic organization [9].

In case of polyblends having 30 ml, 25ml, 15ml and 10ml of cyclohexane (as a solvent) i.e. with increasing thickness of thin films it is found that the current linearly increases from 50V to 600V, hence indicates the ohmic conduction in higher as well as lower voltage region for all the samples. On application of step voltage across the specimen orientation of dipoles occur at low voltages as well as high voltages; the mobility of charge carriers increases resulting into the increase in current density with respect to applied voltages .Among the two polymers, PVC is strongly polar and high dielectric constant. Also it acts as an electron withdrawing group i.e. acceptor, which pulls electrons from neighboring atoms and hence tends to become a more reactive compound .While PMMA is weakly polar and it is a hard rigid, transparent thermoplastic. PMMA contains electrons releasing methyl group (CH_3) i.e. it acts as an electron donor, which supplies electrons and tends to become a stronger bond. PMMA also contain acrylate group (−CH-CO-O-R), which is a bulky side group. Hence introduction of methyl constituent in the polymer decreases the C-C bond stability [10].

The electrical conductivity of PVC, as reported by standard literature is between 10^{-31} - 10^{-34} Ωcm^{-1} and of PMMA is in the range of 10^{-13} to 10^{-15} Ωcm^{-1}. This suggest that PVC is slightly better conducting material as compared to PMMA .The conductivity of PVC-PMMA polyblends as determined from our experimentation lies between 10^{-14} to 10^{-15} Ωcm^{-1}. This dc conductivity lies intermediate between that PVC & PMMA .Thus combination of PVC & PMMA slightly increases the conductivity of PMMA but decreases that of PVC.

4. Conclusions:

PVC-PMMA polyblends having different quantity of cyclohexane show semi conducting properties .The fact that the conductivity of sample increases with the increase of temperature (The rate of increase of conductivity with temperature is comparatively less than the conventional semiconductors such as Ge and Si). But this property is exhibited by the polyblends films. For all the samples, the conductivity increases with the increase in temperature. The conduction has been almost ohmic in low voltage region as well as in high voltage region. The conductivity of sample has also been found thickness dependent. The conductivity has been found to increase with the increase in thickness of sample films. The blending of PVC and PMMA retain the insulating properties quite intermediate between those two of component polymers.

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Zn_2SnO_4 modified ZnO thick film resistors as LPG sensor

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Abstract : Zinc oxide nanostructures were synthesized by chemical route method. The XRD spectrum indicates that the sample is wurtezite (hexagonal) structured ZnO with lattice constants of a = 3.249A°, c = 5.206 A°. Thick films of synthesized ZnO were prepared by screen printing technique. The Zn_2SnO_4 modified ZnO were obtained by dipping them into an aqueous solution of $SnCl_4.5H_2O$ for different interval of time. Gas sensing properties of pure and modified ZnO thick films were investigated. The Zn_2SnO_4 modified ZnO thick film dipped for 3 min was observed to be more sensitive to LPG as compared to other modified thick films at 240°C. The effect of surface microstructure and Zn_2SnO_4 concentrations on the sensitivity, selectivity, response and recovery of the sensor in the presence of LPG and other gases were studied and discussed.

Keywords : ZnO nanostructure, Zn_2SnO_4 modified ZnO thick films, LPG Sensor.

1. Introduction:

The detection of toxic and inflammable gases by a sensor was extremely important for human and environmental protection. Research on the gas sensors was aimed to obtaining new sensing materials to achieve highly sensitive and selective devices. ZnO has proven to be highly sensitive materials for the detection of both reducing and oxidizing gases [1-10]. Though, poor selectivity is one of its disadvantages.

Semiconductor gas sensors based on SnO_2 and ZnO have been studied for the detection of toxic or inflammable gases [11-14]. However, high operating temperature is one of their disadvantages. In order to modify the gas sensing properties, the use of metal additives such as Ag, Pt and Pd as catalysts were widely studied [15]. Another approach was the utilization of the interfaces between two different oxides such as hetero contact of p-n junction with new sensing mechanism was proposed to improve its sensing properties. However, the hetero contact type sensors have the poor reliability due to its pressed contact [16]. Composite type sensors were suggested to improve the reliability since they contain many heterogeneous interfaces between different phases. However, the composites make the study of the individual interface difficult. To overcome these problems, only surface of metal oxides were modified with other oxides by using dipping technology. In present work, the efforts were made to modify surface of ZnO nanostructure thick film with Zn_2SnO_4 crystals by using dipping technique to improve sensing properties.

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2. Experimental

2.1 Synthesis of ZnO nanostructure

All chemicals were of analytical grade and used as purchased without further purification.

In present work, 2.974 g Zinc nitrate hexahydrate was dissolved in 100 ml distilled water and 2.0g of NaoH was dissolved in 100 ml distilled water. The zinc nitrate solution was added drop wise to the NaoH solution to form white solution. Then, white solution was subsequently kept at 75°C for 12h. The resulting white precipitates were collected by centrifugation, washed with distilled water and ethanol several times and then dried at 80°C in vacuum oven for 2h. The synthesized ZnO nanostructure was used for further study.

2.2 Preparation of thick films

Thick films of ZnO nanostructure were prepared by using screen printing technique. In present process, paste was formulated by mixing the ZnO nanostructure powder with ethyl cellulose in a mixture of organic solvents. The ratio of ZnO to ethyl cellulose was kept 93:07. The paste was screen printed on a glass substrate in desired patterns. The films were fired at 500°C for 2h to remove temporary binder. Prepared thick films termed as pure ZnO thick films.

2.3 Zn_2SnO_4 modified ZnO thick films

Surface of pure ZnO thick film were modified by dipping them into a 0.01 M aqueous solution of $SnCl_4.5H_2O$ for different intervals of time (1, 3, 5 & 7 min). After dipping, thick films were dried under IR lamp for 45 min. and calcinated at 700°C for 4h in air ambient. In calcination process, tin chlorides dispersed on the film surface were reacting with surface ZnO molecules and oxidized. Therefore sensor elements with different mass% of Zn_2SnO_4 on the surface of ZnO thick film were obtained. These surface activated films are termed as Zn_2SnO_4 modified thick films.

2.4 Characterization

The synthesized ZnO were characterized for structure and morphology by power X-ray diffraction (Philips PW 1710) and transmission electron microscopy (TecnaiG2 20 ultra-twin). The microstructure and chemical composition of the films were analyzed using a field emission scanning electron microscope (ZEISS SUPRA-55) coupled with an energy dispersive spectrometer. Thickness measurements were carried out using Marutek film Thickness Measurement System. Electrical and gas sensing characteristics were measured using a static gas sensing system.

2.5 Static gas sensing system

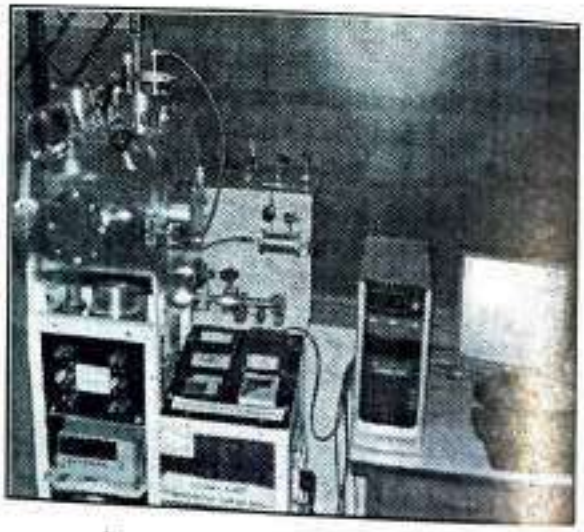


Fig. 1 Photograph of computerized gas sensing system

Fig. 1 represents photograph of computerized static gas sensing system to examine the sensing performance of the thick films. A constant voltage was applied to the sensor element and current was measured with the help of voltage source cum picoammeter (Keithley 6487). Heating element and thermocouple were connected to temperature controller (Nippon NC 2638). Sensor element and thermocouple were kept on the insulating surface of the heating element. The required gas concentration inside the static system was

achieved by injecting a known volume of test gas using a syringe. The vacuum pump is attached to chamber to create vacuum or to remove test gas.

3. Material Characterization:

3.1 X-ray diffraction

The recorded X-ray diffraction pattern (Fig. 2) confirmed that synthesized ZnO is highly crystalline in nature. The corresponding X-ray diffraction peak for (100), (002), (101) and (102) planes confirm the formation of hexagonal wurtzite structure of ZnO, which are in good agreement with the literature values (JCPDS card No. 36-1451). In this X-ray diffraction pattern, extra pick appear at $2\theta = 44^{\circ}$. This peak was identified as surface hydroxyl groups, which can be related to the formation of water on the ZnO nanostructure surface [17]. The crystallite size was calculated by using Scherrer's formula [18] and found to be 16nm.

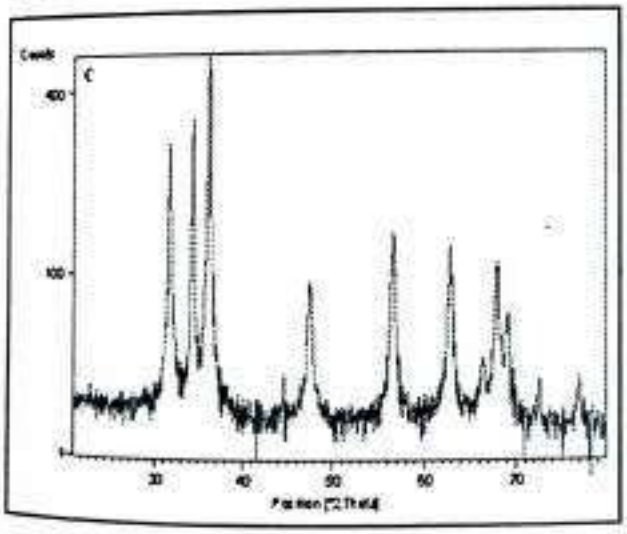


Fig. 2 powder XRD pattern of ZnO nanostructure synthesized by chemical route method

3.2 Transmission electron Microscope

Fig.3 illustrates the TEM image of the ZnO nanoparticles. TEM pattern shows that the particles are agglomerated up to some extent.

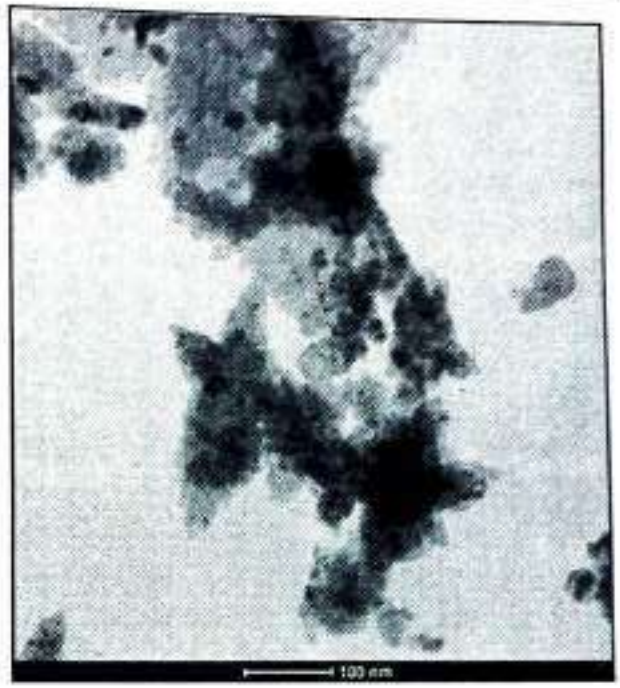


Fig. 3 TEM image of ZnO nanostructure synthesized by chemical route method

3.3 Scanning Electron Microscope:

The FE-SEM micrograph of the pure ZnO thick film prepared by screen printing technique is shown in Fig. 4a. Pure ZnO thick film consists of randomly distributed nanosheets. Fig. 4b corresponds to surface modified ZnO thick film with dipping time 1 min, clearly indicate that, growth of nanosize octahedral crystal began to occur on the surface of ZnO thick films. These nanosize octahedral crystals attributed to Zn_2SnO_4. Thus effective surface area of thick film gets increased. As dipping time increases to 3 min, growth of more and more Zn_2SnO_4 crystals on the surface of ZnO thick films occur (Fig. 4c). Further increasing in dipping time to 5min and 7min, these nanoscale Zn_2SnO_4 crystals start to disperse core of ZnO nanostructure as shown in Fig. 4d and 4e respectively. Fig. 4f shows high magnified FE-SEM image of Zn_2SnO_4 crystal created on the surface of modified ZnO thick film (dipped for 3 min.).

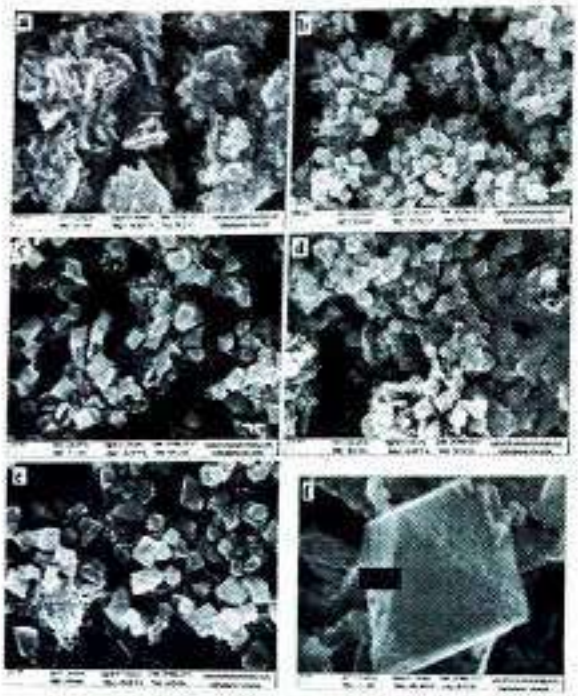


Fig. 4 FE-SEM images of a) pure ZnO thick film & modified ZnO thick film b) dipped for 1 min. c) dipped for 3 min. d) dipped for 5 min. e) dipped for 7 min. f) Highly magnified modified ZnO thick film (3 min dip.)

3.4 Elemental analysis

Fig. 5a-e represents the EDS patterns of pure and modified ZnO Thick films. These Figures illustrate that as the dipping time increases intensity of tin peak increases, which indicate the increasing in mass percentage of tin element on the surface of the ZnO thick film.

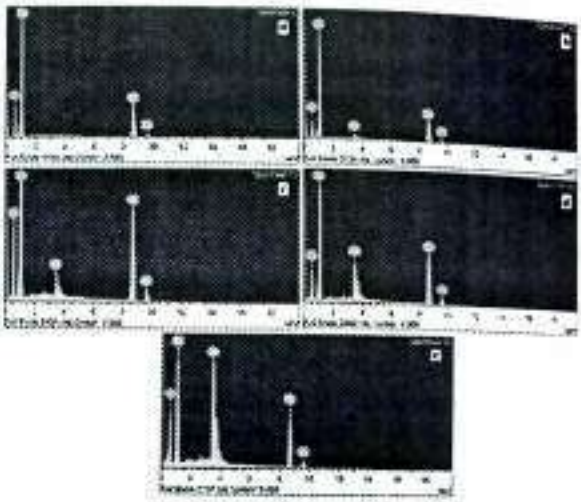
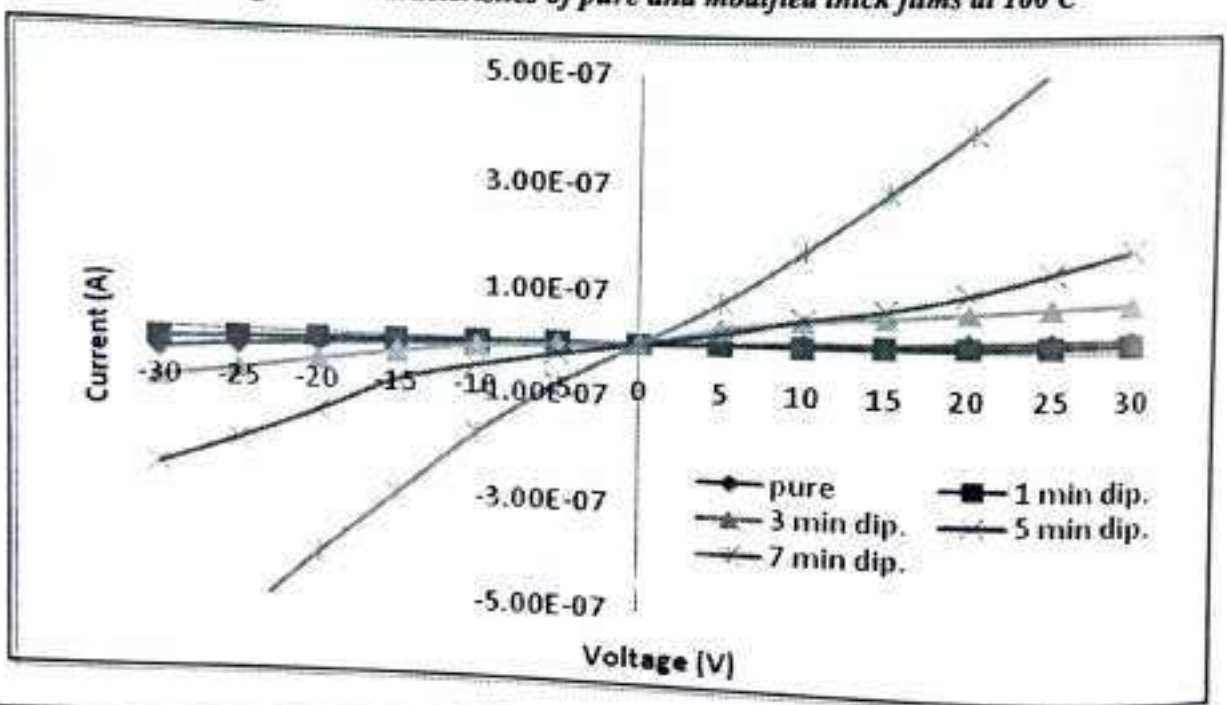


Fig. 5 EDS patterns of a) pure ZnO thick film & modified ZnO thick film b) dipped for 1 min. c) dipped for 3 min. d) dipped for 5 min. e) dipped for 7 min.

Fig. 6 I-V characteristics of pure and modified thick films at 100°C



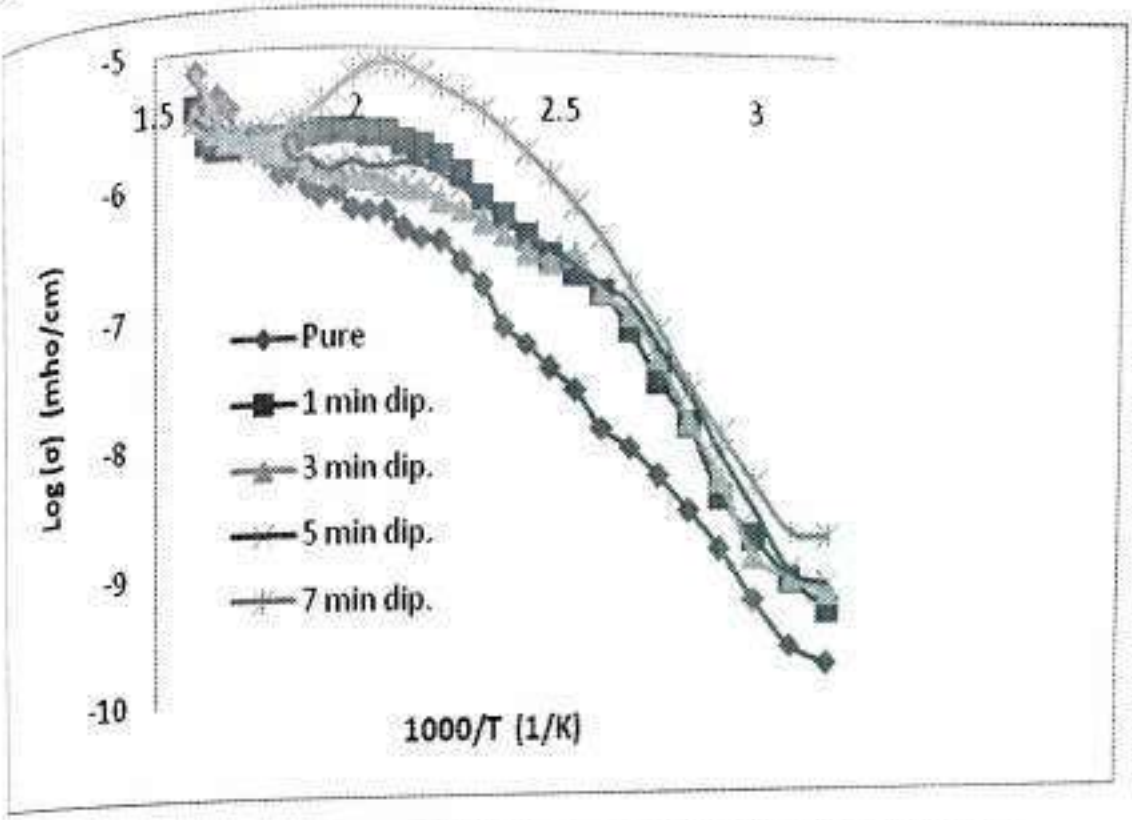


Fig. 7 Variation of log σ with 1000/T of pure and Zn_2SnO_4 modified thick films

4.2 Electrical conductivity

Fig. 7 depicts that, for all the samples conductivity increases with increasing in temperature. It is observed that, the conductivity of pure ZnO thick film is less than Zn_2SnO_4 modified ZnO thick films. Higher conductivity of Zn_2SnO_4 modified ZnO thick films are attributed to growth of Zn_2SnO_4 crystal over the surface of ZnO thick films. Zn_2SnO_4 has high electronic mobility and thermal stability.

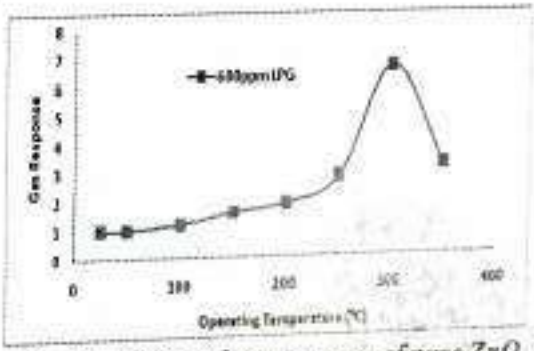


Fig. 8 variation of gas response of pure ZnO thick film with temperature

5. Sensing performance

5.1 Pure ZnO thick film

The gas response of the sensor was defied as the ratio of the change in conductance of a sample upon exposure to the target gas to the original conductance in air. The variation of gas response of ZnO thick film to 600ppm LPG with operating temperature is represented in Fig. 8. The response to LPG increases with increasing the operating temperature, reaches to the maximum (6.7) at 300°C and decreases with further increasing operating temperature. Response to a gas is due to the interaction between hydrocarbons (propane and butane present in LPG) and adsorbed oxygen ions present on the surface of the thick film. When hydrocarbons interact with the adsorbed oxygen ions on the surface of ZnO thick film they are converted to CO_2 and H_2O and releases the trapped electrons back to the conduction band of the zinc oxide thick film. As a result the

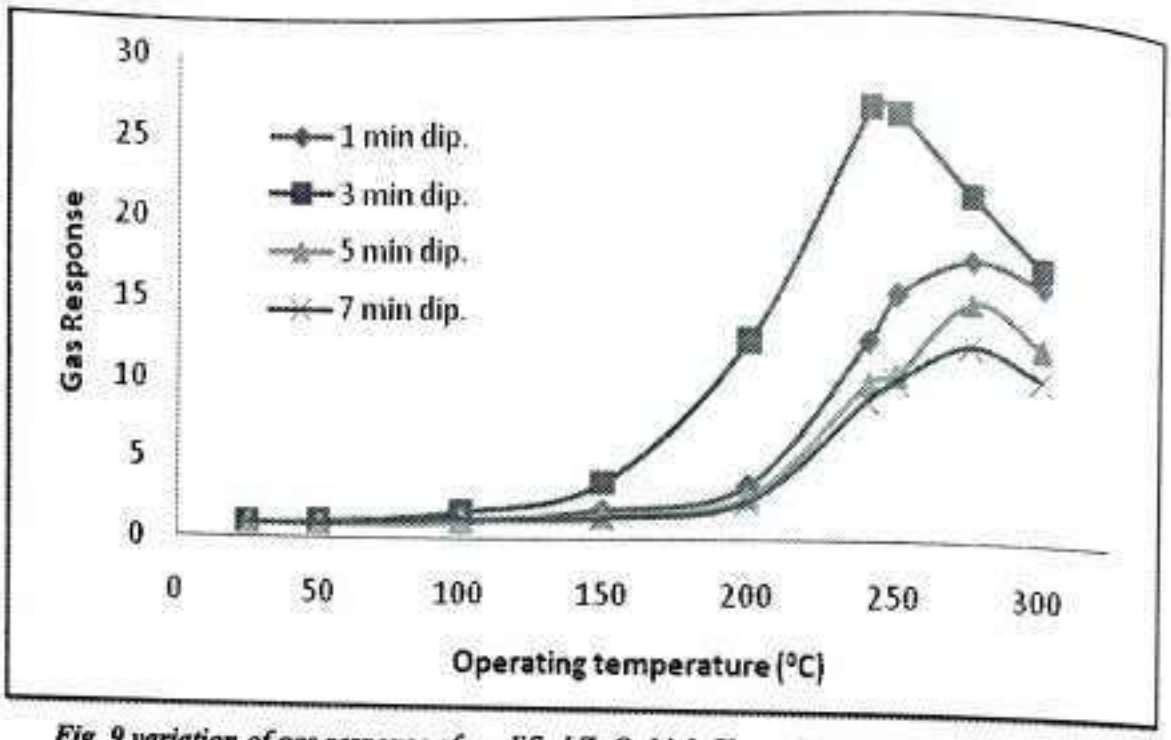


Fig. 9 variation of gas response of modified ZnO thick films with operating temperature.

conductance of ZnO thick film increases in existence of LPG.

5.2 Zn2SnO4 modified ZnO thick films

5.2.1 Gas response and operating temperature

The variation of gas response of modified ZnO thick films to LPG as a function of operating temperature is shown in Fig. 9. It represent that modified ZnO thick films with different dipping time are sensitive to 600 ppm LPG in the temperature range 200-300°C. The highest response of all thick films was observed around temperature 250°C.

5.2.2 Selectivity for LPG against various gases

Fig. 10 demonstrate the selectivity of all modified ZnO thick films for 600 ppm LPG, NH_3 and CO_2 gas at operating temperature 240°C. These modified thick films showed high selectivity to LPG among the gases such as CO_2 and NH_3.

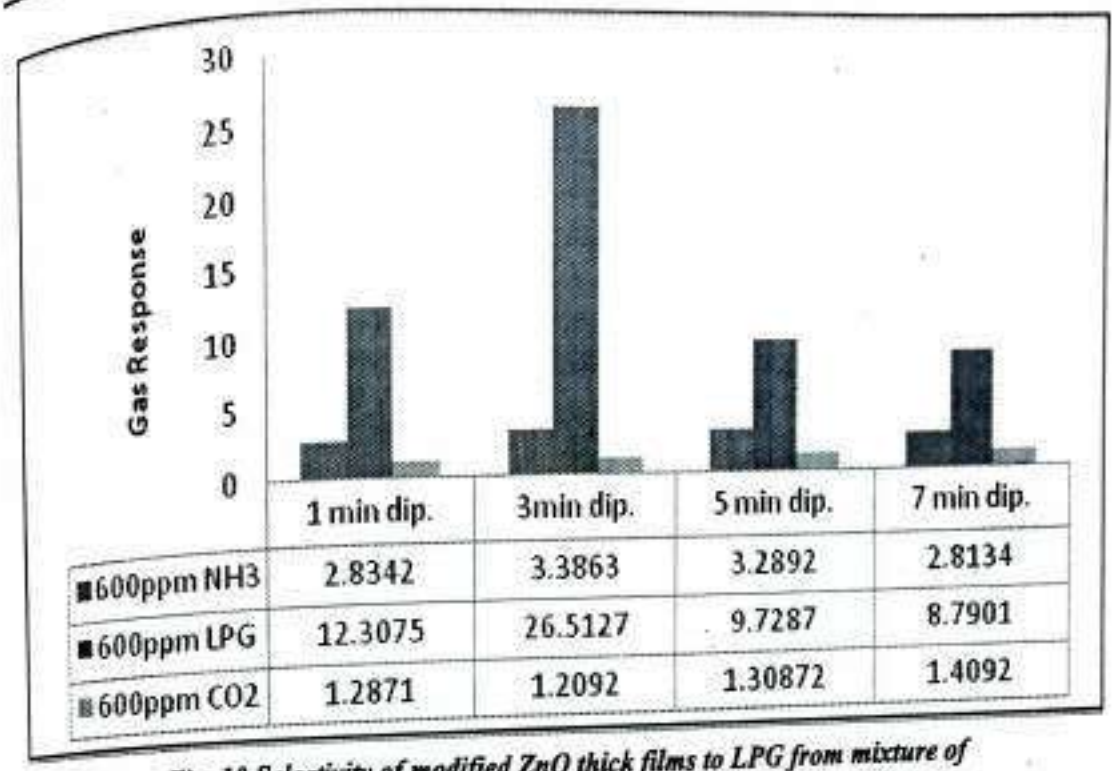
5.3.3 Response and recovery time of the sensor

Fig. 11 illustrates the response and recovery of the modified ZnO thick (3 min dip). It indicates that the response was quick (6 s) to 600 ppm of LPG, while the recovery is also fast (8 s) at operating temperature 240°C.

All modified ZnO thick films gives quick response to LPG at higher operating temperature and fast recovery when sensor element keeps in air atmosphere. Such quick response and fast recovery can be explained on basis of adsorption and desorption process of oxygen ions on surface of Zn_2SnO_4 modified ZnO thick film.

6. Discussion

Enhancement of sensing performance of Zn_2SnO_4 modified ZnO thick film to LPG



	1 min dip.	3min dip.	5 min dip.	7 min dip.
600ppm NH3	2.8342	3.3863	3.2892	2.8134
600ppm LPG	12.3075	26.5127	9.7287	8.7901
600ppm CO2	1.2871	1.2092	1.30872	1.4092

Fig. 10 Selectivity of modified ZnO thick films to LPG from mixture of gases at operating temperature 240°C.

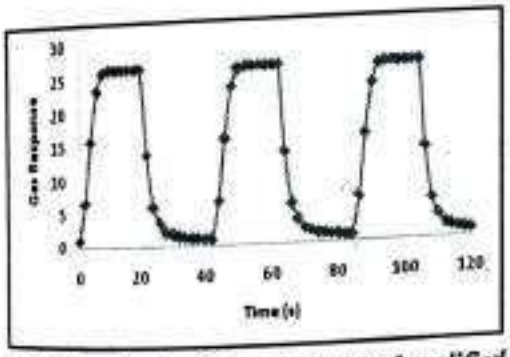


Fig. 11 variation of gas response of modified ZnO thick film (dipped for 3 min) to 600ppm LPG with time

[Fig. 9] as compared to pure ZnO thick films [Fig. 8] can be attributed to growth of zinc stanate crystals on the surface of ZnO thick film. This will increase the surface to volume ratio of the sensor material. The chemical composition and crystal morphology of Zn_2SnO_4 offers enhanced active sites for reactions of LPG molecules with adsorbed oxygen.

When Zn_2SnO_4 modified thick film exposed to air, oxygen molecules were adsorbed on the Zn_2SnO_4 surface, which generate ionized oxygen species by trapping electrons from the conductance band of Zn_2SnO_4. These generated ionized oxygen species react with reducing gas such a LPG, which resulted in the release of electrons to the surface of Zn_2SnO_4 modified ZnO thick film. Thus the conductivity of Zn_2SnO_4 modified ZnO thick films were increases gradually.

Fig. 9 shows that the sensitivity of Zn_2SnO_4 modified ZnO thick film (dipped for 3 min) is highest among other thick films in the temperature region 200-300°C, it may be attributed to morphology of Zn_2SnO_4 crystals developed on the surface of ZnO thick film. The adsorption and desorption processes, which determine the sensor response mainly depends on the orientation and morphology of the crystals. As the size of the crystal domain becomes smaller, the ratio of edge and corner atoms increases and also the surface topology

becomes increasingly roughened [19]. Control of crystal size distributions and resulting changes in electronic and surface states provides an opportunity to tailor the interaction and adsorption of gas molecules on the exposed surfaces of Zn,SnO_4 cubic structures and ZnO nanostructure resulting in enhanced sensor performance.

7. Summary

The sensing performance of pure and modified ZnO thick films can be summarized as

1. Zinc oxide power synthesized by chemical route method consists of nanoparticles and nanorods.
2. Pure ZnO thick films are less conductive as compared to modified ZnO thick films.
3. Pure ZnO thick films showed higher sensitivity and selectivity to 600 ppm LPG gas at 300°C.
4. In case of surface modified thick films, thick film (dipped for 7 min.) shows higher conductivity.
5. All modified ZnO thick films shows sensitive to 600ppm of LPG in the temperature range 200-300°C.
6. At 240°C, modified ZnO thick film (dipped for 3 min.) shows higher sensitivity to 600 ppm of LPG as compared to other modified ZnO thick films.
7. Modified ZnO thick films showed very rapid response and fast recovery as compared to pure ZnO thick films.

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Electrical Conductivity of Surface Activated Nanostructure ZnO Thick Films

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Abstract: Zinc Oxide particles were synthesized by Chemical Precipitation Method. The average particle size of ZnO is found to be 19 nm. Thick films of ZnO were prepared by screen printing technique and Al_2O_3 -surface activated ZnO films were prepared by dipping method. The variation of electrical conductivity of pure and surface activated films was studied with temperature. The results of electrical measurement at the room temperature show that, pure ZnO and surface activated thick films are semiconducting in nature. The decrease in conductivity of surface activated thick films may be due to presence of potential barrier at the intergrain boundaries of ZnO-Al_2O_3 and hence the grain boundary region becomes more resistive.

Keywords: ZnO, Chemical Precipitation Method, XRD, Surface activated thick film, Electrical conductivity.

1. Introduction

Today, when the world is prevailing on the roof of technology and electronics, mostly dominated by compatible electronic equipments and thereby creating the need for materials possessing useful properties. The world now demands a material that should possess inherent properties like larger band gap, higher electron mobility as well as higher breakdown field strength. So on making investigation about such a material the name of compound comes out is "Zinc Oxide" which is a wide gap semiconductor material very well satisfying the above required properties.Zinc oxide possessed many versatile properties for UV electronics, spintronic devices and sensor applications. This ignites many research minds all over the world and creates interest to develop proper growth and processing techniques for the synthesis of Zinc oxide.

The electrical, optical, magnetic, and chemical properties can be very well tuned by making permutation and combination of the two basic structural characteristics that is cations with mixed valence states, and anions with deficiencies(vacancies). Thus, making them suitable for several application fields such as semiconductor, superconductor, ferroelectrics, magnetic and gas sensing.

Nanostructured materials such as ZnO, SnO_2, and WO_3 have shown good electrical properties [1-12]. Among these nanostructure-semiconducting materials, ZnO has been studied extensively for electrical application. Due to its versatility and multifunctionality creates attention in the research field related to its electrical applications. A wide number of synthesis techniques also been developed by which ZnO can be grown in different nanoscale forms. Efforts were made to synthesize ZnO nanostructure with innovative morphology by chemical route method. The synthesized ZnO shows good electrical conductivity. In the present work, the efforts are made to study electrical conductivity with a low cost additive (Al_2O_3) using dipping technique which is a simplest method of surface modification.

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2. Experimental

2.1. Synthesis of ZnO Nanostructure

All chemicals were of analytical grade and used as purchased without further purification. In present work, Zinc nitrate hexahydrate was dissolved in distilled water such that to make 0.15M solution. Subsequently, 0.5 M NaOH aqueous solution was introduced into the above aqueous solution drop by drop with constant stirring. The resultant white solution was subsequently kept at 75 °C For 12 hrs.and then cooled room temperature naturally and sonicated (Ultrasonic wave treatment) for 30 min. The resulting white precipitates were collected by centrifugation, washed with distilled water and ethanol several times and then dried at 80°C in vacuum oven for 2hr. Obtain ZnO nanostructure product were used for further study.

2.2. Preparation of Thick Films

Thick films of synthesized nanostructure ZnO were prepared by using screen printing technique. In present process, thixotropic paste was formulated by mixing the synthesized ZnO powder with ethyl cellulose (a temporary binder) in a mixture of organic solvents such as butyl cellulose, butyl carbitol acetate and turpineol. The ratio of ZnO to ethyl cellulose was kept at 95:05. The ratio of inorganic to organic part was kept as 75:25 in formulating the pastes. The thixotropic pastes were screen printed on a glass substrate in desired patterns. The films prepared were fired at 500°C for 12 hr. Prepared thick films were called as pure ZnO thick films.

3. Materials Characterization

3.1. Thickness Measurement

Thickness of all ZnO thick films were measured by using technique "Marutek film Thickness Measurement System" with the help of provided equipment. The thicknesses of all films were observed in the range from 31 to 35 µm. Thick films of approximately uniform thick-nesses were used for further characterization.

3.2. X-Ray Diffraction Studies

The crystallographic structure of the synthesized ZnO nanostructure was characterized by powder X-ray diffraction (Philips X-ray diffractometer) with Cu-α source and 2θ range of 10° - 70°. Fig 1shows the XRD pattern of the ZnO nanostructure. The recorded XRD pattern confirmed that synthesized ZnO are highly crystalline in nature. The corresponding X-ray diffraction peak for (100),

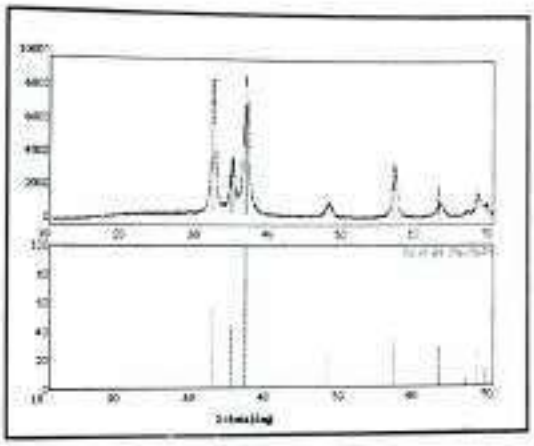


Fig1:XRD Pattern of Pure ZnONanostructure

(002), (101), (102) (110), (103) and (112) planes confirm the formation of hexagonal wurtzite structure of ZnO (JCPDS card no.-01-080-0075). The domain size of the crystal can be estimated from the full width at half maximum (FWHM) of the peaks by means of the Scherrer formula,

$$D = \frac{k\lambda}{\beta \sin\theta}$$

whereλ is the wavelength of incident beam (1.5406 Å), β is the FWHM of the peak in radians, θ is the diffraction angle and K is Scherrer constant. The average particle size was calculated from (101) peak ZnO is found to be 19 nm.

Using X'pert High Score Plus software it is confirm that synthesized zinc oxide powder contains Zn and O elements only, not any impurity and another element.

4. Surface Modification of ZnO Thick Film

The pure ZnO thick film was surface activated by dipping it into a 0.01M aqueous solution of Aluminium chloride anhydrous $[Al(H_2O)_6Cl_3]$ for 2 min and was dried at 90°C, followed by firing at 500°C for 12 h in ambient air. The particles of Aluminum chloride dispersed on the film would be transformed to Aluminum oxide (Al_2O_3) during firing process. This surface-activated filmis termed as Al_2O_3-activated film. Silver contacts were made by vacuum evaporation for electrical measurements

5. Electrical properties

5.1. I–V characteristics

Fig. 2 depicts the I–V characteristics of the pure and Al_2O_3-activated ZnO films at room temperature. The symmetricalnature of I–V characteristics shows that silver contacts on the film are ohmic in nature[13].

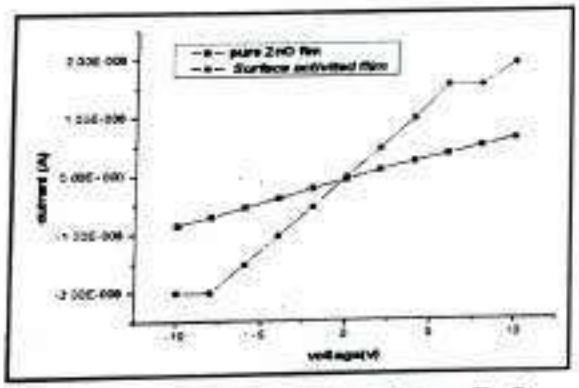


Fig 2:I-V Characteristics of pure ZnO and surface activatedthick film at room temperature

5.2. Effect of Temperature on Current

Fig. 3 shows the variation of current with temperature. The current values of all samples increase with operating temperature which shows good conduction in given samples.

5.3. Electrical conductivity

Fig. 4shows the variation of log σ

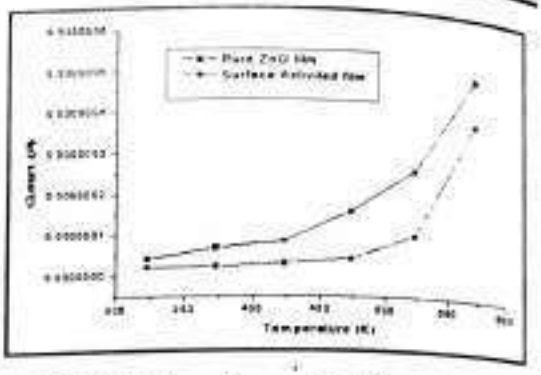


Fig 3: Variation of current with temperature

(conductivity) with reciprocal of temperature of pure and activated films. The conductivity values of all samples increase with increasingtemperature. They are nearly linear to 1000/T in the range from 100 to 250°C. The increase in conductivity with increasing temperature could be attributed to the negative temperature coefficient of resistance and semiconducting nature.

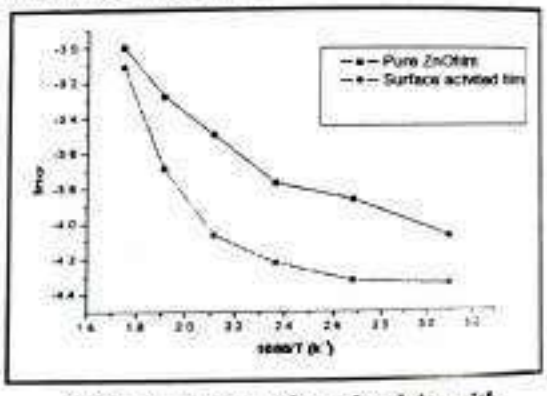


Fig 4: Variation of conductivity with reciprocal of temperature

6. Discussion:

Increasing in conductivity with temperature of ZnO may be due to large oxygen deficiency which could adsorb oxygen species at higher temperature. The adsorption phenomena of the Al_2O_3 modified ZnO thick film surface may be different form the pure ZnO thick films surface. The Al_2O_3 misfits on the surface are the places where the oxygen species adsorb. The Al_2O_3 misfits distributed evenly on the surface

would have made it possible to adsorb the oxygen ions even at low temperature. [14] Formfig 4 it is clear that conductivity of pure and Al_2O_3- modified ZnO films increases with an increase in temperature, indicating a positive temperature coefficient of conductance. This behavior confirmed the semiconducting nature of the pure and modified ZnO [15].

It is observed from fig 4 that the electrical conductivity of the pure ZnO film is higher than modified ZnO film in ambient air. It may be due to the intergranular potential barrier [14]. Pure ZnO has only one kind of grains arranged uniformly, where in the case of Al_2O_3 modified films the grains are of different natures such as Al_2O_3 and ZnO. The modification causes the formation of heterogeneous intergrain boundaries of the Al_2O_3-ZnO. Thus increased barrier heights of the intergranular regions of activated ZnO may be responsible to decrease the conductivity.

7. Summary :

Thick filmsof ZnO nanostructures were synthesized by a chemical precipitation method followed by sonication and their electrical properties were measured. The results demonstrated that the electrical conductivity of the pure ZnO film is higher than modified ZnO films in ambient air. Such nanomaterials with innovative structure can be used for future work such as gas sensing area.

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Study of variation dielectric constant of 4:1 PS PMMA Polyblend thin films doped with Oxalic Acid in different weight proportions

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Abstract: The measurements of the dielectric constant (ε_r) of 4:1 PS PMMA polyblend systems doped with 0%, 5%, 10%, and 15%, Oxalic acid (OA) have been carried out in the temperature range 323 K - 373 K and at frequencies in the range1 kHz – 1 MHz. The experimental results reveal that, dielectric constant (ε_r) increases with increase in temperature and concentration of dopant Oxalic acid (OA), whereas, $_r$ decreases with the increase of frequency.

Keywords: Polymethyl Methacrylate (PMMA),Polystyrene (PS), Oxalic Acid (OA), dielectric constant (ε_r),

Introduction:

We have used the polymers namely PS and PMMA. Among these PS is non-polar and PMMA is weakly polar. In the polar polymers, permanent dipoles can be assumed to be present. Such polymers can be treated as dielectrics. Such dielectrics have special properties of storing and dissipating electrical energy when subjected to electromagnetic fields. Studies of these materials particularly in a. c. fields provide an insight of the electrical nature of the molecular or atomic species which constitute the dielectric materials. This energy storing capacity of dielectric leads to the fabrication of capacitors (capacitance elements). In thin film capacitors, the dielectric materials are sandwiched between two electrodes. In our case, sample polyblend films had been sandwiched between two brass electrodes of the sample holder and as such the system constituted the capacitor. The presence of dielectric material between two electrodes increases the capacitance i.e. the storage capacity of electrical energy. The thin film capacitors are therefore extensively used in various devices such as in micro-miniature electronic circuits, memory devices, transducers in ultrasonic applications, etc. The study of a. c. field behaviour has been extensively carried out{Rajendran *et al.*(2002), Khaled *et al.* (2003), Raghavendra *et al.* (2003),} The behaviour of dielectrics in a.c. field gives us an idea about their polarization effects, dispersion of electromagnetic fields, both at audio and high frequency regions, relaxation phenomenon and a.c. conductivities.

Experimental Techniques

Sample Preparation:

Method of preparation of PS- PMMA Films without Dopant:

In the present work, Isothermal Evaporation Technique (Bahri and Sood 1983; Sangawar 1995) has been used, as it is best suited to the conditions in the laboratory. The two polymers PS and PMMA taken in the ratio 4:1 were dissolved in the common solvent Tetrahydrofuran (THF).The solution was kept for 3-4 days to allow polymers to dissolve completely to yield uniform solution. The solution mixture was then heated for 1 hour at 60°C to get completely homogeneous solution. A glass plate thoroughly cleaned with water and later with acetone was used as a substrate. To achieve perfect leveling a pool of mercury was

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used in a plastic tray. The solution was poured on the glass plate and was allowed to spread uniformly in all directions on the substrate. The film on the glass substrate was then removed and cut into small pieces of suitable sizes. In this way the films were prepared by isothermal evaporation technique.

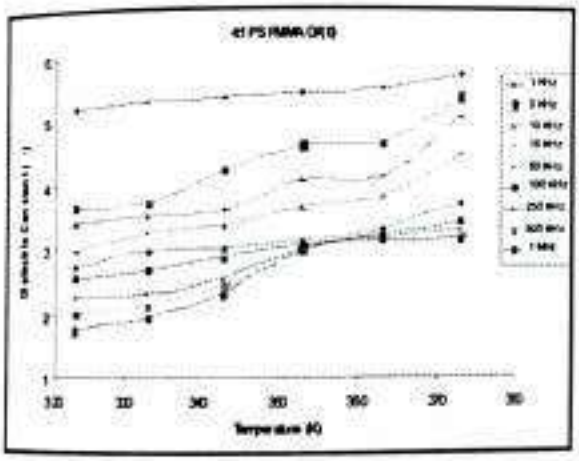
Method of preparation of PS PMMA Films Using dopant Oxalic Acid:

The 5 %, 10 %, and 15% of Oxalic acid (dopant) (means 0.125 gm, 0. 25 gm, 0.375 gm) were taken and dissolved in the mixture of 4:1 PS PMMA solution. After getting homogenous solution, the same procedure was repeated to prepare the films. The present study has been carried out with the following samples:

1) PS PMMA + 0% Oxalic acid [4:1 PSPMMA OA(0)]
2) PS PMMA + 5% Oxalic acid [4:1 PSPMMA OA(5)]
3) PS PMMA +10% Oxalic acid [4:1 PSPMMA OA(10)]
4) PS PMMA +15% Oxalic acid [4:1 PSPMMA OA(15)]

Prominent Findings:

1.At constant frequency, Dielectric Constant (ε_r) increases with the increase of temperature. [Fig. 1 (a) to (d)]



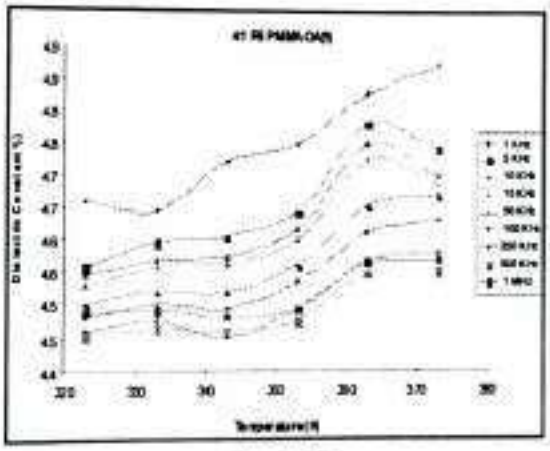


Fig. 1 (b)

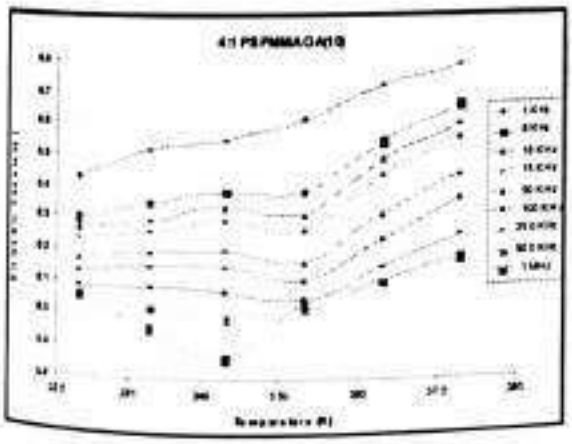


Fig. 1 (c)

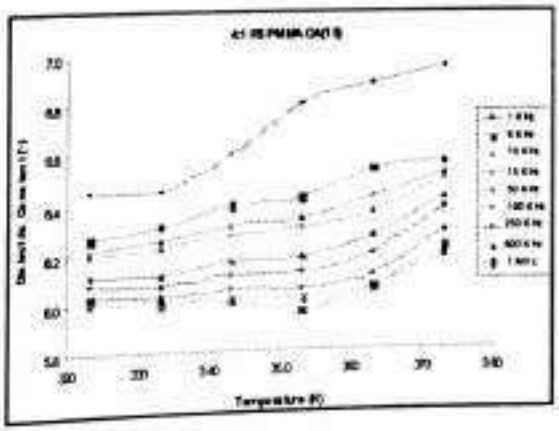


Fig. 1 (d)

Fig. 1 : Variation of Dielectric Constant (ε_r) with temperature at different frequencies for 4:1 PS PMMA OA system

2.At constant temperature, Dielectric Constant (ε_r) decreases with the increase of frequency. [Fig. 2 (a) to (d)]

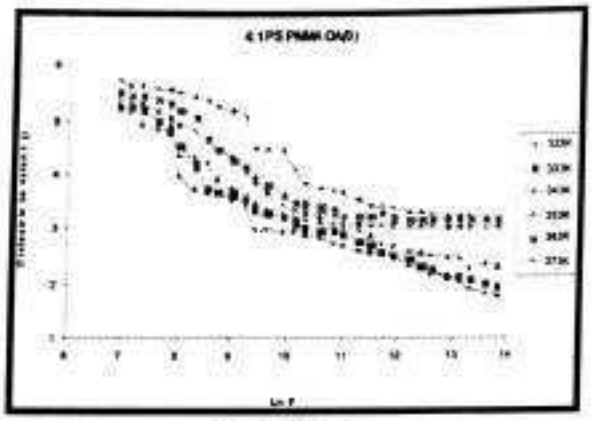


Fig. 2 (a)

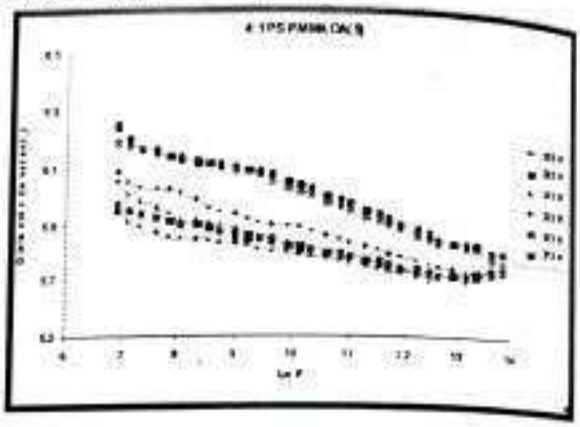


Fig. 2 (b)

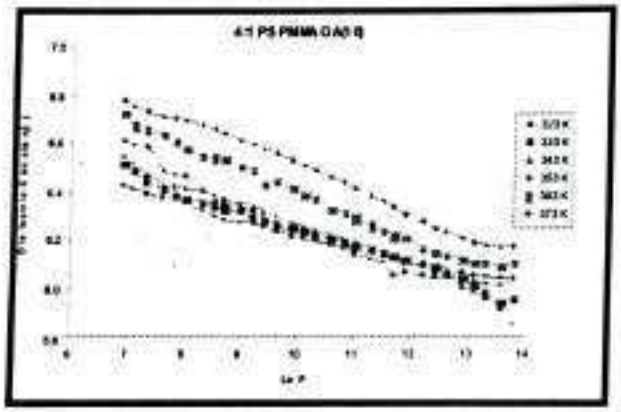


Fig. 2 (c)

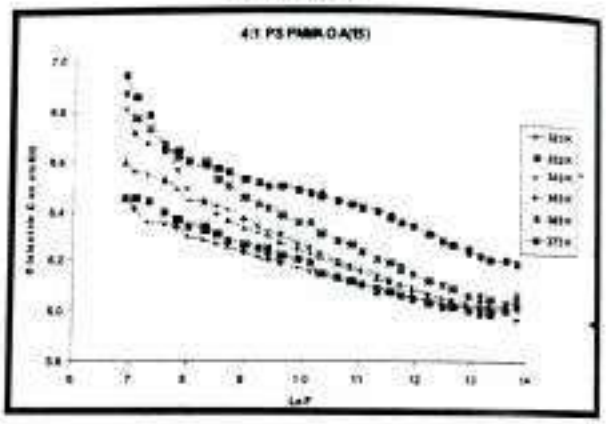


Fig. 2 (d)

Fig. 2 : Variation of Dielectric Constant (ε_r) with frequency (Ln f) at different constant temperatures for 4:1 PS PMMA OA system

3.At constant temperature and frequency Dielectric Constant (ε_r) increases with the percentage of dopant. [Fig. 3 (a) to (c)]

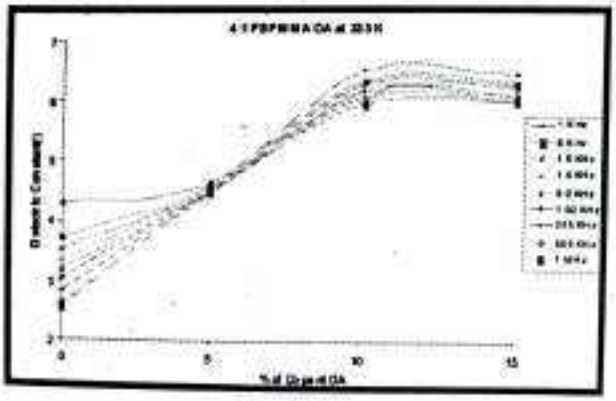


Fig. 3 (a)

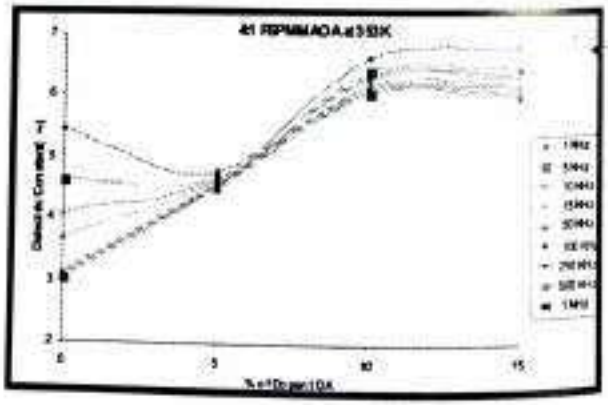


Fig. 3 (b)

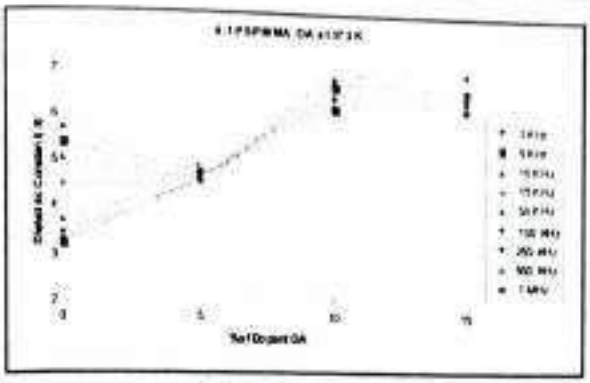


Fig. 3 (c)

Fig. 3 : Variation of Dielectric Constant (ε,) with Concentration of dopant at various frequencies at temperatures (333K, 353 K, 373K) for 4:1 PS PMMA OA system

Discussion of Results:

Effect of frequency and temperature on dielectric constant:

In the present study we have noticed that 1) At constant frequency, Dielectric Constant (ε_r) increases with the increase of temperature. 2) At constant temperature, Dielectric Constant (ε_r) decreases with the increase of frequency. 3) At constant temperature and frequency Dielectric Constant (ε_r) increases with the percentage of dopant.

We have observed that the dielectric constant of our sample decreases with frequency and increases with temperature. This can be explained on the basis of the polarization and polarisability of the dielectric samples as follows:

When a dielectric is introduced in an electric field applied across two plates of a capacitor (two metal electrodes), the polarization of the dielectric takes place. This (polarization) is accompanied by the neutralization of some charges on the plates of the capacitor due to the induction resulting in the increase of the storing capacity of electric field. This arises from two main causes, namely:

a) aligning the polar species in conformity with the applied field.

b) altering the distribution of electric charges of the molecules constituting the dielectric.

The latter process (b) occurs for the polar (**PMMA**) and non-polar (**PS**) species. The effect of high frequency field in (b) is less than that of the slow varying or static fields (except for cases where the field frequency is in resonance with the natural frequency of the molecules).

Thus the dielectric behavior of *a* macroscopic body is due to the dipolar nature of the constituent atoms or molecules. As such, there is a definite link between the macroscopic polarization and the molecular dipole moments.

The microscopic behaviour of a dielectric material such as the doped polyblends **PS-PMMA** under an electric field can be understood from the polarization phenomenon of the charged species which constitute a dielectric or which are introduced during its preparation. These may be extra-nuclear electrons and positively charged nuclei, anions and cat-ions, oppositely charged ionized impurities, charged molecular species, etc.

The oppositely charged species (i.e. having equal and opposite charges) with a reasonable bond (attractive force) between them will form a dipole. This dipole will behave as one unit. These dipoles under an electric field may undergo spatial translational or rotational displacement which will be reflected in the macroscopic behaviour of the dielectric. The polarization effect will also be dependent on the nature of the dipoles and the

frequency of applied electric field.

Dielectric constant or relative permittivity (ε_r) is the ratio of absolute magnitude of the permittivity (ε) of a medium to the permittivity (ε_0) of free space. Or it is also defined as the ratio of the capacitance (C) of the capacitor with dielectric to that of capacitance (C_0) without dielectric. (Keeping the plate dimensions and separation distance same).

$$\varepsilon_r = \frac{\varepsilon}{\varepsilon_0} = \frac{C}{C_0}$$

Thus the increase in dielectric constant is due to the greater freedom of moment of dipole molecular chains within the polymers blends. At lower temperatures as the dipoles are rigidly fixed in the dielectric, the field cannot change the condition of dipoles. As the temperature increases, the dipoles comparatively become free and they respond to the electric field. This causes the increase of polarization and hence the dielectric constant increases with temperature. {H. Frohlick, Theory of Dielectrics, University Press (Oxford 1956), p.13}.

Effect of dopant on Dielectric Constant:

It has been made clear that the addition of dopants Oxalic Acid impart polar character to PS PMMA polyblends. As a result the number of charge carriers and dipoles increases with the increase in the concentration of dopant. Consequently the dielectric constant increases with the dopant concentration.

Conclusions:

For the samples under investigation i.e. blends of 4:1 PSPMMA doped with 0%, 5%, 10% and 15% Oxalic acid:

1) At constant frequency, Dielectric Constant (ε_r) increases with the increase of temperature.

5) At constant temperature, Dielectric Constant (ε_r) decreases with the increase of frequency.

6) At constant temperature and frequency Dielectric Constant (ε_r) increases with the percentage of dopant.

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Effect of UV Radiation Exposure on The Dielectric Constant of Salicylic Acid Doped Polymer Thin Film of PMMA.

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Abstract : The thin films of PMMA, pure and doped with 1%, 3%, 5%, 7%, 9% salicylic acid (SA) were prepared by using isothermal evaporation technique .The measurement of dielectric constant (ε_r) for all above samples have been carried out within the temperature range 323k-363k and at frequencies in the range 1KHz-1MHz.The results reveal that the dielectric constant decreases with the increase in the exposure time of UV radiations. The samples were characterized by XRD, SEM and FTIR

Keywords : PMMA-Polymethylmethacrylate, SA-Salicylic acid, UV- Ultraviolet Radiation.

Introduction:

Low dielectric materials have been intensively researched by ceramic and polymer scientists [1-3] . However, these materials posses a vast myriad of electrical, thermal, chemical and mechanical properties. Therefore, in many cases, the application of low dielectric constant materials are dictated by these other properties and the choice of low dielectric material may have a tremendous effect on a device's performance and lifetime.

Modern ultra-large scale integration (UWI) devices contain 10^8-10^9 transistors in an area smaller than 1 cm^2 and operate at a clock frequency approaching several GHz. As device dimensions shrink, the switching speed of its basic element increases as a consequence of the decrease in carrier's transit time across the length of a transitory channel, Of course, these basic elements must be interconnected to make the ULSI device functional.

As the functional complexity of devices increases, the number of interconnections levels and metal length continue to increase to the extent that an advanced ULSI device may consist of 8-10 levels of metal lines. For this reason, the effective speed of the device is becoming ever more dominated by the signal propagation through the horizontal and vertical metal interconnects of components with various functions. It is here that the resistance (R) and capacity (C) characteristics of the interconnect materials become important. In fact, the rapid increase in RC delay time is one of the main bottlenecks in deep submicron devices. The RC delay is given by

$$RC = 2\rho k\varepsilon_0 = (4L^2/P^2 + L^2/T^2) \quad \ldots\ldots\ldots\ldots (1)$$

ρ – is the metal resistivity, ε_0 is the vacuum permittivity, k is the relative dielectric constant of interlayer dielectric (ILD), P is the metal line pitch (Sum of the line width and line spacing), T is the metal thickness and L is the metal line length. This equation demonstrates that RC delay can be reduced using metals with

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low resistivity and dielectric materials with a low dielectric constant. The introduction of copper and low dielectric const materials has improved the situation as compared with the conventional Al/SiO, technology by reducing both the resistivity and capacitance between wires.

Copper is becoming the common metallization material. Further lowering of the signal delay by introducing low-k dielectrics is one of the main challenges today (Maex et al, 2003). A description of all the problems related to the introduction of copper and low-k dielectrics is beyond the scope of this paper and hence we have limited our discussion to approaches to decreasing the dielectric constant of polymer thin film of PMMA, So that it will act as interlayer dielectric (ILD).

Classically, the dielectric constant of materials is described by Clausius- Mossoti Equation

$$(k-1)/(k+2)=4\pi N\alpha \quad \ldots\ldots\ldots\ldots (2)$$

Where, $k = \varepsilon/\varepsilon_0$

εAnd ε_0 are the dielectric constants of material and vacuum, N is the number of molecules per unit volume (Molecular density) and α is total polarizability, including electronic (α_e), distortion (α_d) and orientation (α_o) polarizabilities. According to equation (2), the dielectric constant of materials can be reduced by decreasing the total polarizability and density. Early generations of low-k dielectrics were obtained by doping the traditional SiO_2 with fluorine and carbon during the chemical vapor deposition (CVD) of the dielectrics which typically have a k value in the range of 3-3.5. Other types of low-k dielectrics are based on organic polymers. Saturated hydrocarbons have a lower polarizability than unsaturated conjugated and aromatic hydrocarbons. Most of the organic low-k films with sufficient thermal stability have dielectric constant close to or in the range of 2.6-3.0. Decreasing the density produces a further reduction in the dielectric constant. Therefore, ultra low k dielectrics with k less than 2.6 must be porous[4].

In this paper, we have discussed the effect of UV radiation on dielectric constant of salicylic acid doped polymer thin films of PMMA. Especially we have focused on lowering dielectric constant of thin films for the development of microelectronic devices based on low dielectric constant polymer films. For this purpose weight of PMMA in all sample remains fixed and salicylic acid doped at different weight percentage, so that we can find the optimum percentage ratio of SA that exhibits lowest dielectric constant value.

2. Experimental Procedure:

2.1 Materials:

In this study, PMMA (Sigma Aldrich), dopant salicylic acid (SA), and solvent THF (J.T. Baker) were used without further purification. Isothermal evaporation technique [5-8] was used to prepare the thin films of polymer.

2.2 Preparation of thin films:

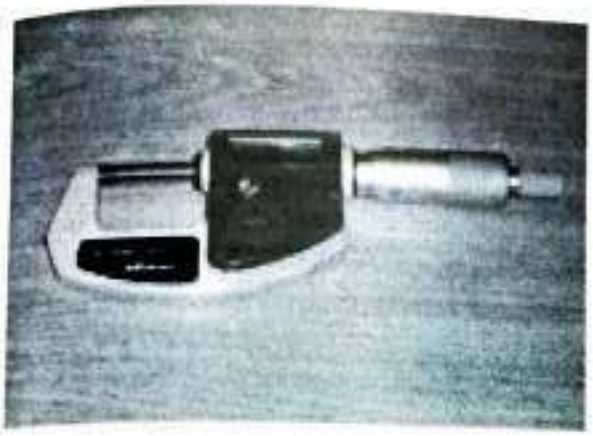
1gm. PMMA was dissolved in THF (Tetrahydrofuran), and doped with salicylic acid in different weight percentage (1%, 5%, 6%, 7%, and 9%). The solution was cast on a glass plate and was allowed to evaporate slowly. This process has produced a mechanically stable and a free standing thin film.

2.3 UV Irradiation

A low pressure mercury vapor lamp (TUV 30W, Philips, Holland), which emits radiation at 254 nm, was used. The intensity of the incident light was 24 W m^{-2}. Films of the same thickness and surface area were placed at 15 cm distance from the light source. Irradiation times were for 0, 5, and 10 minutes. All irradiations were performed at room temperature in air.

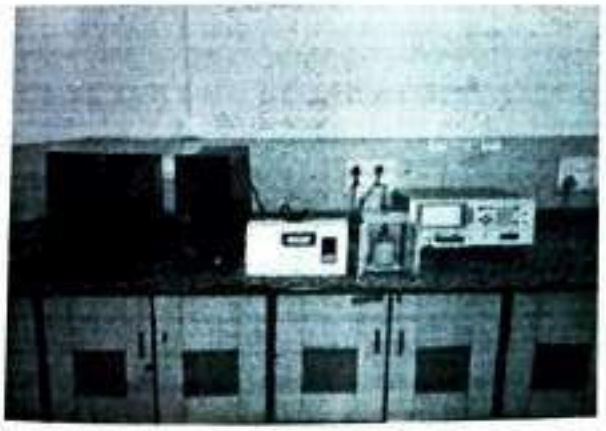
2.4. Thickness Measurement:

The thickness of the film was measured by digital micrometer (Mitutago Corporation, Japan)



2.5 Dielectric constant measurement:

The AC conductivity of the samples was determined by 4284 A precision LCR meter over the frequency range 20 H_z to 1MH, supplied by Agilent Technology, Singapore and corresponding dielectric constant (ε_r) was measured in the temperature range 323 K- 363K.



2.6 Characterization

2.6.1 X-ray diffraction (XRD)

The amorphousity of polymer thin films was investigated using XRD. The XRD pattern were recorded on Siemens D 5000 diffractometer with Cu-K α radiation (λ=1.54060A) over the range of 2θ=10°-60° at ambient temperature.

2.6.2 Scanning Electron Microscopy (SEM)

The morphology of polymer thin films at room temperature was studied by SEM.

2.6.3 FTIR Study:

To study the structural changes including the alteration in position and intensity of the characteristic bands Fourier Transform Infrared (FTIR) spectroscopy using Shimazu FTIR spectrophotometer 8300) over the range 400- 4000 cm-1 was used.

2.7. Prominent findings

Dielectric constant

i) decreases with increase in frequency at different constant temperatures.

ii) increases with increase in temperature at different constant frequencies

iii) decreases with increase in dopant percentage at constant temperature and constant frequency

iv) decreases with increase in time of exposure to UV radiation at constant temperature, frequency and dopant percentage.

3. Results and Discussion

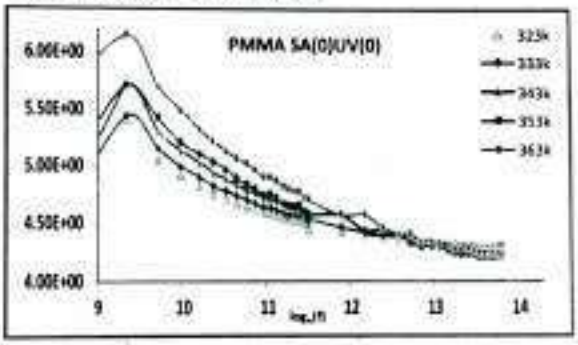


Fig 1: Variation of dielectric constant with log f at different constant temperatures

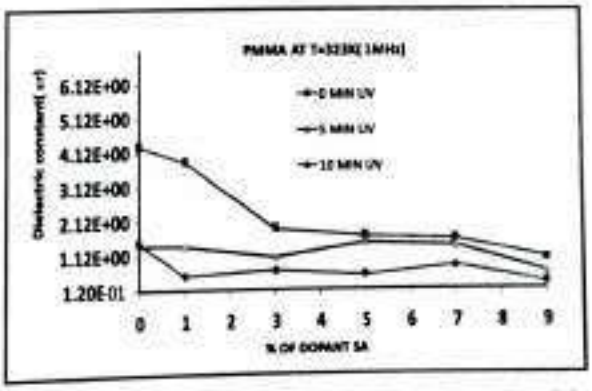


Fig 2: Variation of dielectric constant with percentage of dopant at increasing time of exposure to UV radiation

From fig.1 it is clear that dielectric constant decreases with the increase in frequency and increases with the increase in temperature. This can be explained as PMMA is weakly polar polymer[9] under alternating electric field, polar polymers require some time to align the dipoles. At very low frequencies the dipoles have sufficient time to align with the field before it changes direction. At very high frequencies the dipoles do not have time to align before the field changes direction. At intermediate frequencies the dipoles move but have not completed their movement before the field changes direction and they must realign with the changed field. The electronic polarization and to some extent atomic polarization, is instantaneous, at high or low frequency for both polar and non polar polymers. Therefore, polar polymers at low frequencies (e.g. 60 Hz) generally have dielectric constants of between 3 and 9, and at high frequencies (eg 1MHz) generally have dielectric constants of between 3 and 5. So as frequency increases, the orientational polarization decreases since it takes more time than electronic and atomic polarization .This decreases the value of dielectric constant with frequency reaching a nearly constant value at high frequency. The motion possibly occurring in amorphous material in the order of increasing temperature are: side chain motion, motion of two four moieties in the main chain (The Schatzki Cruck shaft effect), motion of moieties containing hetero atoms in polymer chain, motion of segments containing 50-100 backbone atoms (corresponding to Tg) and motion of the entire chain as a unit (Seanor1982). These motions are responsible for the freeing of change carriers and assisting the orientation of polar species as per the variation in the direction of applied AC electric field of constant frequency. The total polarization of the sample arises from the electronic polarization, atomic or ionic polarization and orientation polarization. Among these three contributions; orientation polarization is greatly assisted by the increase of temperature. This result is in agreement with those reported in the literature [10-12]. The dielectric polarization results from molecular dipoles [13,14] ,which remain frozen at lower temperature and attains rotational freedom at higher temperature ,when the effect of molecular interaction energy becomes weaker than that of the thermal energy [13] .Therefore dielectric constant increases with temperature.

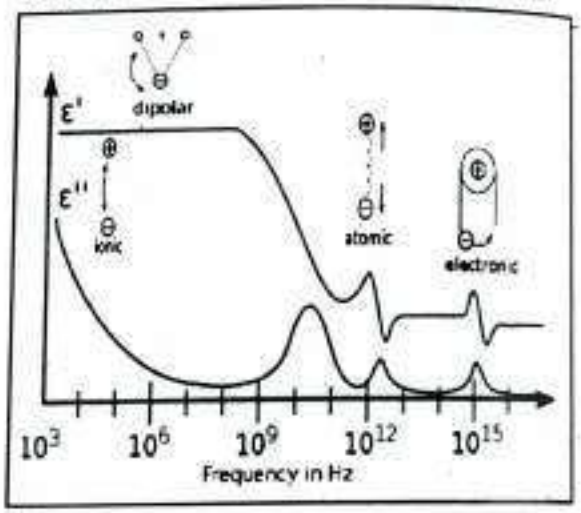


Fig 3 Dielectric constant and loss dispersion of dielectric materials against frequency.

The dielectric constant gets decreased with the increase in dopant percentage (Fig 2). As the dopant salicylic acid has –OH and –COOH groups ortho to each other, both these groups have tendency to release their hydrogen atoms as H^+ ions and the –COO group is electron hungry segment of PMMA that attracts the electrons present in C-CH and O-CH,bonds towards itself. As a result of this, a drift of electrons from nearby bonds starts flowing towards the COO group that imparts polarity in the parent molecule. But due to proximity and availability of electron rich centers within the molecule, the H^+ ions of Salicylic acid tend to form intramolecular hydrogen bonding. As a consequence of this, dopant salicylic acid remains unmoved. Under vigorous conditions, these H^+ ions may get departed partially but it is difficult to break their association completely from parent molecule. In this situation if we go on increasing the percentage of doping that may

enhance the complexity due to which the dielectric constant gets decreased with the increase in dopant percentage.

From fig 2 it is clear that, before irradiation value of dielectric constant is in the range of 4.3-1.03. After irradiation the value of dielectric constant is in range 1.5-0.64 for 5 min irradiation and for 10 min irradiation value is in the range of 1.5- 0.30.This means the dielectric constant gets decreased with the increase in time of exposure and the rate at which the dielectric constant decreases also becomes higher with the increase in time of exposure. This can be explained as; the bonds between the atoms in many polymers have dissociation energies that are very similar to the quantum energy present in UV radiation which is capable of breaking the bonds in the polymer chain to generate a cascade of reaction, oxygen radicals, hydro peroxide unit's carbonyl group formation, chain cleavage. As a result, the polarization group may get reduced and dielectric constant gets decreased as shown in fig (2)[15].Also the evaporation of THF solvent during the preparation of thin film may have led to the formation of pores in the thin film[16]. It should be emphasized that the formation of porous film follows the principle of phase separation. In this principle one phase is induced to create the matrix and the other (i.e. solvent) to create convex surface shapes, which can be removed to leave free space by evaporation. Decreasing the density produces a further reduction in the dielectric constant. Therefore, ultra low k dielectrics with k less than 2.6 must be porous [17]. So from above explanation, we can say that after exposure the porosity in film gets increased [18] .But lowest value of dielectric constant observed for PMMA SA (9) at 5 and 10 min exposure is 0.60 and 0.30 which is very less than dielectric constant of air .As reported by Mikaail Ballanov et al, the material with dielectric constant less than 2.6 must be porous and materials with dielectric constant less than one is called metamaterials (Dixon 2012). These materials are made with high dielectric inclusions with specific shapes and sizes in a lower dielectric matrix.

So here we conclude that, the dielectric constant of material can be reduced by doping with salicylic acid and increasing time of exposure to UV radiation and with increase in time of irradiation the porous material becomes to metamaterials.

The FTIR spectra of PMMA shows the presence of C=O stretching at 1064cm^{-1} confirms the presence of ester moiety. The bend for CH_2 is observed at 1442cm^{-1} also for CH_3 at 1367cm^{-1}.The sp^3 C-H stretching has been observed at 2854cm^{-1} .The IR spectrum of PMMA SA (3) and PMMA SA (9) shows the C=O stretching at 1612.49 cm^{-1}.The SEM photographs (Fig 5) shows the amorphous nature of PMMA SA (0), PMMA SA (3), PMMASA (9) which is in agreement with XRD results (Fig 6)

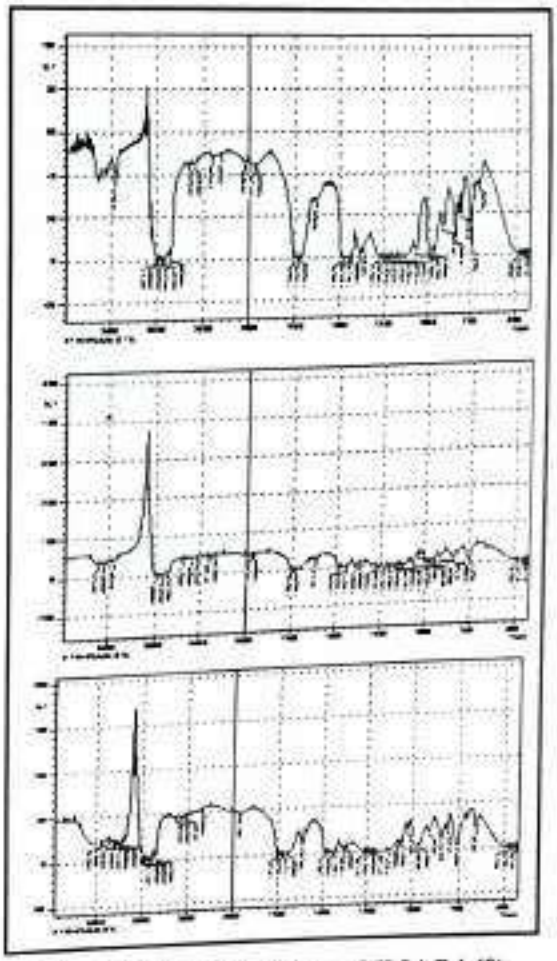


Fig 4: FTIR spectra of a) PMMA SA (0) b) PMMA SA (3) c) PMMA SA (9)



Fig 5: SEM images for a) PMMA SA (0) b) PMMA SA (3) c) PMMA SA (9)

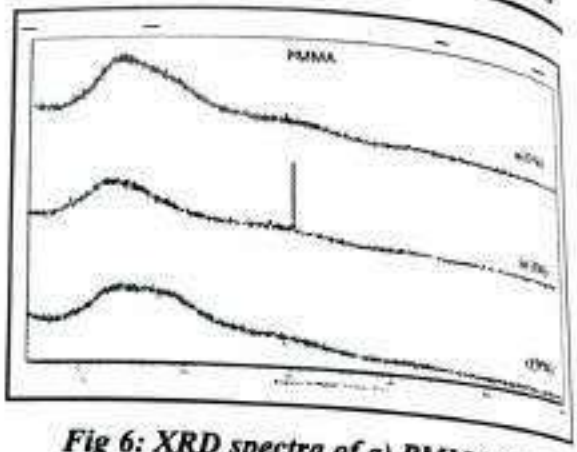


Fig 6: XRD spectra of a) PMMA SA (0) b) PMMA SA (3) c) PMMA SA (9)

4. Conclusion:

The dielectric constant of thin films of PMMA, pure and doped with salicylic acid at different weight percentage, can be reduced by doping with salicylic acid and by exposure to UV radiation so that it can be used as interlayer dielectrics in microelectronic devices.

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Temperature and Electric Field Dependence of DC Electrical Conductivity of 4:1 PVC-PMMA Polyblend thin films doped with Cinnamic Acid.

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Abstract : DC electrical Conductivity of Cinnamic Acid doped **4:1 PVC- PMMA** has been investigated as a function of i) Electric Field ii) Temperature and iii) Concentration of Cinnamic Acid (CA) used as a dopant. The Current – Voltage (I-V) measurements were carried out by applying the voltages ranging from 50V to 800V at various constant temperatures viz. 323 K, 333 K ,373 K. Films prepared by using Isothermal Evaporation Technique consisted of two commercial grade polymers PS and PMMA in the weight ratio 1:1. The weight percentage of dopant was 0%, 5%, 10 %, 15 %. The conductivity has been found to increase with electric field, temperature and also the concentration of dopant.

Keywords: Polymethyl Methacrylate (PMMA), Polystyrene (PS), Tetrahydrofuran (THF), Cinnamic Acid(CA)

1. Introduction

The d.c. electrical conductivity studies are aimed at understanding the origin of the charge carrying species, their numbers and ways in which they move through the bulk materials. These parameters are related with the morphology, microstructure and chemical compositions of the materials (Seanor, 1982). For thin films, the mechanisms generally discussed are tunnelling (Ochiai, Maeda, Ogawa *et al.*,1993), Schottky (Thomas, Pillai and Jayalakshmi, 1988: Mujairi and Kondo, 1991), Poole-Frenkel emission (Rao, Rao KVS, Reddy *et al.*, 1991: Bahri and Seth, 1997) and Space Charge Limited Conduction (SCLC) (Sessle, Hahn and Yoon, 1986). The depolarising current increases with the increase in the percentage of PMMA (Keller, Dubey and Datt, 1991).

The electrical properties of thermoplastics are measured to determine performance capability in electrical properties (Mark *et al.*,1985). Materials such as polyethylene, polystyrene find an extensive usage as an electrical insulator (Goosey, 1985). PS is a non-polar, low loss polymer and hence has desirable electric properties for the use in the insulation (Chutia and Baru, 1981). PMMA is hard, rigid, transparent thermoplastic, which has good weatherability. PMMA is weakly polar (Blythe, 1979). The blends PS/PMMA doped with iodine (Belsare and Deogaonkar, 1998) and PNA (Waghmare *et al.*, 2007) have been studied earlier. The present study is aimed at finding the effect of percentage of dopant Cinnamic Acid (CA) on the dc electrical conductivity of PVC-PMMA polyblend thin films by applying electrical field in the range 50V-700V at various thermostatically controlled temperatures in the range 323 K -373 K.

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2. Experimental:

2.1 Sample Preparation:

The Polyvinylchloride (PVC) of commercial grade and Poly Methylmethacrylate (PMMA) were used for the present study. The two polymers were taken in the ratio 4:1, were dissolved in the common solvent Tetrahydrofuran (THF). The solution was kept for 3-4 days to allow polymers to dissolve completely to yield uniform solution. The solution mixture was poured on a perfectly plane glass plate kept floating freely in a pool of mercury for perfect levelling. Then the solvent was allowed to evaporate in air at room temperature. In this way the films were prepared by isothermal evaporation technique (Narayan and Singh, 1987: Bahri and Sood, 1983). Further it was dried for 3 days to remove any trace of solvent. The dry film was removed from the plate and then it was coated with silver paint. The Cinnamic Acid doped blend films have been prepared by taking CA in the percentage weights 5%, 10%, 15%. The films were prepared by using the same technique and were subjected to outgassing described above. The present study has been carried out with the following samples:

1) PVC PMMA + 0% Cinnamic acid [4:1 PVC-PMMA CA(0)]
2) PVC PMMA + 5% Cinnamic acid [4:1 PVC-PMMA CA(5)]
3) PVC PMMA +10% Cinnamic acid [4:1 PVC-PMMA CA(10)]
4) PVC PMMA +15% Cinnamic acid [4:1 PVC-PMMA CA(15)]

2.2. Measurement of DC Electrical Conductivity:

The thin film sample prepared by using isothermal evaporation technique, was coated with the silver paint and then loaded into the sample holder(Fig.) which was kept in thermostatically controlled oven. The DC voltage was applied (in the range 50 V-800 V) across the sample by using highly regulated DC power supply (model EHT-111). The corresponding DC current was measured by using digital pico-ammeter (model DPM-111). Such current – voltage (I-V) measurements were taken at different constant temperatures (323 K, 333 K, 343 K, 353 K, 363 K, 373 K.) From these measurements the DC conductivity for all the samples was calculated.

Results and Discussion:

As stated earlier, the DC Conductivities of each of these Samples have been investigated by carrying out current- voltage (I –V) measurements at various constant temperatures: 323 K, 333 K, 343 K, 353 K, 363 K, 373 K.

The DC currents were recorded at each of above constant temperatures by applying the DC voltages: 50 V, 100 V, 150 V,800 V.

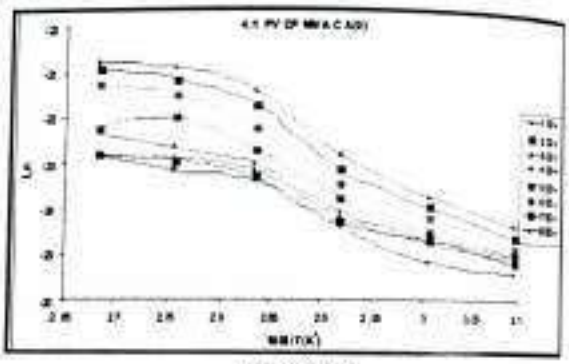


Fig.1 (a)

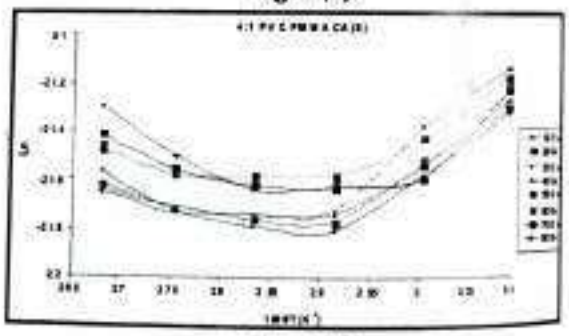


Fig.1 (b)

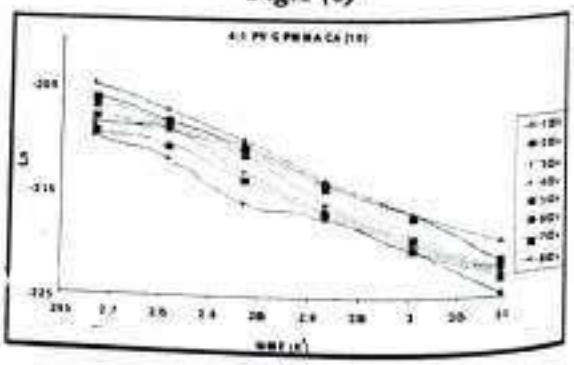


Fig.1 (c)

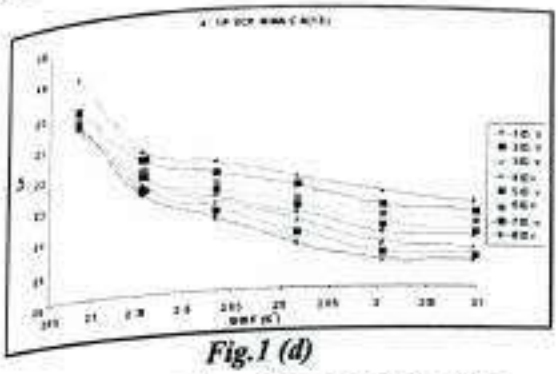


Fig.1 (d)

Fig. 1: Variation of Conductivity with Temperature at different constant voltages for 4:1 PVCPMMA CA system{Arrhenius Plot}

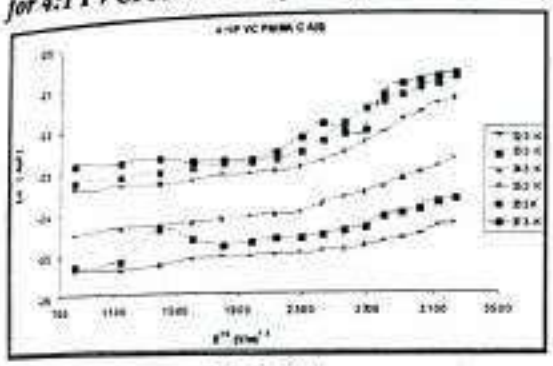


Fig.2 (a)

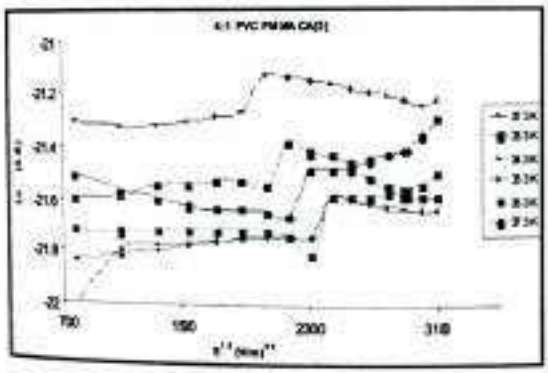


Fig.2 (b)

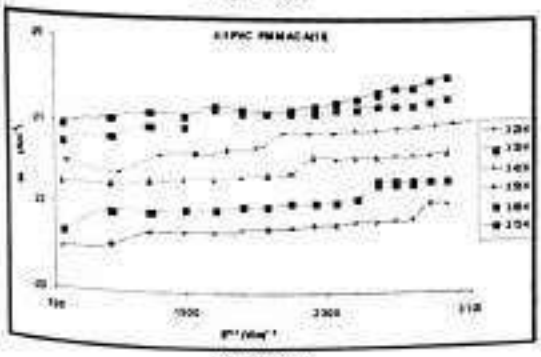


Fig.2 (c)

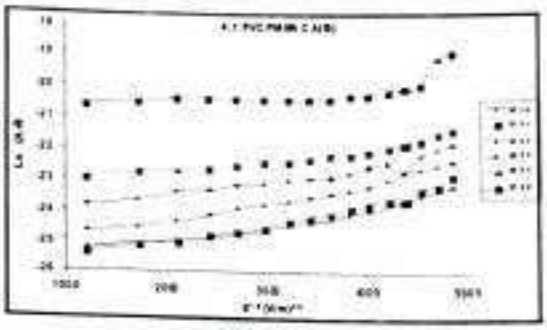


Fig.2 (d)

Fig. 2:Variation of Conductivity with $(E)^{1/2}$ at different constant Temperature for 4:1 PVCPMMA CA system {Poole- Frenkel mechanism}

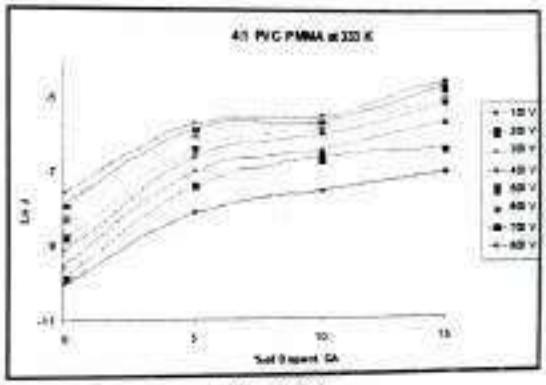


Fig.3 (a)

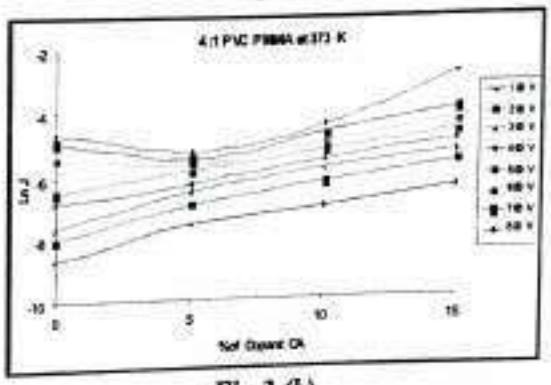


Fig.3 (b)

Fig. 3: Variation of Current density (Ln J) with Concentration of dopant CA at various voltages at temperatures(333K,373K) for 4:1 PVC PMMA CA system

Prominent Findings:

On the basis of the analysis of the results, the prominent findings of this part of the study can

be summarized as under:

1) The electrical conductivity (σ) increases with the increase in temperature at every applied voltage. Fig 1:(a) to (d)

2) The Increase in electrical conductivity (σ), shown in the following results from 1) Increase in Electric Field, 2) Increase in Temperature, 3) Increase in percentage of Dopants Cinnamic Acid. Fig 2:(a) to (d) Fig 3:(a) and (b)

Discussion of Results:

In case of PVC PMMA polyblend, the conductivity undergoes almost similar variations with respect to temperature, voltage and dopant (Cinnamic Acid) concentration.



Structurally Polyvinyl Chloride (PVC) molecule is syndiotaetic so it has low Crystallinity. It is relatively unstable to heat and light. Thermal initiation involves loss of chlorine atom adjacent to some structural abnormality which reduces the stability of C-Cl bond. A hydrogen atom forms HCl. The resulting chain radical then reacts to form chain unsaturation with regeneration of chlorine radical.

PVC PMMA is commercial copolymer combination having more solubility and workability. The addition of Cinnamic acid as a dopant in the PVC PMMA polymer blend may provide a new site for chlorine exchange. An unsaturated substituent of Cinnamic acid easily add-up to PVC which liberate chlorine. Similarly the carboxylic proton with its natural affinity reacts with chlorine radical to form HCl molecule which, under the influence of heat or UV light, regenerates chlorine radical. This process of formation of HCl molecule and regeneration of chlorine radical continues till the removal of external energy disturbances.

Liberated chlorine and hydrogen from PVC and Cinnamic acid respectively have natural fascination towards carbonyl group of PMMA molecule. With this interaction, several reactive sites come into force to create new oppositely charged associations. As a result of this, there is a great possibility of increase in conductivity with temperature.

Khan *et al.* (2008) carried out the Viscometric Study of PSPMMA and PVC PMMA systems. Their Study reveled immiscibility for PS PMMA miscibility for PVC PMMA. Their findings from FTIR spectroscopy suggested specific interaction between PVC and PMMA. The results of FTIR spectroscopy carried out in the present work are in agreement with the above findings.

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Investigation of Temperature Dependence of Electrical Conductivity of PVAC-PPy-CrCl3 Composite Polymer Film

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Abstract : PVAC-PPy-CrCl, composite polymer thin film prepared by using isothermal evaporation technique. The electrical conductivity measurements were taken at different constant temperatures (313K, 323 K, 333 K, 343 K, 353 K, and 363 K). The current density, electrical conductivity was increases with temperature. The enhancement in electrical conductivity is due to mobility of free charge carriers. The current- voltage relation obeys the Ohm's law.
Keywords: Polypyrrole, Polyvinyl acetate, electrical conductivity.

1. Introduction:

In this present work our aim is to determine electrical conductivity of PVAC+PPy and to study variation of conductivity with the doping of CrCl3.

Over the years, electrical application of polymers has been extensively explored. Traditionally the electrical applications of polymers have been as an electrical insulation and therefore major emphasis has been placed on the study of properties which help polymers act as passive electrical elements. But in recent times highly conducting polymers materials have been discovered. There are polymeric materials, which exhibit piezoelectric and pyroelectric properties too. Such materials have the potential to act as active elements. There has been the major stress worldwide to explore non-conventional energy sources, and finding ways of exploring solar energy has been major feature of human endeavour to meet the growing energy requirements of the mankind. Consequently there has been a developing need for large area photoactive materials that converts the solar energy into the usable electrical energy. Polymers, being disordered materials, have some unique properties that are based upon them. The capability is being utilized as active electrical elements.

Among all of them, polypyrrole (PPy) has obtained much interest due to its properties such as good processability, relatively high conductivity, cheap and commercially available. One of the approaches that have been used by global researchers to improve the limitation of PPy is by introducing PPy in polymer matrix making as composite polymer. The examples of well- known matrices that have been studied include polyvinyl acetate (PVAc), polyvinyl alcohol (PVA), Polymethyl methacrylate (PMMA) and Polyvinyl chloride (PVC). Polypyrrole is a heterocyclic polymer (-C4H4NH-) n which has attracted great attention due to its high electrical conductivity and good environment stability and relative ease of synthesis. During the last two decades there have been a lot of research works in the literature about the preparation of the polypyrrole (PPy)-polymer composite or blend coatings by chemically repared [1]. In general, electrochemically deposited PPy composites films show a high electrical conductivity, whereas the chemically prepared PPy blends are less co[illegible] transparent. As for the

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host polymers, several well-known polymers have been used in the chemically prepared PPy composite materials, such as polymethyl methacrylate [2], rubber [3], poly(styrenebutyl acrylate- hydroxyethyl acrylate) [4], polyvinyl alcohol [5], polyvinyl acetate [6] and polyethylene oxide [7]. Polypyrrole (PPy) is a poly conjugated polymer that is one of the most frequently used and studied polymers owing to its suitable properties and easy preparation. PPy can be prepared by chemical or electrochemical oxidation of pyrrole in various organic solvent and in aqueous Media [8-12]. The preparation conditions and various additives introduced into reaction mixture influence the properties of final conducting polymer [13-14]. The properties of fabricated conducting polymers are strongly dependent on the preparation conditions and various additives introduced into reaction mixture [14,15].

The incorporation of polymer matrices significantly changes their physical properties, which make the samples more resistive to chemicals, ambient and physical action. PVAc has been the main focus to be used as matrix because it is water soluble, good polarity and good mechanical strength. However, the transport properties in which related to free charges become more complicated as the system becomes disordered. Polarons is a defect as a result of doping encompasses reaction between pyrrole monomer and dopant whereas free ions come from dopant which does not take place upon polymerization of polypyrrole. Therefore, it is recognized to use dc conductivity for quantifying and investigating the disordered composites system. The ariation of temperature can provide more detail on the behaviour of charges and ability to enhance the electrical conductivity. In this paper, the dc electrical conductivity of the blend of polypyrrole doped with chromium (III) chloride in PVAc matrix at different temperatures has been studied. The results cover direct current (dc).

2. Method of preparation of pure film:

A solution containing 0.6g of PVAC in 100ml distilled water was prepared by constant stirring and heating the mixture up to 95°C for an hour. Then the mixture was left to cool down to laboratory temperature while the stirring of the mixture was carried out to ensure a homogenous composition.

3. Method of preparation of doped film:

PVAC and polypyrrole (PPy), supplied by Fluka, were used and pyrrole was distilled for purification prior to use. Reagent Chromium (III) Chloride (CrCl3) (99% purity) supplied by Riedel de Haen was used as received. The sampling process was carried out at room temperature (27°C).

A solution containing 0.6g of PVAC in 100 ml distilled water was prepared by constant stirring and heating the mixture up to 95°C for an hour. Then the mixture was left to cool down to laboratory temperature while the stirring of the mixture was carried out to ensure a homogenous composition. From the cooled mixture, 30 ml was taken and was mixed with 0.67 ml polypyrrole in 15 ml of distilled water and stirred for 5 minutes at the room temperature in order to get homogenous solution. Finally, 4.8gm of CrCl3 was added in the mixture and stirred for 10 minutes. The concentration of dopant is 0.01 mol. concentrations.

The solution was then poured into a casting glass plate 14cm×14cm and dried at the room temperature for ca.120 hours. After drying, the composite polymer films were stripped from the plate and cut into 4cm × 4cm pieces for electrical conductivity. The reaction mechanism to form PVAC-PPy-CrCl3 composite is shown below (this mechanism is proposed by Benseddik and his co-workers in 1995):

$nC_4H_4NH(PVAC)+2.25nCrCl_3 \; C_4H_4N^{0.25}+Cl^{0.25}]$

$n(PVAC)+2nHCl+2.25nCrCl_3(H_2O)$

4. Results:

1. V- (Voltage) V
2. I- (Current) Amp.
3. R- (Resistance) Ohm
4. E- (Electric field) = V/d, Volts/cm
5. P- (Specific resistivity) σ=AR/d (Ωcm)

6. σ- conductivity (Mho cm^{-1})
7. J- current density (J) = I/A (Amp cm^{-2})

In order to present the result we should consider the nature of graph.

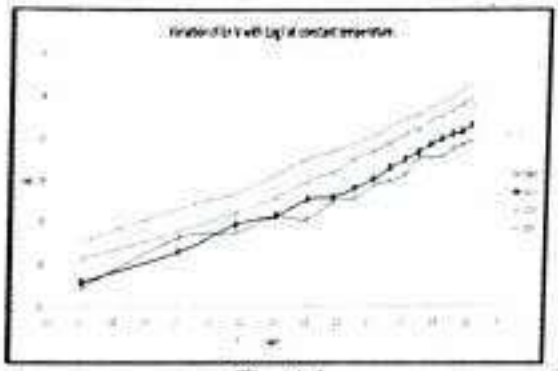


Fig. A.1

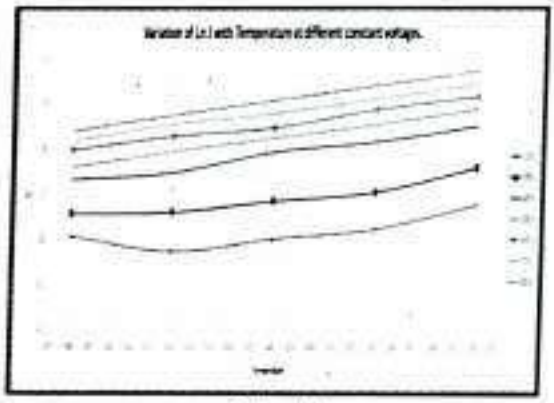


Fig. A.2

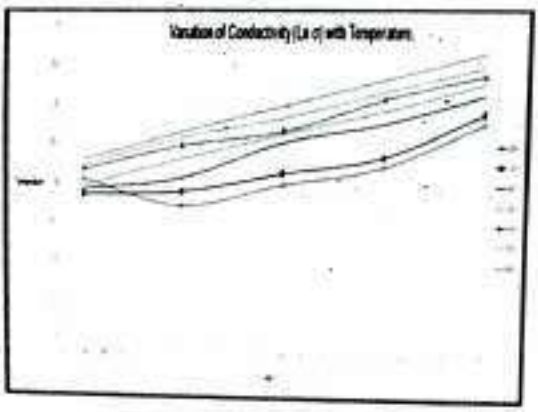


Fig. A.3

Fig. A.1, Fig. A.2, Fig. A.3 shows the results of pure material i.e. (PVAC+PPy).

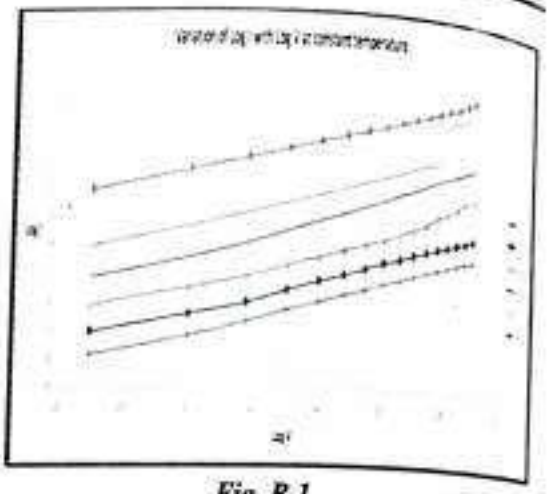


Fig. B.1

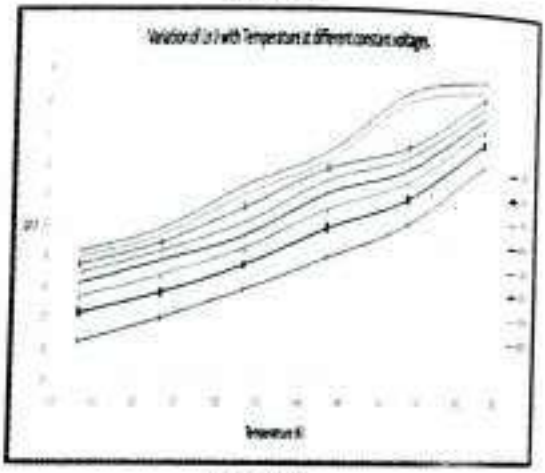


Fig. B.2

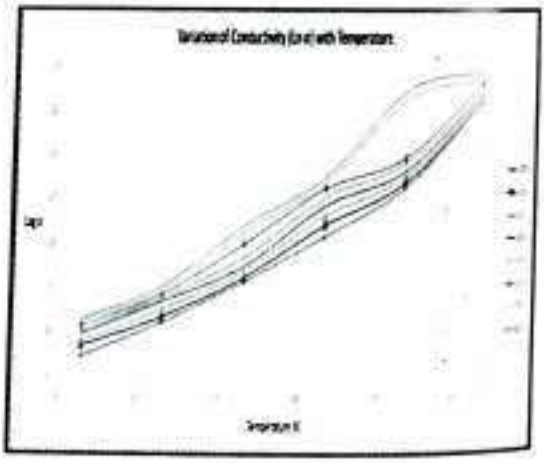


Fig. B.3

Fig. B.1, Fig. B.2, Fig. B.3 shows the results of doped material i.e. (PVAC+PPy+CrCl).

5. Discussion:

From Fig. A.1 and Fig. B.1 it is revealed that as we increase the voltage, current I also increase linearly at constant temperature i.e. it obeys Ohm's law.

From Fig. A.2 and Fig. B.2 it is revealed that current density of material increases with increasing temperature.

From Fig. A.3 and Fig. B.3 it is revealed at high temperature conductivity of PVAC bearing high value due to negative temperature coefficient of resistance while as temperature goes on decreasing then conductivity also decreases.

6. Conclusion:

Extensive study on temperature dependence of dc electrical conductivity of PVAC+PPy+CrCl3 had been carried out. The dc conductivity increases with the increment of temperature. An increase of the values of the dc electrical conductivity is driven by mobility of free charges (i.e. polarons and free ions) as temperature is increased. It becomes more conductive as the temperature applied was increased. This finding is confirmed with the gradual increment of values of the dc electrical conductivity obtained from different temperatures.

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The Study of Molecular Interaction of Proton Polymer Electrolytes Using Ultrasonic Technique

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ABSTRACT : The Ultrasonic velocity, density and viscosity have been measured for aqueous electrolyte solution of ammonium acetate. The samples were prepared by using different concentration of ammonium acetate doped with polyvinyl alcohol. These experimental data have been used to estimate the physical parameter such as adiabatic compressibility, free path length, internal pressure, relaxation time, acoustic impedance, Gibb's free energy for the aqueous electrolyte solution. The strength of intermolecular interaction between component of liquid have been successfully investigated by ultrasonic method.

KEYWORDS: PVA solution, ultrasonic velocity, Acoustic parameters.

INTRODUCTION

Polyvinyl alcohol is a water soluble polymer. It is used to study the physical parameter of polymer polyvinyl alcohol in solvent distiled water. Ultrasonic is a versatile nondestructive technique and powerful tool for characterization of various acoustic parameters of solution of different concentration [1, 2, 3]. Acoustic parameters provide the information to understand the solute-solvent interaction in proton conducting polymer electrolyte solution [4]. The development of molecular sciences with the help of intermolecular interaction. In this work, we have studied important acoustic parameter like adiabatic compressibility, free length, internal pressure, relaxation time, acoustic impedance, Gibb's free energy of proton conductor PVA solution at different concentration. The ultrasonic velocity and their related acoustic parameters were provides information to understand the molecular interaction in proton conductor polymer blend.

Materials and methods:

Polyvinyl alcohol was procurred from merck and the Aq. Polyvinyl alcohol mixture were made with masses weigh by analytical balance. Distilled water was use as a solvent. Similarly the aq. Solution of ammonium acetate was prepared. As polyvinyl alcohol has remarkably slow rate of dissolution in water at room temperature. Therefore it is warming up with continuous stirring and obtained one phase solution. After cooling solution were weighed again and evaporated water in the process of warming up were compensated by adding the distilled water similarly the Aq. solution of ammonium acetate was prepared. As per weight percentage sample were mixed and prepared the sample of 10%, 20% and 30% concentrated of ammonium acetate with polyvinyl alcohol. In the present study the physical parameter of polymer electrolyte solution were studied by using ultrasonic technique.

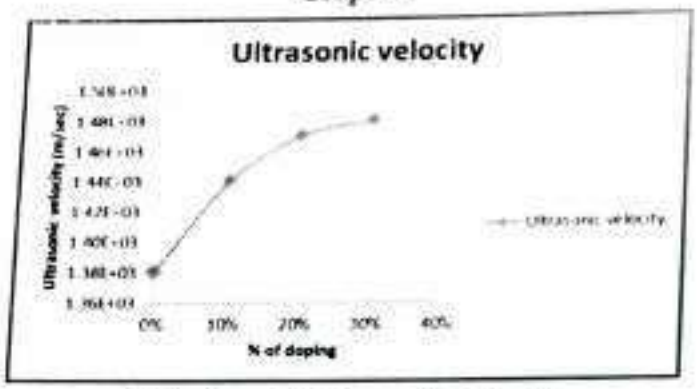
Result and Discussion

The experimental value of ultrasonic velocity, density and viscosity for the binary solution of polyvinyl alcohol and ammonium acetate are given in Graph 1, 2, 3.

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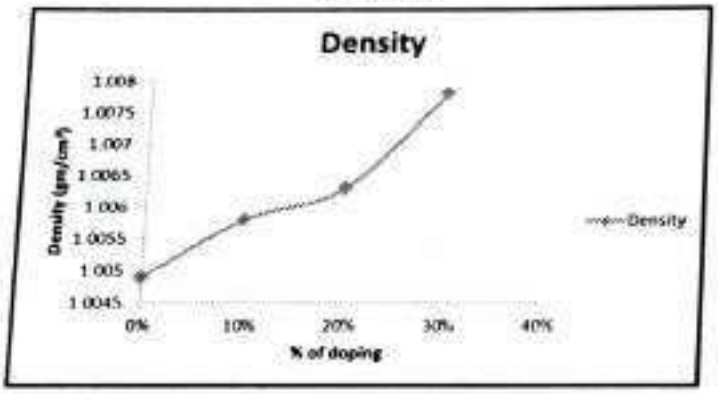
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Graph-1



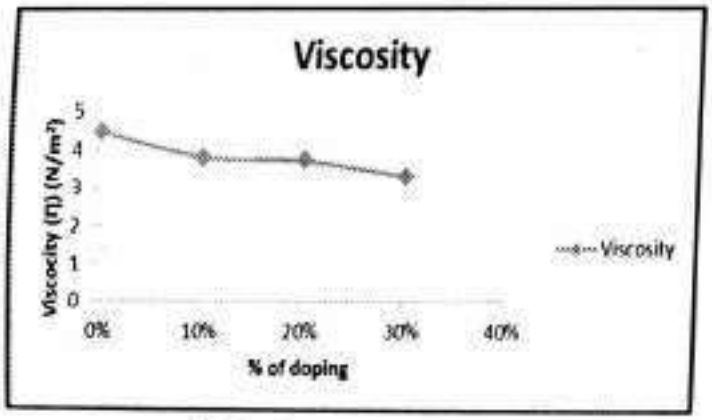
Variation of ultrasonic velocity with % of doping

Graph-2



Variation of density with % of doping

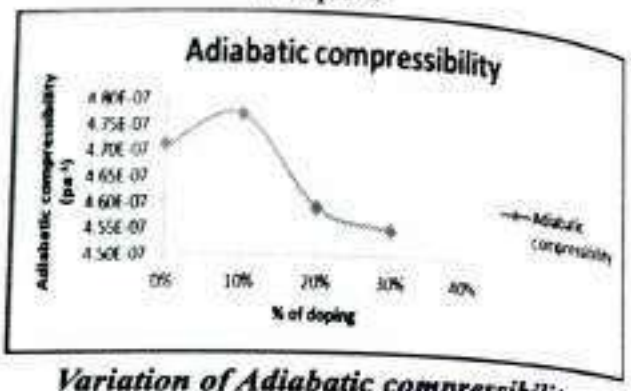
Graph-3



Variation of viscosity with % of doping

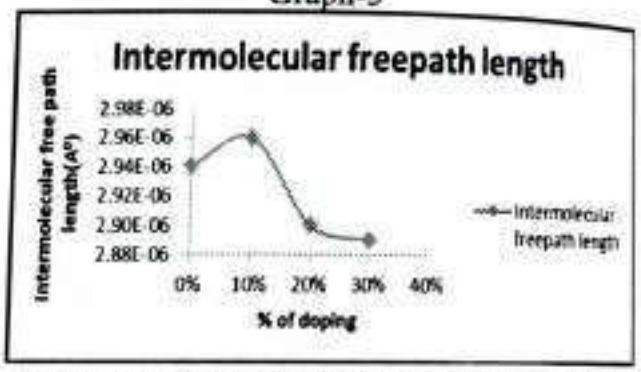
The graph of the adiabatic compressibility, Intermolecular free path length, Free volume, Acoustic Impedence , Relaxation time , and Internal pressure are given

Graph-4



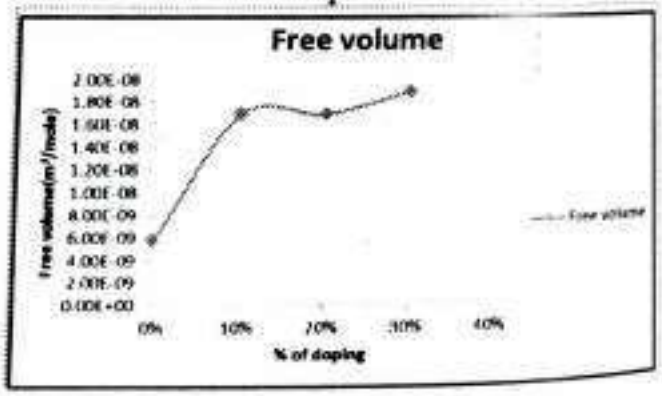
Variation of Adiabatic compressibility with % of doping

Graph-5



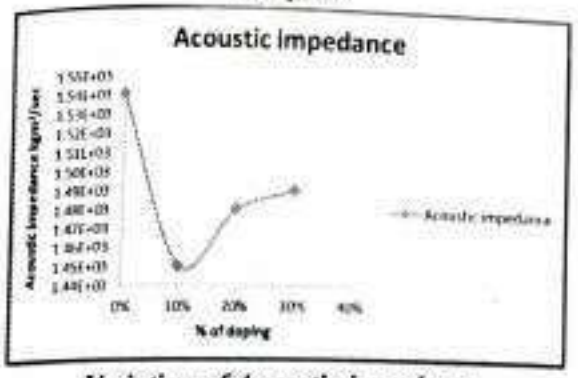
Variation of intermolecular free path length with % of doping

Graph-6



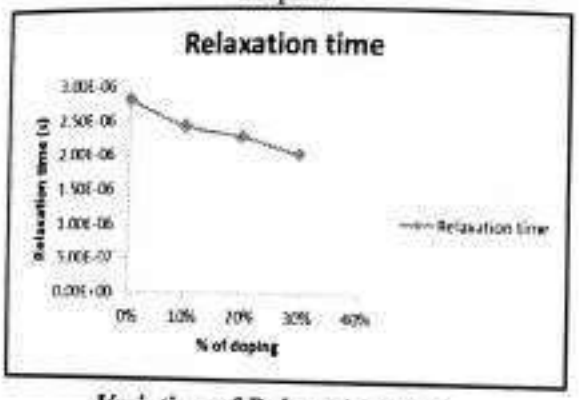
Variation of Free Voluma with % of doping

Graph-7



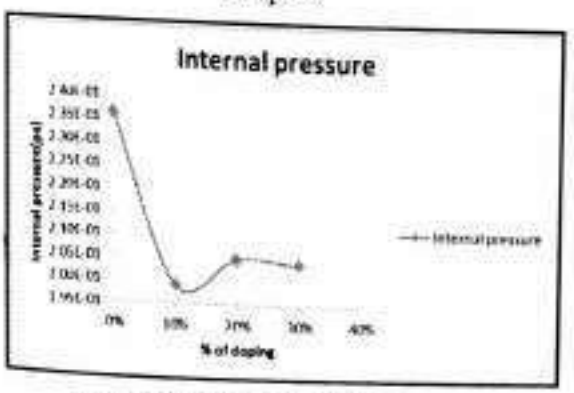
Variation of Acoustic impedance with % of doping

Graph-8



Variation of Relaxation time with % of doping

Graph-9



Variation of Internal pressure with % of doping

From graph-1, 2 and 3 it is noted that density and ultrasonic velocity increases with increasing percentage of doping and viscosity decreases. The increase in velocity is due to the decrease in intermolecular free length and adiabatic compressibility of the liquid solution. The adiabatic compressibility and intermolecular free length are the deciding factor of the ultrasonic velocity in the liquid solution. The interdependences of intermolecular free path length and ultrasonic velocity has been evolved. The internal pressure decreases and free volume increases with increasing percentage of doping. The internal pressure may give information regarding the nature and strength of force existing between the molecules. The increase in free volume shows that the strength of interaction decreases gradually with the increase in ammonium acetate. The relaxation time decreases with increase in percentage of doping. The dispersion of ultrasonic velocity is the system should contain information about characteristic time T of the relaxation process that causes dispersion. The relaxation time which is in the order of 10^{-6} sec is due to the structural relaxation process and such situation it is suggested that the molecules get arranged due to co-operative process.

Conclusion

From the data of ultrasonic velocity, density and viscosity, computed acoustical parameters and their values point to the presence of specific molecular interaction in the electrolyte solution. The increase in free volume show that strength of interaction decreases gradually hence it is conclude that there exist weak interaction between molecules of electrolyte solution of polyvinyl alcohol and ammonium acetate with distilled water at room temperature. Molecules in the electrolyte solution get arranged due to co-operative process as relaxation time is in the order of 10^{-6} sec. From it is conclude that , a very less attenssion is paid to the study of physical parameter of protonic electrolyte PVA and ammonium acetate and which is useful for to study of protonic electrolyte use as a fuel cell in various devices.

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Stannic Oxide Doped with Zinc Oxide based for CO_2 gas Sensing

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Abstract: Metal Oxide (SnO_2–ZnO) thick films have been prepared by screen printing technique. Sensitivity of these sensors to CO_2 gas was examined found to be better sensitive to CO_2 gas than pure SnO_2 films may be due to porosity created by ZnO into SnO_2 matrix.

CO_2 gas sensor the p-n junction like structure is formed of (SnO_2–ZnO) film where at equilibrium flow of electron form lower work species to the higher work species. As the CO_2 gas concentration increases the flow of electron increases and there will be decrease in the electrical resistance of the sensor with respect to CO_2 gas.

Keywords: SnO_2–ZnO; CO_2 gas sensor

1.Introduction:

Recently various materials are used to sense for various gases. These semiconducting materials include electronics ceramic and often a combination of various metals oxides. The SnO_2 based gas sensor are widely used for the detection of CO_2, H_2S, NOx, LPG,C_2H_5OH, H_2 etc[1]. There are many conducting polymers such as polypyrrole, polyacetylene, polyaniline and polythiophene are recently useful for the gas detection [2,3]. K. Suri *et al* [4] reported that iron oxide polypyrrole nanocomposite sensors showed the maximum response to CO_2 gas compared to N_2 and CH_4 gases. ZnO, TiO_2 , SnO_2 are the n-type semiconductor materials , which are most promising candidates for the gas sensors [5]. The metal oxide doped with different semiconducting metals is good sensing materials for gas detection.

The sensors shows the parameter such as response magnitude and dynamic response were studies at the room temperature (303K) for different concentrations of CO_2 gas with an aim to know the behaviors of electrical properties of ZnO-SnO_2 under concentration of CO_2 gas.

2. Experimental

The ($60SnO_2$ - 40ZnO) sensor was prepared by using screen printing technique, followed by an adequate heat treatment. The binder was prepared by thoroughly mixed 8 wt.% of butyl carbitol with 92 wt. % of ethyl cellulose. The material ZnO and SnO_2 was calcinated at 700°C for 4 Hr. in air atmosphere in furnace to remove the impurities. After calcinations the fine powder was formed by using agated motor pestle. The calcinated chemicals are of (A R grade) are weighted on monopan balance (K-Roy, India) with proper wt.% of ZnO and SnO_2. The two components are mixed together to form a homogeneous mixture. The mixture is then placed in porcelain crucible and subjected to heating at 700°C for 1Hr. The paste for screen printing was prepared by taking materials in different ratios of wt.% with a binder in a moter pestel for mixing it. The paste thus prepared was screen printed on a chemically cleaned glass substrate of size 75x25 mm^2 and dried at room temperature at (303K). Th
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Table 2.1. Composition of sample.

Sample code	Composition	Thickness of film(mm)
P1	100 SnO_2+Al_2O_3	1.383 mm
P2	80SnO_2+20ZnO+Al_2O_3	1.381 mm
P3	60SnO_2+40ZnO+Al_2O_3	1.939 mm

the volatile organic solvent was removed via decomposition and the prints adhered to the glass substrate of basic layer of Al_2O_3. For the surface resistance measurement the electrodes of conducting silver paint were formed on adjacent sides of the films and then films were subjected to heating at 80°C for again 15 min. for drying the silver paste and the sample code and thickness of the film are listed in table. The electrical resistance of the films was measured by using a voltage drop method adopted by Yawale et al. [6]. We have compared the various sample with composition given in the table 2.1.

3.Results and Discussion:

In the present study the variation of CO_2 gas concentration with the sensitivity have been studied. Figure (3.1a, 3.1b, 3.1c) shows the variation of sensitivity with CO_2 gas concentration at the room temperature for the multilayer thin films of samples with different ratios P1,P2 and P3 respectively.

From figure it is observed that, P3 sensor has maximum sensitivity and P1 and P2 sensor showed minimum sensitivity. Also change in sensitivity of P3 sensor is more as compare to P1 and P3 sensors. The Sensitivity linearly increases with the increase in CO_2 gas concentration for P3 sample be after 20 ppm of CO_2 gas. It is found that sensitivity of P3 sensor in more than P1 and P3 sensors. Sensitivity is nearly constant i.e. it is goes in saturation region after the range 100 ppm of CO_2 gas.

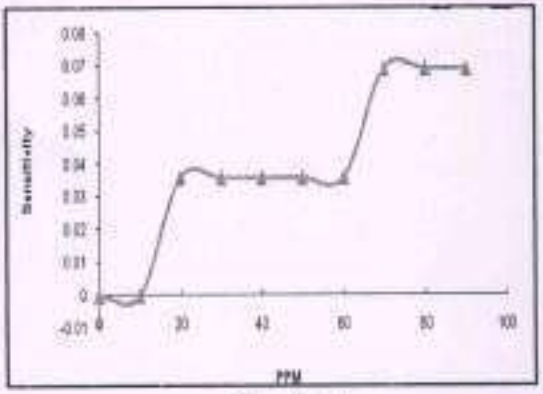


Fig. (3.1a)

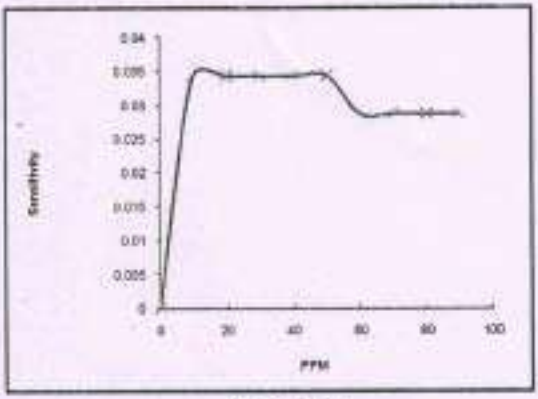


Fig. (3.1b)

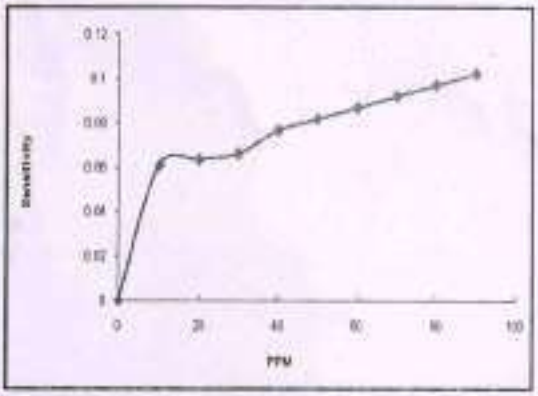


Fig. (3.1c)

The surface morphology of polypyrrole material was studied by SEM and its picture is shown in the Figure (3.2a, 3.2b, 3.2c)

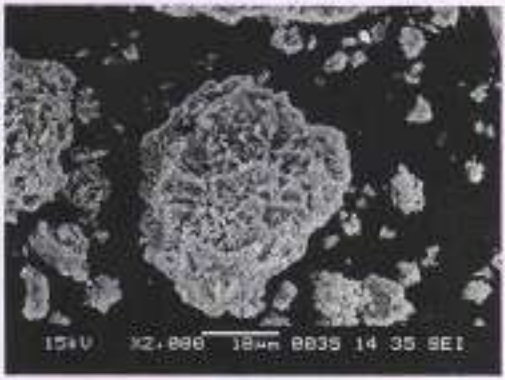


Fig.3.2a SEM pictures of pure SnO_2



Fig. 3.2b SEM picture of ZnO

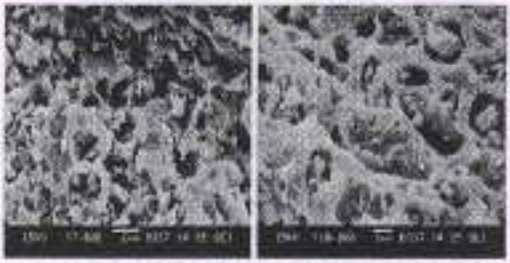


Fig. 3.2c SEM pictures of ($60SnO_2$–40ZnO) at different magnifications.

From SEM picture, it is observed that ($60SnO_2$-40ZnO) is more porous in nature and average diameter pore size found to be 360nm. Due to small pores size, its surface area is more and it shows more sensing nature. Some portion of SEM picture shows some rods with fine voids over them which helps to increase sensing properties.

Table 3.2. Shows the average diameter of pore and number of pores per inch of pure samples and their compositions.

Sr. No.	Pure sample and their compositions (mole %)	Average diameter of pore (nm)	Number of pores per inch (in x 2000 magnification)
	SnO_2 (Pure)	590	65
	ZnO (Pure)	760	62
	$60SnO_2$:40ZnO	360	109

It was concluded that the Sensitivity linearly increases with the increase in CO_2 gas concentration for P3 sample be after 20 ppm of CO_2 gas. From SEM picture, it is observed that $60SnO_2$:40ZnO is more porous in nature and average diameter pore size found to be 360nm. In CO_2 gas sensor the p-n junction like structure is formed of (SnO_2–ZnO) film where at equilibrium flow of electron form lower work species to the higher work species. As the CO_2 gas concentration increases the flow of electron increases and there will be decrease in the electrical resistance of the sensor with respect to CO_2 gas.

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Schottky -Richardson Mechanism in Oxalic acid Doped (PVC-PMMA) Blends

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Abstract: ***We have measured the electrical conductivity of Oxalic acid doped Polyvinyl Chloride (PVC)- Polymethyl Methacryalate (PMMA) blends at temperatures (313K - 373K). The current voltage characteristic of blends does not obey the power law and there is absence of ohmic conduction. The electrical conduction mechanism discussed by various models such as Poole–Frenkel, Fowler–Nordheim, Schottky ln(J) Vs T plots, Richardson and Arrhenius Plots. Out of this, Schottky - Richardson mechanism is conscientious for the observed conduction mechanism in the Polyblends.***

Keywords: PVC, PMMA, Polyblends, Oxalic Acid

1. Introduction

The blending of two polymers is found to be new polymeric material which new materials may be promising candidate than indivisible polymer [1]. There are many investigations on polymer blending [2]. The conductivity study gives the origin of the charge carrying species, their number, and the way in which they move through the bulk of the material. These parameters are interlinked with the chemical composition of the microstructure and the morphology of the particular material.

The electrical conductivity of organic solid shows complex conduction behavior, while the conductivity due to electrons excited from valence band to conduction band is negligible [3,4]. The complex conduction behavior can be explained in terms of electron emission from cathode i.e. Schottky - Richardson mechanism [4] or by liberating electron from the traps in the bulk material, i.e. Poole–Frenkel mechanism [5]. In addition to there is also possibility of tunneling [6] or Fowler–Nordheim mechanism [7], space charge limited conduction [8], etc occurs. In case of polymer films space charge limited conduction, Poole-Frankel and Richardson-Schottky emission and tunneling mechanism generally discussed. When the applied field is sufficiently high and the electrode makes ohmic current with the polymer then the charge carriers are injected into the polymer by lowering of the barrier at the metal – insulator interface, this effect is known as Richardson-Schottky (RS) emission.

PVC is a polar molecule and one of the most important commercially available polymer due to its light, electrical & chemical resistant and it has the ability to get mixed with other to produce verity of compounds which has a wide range of physical & chemical properties.

PMMA is strongly polar and it is a hard, rigid and transparent polymer which has good outdoor weatherability and it has more impact resistance than glass. PMMA is a versatile polymer showing plenty of application. Blends of these two polymers are expected to yield strong and long lived electrets useful for industrial application. Both PVC-PMMA are rigid polymers but by blending PVC with PMMA make the resultant blend soft & open to make useful applications. Many researchers reported the electrical conductivity and experimental observations in PS-PMMA [9], PVC-PMMA blends [10], [11], [12]. The conductivity studies on PVC-PMMA polymer blends electrolytes shows stability [10].

In the present study, the electrical conductivity of PVC-PMMA blends doped with Oxalic acid was measured to identify the mechanism of electrical conduction in the polyblends. The electrical conduction mechanism discussed by various models such as Poole–Frenkel, Fowler–Nordheim, Schottky ln(J) Vs T plots, Richardson and Arrhenius Plots.

2. Experimental

The polymers, PVC (Aldrich) and PMMA (Otto kemi, Mumbai) in 1:4 weight proportions were dissolved in 20 ml solvent cyclohexanone (SD Fine Chemicals, Mumbai) respectively. Oxalic acid used as a dopant in these selected polymers. The dopant & polymer mixture were mixed together and this mixed solution was kept in a stand for three days so as to get the complete homogenous dissolution of blends. After three days, the solution mixture was poured on perfectly plane and chemically clean glass plate, which is kept floating freely in a pool of mercury for perfect horizontal leveling. It was, thereafter, allowed to evaporate in air at room temperature. Further, it was dried for 48 hrs. to remove any traces of solvent.

The dried film was removed from the plate and cut into small pieces (samples) of desired size, which were then coated on both sides with silver paste (Eltecks Corporation, Bangalore) so that electrical contact hold very well. The polyblends films of PVC-PMMA doped with 5%, 10%, 15% Oxalic acid (wt. percentage) were prepared by the same method given above but the results are only interpreted for doping of 15% Oxalic acid due to the significant change in conduction of blends. The thickness of the polyblends film was measured

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by using Digital Micrometer screw gauge (Mitutoyo Corporation, Japan, Least Count 0.001mm) is found to be 56 μm. These polyblends films were kept between the electrodes of a specially designed sample holder having gold plating. The variation between current and voltage measured by using Keithley 6487 Picoammeter / Voltage source meter instruments at various constant temperature.

3. Results & Discussion

3.1. I-V characteristics of Polyblends

The I-V characteristics of 1: 4 **(**PVC-PMMA) doped with 15% Oxalic acid is represented by lnI - lnV plots at various temperatures 313K, 323K, 333K, 343K, 353K, 363K and 373K are shown in figure 3.1. The current increases non-linearly with the applied voltage and does not follow a Power law $I = kV^m$ where, k and m are constant.

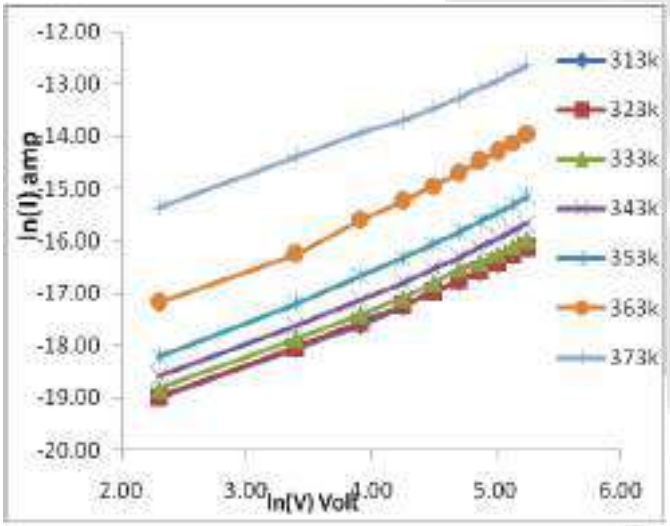


Figure 3.1: I-V characteristics

It is seen from the figure 3.1 that, the current increases nonlinearly with applied voltage at constant temperature and also the current increases with increase in temperature at constant applied voltage). The possibility of ohmic conductions as well as space charge limited conduction is ruled out from the observed behavior of *I–V* characteristics. As we know the compositions of blends are insulators and blends are almost non-crystalline, which give rise to wide scope for irregularities in the structure therefore there is absence of ohmic conduction.

3.2. Poole–Frenkel Mechanism

The Poole-Frenkel relation [5] for the current density is given by the equation 3.1 ,

$$J = B \exp\left(\frac{-\phi}{KT} + \beta_{PF} E^{\frac{1}{2}}\right) \quad (3.1)$$

Where, $\beta_{PF} = \frac{e}{KT}\left(\frac{e}{\pi \varepsilon \varepsilon_0 d}\right)^{\frac{1}{2}}$ = constant

and e = electronic charge which predicts a field -dependent conductivity as,

$\sigma = \sigma_0 e^{\frac{\beta_{PF} E^{\frac{1}{2}}}{2KT}}$ or

$$\log\sigma = \log\sigma_0 + \frac{\beta PF}{2KT} E^{\frac{1}{2}} \quad (3.2)$$

So that, the Poole -Frenkl mechanism is characterized by linearity of logσ Vs $E^{\frac{1}{2}}$ plots with positive slope. In this present case of 1: 4 **(**PVC-PMMA) doped with 15% Oxalic acid the lnσ Vs $E^{\frac{1}{2}}$ plots are linear with negative slope (figure 3.2) indicating the absence of Poole-Frenkl mechanism.

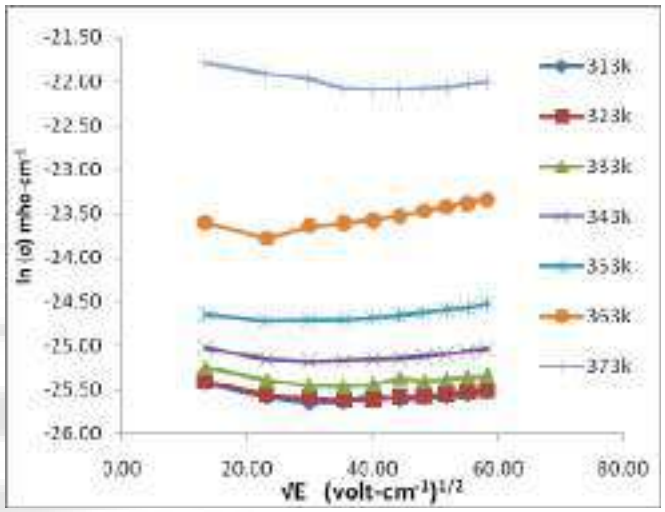


Figure 3.2: Poole-Frenkel Plot

3.3. Fowler– Nordheim Mechanism:

The Fowler -Nordheim Relation for [7] current density J can be expressed by equation 3.3.

$$\log\frac{J}{V^2} = \log A - \frac{\phi}{V} \quad (3.3)$$

and $\log\frac{J}{V^2}$ Vs $\frac{1}{V}$

Plots is expected to be a linear With a negative slope .

In this present case the $\log\frac{J}{V^2}$ Vs $\frac{1}{V}$ plots for 1: 4 **(**PVC-PMMA) doped with 15% Oxalic acid is represented by figure 3.3. Excepting few plots which have strayed away the graph are nearly straight lines with a positive slope indicates the absence of tunneling current as is suggested by Fowler - Nordheim mechanism.

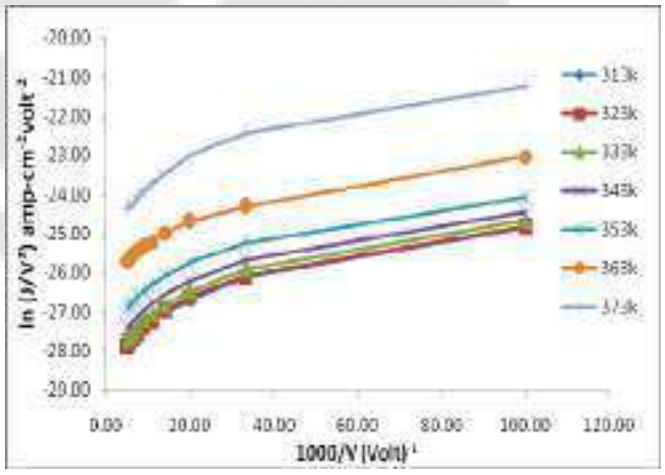


Figure 3.3: Fowler-Nordheim Plot

3.4. Schottky – Richardson Mechanism

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The Schottky – Richardson current voltage relationship is expressed by the equation 3.4.,

$$\log J = \log AT^{\frac{3}{2}} - \frac{\phi_B}{KT} + \beta_{SR} E^{\frac{1}{2}} \qquad (3.4)$$

and that log J Vs $\sqrt{E}$ Plot referred to a Schottky Plots should be a straight line with positive slope.

For the present case, Schottky plot are shown in figure 3.4.1 below. The linear positive slope indicates that Schottky - Richardson mechanism is applicable to the process in 1:4 (PVC-PMMA) with 15% O.A.

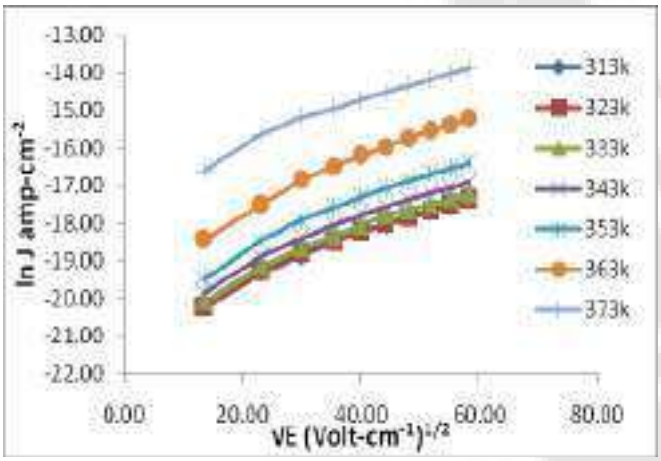


Figure 3.4.1: Schottky Plot

Further, in the case of Schottky – Richardson mechanism the current shows strong temperature dependence but not in case of Poole -Frenkel mechanism. The study of temperature dependence of current density is therefore of great importance.

The temperature dependence of current density is represented plot of ln (J) verses temperature shown in the figure 3.4.2, observed that ln (J) increases almost linearly with change in the temperature. The temperature dependence is great agreement with the Schottky -Richardson Mechanism. Further that the slopes of all the lines are nearly same for all the fields, shows that, no thermodynamic transition occurs in the temperature range studied.

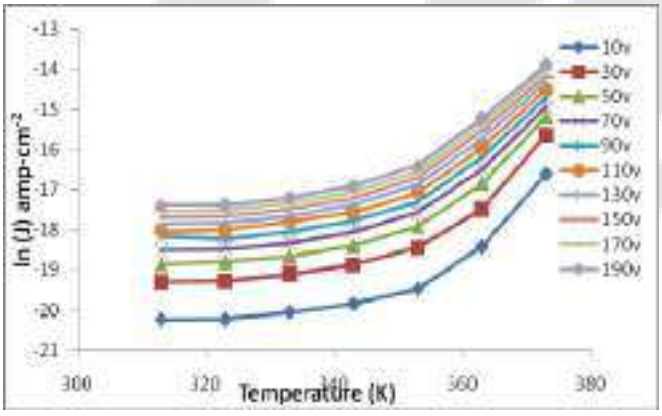


Figure 3.4.2: Current density Ln (J)Vs Temperature Plot

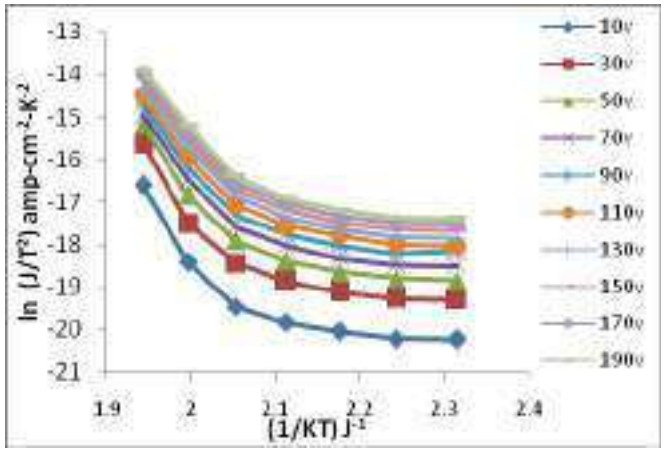


Figure 3.4.3: Richardson Plot

From the relation 3.4 we can plot the variation between Ln(J/T^2) versus (1/KT) shown in fig. 3.4.3 Richardson Plot, it is observed from plot, it should be a straight line with a negative slope. In our case such a straight line graph have been obtained with a negative slope. This shows the linearity of the plot which supports to Schottky- Richardson Mechanism.

3.5. Arrhenius Mechanism

The ln (σ) verses 1/T plots at all values of applied voltage is shown in figure 3.5., the conductivity of polymer is mostly dependent on the temperature. As the temperature increases polymer becomes soft and mobility of the main chain segment as well as the rotation of the side group becomes easier [13]. Thus at higher temperature more & more dipoles are oriented resulting in the higher equivalent surface charge density i,e. as the temperature increases conductivity also increases in accordance with the Arrhenius equation given by relation 3.5.

$$\sigma = \sigma_0 \exp\left(\frac{-E_a}{KT}\right) \qquad (3.5)$$

where , σ_0 - is the pre-exponential factor, E_a- is activation energy and K- Boltzmann constant

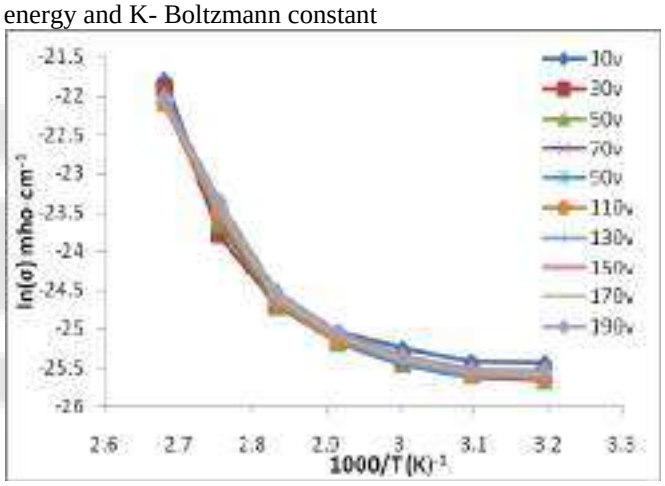


Figure 3.5: Arrhenius plot

From the slope of straight line the activation energy is calculated & is found to be in the neighbored of 0.1eV.This is in good agreement with the reported earlier.

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4. Conclusions

The observed conduction nature at higher fields and temperatures is found to be Richardson-Schottky emission. Due to the formation of charge transfer complex, there exist a link between the dopant molecules and polymer molecules in amorphous region. Schottky and Richardson mechanism of conduction predominates over other mechanism in the doped sample. The applied field seems to be insufficient to liberate electrons from the trapping centers (dopant molecules) showing absence of the Poole–Frenkel mechanism.

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"Appliaction of Polypyrrole for CO_2 Gas Sensing at Different Tempetetures"

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Abstract: In this paper we have prepared the Al_2O_3-ppy multilayer thin films sensor for the CO_2 gas detection. The sensor (Al_2O_3+PPY) shows the maximum sensitivity towards CO_2 gas detection at room temperature (303K). The plot showed the linear nature against concentration of CO_2 gas. The sensitivity of the different sample difference is due to the properties of metal oxide material and high porosity of materials. The sensitivity of the samples was found to be increasing with the change in the concentration of CO_2 gas.

The sensing mechanism is described as the surface oxygen atom absorbed when the sensor is exposed to the CO_2 gas. A p-n junction like structure is formed where at equilibrium flow of electron form lower work species to the higher work species. As the flow of electron increases there will be decrease in the electrical resistance with the increase in CO_2 gas concentration.

Key Words: Polypyrrole, Al_2O_3, CO_2 Gas.

1. Introduction: Recently, the solid state gas sensor based on the semiconducting metal oxides has becoming a promising alternative and have a good sensing properties. There have been several oxides tested Al_2O_3 doped with the polypyrrole has been reported. Electronic polymer has many excellent features: flexibility, functionality, processing and economics, etc.; among them, electronic function sensitive polymer, such as physical, chemical and biological, and their composites have been especially notable in the improvement of the modern electronic materials [1-4]. However, compression of the response of Al_2O_3 doped described in these studies gives discrepancies variation in the resistance. In the present study (Al_2O_3+PPY) multilayer thin films response only become applicable at CO_2 gas concentration so these sensor is more suitable for the high concentration application.

2. Experimental:

In the present work we have selected semiconducting metal oxides Al_2O_3 and Polypyrrole (AR grade).The chemicals in the powder formed are mixed with different stiochiometery in mol % as (Al_2O_3-ppy). The Polypyrrole (ppy) was prepared by taking 1.892 gm of Ferric chloride ($FeCl_3$) which was added with the 7 ml of methanol. 0.84 ml of Polypyrrole monomer was taken in beaker. After that, these two solutions are combined with the constant string. This processes is done in the dark place and then it was allowed to kept it for 8 Hr. Then the above solution is washed with the methanol and dried it. After drying we get black colour precipitates as the ppy. The materials used for gas sensor are generally prepared in the form of multilayer thin films.

Initially, the material was calcinated at 700°C for 5 Hr by using the furnace in the air atmosphere, so as to remove the impurities. Then the material was crushed to make a fine powder by using moter pestel. This calcinated pow
Roy
Al_2O





Butyl Carbitol acetate (BCA) used as a binder for making multilayer thin film by using screen printing technique. After making these thin films the film were subjected to heating at 80°C for 1 hrs in the vacuum oven.

In the multilayer thin film for the surface conductance measurement the electrode was made on film by using silver paint which was formed on adjacent sides as shown in fig 1.

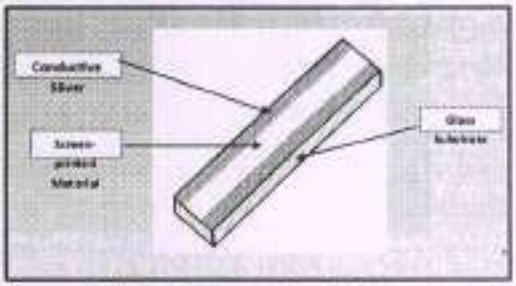


Fig 1. Screen- printed glass substrate (Sensor)

Again, these multilayers thin films were subjected to heating for 50°C for 15 min for drying the silver paint and the sample code surface area weight of film and thickness are listed in Table 1.

Sample code	Composition	Thickness of film(mm)
P1	Al_2O_3	1.38 mm
P2	Al_2O_3+Ppy	1.343 mm
P3	Ppy	1.313 mm

Table. 1

The crystalline size was calculated from the full width at hail maximum of the first peak using the Scherer's formula [5]. The electrical resistance of the thin films was measured by voltage drop method which was adopted by Yawale *et al* [6]. When CO_2 gas starts to flow via inlet to the chamber, then resistance of the thin film is change. We measured the output voltage by using voltage drop method at specific time instant with the help of stopwatch. With the help if this voltage, study the variation of sensitivity with CO_2 gas concentration was done. The constant flow of CO_2 gas, a gas flow meter (FLOWTRAN make, India) was used. The sensitivity the device characteristics of perception a variation in electrical properties of the sensing material under gas exposure and it can be defined as in the equation

Sensitivity (S) = (Rg-Ra)/Ra If Rg > Ra (1)

Sensitivity (S) = (Ra-Rg)/Ra If Ra > Rg (2)

where, Rg is the change in resistance of the sensor in presence of gas /vapors and Ra is the original resistance of sensor in presence of air. Where Rg is the change in resistance of the sensor in the presence of gas vapors and Ra is the original resistance of sensor in the presence of air.

3. Result and Discursion:

In the present study the variation in CO_2, gas concentration with the electrical resistivity, conductivity and sensitivity have been studied. Figure (a,b,c) shows the variation of sensitivity with CO_2 gas concentration at room temperature for multilayer thin film P1,P2 and P3 respectively.

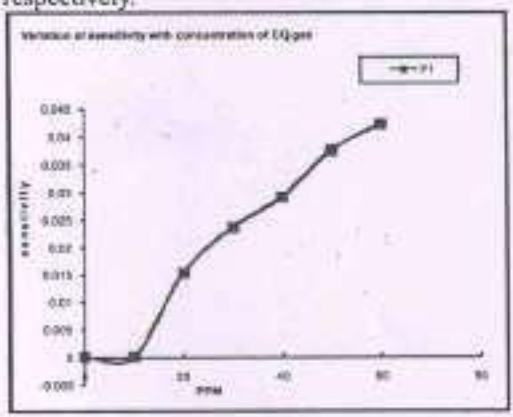


Figure (a)

From figure it is observed that, P2 sensor has maximum sensitivity and P1 and P3 sensor showed minimum sensitivity. Also change in sensitivity of P2 sensor is more as compare to P1 and P3 sensors. The Sensitivity

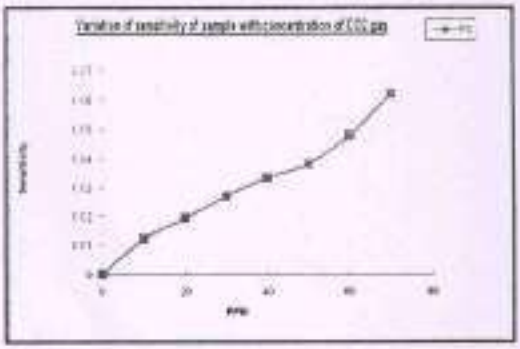


Figure (c)

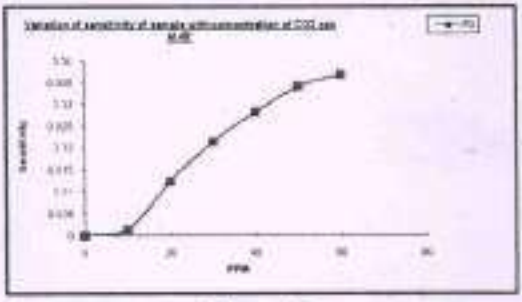
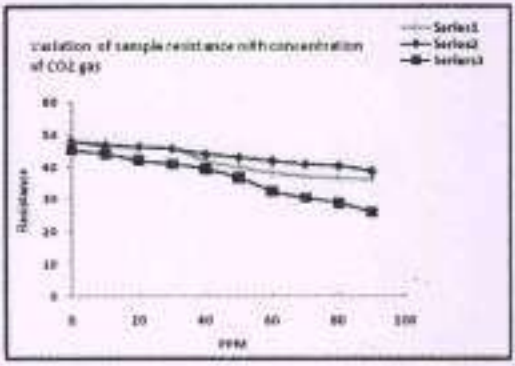
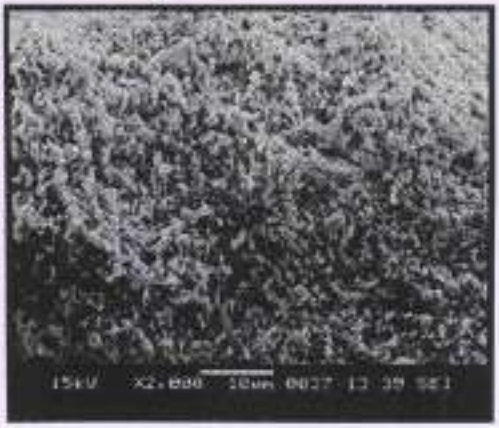


Figure (d)

The resistance of the sample decreases with increase in the concentration of CO_2 gas. The resistance of the P2 is more than the resistance of P1 and P2.As the resistance of the sample decreases the conductivity of sample increases.



The surface morphology of polypyrrole material was studied by SEM and its picture is shown in the Fig.



From SEM picture, it is observed that Ppy is more porous in nature and pore size varies from ~ 0.5 to 3 µm. Due to small pores size, its surface area is more and it shows more sensing nature. Some portion of SEM picture shows some rods with fine voids over them which helps to increase sensing properties.

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Research Paper Zoology

Effects of Cypermethrin on Lipid and Cholesterol Contents of Freshwater Fish *Channa Orientalis* (Bloch).

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ABSTRACT

Water pollution is a major global problem that requires ongoing evaluation and revision of water resource policy at all levels. The water pollution is an acute problem in developing and industrialized countries. Fishes are very sensitive to a wide variety of toxicants in water and the deleterious effects of pesticides on fishes can be easily established. Ophiocephalus orientalis, freshwater fish exposed to sublethal concentration(0.0007µ/lit) of cypermethrin at different time intervals. Lipid and cholesterol contents were observed from liver and muscle after exposure period. There were decreased in lipid and cholesterol content at different time intervals.

KEYWORDS | Ophiocephalus orientalis, cypermethin, lipid, cholesterol.

INTRODUCTION:-

Pesticides are an integral part of present day agricultural technology. They are greatly contributing towards increasing world food supply by protecting the crop yield. Due to intensive development of agriculture in recent years and rapid growth of industrialization in our country, there has been a great increase in manufacture and utilization of fertilizers, pesticides, petrochemical products, detergents and other synthetic chemicals and pose a serious threats to the water ecosystem. Pesticides and related chemicals destroys the delicate balance between species and a functioning ecosystem (Khan and Francis,2005).

Pesticides are not highly selective but are generally toxic to many macrophytes, non-target organisms such as fish (Ayoola,2008; Franklin et al.,2010). Acute exposures of fish to pesticides result in some biochemical changes, causing some interference. Every living organism has its own so called detoxification mechanism to get rid of foreign substances in the body, however if toxic substances are encountered in higher concentration, they are bound to bring severe adverse effects (Satyavardhan 2010).

Some of the biochemical alteration occurring in the body gives the first indication of the stress in the organism and hence effect on the part of the pollution (Venkataramana et al.,2006; Rathod et al.,2009). The biochemical studies are good parameters which help to see the effects of toxicants on metabolism of fish (Kajare et al.,2000). In present investigation, an attempt has made to find out effect of cypermethrin on lipid and cholesterol constituents from liver and muscles of experimental fish, Ophiocephalus orientalis.

MATERIALS AND METHODS

The freshwater fish Ophiocephalus orientalis were collected from Wadali lake around Amravati region. The fishes were acclimatized at laboratory condition for 1 week. The LC_{50} value was calculated by probit analysis method (Finey,1971) . The LC_{50} value is 0.0007µ/lit. at 72hrs. The acclimatized fishes were exposed to sub lethal concentration for 24hr, 48hr, 72hr and 96hrs. Simultaneously a control group of healthy fishes were maintained under identical conditions. The fishes were sacrificed at the end of exposure period and liver and muscle were processed for the biochemical estimation. Lipids were estimated according to the method of Floch et al., (1957) . and cholesterol content was estimated with the help of Leiberman Burchad method by King and Wolten (1959).

RESULTS:-

The sublethal concentration of cypermethrin treated with Ophiocephalus orientalis at different time interval and observed that in the liver and muscle lipid showed declined trend. The lipid level declined in liver that is, 19.85±1.58, 18.67±1.68, 16.32±1.78, 15.66±1.79 as compared to control value 20.30±2.00 and in muscles that is, 9.89±1.58, 8.88±1.78, 7.45±1.68, 6.96±1.48 as compared to control value 10.30±3.00.

Lipids in liver and muscles of fish Ophiocephalus orientalis were decreased due to exposure to cypermethrin. Lipids constitute very rich energy reserve, it showed decrease trend indicates the changes in energy demand of fish during exposure to cypermethrin.

The sublethal concentration of cypermethrin treated with Ophiocephalus orientalis at different time interval and observed that in the liver and muscle cholesterol showed declined trend. The cholesterol level after exposure to cypermethrin was declined in liver that is, 10.38±0.07, 10.38±0.07, 10.36±0.02, 10.15±0.03 as compared to control value 11.45±0.70, 10.97±0.50, 10.96±0.50, 10.30±1.02 respectively. The cholesterol level declined in muscle that is, 0.89±0.06, 0.62±0.02, 0.51±0.03, 0.47±0.02 as compared to control value 1.35±0.93,1.24±1.00, 1.11±0.1, 1.00±0.5. The reduced cholesterol level due to the inhibition of cholesterol biosynthesis in the liver and reduced absorption of dietary cholesterol.

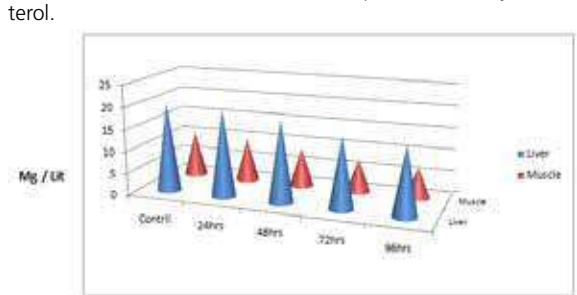


Fig.No.1Changed in the Liver and muscle lipid of the freshwater fish Ophiocephalus orientalis exposed to sublethal concentration of cypermethrin at different time interval. (Mg/lit).

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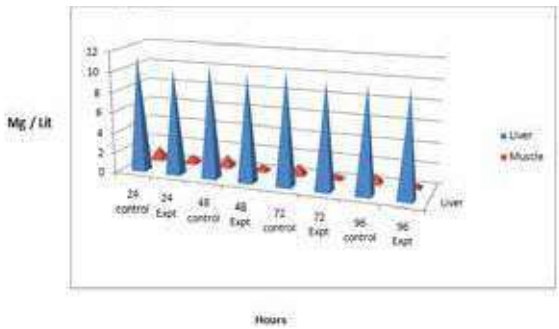


Fig.No.2 Changed in the Liver and muscle cholesterol of the freshwater fish Ophiocephalus orientalis exposed to sublethal concentration of cypermethrin at different time interval.(Mg/lit).

DISCUSSION:-

In the present investigation, cypermethrin exposed to freshwater fish Ophiocephalus orientalis. The level of lipid content decreased in liver and muscle tissues. Lipid plays an important role in energy metabolism and provide energy to metabolic processes. They are also important for cellular and sub-cellular membrane. It is used as energy reservoir, stored and transported in the form of glycerol ester. These decreased in lipid content in tissues suggested that the lipid have been channelized to meet the metabolic demand for extra energy needed to mitigated the toxic stress. Similar finding was given by Patil and Patole,(2012) that the effect of malathion and cypermethrin on lipid constituents of freshwater fish Lepidocephalicchthys guntea. They observed that, the level of lipid content decreased significantly in all treated groups,.

Lipid level decreases significantly because liver is the principle site of detoxification in fishes (Dixith, 2005). Stalin and Das, (2012) were observed the decrease in lipid levels in the liver tissues of Cirrhina mrigala exposed to fenthion.

The level of cholesterol content decreased in liver and muscle tissues. The reduced cholesterol level due to the inhibition of cholesterol biosynthesis in the liver and due to reduced absorption of dietary cholesterol. There was also depletion in the lipid content of fish Tilapia mossambica exposed to monocrotophos reported by Remia et al., (2008).

Ganeshwade (2012), reported that there was decrease in cholesterol content in the liver and muscle tissues of freshwater fish Punctius ticto. Due to dimethoate toxicity stress which suppressed lipid metabolism and leads decrease value of cholesterol Choudhary and Gaur (2001); Shindhe et al., (2002). Cholesterol is an important normal body constituent used in the structure of cell membrane synthesis of bile acid and synthesis of steroid hormones. Significant decrease in cholesterol content is studied in fish Oreochromis niloticus by Kahtani, (2011).

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MORPHOMETRIC AND MERISTIC VARIATIONS IN FINS OF *CHANNA PUNCTATUS* FROM FRESH WATER HABITATS IN AMRAVATI REGION (M.S.)

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ABSTRACT

The freshwater fish which has been selected for present study were *Channa punctatus* which is locally called as dhok. Fishes were collected from the local wadali lake of Amravati region. Morphometric study of fins were done by the measured as different fins their characterstics such as fin length, fin width and number of fin rays. Fin variables relationship were observed with standard lengths of fish *Channa punctatus.* The meristic characters are the countable structure useful for differentiation and identification of species and populatiom. Channa *punctatus* showed L/W ratio and also gave phenotypic differences between different fins regarding its length, width and number of fin rays and growth pattern with their increasing body length.

KEYWORDS: Morphometric, Meristic, variation, fin, *Channa punctatus*

The success of fishery industry largely depends on the growth and reproductive potential of the concerned fish species. The development and improvement of the species mostly depends on the knowledge of the biology. Majority of the people need fish throughout the year as a necessary food, its demands the wide aquaculture resources are utilized widely. The shape and structure of fins and fin rays of fishes show modifications due to varied swimming habits, habitat, sex, growth factors, age and size of the fishes, **Ugwumba and Adebbisi (1992)**, **Ugwumba and Ugwumba (1993), Weisel (1995), Oyekanmi (2000),**. It is also known that the morphometric and meristic parameters are influenced by environmental factors, **Dynes *et. al.,* (1999).** Information on the morphometric and meristic characterstic of fins of fishes are useful in marking sex determination, species identification and in ascertaining the suitability of cultivable species.

Channa punctatus, locally known as Dhok, were found in rivers, canals, lakes and other aquatic habitats along with other species of same genus **Wee (1982)**. The fish belonging to genus *Channa* contribute a lot to the commercial fishery of inland waters of India high market price, tolerance to a variety of habitats and carnivorous food habitat make them an important element of fish farming which demands an understanding of their biology and ecological requirements **Omnoniyi and Agborn (2008)**. These fishes contain high protein, substantive iron and low fat content which is beneficial for human health.

It is not easy to identify the different species through colour and marking as it is with other fish. Nearly all snakeheads have different colours and making as juveniles compared to an adult species. Also some snakeheads can change their colour and marking within seconds depending on the situation. Thus in present investigation morphometric and meristic study such as fins length, width and finrays numbers were studied to give clear idea and identification of *Channa punctatus* fish from other species of same genus.

MATERIAL AND METHODS

The *Channa punctatus* which is locally called as dhok were collected from the local wadali lake of Amravati region. After collection healthy fishes were selected (size 30-150mm in length and 30-60gm in weight) and washed with dilute solution of potassium paramagnet (KMno4, 1.0mg/l) to remove dermal infection and acclimatized in laboratory condition for 10 days.

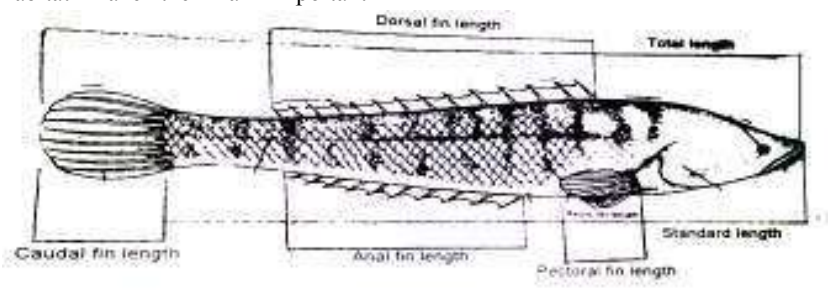


Figure 1: Measurement of *Channa Punctatus*

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Morphometric and meristic study of fins was done by the measurement of different fins their characterstics such as fin length, fin width and number of fin rays. Fin variables relationship is observed between standard length of fish *Channa punctatus.*

OBSERVATION AND RESULTS

Morphometrically dorsal fin length measured as 4.28 + 2.36, width 0.46 + 0.19, and fin rays were 24.48 + 4.89, anal fin length 3.2 + 2.36, width 0.3 + 0.005, fin rays were 18.8 + 2.77, caudal fin length 1.58 + 1.14, width 0.66 + 0.42 and finrays was 13.18 + 5.26, pectoral fin 1.56 + 0.82, width 0.66 + 0.42, and fin rays were 13.18 + 5.26, pectoral fin 1.56 + 0.82, width of fin 0.56 + 0.36 and fin rays were 12.22 + 3.50. Pelvic fin length 0.94 + 0.01, width 0.31 + 0.12, and fin rays were 6.02 + 0.33 observed in fish length of *Channa punctatus* were ranges 30-130 mm respectively (Table 1) were found in between 18-30; mean 24.48 respectively. While relationship between body length of fish and dorsal fin length of *Channa punctatus* fish was found to be Y= -0.2179 + 0.49X

The coefficient of correlation of the fish *Channa punctatus* was r = 0.63 showed Substantial degree of co-relation. The relationship between body length and dorsal fin width were found to be Y= -0.7916 + 0.04X. The coefficient correlation r=0.64 showed substantial degree of correlation. While the relationship between body length and dorsal fin rays was found to be Y= -14.366 + 1.22X

The coefficient correlation r= 0.76 showed substantial degree of correlation. The relationship between body length and anal fin length was found to be Y = -0.8621 + 0.49X.

Table 1: Morphometric and Meristic study of different fins with their fin length, width and fin rays numbers of freshwater fish *Channa punctatus*

Fins	Fish length (Ranges)	Length	Width	Fin Rays
Dorsal Fin	30-130 mm	4.28 ±2.36	0.46 ± 0.19	24.48 ± 4.84
Anal Fin		3.2 ± 2.36	0.3 ±0.005	18.8 ±2.77
Caudal Fin		1.58 ± 1.14	0.66 ± 0.42	13.18 ± 5.26
Pectoral Fin		1.56 ± 0.82	0.56 ± 0.36	12.22 ± 3.50
Pelvic Fin		0.94 ± 0.00	0.3 ± 0.12	6.02 ± 0.00

Table 2: Relationship between fish length and Morphometric and Meristic study of different fins of freshwater fish *Channa punctatus*

Fins	Fin length	Fin Width	Fin Rays
Dorsal Fin	y = -0.2179+0.49X r= 0.63	y = -07916+0.04x r = 0.64	y = -14.366+1.22x r = 0.76
Anal Fin	y = 0.8621+ 0.49x r = 0.63	y = 0.183+0.014x r = 0.60	y = -12.997+0.70x r = 0.76
Caudal Fin	y = - 0.5754+ 0.26x r = 0.69	y = -0.0382+0.07x r = 0.54	y = -6.548+0.80 r = 0.46
Pectoral Fin	y = 0.0151+0.19x r = 0.70	y = 0.708+0.059x r = 0.49	y = -4.759+0.90x r = 0.77
Pelvic Fin	y = 0.6351+0.19X r = 0.66	y = 0.151+0.017x r = 0.43	y = -6+0x r = 0.0

The coefficient of correlation r = 0.63 showed substantial degree of correlation. The relationship between body length and anal fin width was found to be Y = -0.183+0.014x. The coefficient of correlation r = 0.60 showed substantial correlation between body length Anal width. The relation between body length and Anal fin rays was found to be Y= -12.997+0.70x. The coefficient of correlation r = 0.76 showed substantial degree of correlation between body length anal fin rays. The relation between fish length and

pectoral fin length was found to be Y= 0.0151+0.19x. The coefficient of correlation r = 0.70 showed substantial degree of correlation. The relation between body length and pectoral fin width of *Channa punctatus* was found to be Y = -0.708+0.059x. The coefficient correlation r = 0.49 showed moderate degree of correlation. The relation between body length and pectoral fin rays was found to be Y = -4.759+0.90x. The coefficient correlation r = 0.77 showed moderate degree of correlation.

In the relationship between body length of fish *Channa punctatus and* different fin length was found that regression coefficient of dorsal fin length and Anal fin length was more than caudal fin length, pelvic fin length and pectoral fin length while coefficient correlation was near about same that was 0.63, 0.63, 0.69, 0.66, and 0.70 respectively. The relationship between body length of *Channa punctatus* fish and different fin width was found that regression coefficient of caudal fin width and dorsal fin width was observed larger as compared to fin width of pectoral fin, pelvic fin and anal fin. While coefficient correlation in dorsal fin width and anal fin width was observed more that is 0.64 and 0.60 and coefficient correlation of caudal fin width, pectoral fin width, pelvic fin width was seen as 0.54, 0.49, and 0.43, respectively. While the relationship between body length of fish and number of fin rays of different fins was found that regression coefficient as dorsal fin rays were more following pectoral, caudal and anal fin rays. But pelvic fin rays showed regression coefficient as 0. Same way coefficient correlation of pelvic fin rays was also found to be 0.The coefficient correlation of dorsal fin rays, Anal fin rays, pectoral fin rays and caudal fin rays was found to be 0.76, 0.76, 0.77, 0.46 respectively; (table no.**2**).

The above values showed that increase in body length; fin length, width and fin rays also changes and showed increase in them with substantial, moderate degree of correlation respectively .In case of pelvic fin, even with increase in body length of the fish *Channa punctatus* there is no increase in number of fin rays thus showed coefficient correlation as r=0.00

DISCUSSION

The present morphometric analysis of different fins of *Channa punctatus* showed variation in length, width and number of fin rays'. It was observed that with the growth of fish, body length, fin length and fin width and fin rays number also increase with high degree of correlation was also shown in fin rays such as 0.76, 0.76, 0.77, 0.46 for dorsal fin, anal fin, pectoral fin and caudal fin respectively. But pelvic fin showed no change or increase in number of fin rays r =0.

According to **Turan *et.al*., (2005)** and **Omoniyi and Agbon (2008)** distinct environmental structure causes the high morphometric variation and plasticity which response to differences in environmental condition such as food abundance and temperature. **Usha (2000)** reported that anal, caudal, pectoral, and pelvic fins of *Catla catla* were longer than *Cyprinus carpio* and *Labeo rohita* due to its surface feeding suited ecologically which is rich in vegetation and species of *Clarias gariepinus.* They belong to benthic habitat and have robust bodies and large pectoral fins which allow them to withstand current on smaller, smoother substratum. **Dynes *et.al.*, (1999)** found that dorsal and pectoral fin lengths of pelagic fish were shorter than littoral ones in brooke chart, *Salvelias fountinalis*. The morphometric study of fins of *Channa punctatus* were seen broadly by their location, shape and size. In *Channa punctatus* species long dorsal fin, anal fin, lobed shaped caudal fin, two pectoral fin, two pelvic fins.and varying number of fin rays were also noticed.

The increase in size of the fins was accompanied by branching and segmentation of fin rays. Such increase was noticed in number of fin rays once these were formed because a constant number of rays are characteristic of a particular species, genus or family **(Lagler 1962, Usha and Prakasam 2005).** The sequential development of pectoral fin followed by caudal and dorsal fins appeared to be related to the timely uses of these fins as suggested by **(Whitehead 1975, Devenport 1993).** In the present analysis of fresh water fish C*hanna punctatus* showed the phenotypic differences between different fins regarding its length, width and number of fin rays and growth pattern with their increasing body length.

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Section A: Green Chemistry

Research Article

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Antimicrobial study of analogues prepared under microwave assistance of active ingredient isolated from *Buteamonosperma* plant and their growth promoting impact on some flowering plants

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Abstract: *Buteamonosperma*is one of the medicinally potential plants found in Melghat region which is frequently used for the eradication of skin diseases. In the present study we have undertaken microwave assisted synthesis the analogues of active ingredient isolated from leaves of *Buteamonosperma*plant extract and screened for their antibacterial activity against pathogens responsible for skin diseases viz. *Streptococcus pyogenes, Nocardiacalcarea, Trichosporoncutaneum, Rhodotorularubra.* The synthesized compounds were screened for their growth promoting impacts on some flowering plants viz. *Papaverrhoeas, Gladiola tristis, Dianthus chinensis, Candy tuft, Gaillardia, Calendula officinalise.*

Key words: *Buteamonosperma,* microwave assisted synthesis of analogues, skin diseases, *Streptococcus pyogenes, Nocardiacalcarea, Trichosporoncutaneum, RhodotorularubraPapaverrhoeas, Gladiola tristis, Dianthus chinensis, Candy tuft, Gaillardia, Calendula officinalise.*

INTRODUCTION

The forest of Melghat Tiger reserve is of deciduous nature and has been categorized as “Dry deciduous forest”. The geological formation of the soil largely determines the type of vegetation it is going to support. The most of the area has the soil of trap origin which is rich in minerals and having a high water holding capacity. The soil strata has a remarkable rate of exchangeable

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calcium and pH varying from 6.5 to 7.5 thus supporting the best form of teak and its associate flora.This is the main reason that to make *Tectonagrandis* (teak) is the most dominant species of Melghat forest. This region is also determined as a unique blend of multiple high hills and deep valleys with terrains and vegetations changing at close intervals.

More than 750 plant species have been enlisted in the Flora of Melghat[1]. These species belong to 400 genera representing as many as 97 families. There are 91 trees, 109 shrubs, 450 herbs, 38 climbers, 23 sedges and 84 grass species.

In the literature, *B. monosperma*is ascribed to have many medicinal properties such as astringent, diuretic, depurative, aphrodisiac, rubefacient, tonic, and anthelmintic. They are effective in leprosy, leucorrhoea, gout, diarrhoea, puerperal women, elephantiasis, night blindness and other defects of sight, dysentery, phthisis and haemorrhage from stomach and bladder, inflammations, ringworm, ulcers and sore – throats[2, 3].

MATERIALS AND METHODS

The leaves of *Buteamonosperma* plant was collected from the Melghat region of Amravati, District of Maharashtra, India seasonally and authenticated by the taxonomists Dr. S. P. Rothe from the Department of Botany, Shri Shivaji College Akola. Voucher specimen (ML – 101) was deposited in the herbarium of Department of Botany, Shri Shivaji College, Akola.

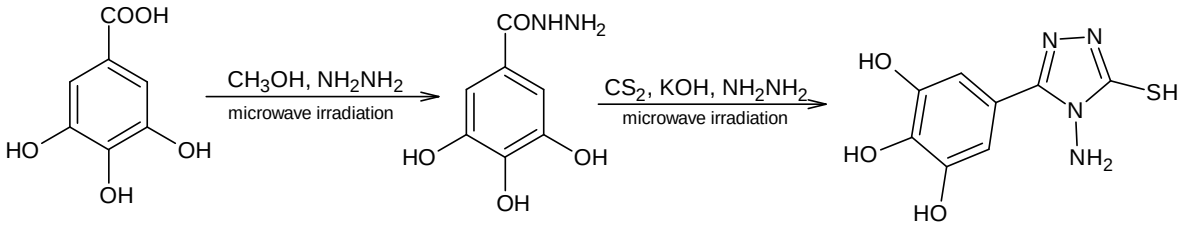
Chemicals: All the chemicals used in the study were obtained commercially and of analytical grade.

Microorganisms: The microorganisms which were used viz: *Streptococcus pyogenes, Nocardiacalcarea, Trichosporoncutaneum,* and *Rhodotorularubra*procured from National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune 411 008.

Experimental: The leaves of *Buteamonosperma* plant was shade dried at room temperature and ground in a manual mill to get coarse powder. It was kept in the air tight polythene bag and stored at a dry place. The powdered material was extracted with water as a solvent by using soxhlet apparatus. The extract was concentrated for further studies at 40 ^{o}C in water bath. The test extract then dried, crushed and stored in air tight bottle for further study. The acidic ingredients present in the extracts were separated by conventional as well as sophisticated chromatographic methods. The major active acidic ingredient i.e. Gallic acid (1a) separated from acidic ingredients was then used for the preparation of analogues under Microwave irradiation.

Synthesis of 3, 4, 5-trihydroxy benzohydrazide (2a): Gallic acid (0.01 mol), methanol (0.03 mol) and hydrazine hydrate (0.02 mol) were mixed and stirred for five minutes. The reaction mixture was exposed to microwave irradiation at low frequency for 45 seconds. The product thus obtained was crystallized by using ethanol.

Synthesis of 5-(4-amino-5-sulfanyl-4H-1, 2, 4-triazole-3-yl) benzene-1, 2, 3-triol (3a):3, 4, 5-Trihydroxy benzohydrazide (II) (0.01 mol), carbon disulphide (0.03 mol), potassium hydroxide (0.02 mol) and hydrazine hydrate (0.03 mol) were mixed together and exposed to microwave irradiation at low frequency for 45 seconds. The yellow colour product thus separated was crystallized by ethanol.



1a 2a 3a

The isolated active ingredient and synthesized analogues were characterized on the basis of elemental analysis, molecular weight determination, and spectral data: The details thereof are as:

COMPOUND (1A):

Yield: 40%, ***M.P.*****:** 250 °C, ***Elemental analysis for $C_7H_6O_5$*****:** Found C =49.40,H = 3.52, O = 47.00, Calculated C = 49.42, H = 3.55, O = 47.02 %. ***UV spectrum (EtOH):***λmax283 nm (n→π*).

IR spectrum, ν, cm^{-1}: 3367.61, 3289.24, 3064.85, 3011.46 (-OH stretching), 3064.85 (Ar-H stretching), 1702.93, 1618.06 (two C=O absorptions), 1600-1450 (aromatic ring), 1300-1000 (C-O). ***^{1}H NMR spectrum (400 MHz, $CDCl_3$):***δ ppm 4.801 (3H, s, aromatic C-O**H**), 7.087-7.221 (2H, s, Ar-**H**).

COMPOUND (2A):

Yield:75%, ***M.P.:*** 192 °C, ***Elemental analysis for $C_7H_8N_2O_4$:***Found C = 45.40, H = 4.32, O = 34.73, Calculated C = 45.66, H = 4.38, N = 15.21, O = 34.75 %.

UV spectrum (EtOH):λmax283 nm (n →π*);***IR spectrum ν, cm^{-1}:*** 3754 (-NH_2 stretching), 3714 (overtone of 1658), 3273 (-NH stretching/-OH stretching), 2375, 2341(-CH stretching) 1658 (-NH bending, primary amine), 1614 (C-O stretching), 1541(NH bending, secondaryamine), 769 (-NH oop). ***^{1}H NMR spectrum (400 MHz, $CDCl_3$):*** δ ppm 1.902 (2H, s, primary amine), 2.007(1H, s, secondary amine), 4.800 (3H, s, aromatic C-OH),7.015 (2H, s,Ar-H).

COMPOUND (3A):

Yield: 70%, **M.P.:** 166 °C, **Elemental analysis for $C_8H_8N_4O_3S$:** Found C =40.00, H = 3.30, N= 23.30, O = 19.92, S = 13.29, Calculated C = 40.00, H = 3.36, N= 23.32, O =19.98, S = 13.35 %. **UV spectrum (EtOH):**λmax366 nm (n →π*). **IR spectrum, ν,cm^{-1}:** 3273 (-OH stretching), 3178 (-NH_2 stretching) 2956 (Ar-H stretching), 2380 (-SH stretching), 1638, 1527 (Ar C=C stretching), 1487 (-CN stretching), 1527 (-NH bending, primary amine), 753-678 (monosubstituted oop).**^{1}H NMR spectrum (400 MHz, $CDCl_3$):**δ ppm1.943 (2H, s,primary amine), 2.054 (1H, s, aromatic C-S**H**), 4.525-5.192 (3H, s, aromatic C-O**H**) 7.033 (2H, s, Ar-**H**).

Antimicrobial Assay: The crude acidic ingredients, major acidic ingredient (1a), analogues prepared (2a & 3a) along with whole extract of leaves were screened for their antibacterial potency

by cup plate agar method[4,5] against bacterial species *viz.*,*Streptococcus pyogenes, Nocardiacalcarea, Trichosporoncutaneum,* and *Rhodotorularubra*. The petriplates were prepared with 25ml sterile Mueller Hinton Agar. A sterile cork borer (8 mm) was used to make wells in each plate.1 ml inoculums' suspension was swabbed uniformly over the agar medium to get uniform distribution of bacteria. After labelling the plates 100µl of each test compound (at concentration of 0.01 mol) was added aseptically into the wells. The petriplates were then incubated at 37°C for 24 hrs during which the activity was evidenced by the presence of zone of inhibition surrounding the well. The negative control was prepared using respective solvent. *Ampicilin disc* (10 mcg/disc) and *Vancomycin disc* (30 mcg/disc) were used as positive control. The zones of inhibition were recorded in millimetres by using Himedia Zone Reader Scale.

Table- 1: Antibacterial activity of test compounds:

Extracts & analogues	**Concentration**	**Inhibitory zones in mm**			
		S. pyogenes	*N. calcarea*	*T. cutaneum*	*R. rubra*
1) Crude acidic ingredients	0.01 mol	18	22	18	20
2) Active acidic ingredient (1a)	0.01 mol	24	24	20	22
3) Analogue (2a)	0.01 mol	30	26	22	24
4) Analogue (3a)	0.01 mol	28	28	26	25
5) Whole extract of leaves	0.01 mol	16	14	18	17
6) *Ampicilin*disc	10 mcg/disc	16	20	18	18
7) *Vancomycin*disc	30 mcg/disc	16	20	22	18

Physiological Activity: The analogues prepared (2a & 3a) were screened for their growth promoting impacts on some flowering plants viz. *Papaverrhoeas, Gladiola tristis, Dianthus chinensis, Candy tuft, Gaillardia, Calendula officinalise.*The experimental set up of the study was divided into seed treatment and field experiment.

Seed treatment: With a view to safeguard dormant seed's potential from harmful external agencies, the seed of the test plants were treated by test compounds before sowing.

Field experiment: Pre-germinated quality seeds of *Papaverrhoeas, Gladiola tristis, Dianthus chinensis, Candy tuft, Gaillardia, Calendula officinalise* were procured from genuine agricultural agencies. The beds of black cotton soil, 2.5 x 2.5m size were prepared on an open field. The sowing of seeds of all six flowering plants under examination were done in beds and in earthen pots separately by conventional methods and irrigated as and when required. The plants from each bed and pot were divided into two groups, i.e. A and B which were designated as *'control'* and *'treated'* group plants respectively. The plants from group B were sprayed with the solution of synthesized compounds at fortnightly intervals. The field experiments were conducted to compare the treated plants of group B with untreated plants of controlled group A. In this context, the observation were recorded on 15, 30, 45, 60, 75 and 90 days after sowing; corresponding to early vegetative, late vegetative, flowering, pod filling and pod maturation stages, with special reference to number of leaves and height of shoots. The results of field's experiments with synthesized compounds are tabulated in **Table 1.**

Table-1: Activity of the synthesized compounds (2a), (3a)

Periodicity ofthe observation(in days)	Poppy (*Papaver rhoeas)*				Calendula (*Calendula officinalise)*				Gladiolus (*Gladiola tristis)*				*Gaillardia (Gaillardia aristata)*				Pink (*Dianthus chinensis)*				Candytuft (*Iberis*sp)			
	Shoot height		No of leaves		Shoot height		No of leaves		Shoot height		No of leaves		Shoot height		No of leaves		Shoot height		No of leaves		Shoot height		No of leaves	
	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
Activity of the synthesized compound3, 4, 5-trihydroxy benzohydrazide (2a)																								
15	3	3	10	10	1	1	8	7	2	2	1	2	4	3	4	5	2	2	4	4	3	2	9	5
30	6	7	14	15	3	7	17	18	6	7	2	3	6	8	15	8	5	4	10	8	6	4	15	20
45	9	10	21	25	9	10	28	30	8	9	4	5	8	15	30	20	7	8	15	16	8	7	45	40
60	11	12	22	30	10	16	52	55	15	16	5	6	12	17	50	38	10	12	25	29	12	11	60	70
75	16	17	31	47	14	20	78	85	18	20	6	8	16	20	60	70	13	17	34	41	15	15	100	105
90	20	23	52	78	16	21	98	115	20	21	6	10	20	21	95	105	18	20	50	63	18	19	130	150
Activity of the synthesized compound5-(4-amino-5-sulfanyl-4H-1, 2, 4-triazole-3-yl) benzene-1, 2, 3-triol (3a)																								
15	3	4	9	7	2	4	9	12	2	3	1	1	4	2	4	5	2	2	4	2	3	4	9	10
30	7	7	15	15	4	5	18	28	6	7	2	2	6	5	15	8	5	4	10	6	6	8	15	27
45	10	12	20	21	8	11	30	40	10	11	4	5	8	8	30	20	7	7	15	15	8	12	45	62
60	12	18	22	25	10	15	55	60	15	16	5	6	12	14	50	38	10	11	25	25	12	15	60	100
75	16	22	30	38	13	20	80	100	20	21	6	8	16	18	70	80	13	14	34	34	15	19	100	145
90	20	25	47	50	15	22	100	130	22	25	6	10	20	22	100	100	18	19	50	50	18	24	130	150

Note: C= Control, T= Treated

RESULTS AND DISCUSSION

The results obtained for the antibacterial test performed with analogues prepared from isolated acidic ingredient along with mixture of acidic ingredients and whole extract of *Buteamonosperma* leaves presented in Table 1. The analogues prepared were found to be most effective against all pathogenic bacteria. The isolated active acidic ingredient was found to be more effective as compared with the mixture of crude acidic ingredients. The whole extract of leaves found to be moderately active. The results obtained were assessed on their comparison with the activities of standard antibacterial agent like *Ampicilin* and *Vancomycin* as control.

The analogues prepared (2a & 3a) were screened for their growth promoting impacts on some flowering plants viz. *Papaverrhoeas, Gladiola tristis, Dianthus chinensis, Candy tuft, Gaillardia, Calendula officinalise.*The efforts have been made to examine and analyze the morphology of treated plants. When the comparison of morphological characters was made between those of treated and control groups plants, it was interesting to note that all the plants exhibited significant shoot growth, and considerable increase in the number of leaves as compared to those of untreated ones.

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Tautomerism and multiple modelling enhance the efficacy of QSAR: antimalarial activity of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Tautomerism and multiple modelling enhance the efficacy of QSAR: antimalarial activity of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl

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Abstract In the present study, sixty phosphoramidate and phosphorothioamidate analogues of amiprophos methyl (APM) previously reported as potential antimalarial agents were selected to build GA-MLR QSAR models to determine the features that govern the antimalarial activity. In addition, field similarity analysis was performed to determine the molecular fields that are responsible for the difference in the activity. The two tautomeric forms, possible for the molecules in the present study, were considered to determine the effect of tautomerism on QSAR modelling. In the present analysis, a simplistic approach was employed with the assumption that all the molecules either exist in keto-type tautomeric form or in enol-type form. To get more results from QSAR analysis, multiple models were developed. All the models have been thoroughly validated according to the OECD principles. The best four-parametric GA-MLR QSAR model is with $R^2 = 0.787$ and $R^2_{ex} = 0.806$ for the keto form, and $R^2 = 0.785$ and $R^2_{ex} = 0.770$ for the enol form. In addition, optimum values for more easily interpretable descriptors like molecular weight (*MW*), lipophilicity (*ALogP*), etc., have been determined. The analysis reveals that consideration of tautomerism and multiple models development enhance the efficiency of QSAR analysis for lead optimization and for prediction of the activities of as-yet untested molecules.

Keywords Antimalarial activity · Amiprophos methyl analogues · QSAR · Field similarity · Tautomerism

Abbreviations

GA	Genetic algorithm
MLR	Multiple linear regression
QSAR	Quantitative structure–activity analysis
WHO	World Health Organization
ADMET	Absorption, distribution, metabolism, excretion and toxicity
OLS	Ordinary least square
QSARINS	QSAR Insubria

Introduction

The recent WHO report on malaria (http://www.who.int/malaria/en/2013) clearly indicates that though malaria has its major presence in undeveloped and developing countries from Africa, Asia and South America, yet, its ill-effects are global. This vector-borne disease is responsible for more than 2 million cases every year (http://www.who.

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int/malaria/en/2013; Mahajan *et al.,* 2012; Masand *et al.,* 2013c). Recently, many researchers have reported the emergence of multidrug-resistant strain of *Plasmodium falciparum* (*P. falciparum*), the main etiological agent of malaria, thereby, making the complete eradication of malaria a more difficult task. To curb this deadly disease, established antimalarial classes like artemisinins, aminoquinolines, etc., and largely unexplored many new compounds such as prodiginines, xanthones, amiprophos methyl derivatives, etc., have been tested in last decade (Hwang *et al.,* 2011; Mahajan *et al.,* 2012; Mara *et al.,* 2011; Mara *et al.,* 2013; Masand *et al.,* 2010b; Masand *et al.,* 2013c; Ojha and Roy, 2012).

Amiprophos methyl derivatives have received considerable attention in the last decade because of their insecticidal, antimicrobial and herbicidal properties, and ease of synthesis with the possibility to vary the structure relatively easy (Mara *et al.,* 2011; Mara *et al.,* 2013). Despite these advantages and the efforts executed, search for amiprophos methyl derivatives with high activity and better ADMET profile still persists.

Computer-assisted drug designing (CADD) has secured a unique place in modern drug designing because of quicker, cheaper and result-oriented analysis. Quantitative structure–activity relationship (QSAR), a thriving branch of CADD technique, is useful to determine the structural and pharmacophoric patterns that govern the activity of congeneric molecules (Scior *et al.,* 2009; Yuriev *et al.,* 2011). Tautomerism is an import molecular phenomenon that has significant influence on the different aspects of molecules, like pKa, LogP, solubility and other properties (Pospisil *et al.,* 2003a). Recently, a minor tautomer (in solution) of barbiturate analogue was found to be the active form in a 1.8 Å crystal structure of matrix metalloproteinase 8. Another example is that of pterin tautomer bound to the 2.3 Å structure of ricin toxin A-chain (Martin, 2010). Thus, a thermodynamically favoured tautomeric form in the solution may not be the 'bioactive tautomeric form' during the course of mechanism. Moreover, a molecule may interact in different tautomeric forms with different receptors (Martin, 2009, 2010; Masand *et al.,* 2013a; Oellien *et al.,* 2006; Pospisil *et al.,* 2003b; Thalheim *et al.,* 2010; Zou *et al.,* 2007). Herein, we have considered the influence of tautomerism on QSAR model development and multiple QSAR modelling with the determination of optimum values for some of the more easily interpretable descriptors for phosphoramidate and phosphorothioamidate analogues of amiprophos methyl. In the present study, we have performed integrated QSAR and field similarity analysis to determine the structural features that steer the antimalarial activity of amiprophos methyl derivatives.

Materials and methods

Dataset

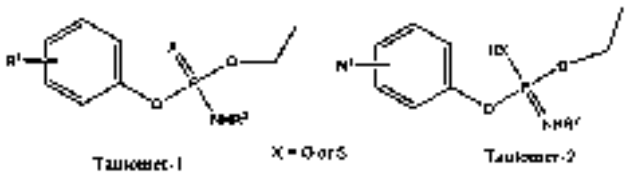
The dataset consists of sixty phosphoramidate and phosphorothioamidate analogues of amiprophos methyl previously reported as potential antimalarial agents (Mara *et al.,* 2011; Mara *et al.,* 2013). The compounds were tested for inhibitory activity against *P. falciparum*. The experimental antimalarial activities reported as IC_{50} (μM) were converted to pIC_{50} (M) for QSAR analysis (Jawarkar *et al.,* 2010; Mahajan *et al.,* 2010, 2012; Masand *et al.,* 2010a; Masand *et al.,* 2010b; Masand *et al.,* 2013b; Masand *et al.,* 2012, 2013c). The compounds possess varying substituents at different positions, cyclic and non-cyclic derivatives and tautomerism also. For the present analysis, both the tautomeric forms were considered. The structures were drawn using ChemDraw 2008 with default settings followed by energy optimization with MMFF94 field. The general structures for both the tautomers are depicted in Table 1 along with the experimental data [IC_{50} (μM) and pIC_{50} (M)].

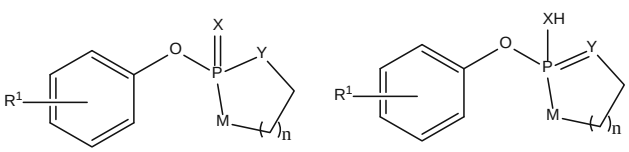
Descriptor calculation and model development

In the present analysis, a simplistic approach was employed with the assumption that all the molecules exist either in first tautomeric (keto-type) form or in other (enol-type) form. Therefore, the first set (Set 1) consists of 60 molecules in keto-type tautomeric form only, while the second set (Set 2) consists of 59 molecules but in enol-type of tautomeric form only. For one of the molecules, **44**, M and Y are oxygen and sulphur, respectively (see Table 1); therefore, enolization was not possible for it, and hence it was excluded from set 2. For both the tautomeric forms, a good number of descriptors were generated for the lowest energy conformer using e-Dragon followed by the removal of highly collinear ($|R| > 0.70$) and constant (>75 %) descriptors to avoid the inclusion of multi-collinear and spurious variables in GA-MLR model, using objective feature selection in QSARINS v1.2 (Gramatica *et al.,* 2013, 2014). This substantially decreased the total set of descriptors from 3,224 to 224 and 334 for sets 1 and 2, respectively. The reduced descriptors pool consists of zero-, one-, two- and three-dimensional descriptors, charge descriptors and molecular properties. Subjective feature selection was used to build the statistically robust OLS QSAR models using genetic algorithm (GA) in QSARINS. Thorough statistical validation of all the models for the two sets was performed according to OECD principles; only models with high internal and external predictivities were considered (Chavan *et al.,* 2013). To develop simple and informative QSAR models, the heuristic search was limited to four variables per model.

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Table 1 Experimental data. IC_{50} and pIC_{50} for phosphoramidate and phosphorothioamidate analogues of amiprophos methyl

S. no.	R^1	R^2	X	IC_{50} (μM)	pIC_{50} (M)
					
1.	4-CH_3-2-NO_2	*i*-Propyl	S	4	5.398
2.	4-CH_3-2-NO_2	*i*-Propyl	O	126	3.900
3.	2-CH_3-4-NO_2	*i*-Propyl	O	128	3.893
4.	2-CH_3-5-NO_2	*i*-Propyl	O	128	3.893
5.	3-CH_3-4-NO_2	*i*-Propyl	O	79	4.102
6.	2-CH_3-3-NO_2	*i*-Propyl	O	128	3.893
7.	2-CN-4-CH_3	*i*-Propyl	O	128	3.893
8.	2-Br-4-CH_3	*i*-Propyl	O	39	4.409
9.	2-CH_3O-4-CH_3	*i*-Propyl	O	128	3.893
10.	2-Cl-4-CH_3	*i*-Propyl	O	39	4.409
11.	2-CF_3	*i*-Propyl	O	87	4.060
12.	3-CF_3	*i*-Propyl	O	50	4.301
13.	4-CF_3	*i*-Propyl	O	50	4.301
14.	2-Naphthol	*i*-Propyl	O	72	4.143
15.	1-NO_2-2-Naphthol	*i*-Propyl	O	87	4.060
16.	4-CH_3-2-NO_2	*n*-Butyl	O	28	4.553
17.	4-CH_3-2-NO_2	*i*-Butyl	O	75	4.125
18.	4-CH_3-2-NO_2	*n*-Pentyl	O	51	4.292
19.	4-CH_3-2-NO_2	Cyclopentyl	O	47	4.328
20.	5-CH_3-2-NO_2	*n*-Propyl	O	102	3.991
21.	4-CF_3	NH_2	O	79	4.102
22.	4-CF_3	*n*-Butyl	O	32	4.495
23.	4-CF_3	sec-Butyl	O	40	4.398
24.	4-CF_3	Cyclobutyl	O	45	4.347
25.	4-CF_3	*n*-Pentyl	S	4.5	5.347
26.	4-CF_3	Cyclopentyl	O	26	4.585
27.	4-CF_3	Cyclopentyl	S	8.6	5.066
28.	4-CF_3	Cyclohexyl	O	43	4.367
29.	4-CF_3	*n*-Heptyl	O	44	4.357
30.	4-CF_3	Piperidino	O	84	4.076
31.	4-CF_3	Pyrrolidino	O	56	4.252
32.	4-CF_3	Morpholino	O	98	4.009
33.	2-CH_3-4-NO_2	*n*-Pentyl	S	6.9	5.161
34.	2-CH_3-4-NO_2	Cyclopentyl	S	1.6	5.796
35.	4-Br	Cyclopentyl	O	17	4.770
36.	4-Br	Cyclopentyl	S	23	4.638

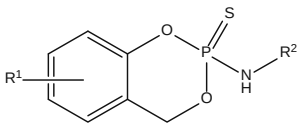
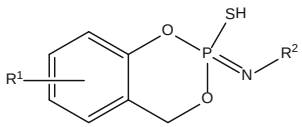
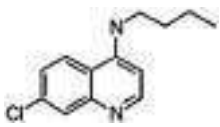
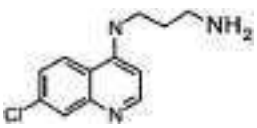


M = O, Y = N/S, n = 1 or 2
Tautomer-1

M = O, Y = N/S, n = 1 or 2
Tautomer-2

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Table 1 continued

S. no.	R^1	R^2	X	IC_{50} (μM)	pIC_{50} (M)
37.	4-CH_3-2-NO_2	–	S	77	4.114
38.	2-CH_3-4-NO_2	–	S	51	4.292
39.	2-CH_3-4-NO_2	–	S	128	3.893
40.	2-CH_3-5-NO_2	–	S	24	4.620
41.	2-CH_3-5-NO_2	–	S	108	3.967
42.	4-CF_3	–	S	108	3.967
43.	4-CF_3	–	S	62	4.208
44.	4-CF_3	–	S	64	4.194
	 Tautomer-1	 Tautomer-2			
45.	H	*i*-Pr	S	62	4.208
46.	H	*n*-Pr	S	95	4.022
47.	H	*i*-Bu	S	58	4.237
48.	4-NO_2	*i*-Pr	S	108	3.967
49	4-NO_2	*i*-Bu	S	118	3.928
50.	Naphtal-2-ol	*i*-Propyl	O	128	3.893
51.	2-OH-4-CH_3-3-NO_2pyridine	*i*-Propyl	O	128	3.893
52.	2-OH-5-CF_3pyridine	*i*-Propyl	O	25	4.602
53.	2-OH-5-CF_3pyridine	*i*-Propyl	S	29	4.538
54.	2-OH-5-CF_3pyridine	Cyclopentyl	O	23	4.638
55.	2-OH-4-CH_3-5-NO_2pyridine	*i*-Propyl	O	25	4.602
56.	4-OH pyridine	i-Propyl	O	128	3.893
57.	8-OH quinoline	Cyclopentyl	S	25	4.602
58.	6-OH quinoline	Cyclopentyl	S	19	4.721
59.	4-CF_3 phenyl		S	0.038	7.420
60.	4-CH_3-2-NO_2		S	0.64	6.194

The general procedure (employed on both the tautomeric forms) for building the GA-MLR QSAR models is as follows:

(1) The set was divided randomly, using random splitting option in QSARINS (Gramatica *et al.,* 2013, 2014), into training and prediction sets of 48 (i.e. 80 % training set) and 12 (i.e. 20 % prediction set), respectively. The training set was used for model development, and the prediction set for the evaluation of predictivity on new chemicals, with the condition that the molecules which constitute the prediction set for set 1 also constitute the prediction set of set 2. In short, prediction sets of both the sets are identical. This was done for the appropriate comparison.

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(2) QSARINS was used to build mono-parametric to tetra-parametric OLS models for both the sets (for sets 1 and 2) using default settings, except that Lack of Fit (LOF) was set to a value of 0.5. The selected fitness function to maximize in GA was Q^2. The descriptors that have been selected in models 1–4 are available in the supplementary information.

(3) All the models were subjected to internal as well as external validation along with Y-scrambling using QSARINS. The various parameters for internal validation include determination coefficient R^2, leave-one-out (LOO) cross-validation Q^2, leave-many-out (LMO) Q^2_{LMO}, coefficient of determination for Y-scrambling R^2_{Yscr}, and root mean squared error (RMSE). The LMO was repeated 500 times with 30 % of the objects left out randomly from the training set each time, and then the mean value of Q^2_{LMO} has been reported. The external validation parameters are $\mathrm{RMSE_{ex}}$, $\mathrm{MAE_{ex}}$, R^2_{ex}, Q^2_{F1}, Q^2_{F2}, Q^2_{F3} and $\mathrm{CCC_{ex}}$ (Chirico and Gramatica 2011, 2012; Consonni *et al.,* 2009; Schuurmann *et al.,* 2008).

(4) Another important step carried out for the model's validation was to check the model applicability domain (AD) and has been represented by Williams plots in Fig. 2. It is a theoretical region defined by the descriptors used in the modelling. It is evaluated by leverage (or hat) analysis using the formula: $h_i = x_i\ (X^{\mathrm{T}}\ X)^{-1}\ x_i^{\mathrm{T}}$, where $(i = 1, \ldots, m)$, x_i is the descriptor row vector of the query compound i, m is the number of query compounds and X is the $n \times p$ matrix of the training set (p is the number of descriptors in the model and n is the number of training set compounds). The limit of the model domain is quantitatively defined by the leverage cutoff h^*, set as $3(p + 1)/n$. A leverage bigger than h^* for the training set means that the compound is very dominant in determining the model, while for the test set (X outlier), it means that the prediction is the substantial extrapolation of the model and could be unreliable. Meanwhile, a compound with a standardized residual greater than 3σ (3 standard deviation units) is recognized as a Y outlier (Masand *et al.,* 2013d; Tropsha and Golbraikh, 2007; Yoona *et al.,* 2013).

Results and discussion

For both the sets, the GA analysis provided a good number of MLR models with almost similar statistical characters comprising different descriptors. Generally, in such a situation, the QSAR modellers choose only one MLR model on the basis of its statistical performance. The drawbacks, however, of this 'first among equals' approach are (1) for a QSAR model comprising esoteric descriptors only, appropriate and feasible interpretation in terms of structural features is more tricky and exigent; (2) a single QSAR model may be influenced by (i) the composition of training and test sets and (ii) some molecules in the dataset. Thus, it seems rational that building and reporting multiple models or consensus modelling (Yoon *et al.,* 2013) are the feasible and appropriate solutions to overcome the drawbacks of 'first among equals' approach. Therefore, in the present study, multiple models have been built for both the sets. The models that do not satisfy the OECD principles were rejected. The GA-MLR QSAR models for both the sets along with their physical interpretation are as follows:

Set 1 (Keto form)

Model 1 $p\mathrm{IC_{50}} = 2.3367\ (\pm 0.7641) + 1.5695\ (\pm 1.7697)\ R6p\ -0.0306\ (\pm 0.0254)\ nBT + 0.4084\ (\pm 0.1941)\ nN + 0.6338\ (\pm\ 0.1605)\ ALogP.$

Model 2 $p\mathrm{IC_{50}} = 2.3499\ (\pm 0.8363) + 0.4006\ (\pm 0.2031)\ nN + 0.6195\ (\pm 0.1657)\ AlogP - 0.0273\ (\pm 0.0260)\ Se + 1.3502\ (\pm 1.8907)\ R6p.$

The above models, with usual meaning of the symbols, are statistically robust and predictive with satisfactory values of the various parameters for internal and external validation (see Table 2). The high values of R^2, Q^2, R^2_{ex}, Q^2_{Fn} and $\mathrm{CCC_{ex}}$ indicate that the models are statistically acceptable and also have good external predictivity (Chirico and Gramatica 2011, 2012). These parameters, additionally vindicated by the low correlation among the descriptors, point out that these models are not fortuitous (see supplementary information). A QSAR model is primarily build for the following two reasons: (1) to predict the activity of as-yet untested molecules and (2) to get the relevant information useful for the lead optimization i.e. interpretation of the model for mechanistic details.

The positive coefficients for *ALogP* (Ghose/Crippen octanol/water partition coefficient, represents lipophilicity of molecule), *nN* (number of nitrogen atoms) and *R6p* (R autocorrelation of lag 6/weighted by atomic polarizabilities) indicate that these descriptors have positive correlation with the activity, whereas the reverse is true for *nBT* (number of bonds) and *Se* (Sum of atomic Sanderson electronegativities). The relatively low value of std. coeff. 0.1491 and −0.2659 for *R6p* and *Se*, respectively, indicates that these descriptors have relatively low influence on the activity profile of the molecules. For lipophilicity (*ALogP*), the standardized coefficient (std. coeff.) is 1.0005 and 0.9780 in models 1 and 2, respectively. However, for the descriptor *nN*, the std. coeff. is 0.4249 and 0.4168 in models 1 and -2, respectively. Thus, these two descriptors play a crucial role in deciding the activity. Of these two descriptors,

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Table 2 Statistical parameters for different GA-MLR models 1–4 and combined set model

S. no.	Statistical parameter	Model 1 Keto form	Model 2 Keto form	Model 3 Enol form	Model 4 Enol form	Combined set model
1.	N_{tr}	48	48	47	47	96
2.	N_{ex}	12	12	12	12	23
3.	Number of descriptors	4	4	4	4	4
Fitting criteria						
4.	R^2_{tr}	0.79	0.78	0.78	0.78	0.72
5.	$R^2_{adj.}$	0.77	0.76	0.76	0.76	0.71
6.	$RMSE_{tr}$	0.28	0.29	0.29	0.29	0.32
7.	MAE_{tr}	0.23	0.23	0.22	0.21	0.26
8.	CCC_{tr}	0.88	0.88	0.88	0.88	0.84
9.	s	0.30	0.30	0.30	0.30	0.33
10.	F	39.69	38.20	37.81	38.09	59.33
Internal validation criteria						
11.	R^2_{cv} (Q^2loo)	0.72	0.71	0.70	0.70	0.68
12.	$RMSE_{cv}$	0.32	0.33	0.34	0.34	0.34
13.	MAE_{cv}	0.27	0.27	0.26	0.25	0.28
14.	Q^2_{LMO}	0.54	0.54	0.58	0.60	0.58
15.	CCC_{cv}	0.83	0.83	0.82	0.82	0.81
16.	R^2_{Yscr}	0.08	0.08	0.09	0.09	0.04
External validation criteria						
17.	$RMSE_{ex}$	0.30	0.30	0.30	0.30	0.27
18.	MAE_{ex}	0.25	0.24	0.27	0.27	0.23
19.	R^2_{ex}	0.81	0.81	0.85	0.85	0.88
20.	Q^2_{F1}	0.78	0.78	0.76	0.77	0.82
21.	Q^2_{F2}	0.77	0.77	0.76	0.76	0.82
22.	Q^2_{F3}	0.76	0.76	0.76	0.77	0.80
23.	CCC_{ex}	0.89	0.89	0.90	0.90	0.92

lipophilicity has more influence on the activity than *nN*, as evident by its higher std. coeff. in models 1 and 2 and difference in the activity of molecules **21**–**32**. The negative influence of *nBT* is further vindicated by the negative std. coeff. of −0.2988 in model 1. A comparison of the following pairs of molecules **50** with **52**, **51** with **53** and **54** with **55** reveals that the values of *nN*, *nBT* and *ALogP* are either same or very close for molecules in these pairs, yet there is good difference in the activity; thus, the descriptor which influences the activity of these molecules is *R6p*. *R6p*, a GETAWAY 3D descriptor, is a type of spatial autocorrelation descriptor. The autocorrelation is weighted by different physicochemical properties such as Sanderson's electronegativities, atomic polarizabilities, etc., at a certain topological distance. It considers the leverage of the atoms and their inter-atomic distance within the molecule relative to each other. For *R6p*, the topological distance is 6 and the weight has been made by atomic polarizabilities as stated above. Thus, it signifies the presence of polar atoms at a relative topological distance of 6 in the molecule, i.e. representing the polar environment within the molecule. A largest value of *R6p* is expected when more number of highly polar atoms are distant from the centre of the molecule at a topological distance of 6 and at the same time close to each other in the molecular space which has, besides, a significant favourable effect on the activity of the molecule. For better clarification, the topological distance of 6, in turn *R6p*, has been highlighted (with pink colour) between the polar atoms for molecules **38** and **40**, as representatives (see Fig. 1).

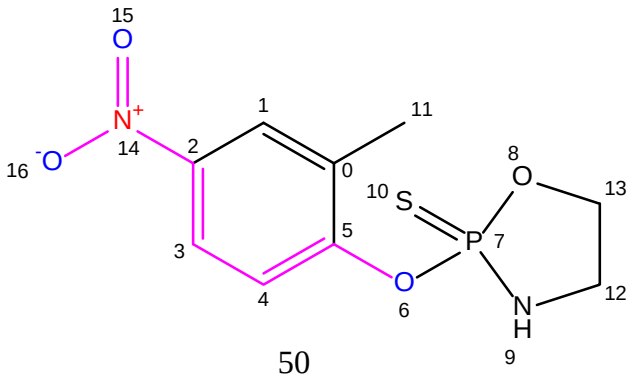
Set 2 (Enol form)

Model 3 $pIC_{50} = 2.1974\ (\pm 0.5893) + 1.3098\ (\pm 1.2403)\ E3m + 0.4230\ (\pm 0.2207)\ nN - 0.1044\ (\pm 0.1144)\ nO + 0.4600\ (\pm 0.1019)\ ALogP.$

Model 4 $pIC_{50} = 1.8452\ (\pm 0.4747) + 1.6878\ (\pm 1.1720)\ E3m + 0.4117\ (\pm 0.2111)\ nN - 0.2181\ (\pm 0.2303)\ nArNO_2 + 0.4701\ (\pm 0.0991)\ ALogP.$

The symbols have their usual meaning (Chirico and Gramatica, 2011, 2012; Gramatica *et al.,* 2013; Yoon *et al.,* 2013). All the above-mentioned models satisfy most of the statistical parameters, i.e. they are statistically acceptable.

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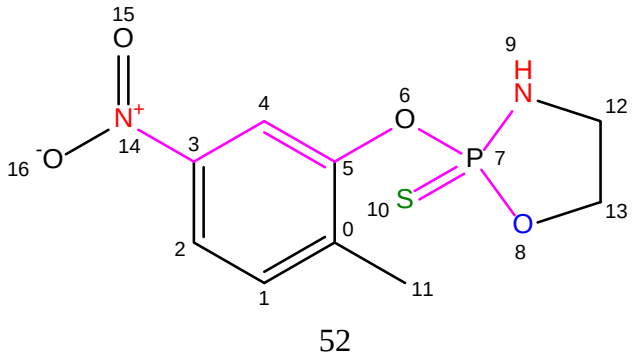


Fig. 1 Physical interpretation of *R6p* using molecule numbers **50** and **52** as representatives

It is clear that lipophilicity (*ALogP*) (Std. Coeff. 0.7246 and 0.7405 in models 3 and 4, respectively) has significant positive role in deciding the activity; the same is acceptable for *nN* (Std. Coeff. 0.3848 and 0.3745 in model 3 and 4, respectively) and *E3m* (Std. Coeff. 0.1837 and 0.2367 in model 3 and 4, respectively). However, *nO* (Std. Coeff. −0.1762 in model 3) and $nArNO_2$ (Std. Coeff. −0.1762 in model 4) have negative influence on activity. The predicted residuals, statistical parameters and correlation matrices for descriptors used for different GA-MLR models 1–4 have been listed in tables 3–5 in supplementary information.

A four-parametric QSAR model based on a dataset comprising both tautomeric forms has also been developed.

Combined set model $pIC_{50} = 2.2298\ (\pm 0.3391) + 0.3463\ (\pm 0.1126)\ nN + 0.2501\ (\pm 0.1349)\ nS + 0.3910\ (\pm 0.2538)\ nArX + 0.4279\ (\pm 0.0775)\ ALogP$.

The graphs for correlation, residuals and Y-randomization have been depicted in Figs. 1 and 2 of supporting information. Further, the Williams plot has been used to represent the AD of the models. From Fig. 2, it is evident that some molecules lie outside the AD of the entire reported model.

It appears that the QSAR models for both the tautomeric forms are statistically significant and independent of tautomerism. The plausible reasons for negligible influence of the tautomerism on QSAR models could the insensitivity of the descriptors in recognization and discrimination of tautomers. Moreover, tautomerization is a natural, rapid and dynamic phenomenon, resulting in rapid equilibrium among the tautomers.

Determination of optimum values of different descriptors

Even though many QSAR modellers report properly validated QSAR equations, which are efficient to guide for the development of novel drugs or modification of existing drugs, they are not practised due to the following reasons: (i) complexity in understanding and interpretation of QSAR equation in terms of structural or pharmacophoric features; (ii) the accurate and reproducible computation or estimation of descriptors is either very complex or resource consuming; (iii) computational facilities/resources like sophisticated and particular softwares may not be accessible to organic chemist to compute the reported descriptors in the QSAR equation; (iv) in addition, some other descriptors may have good correlation with the activity but are not included in QSAR equation due to some reasons; and (v) the organic chemist may not be well skilled or trained in QSAR.

Therefore, in the present study, we have determined the optimum values for more easily interpretable different descriptors to gauge the discovery of novel small molecules with the specified chemical properties. A very simple yet effective method to establish the optimal value of any descriptor is to develop either parabolic (quadratic) or bilinear equation (Pinto *et al.,* 2005; Abreu *et al.,* 2009). These functions presume that the correlation between the descriptor and the activity is non-linear in nature with the peak of the curve representing the optimum value. R, R^2, R^2_{adj}, F, *Spress*, *SDEP* and s were calculated to check the robustness of the bilinear/parabolic equations. Though we have compared the activities of the molecules of the dataset in terms of descriptors like lipophilicity/hydrophobicity, number of bonds, molecular weight, etc., for which we have determined the optimum value, we make it clear that the combined or converse effect of confounding factors/descriptors do have additional influence on the activity profile of the compounds. The optimum values will be the handy tool for medicinal chemists in developing novel amiprophos methyl analogues with improved antimalarial activity profile.

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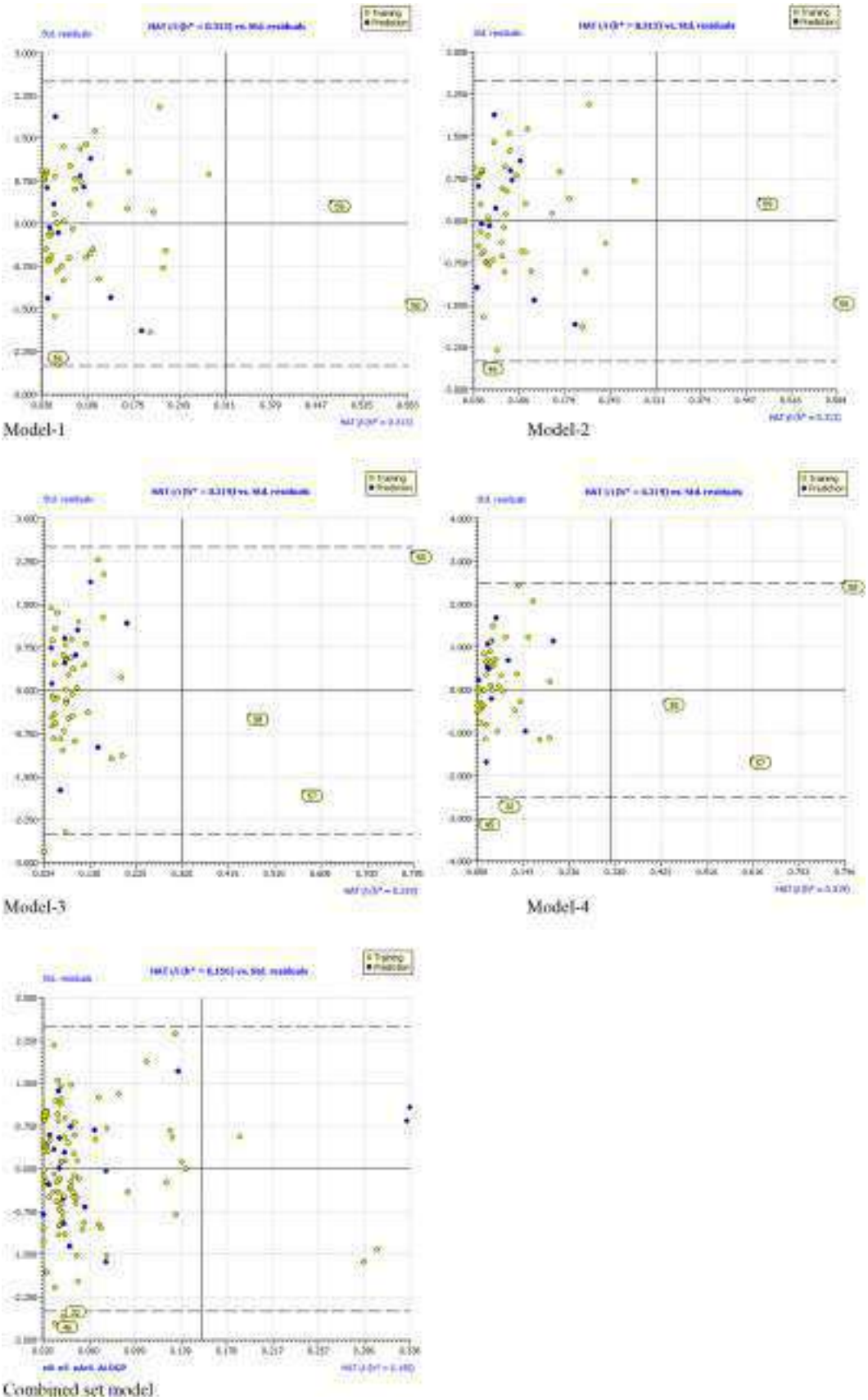


Fig. 2 Applicability domain representation using Williams plot for models 1–4 and combined set model

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Molecular weight (*MW*)

Model 5 $p\mathrm{IC}_{50} = +0.0002\ (\pm 0.0070)\ MW + 0.0117\ (\pm 0.0081)\ \mathrm{Log}\ (\beta\ 10^{MW} + 1) + 4.0275\ (\pm 2.0353)$.

$N\mathrm{tr} = 60$, $R = 0.808$, $R^2 = 0.6522$, $R^2_{\mathrm{adj.}} = 0.634$, $Q^2 = 0.573$, $s = 0.375$, $F = 34.997$, $p < 0.0001$, *SPress* = 0.415, *SDEP* = 0.408, *Log* $\beta = -299.441$, *MW-Optimum* = 297.777, Outliers = compound numbers **32** and **46.**

Number of carbon atoms (*nC*)

Model 6 $p\mathrm{IC}_{50} = +0.0763\ (\pm 0.0550)\ nC + 1.1983\ (\pm 0.4840)\ \mathrm{Log}\ (\beta\ 10^{nC} + 1) + 3.3909\ (\pm 0.6794)$.

$N\mathrm{tr} = 60$, $R = 0.783$, $R^2 = 0.613$, $R^2_{\mathrm{adj.}} = 0.593$, $s = 0.395$, $F = 29.607$, $p < 0.0001$, $Q^2 = 0.588$, *SPress* = 0.407, *SDEP* = 0.400, *Log* $\beta = -20.043$, *nC-Optimum* = 18.875, Outliers = compound numbers **23**, **32** and **46.**

Lipophilicity (*ALogP*)

Model 7 $p\mathrm{IC}_{50} = +0.2074\ (\pm 0.1638)\ \mathrm{ALogP} + 0.7029\ (\pm 0.3499)\ \mathrm{Log}\ (\beta\ 10^{\mathrm{ALogP}} + 1) + 3.6044\ (\pm 0.4805)$.

$N\mathrm{tr} = 60$, $R = 0.836$, $R^2 = 0.699$, $R^2_{\mathrm{adj.}} = 0.683$, $s = 0.349$, $F = 43.270$, $p < 0.0001$, $Q^2 = 0.664$, *SPress* = 0.368, *SDEP* = 0.362, *Log* $\beta = -4.123$, *ALogP-Optimum* = 3.745, Comment: No outlier.

Sum of atomic polarizabilities (*Sp*)

Model 8 $p\mathrm{IC}_{50} = 0.0186\ (\pm 0.0502)\ Sp + 0.1706\ (\pm 0.0774)\ \mathrm{Log}\ (\beta\ 10^{\ Sp} + 1) + 3.7687\ (\pm 1.2016)$.

$N\mathrm{tr} = 60$, $R = 0.796$, $R^2 = 0.634$, $R^2_{\mathrm{adj.}} = 0.614$, $s = 0.384$, $F = 32.298$, $p < 0.0001$, $Q^2 = 0.554$, *SPress* = 0.424, *SDEP* = 0.417, *Log* $\beta = -26.248$, *Sp*-Optimum = 25.337, Outliers = compound numbers **32** and **46.**

In the above models, the symbols have their usual meanings. A better statistics is possible if the number of congener compounds in the dataset and also the range of the biological data are augmented. In many cases, the acceptable fitting of the equation ($R^2 > 0.60$), though statistically not outstanding, indicates that there prevails optimum value of lipophilicity, molecular weight (*MW*), Sum of atomic polarizabilities (*Sp*) and Number of carbon atoms (*nC*).

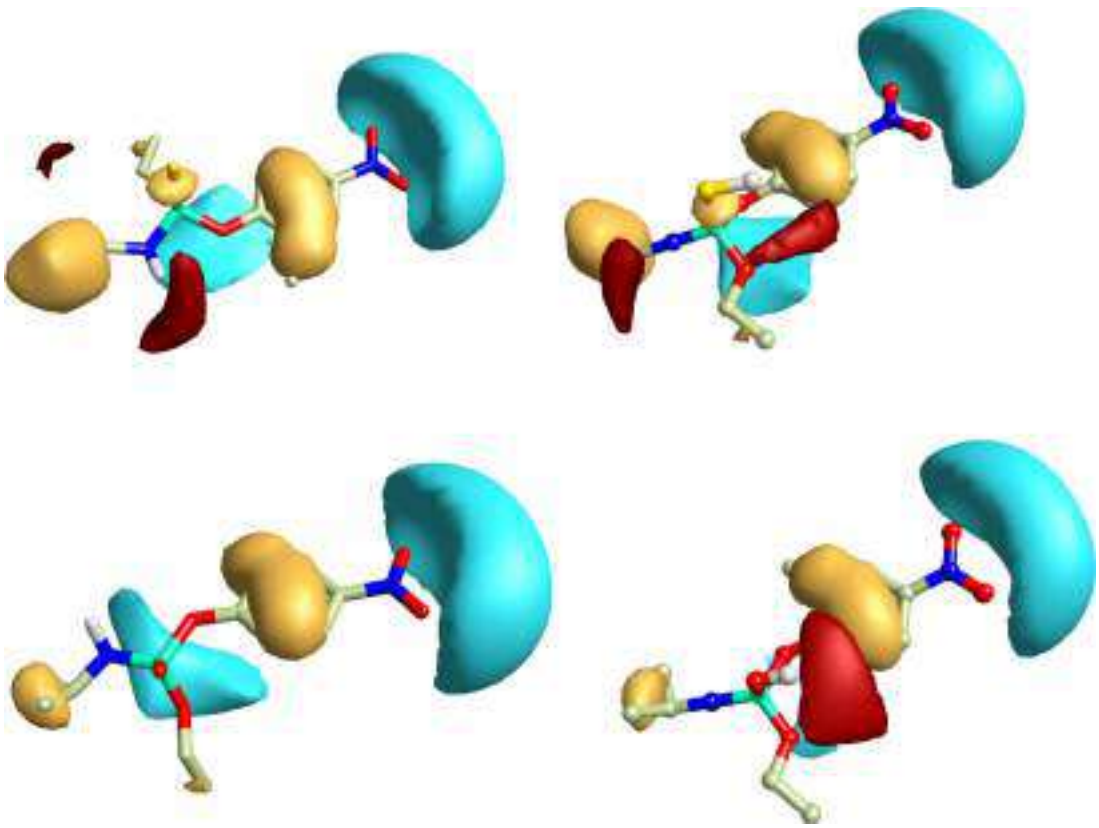


Fig. 3 Field similarity analysis of Mol id **34** (Most active) and Mol id **3** (least active) **34** (Most active) with side view of Keto form (*left*) and enol form (*right*) (*red* positive field, *blue* negative field and *yellow* hydrophobic region) **3** (least active) Side view of Keto form (*left*) and enol form (right) (Color figure online)

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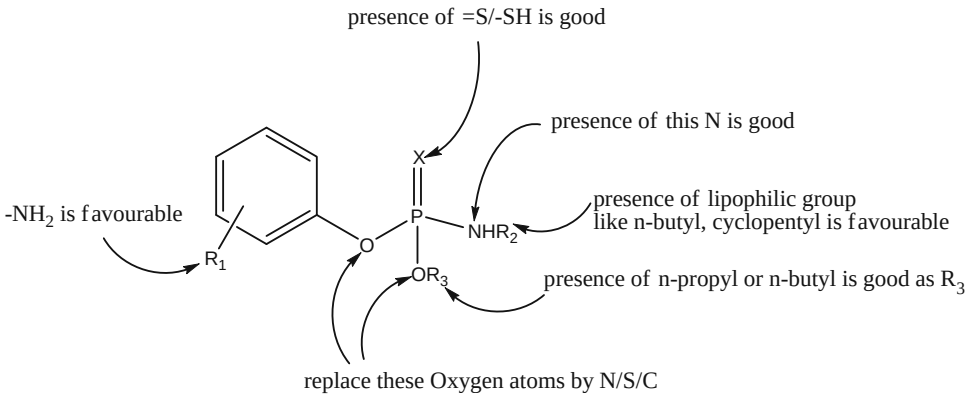


Fig. 4 Summary of SAR, QSAR and field similarity analysis

Field similarity analysis

Field similarity analysis was performed to compare the fields of tautomeric forms of the most active and least active compounds, as representatives, to identify the key features that control the biological activity. The results are as shown below in Fig. 3.

From Fig. 3, it is clear that sulphur is very important for enhancing the activity due to its lipophilicity. The presence of red contour near N reveals that the presence of this positive field is very important for activity. This positive field is also present in the enol form of the least active molecule (compound **3**). This positive field could be a possible reason for the lesser activity of the primary amido **21** ($IC_{50} = 79$ μM) than the tertiary amides **30–32**. In their previous publication, Mara *et al.* (2011) obtained a modest relation ($R^2 = 0.504$) between activity and *clogP* (represents lipophilicity). It is evident from the above figure that the pharmacophoric pattern consists of not only lipophilic region, but also positive and negative fields. Another observation is that a possible reason for the difference in the activities of **34** and **3** could be the presence of bigger lipophilic region due to cyclopentyl ring in **34** (depicted by the yellow-coloured contour) than a relatively small lipophilic region in **3** due to iso-propyl group.

The summary of SAR, QSAR and field similarity analysis are depicted in Figs. 4 and 5.

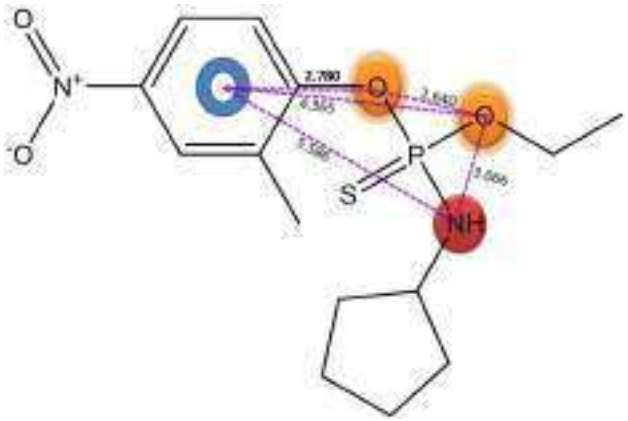


Fig. 5 Summary of SAR, QSAR and field similarity analysis in terms of pharmacophoric pattern. *Blue*, *golden* and *red circles* represent aromatic, H-bond acceptor and H-bond donor, respectively. All the values are in Å (Color figure online)

Conclusions

In the present study, we have investigated the influence of tautomerism on the predictive QSAR model development for antimalarial activity of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl. The four-parametric models satisfy the threshold values for many statistical parameters like R^2_{ex}, Q^2_{F1}, Q^2_{F2}, $Q^2_{F3}$and CCC_{ex}, which are essential to judge the real external predictivity. The analysis indicates that tautomerism has no influence on the statistical performance of QSAR models built using different tautomeric forms. However, important information in terms of structural and pharmacophoric patterns that affect the activity can be extracted when multiple models are built for the different tautomeric forms for the congeners. Thus, tautomerism and multiple modelling improve the efficacy of QSAR for lead optimization and to predict the activities of as-yet untested molecules.

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Disclosure The authors have no other relevant affiliations or involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Original article

Synthesis of α, β-unsaturated carbonyl based compounds as acetylcholinesterase and butyrylcholinesterase inhibitors: Characterization, molecular modeling, QSAR studies and effect against amyloid β-induced cytotoxicity

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ABSTRACT

A series of novel carbonyl compounds was synthesized by a simple, eco-friendly and efficient method. These compounds were screened for anti-oxidant activity, *in vitro* cytotoxicity and for inhibitory activity for acetylcholinesterase and butyrylcholinesterase. The effect of these compounds against amyloid β-induced cytotoxicity was also investigated. Among them, compound **14** exhibited strong free radical scavenging activity (18.39 μM) while six compounds (**1**, **3**, **4**, **13**, **14**, and **19**) were found to be the most protective against Aβ-induced neuronal cell death in PC12 cells. Compounds **4** and **14**, containing *N*-methyl-4-piperidone linker, showed high acetylcholinesterase inhibitory activity as compared to reference drug donepezil. Molecular docking and QSAR (Quantitative Structure–Activity Relationship) studies were also carried out to determine the structural features that are responsible for the acetylcholinesterase and butyrylcholinesterase inhibitory activity.

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1. Introduction

According to the World Alzheimer Report 2013, Alzheimer's disease and other forms of dementia are among the biggest global public health issues facing our generation. Currently, over 35 million people around the world live with these conditions and this number is likely to increase threefold by 2050, to 115 million people [1]. Alzheimer's disease (AD), the most common form of dementia amongst the aged, is a deadly neurodegenerative disease categorized by the loss of mental abilities and a diversity of neuropsychiatric symptoms and behavioral disorders [2,3]. Neurofibrillary tangles and amyloid β (Aβ) plaques are found in the brain. The cholinergic system is predominantly vulnerable to synapse loss, particularly in cortical regions related with memory and executive function [4]. Most treatment approaches to date have been based on the cholinergic hypothesis which assumes that memory loss in patients suffering from this disease result from a loss of cholinergic function in brain for cholinergic neurotransmission is specifically affected in patients suffering from Alzheimer's disease.

For the treatment of AD, one of the most common methods is to increase the acetylcholine levels in brain with acetylcholinesterase inhibitors [5]. The best characterized therapeutic effect of cholinesterase inhibitors (ChE) in Alzheimer disease patients is to maintain cognitive function for a 1-year period in about 50% of the patients [6]. Two kinds of cholinesterase enzymes are found in the central nervous system; acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Both enzymes are capable of hydrolyzing acetylcholine, but AChE has a 10^{13}-fold higher hydrolytic acetylcholine activity than BuChE, at the similar temperature and pH [7]. In the healthy brain, BuChE is thought to play a trivial role in regulating brain acetylcholine levels. In the AD brain, BuChE activity rises while AChE activity remains unchanged or declines. Hence, both enzymes may contribute to regulating acetylcholine levels and are appropriate therapeutic targets to enhance the cholinergic deficit. The two enzymes vary in location, substrate specificity and kinetics. The most recent studies suggest that

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BuChE might also have a part in the etiology and development of AD beyond the regulation of synaptic acetylcholine levels. Experimental evidence from the use of agents with improved selectivity for BuChE and ChE, such as rivastigmine (having dual inhibitory action on both AChE and BuChE), shows that there are possible therapeutic benefits of inhibiting both AChE and BuChE in AD and associated dementias. The development of specific small molecule drugs BuChE inhibitors with the capability to inhibit BuChE together with AChE should lead to better clinical outcomes [8].

In our previous studies, we synthesized and screened the series of novel chalcone derivatives and curcumin analogues with α, β-carbonyl linkers for their activity against phagocytic chemotaxis and the production of reactive oxygen species (ROS) from zymosan stimulated human phagocytes. On the basis of these findings and a those of other scientists, it was determined that chalcone derivatives and curcumin-like compounds bearing α, β-carbonyl group have a wide diversity of pharmacological activities [9–14]. Our latest studies showed that a range of compounds with a α, β-unsaturated moiety are capable of inhibiting both AChE and BuChE and can be possible candidates for the treatment of Alzheimer's disease [15,16].

Numerous studies have documented increased protein oxidation [17] and reactive oxygen species (ROS) formation [18] in the brain tissue of AD patients. Aβ is considered to be a cause of lipid peroxidation in brain cell membranes that may contribute to neurodegeneration [19,20]. Encouraged by these results, we continued our work in this area, and in the current study we synthesized thirty novel compounds bearing the α, β-carbonyl moiety and have screened them for their effects on the AChE/BuChE activities in addition to amyloid β-induced cytotoxicity in PC12 cells. Lastly, molecular modeling calculations and QSAR studies were performed to understand the structural basis for the biological activity of compounds.

2. Results and discussion

2.1. Chemistry

Thirty novel compounds of ten different types were synthesized in the current study as reported previously [21,22]. To synthesize the desired α, β-unsaturated carbonyl based compounds, Claisen–Schmidt condensation was used [23] between different ketones and suitable aryl aldehydes at a molar ratio 1:2, (twenty one compounds, **1**–**7**; **11**–**17**; **21**–**27**) in the presence of NaOH in ethanol. Some compounds were synthesized in acetic acid in the presence of dry HCl gas. Nine compounds (**8**–**10**; **18**–**20**; **28**–**30**) resembling chalcone analogues were synthesized by same Claisen–Schmidt condensation using molar ratio 1:1 of ketone and aldehyde (Scheme 1). Eight compounds (**7**, **8**, **10**, **17**, **18**, **20**, **27**, **28**) were synthesized using both types of catalytic systems comprising NaOH and the dry HCl gas mixture. As compared to NaOH, the catalytic system with HCl gas mixture produced compounds more efficiently with a higher yield. When using NaOH, a mixture of numerous unidentified products was obtained requiring extensive purification by column chromatography.

All synthesized new compounds were characterized by spectrophotometric techniques as well as elemental analysis of C, H, and N, and melting points. Carbon nuclear magnetic resonance spectra were also obtained. For compounds **3**, **13** and **23**, the NH absorption peaks were not seen in the ^{1}H NMR spectra of the compounds. Absence of NH absorption peaks is also reported previously by other researchers [24,25].

2.2. Antioxidant activity of α, β-unsaturated carbonyl based compounds

The DPPH (1,1-diphenyl-1-picrylhydrazyl) assay was performed to assess the compounds for their antioxidant activity. The data of the antioxidant assay is summarized in Table 1. According to the data, five compounds (**1**, **3**, **4**, **14** and **19**) were found to possess potent DPPH radical scavenging activity with IC_{50} in the range of 18.39–22.99 μM. Compound **14**, having a *N*-methyl-4-piperidone linker and diethoxymethyl substitution at position 4 of aromatic rings, showed the strongest antioxidant activity (18.39 μM), even more than the positive control (ascorbic acid; 19.36 μM). Among all thirty compounds, only eleven compounds have poor antioxidant activities, exhibiting IC_{50} values greater than 50 μM.

2.3. Cytotoxicity of synthetic compounds in PC12 cells

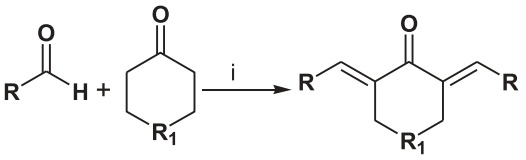
To investigate the effect of the new compounds on cell viability, the MTT assay was conducted on PC12 cells. The cells were incubated with varying concentrations (0.01–100 μM) of the test compounds for 24 h and under these conditions the α, β-unsaturated carbonyl based compounds were nontoxic to PC12 cells at any of the concentrations tested.

2.4. Neuroprotective effect of synthetic compounds against Aβ-induced cell cytotoxicity

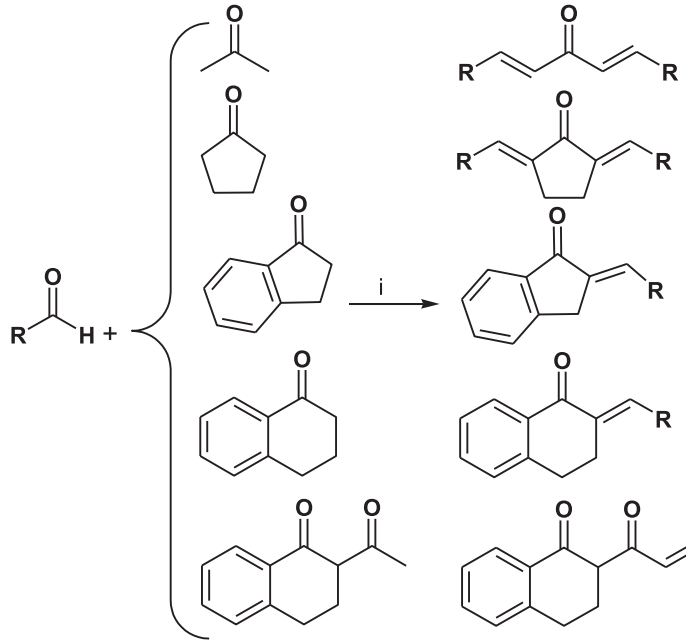
The MTT assay was performed to evaluate the effect of novel synthetic compounds on Aβ-induced PC12 cell toxicity. The cells treated with Aβ exhibited significantly reduced cell viability as compared to control cells (decreased cell viability by 48%). Pretreatment of cells with the synthetic compounds protected against Aβ-induced cell death up to 87%, at a concentration of 100 μM. Six compounds (**1**, **3**, **4**, **13**, **14**, **19**) were the most protective against Aβ-induced PC12 cell toxicity (Fig. 1). As compared to the positive control selegiline, the protective effect of the synthetic compounds was significantly higher with compound (**14**) being the best. Amongst the tested compounds, all those possessing 2-nitro and 4-dimethylamine groups (**11**–**20**) had extremely high protective activities, while a diethoxymethyl group at position 4 of the rings (**1**–**10**) lead to significantly less protective activity. The presence of pyrolidine at position 4 of compounds (**21**–**30**) decreased the protective activity against Aβ-induced cytotoxicity. Compounds having a 4-piperidone (**3**, **13**) and those possessing *N*-methyl-4-piperidone (**4**, **14**) linker exhibited somewhat more protection as compared to all other compounds. These results suggest that a few of the novel α, β-unsaturated carbonyl based compounds may reduce cell damage caused by Aβ-induced cytotoxicity.

2.5. Acetylcholinesterase and butyrylcholinesterase inhibition activity

Evaluation of new compounds for their inhibitory effects on AChE and BChE was done by Ellman's method. The screening of novel α, β-unsaturated carbonyl based compounds against AChE and BChE demonstrated that nearly all these were moderate to strongly active against AChE (Table 1). The compounds were found to be less active on BChE but most inhibited AChE to various extents. The IC_{50} values of the compounds **8**, **9**, **15**–**18**, **21**, **22**, **25**, **26**, and **28**–**30** could not be calculated owing to their weak inhibition potency, which did not surpass 50% at the highest concentration (100 μM). In contrast, the compounds **3**, **4**, **12**–**14**, **23** and **24** exhibited IC_{50} values ranging from 0.042 to 9.52 μM for inhibition of AChE. In addition, the compounds **3**, **4**, **13** and **14** showed substantial AChE inhibitory activity below 1 μM, which is similar to



	R	R_1
1	4-Diethoxymethyl-benzene	CH_2
2	4-Diethoxymethyl-benzene	O
3	4-Diethoxymethyl-benzene	NH
4	4-Diethoxymethyl-benzene	NCH_3
5	4-Diethoxymethyl-benzene	NCH_2-benzene
11	Phenyl-2-nitro-4-dimethylamine	CH_2
12	Phenyl-2-nitro-4-dimethylamine	O
13	Phenyl-2-nitro-4-dimethylamine	NH
14	Phenyl-2-nitro-4-dimethylamine	NCH_3
15	Phenyl-2-nitro-4-dimethylamine	NCH_2-benzene
21	Phenyl-4-pyrrolidine	CH_2
22	Phenyl-4-pyrrolidine	O
23	Phenyl-4-pyrrolidine	NH
24	Phenyl-4-pyrrolidine	NCH_3
25	Phenyl-4-pyrrolidine	NCH_2-benzene



	R
6	4-Diethoxymethyl-benzene
16	Phenyl-2-nitro-4-dimethylamine
26	Phenyl-4-pyrrolidine
7	4-Diethoxymethyl-benzene
17	Phenyl-2-nitro-4-dimethylamine
27	Phenyl-4-pyrrolidine
8	4-Diethoxymethyl-benzene
18	Phenyl-2-nitro-4-dimethylamine
28	Phenyl-4-pyrrolidine
9	4-Diethoxymethyl-benzene
19	Phenyl-2-nitro-4-dimethylamine
29	Phenyl-4-pyrrolidine
10	4-Diethoxymethyl-benzene
20	Phenyl-2-nitro-4-dimethylamine
30	Phenyl-4-pyrrolidine

Scheme 1. Structures and synthesis scheme of α, β-unsaturated carbonyl based compounds. Reagents and conditions: (i) NaOH, EtOH, Room temperature.

that of donepezil (0.062 μM). The compounds **4** and **14**, having *N*-methyl-4-piperidone linker, had a better inhibitory potency than the reference drug donepezil. For the inhibition of BuChE, compounds **3**, **7** and **12** displayed IC_{50} below 20 μM, but none was found more active than donepezil (6.92 μM).

These findings encouraged us to explore the relationship between AChE inhibitory activity and the chemical structures of the compounds. Ten varying types of ketones were used as linkers, but only three types of linkers present in compounds (**3**, **4**, **12**, **13**, **14**, **23**, and **24**) were found to be the most effective. The presence of tetrahydropyran-4-one linker displayed good inhibition but only in the presence of 2-nitro and 4-dimethylamine substitution patterns (compound **12**). Table 1 shows that the compounds (**4**, **14**, and **24**) having *N*-methyl-4-piperidone linker were strong inhibitors of AChE. Synthetic α, β-unsaturated carbonyl based compounds possessing the 4-piperidone moiety (**3**, **13**, and **23**) were also good inhibitors but relatively weaker than those with 4-piperidone linker. In an earlier study, Yalda et al. reported the synthesis of piperidone-grafted novel mono- and bisspiro heterocyclic hybrids containing functionalized piperidine, pyrrolizine and oxindole rings. The cholinesterase inhibitory activity of those cycloadducts revealed that monospiripyrrolizines were more active with IC_{50} in the range of 3.36–20.07 μM than dipolarophiles or bisspiropyrrolizines [26]. The current investigation shows that the increased activity is the result of specific linkers, whereas substitution patterns on the linked aromatic rings participated to lesser extent. The comparison amongst the three active compounds with same linker (**4**, **14**, **24**) revealed that compound **4** with diethoxymethyl group at position 4 of the aromatic rings showed more activity than compound **14** possessing a 2-nitro and 4-dimethylamine substitution pattern. The introduction of pyrrolidine at position 4 of compound **24** reduced the inhibition of AChE. A similar like activity relationship was also observed amongst compounds (**3**, **13** and **23**), having 4-piperidone groups on the aromatic rings. The activities of these compounds showed that the linkers derived from ketones during synthesis play key roles in terms of inhibitory activity. Compounds (**1**–**10**) have similar substitution pattern, but only two compounds (**3**, **4**) with 4-piperidone and *N*-methyl-4-piperidone moieties are potent inhibitors. Similar results were seen amongst other two series of synthetic compounds (**11**–**20** and **21**–**30**). Contreras et al. reported the synthesis of novel compounds by using 1-benzyl-4-piperidone and a conventional structure–activity relationship examination proposed that the presence of a central pyridazine ring is vital for high AChE

Table 1
Antioxidant activity and inhibitory effects of synthetic α, β-unsaturated carbonyl based compounds against AChE and BChE.

Compounds	IC_{50} AChE (μM)	IC_{50} BuChE (μM)	Selectivity for AChE[a]	IC_{50} DPPH (μM)
1	12.43 ± 1.22	43.66 ± 1.93	3.51	20.12 ± 1.20
2	41.22 ± 2.20	38.53 ± 1.64	0.93	29.30 ± 1.83
3	0.92 ± 0.73	12.34 ± 0.67	13.41	19.29 ± 3.20
4	0.042 ± 0.01	>100	–	20.40 ± 1.93
5	27.54 ± 2.21	65.27 ± 0.52	2.37	28.22 ± 0.96
6	55.34 ± 1.76	88.93 ± 2.37	1.61	>50
7	76.64 ± 3.21	14.66 ± 0.68	0.19	>50
8	>100	>100	–	37.22 ± 2.54
9	>100	>100	–	39.45 ± 5.44
10	76.93 ± 1.89	>100	–	>50
11	45.29 ± 2.71	>100	–	32.46 ± 2.16
12	1.54 ± 0.02	19.74 ± 1.22	12.82	29.22 ± 1.34
13	0.88 ± 0.04	22.65 ± 1.28	25.74	25.67 ± 0.45
14	0.057 ± 0.05	>100	–	18.39 ± 1.75
15	>100	>100	–	>50
16	>100	>100	–	>50
17	>100	>100	–	47.77 ± 4.27
18	>100	>100	–	>50
19	79.31 ± 2.84	>100	–	22.99 ± 2.14
20	39.44 ± 1.73	>100	–	49.10 ± 1.76
21	>100	>100	–	31.29 ± 2.43
22	>100	>100	–	>50
23	9.52 ± 0.45	>100	–	26.94 ± 0.85
24	2.78 ± 0.55	66.75 ± 5.76	24.01	43.28 ± 1.48
25	>100	56.92 ± 2.87	–	>50
26	>100	>100	–	>50
27	66.43 ± 2.91	>100	–	>50
28	>100	>100	–	>50
29	>100	>100	–	29.22 ± 1.67
30	>100	>100	–	27.87 ± 2.51
Donepezil	0.062 ± 0.08	6.92 ± 0.21	111.61	–
Ascorbic acid	–	–	–	19.36 ± 1.55

[a] AChE selectivity index defined as IC_{50} BChE/IC_{50} AChE affinity ratio.

inhibition [27]. The data in our current investigation support the significance of the piperidone moiety for the inhibition of AChE.

2.6. Docking and QSAR analyses

Molecular docking analysis was performed to obtain better insight into mechanism of action of the AChE inhibitors. The active site of AChE is located at the base of ~20 A° deep and narrow gorge, from the surface of the enzyme and is composed by two subsites [28,29]: (1) catalytic esteratic site (CES) and (2) peripheral anionic site (PAS). The active site consists of Gln71-Tyr-Val-Asp-Thr-Leu76, Gly82-Thr-Glu84, Trp86-Asn-Pro88, Tyr121, Leu130, Tyr133, Glu199, Ser200, Glu202-Ser-Ala204, Trp279, Trp286, Phe295, Phe297, Glu327, Phe330, Tyr334, Tyr337-Phe338, Tyr341, Trp439, His447-Gly-Tyr449, and Ile451. The mechanism of acetylcholine (ACh) hydrolysis involves trapping of ACh to PAS, followed by the transfer of ACh to the active site.

From Figs. 2 and 3, it is clear that the most active AChE inhibitor (compound **4**) interacts with the receptor mainly due to hydrophobic and mild polar interactions. The close proximity of compound **4** with Tyr334 and Trp279 is due to mild polar interactions, indicating that it binds reversibly with the receptor (see Fig. 3).

QSAR analysis: For QSAR analysis, a myriad number of descriptors were calculated followed by elimination of redundant descriptors using QSARINS. Then, GA–MLR (Genetic Algorithm–Multilinear Regression) was performed to develop robust QSAR model. The best two parametric QSAR model along with its statistical parameters is as following:

pIC_{50} = 126.3811 (±28.0863) −7.2606 (±2.3866) RDF090m −4.8896 (±2.0119) F01[C–N].

N_{tr} = 14, N_{ex} = 3, R^2 = 0.8558, R^2_{adj} = 0.8296, CCC_{tr} = 0.9223, F = 32.6359, Q^2_{LOO} = 0.7924, CCC_{cv} = 0.8897, R^2_{ex} = 0.7718, CCC_{ex} = 0.8578.

The symbols have the usual meaning [30–33]. The high value of R^2, R^2_{adj}, CCC_{tr}, F, Q^2_{LOO}, CCC_{cv} and R^2_{ex} indicates that the QSAR model is not only robust but also possesses good predictive ability (see Fig. 4) [30–35]. Since the model is based on a data set of seventeen molecules only, further improvements in the external predictive ability are also possible. From the QSAR model, it is clear that activity has correlation with RDF090m (Radial Distribution Function – 9.0/weighted by atomic masses, RDF descriptors) and F01[C–N] (frequency of C–N at topological distance of 01, a 2D frequency fingerprints descriptor). It is quite clear that the docking and the QSAR analyses not only support each other but are complementary to each other also.

3. Conclusion

In the work described above, we report the synthesis, pharmacological evaluation and molecular modeling of thirty novel α, β-unsaturated carbonyl based compounds. From docking and QSAR analyses, it can be stated that lipophilicity steers the AChE activity which is additionally supported by the hydrophobic interactions between the ligand and the receptor. We propose that the free radical scavenging activity of these novel compounds is responsible for their neuroprotective effects as it was seen that all strong antioxidant compounds possess more protective effect against Aβ-induced PC12 cell death. The most potent AChE inhibitors in this series correspond to *N*-methyl-4-piperidone and 4-piperidone moieties. The type of the substituent at the aromatic rings in compounds does not appear to have a strong influence on the inhibitory activity. Overall, the substitution of benzene rings by diethoxymethyl group at position 4 and presence of piperidone moiety imparts strong acetylcholinesterase inhibition. The multiple activities of these compounds suggest that they may be useful for the treatment of neurodegenerative diseases such as AD that involve a loss of cholinergic neurons.

4. Experimental

4.1. Materials

All chemicals and reagents were purchased from Sigma–Aldrich, Merck and Acros Organics (above 98% purity) and were used without additional purification. MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] was procured from Sigma–Aldrich (St. Louis, MO, USA). AChE, (E.C.3.1.1.7 from Electric Eel, 500 units), BChE, (E.C. 3.1.1.8, from horse serum, 1000 units) and donepezil hydrochloride were also purchased from Sigma–Aldrich. $Aβ_{1–42}$ was purchased from Bachem (Bubendorf, Switzerland). Potassium dihydrogen phosphate, 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), potassium hydroxide, sodium hydrogen carbonate, gelatine, acetylthiocholine iodide (ATC) and butrylthiocholine iodide (BTC) were supplied by Fluka (Buchs, Switzerland). Spectrophotometric analyses were performed using a Shimadzu UV-1700, UV–Vis spectrophotometer. Phosphate buffer (100 mM, pH 8.0) at 25 °C was used to measure cholinesterase activity of the compounds, using ATC and BTC (75 mM) as substrates. In both cases, DTNB (10 mM) was used to observe absorbance changes at 412 nm. Donepezil hydrochloride was used as a positive control [36].

4.2. General procedures

^1H and ^{13}C NMR spectra were recorded on a JEOL ECP spectrometer operating at 500 MHz, with Me4Si as internal standard

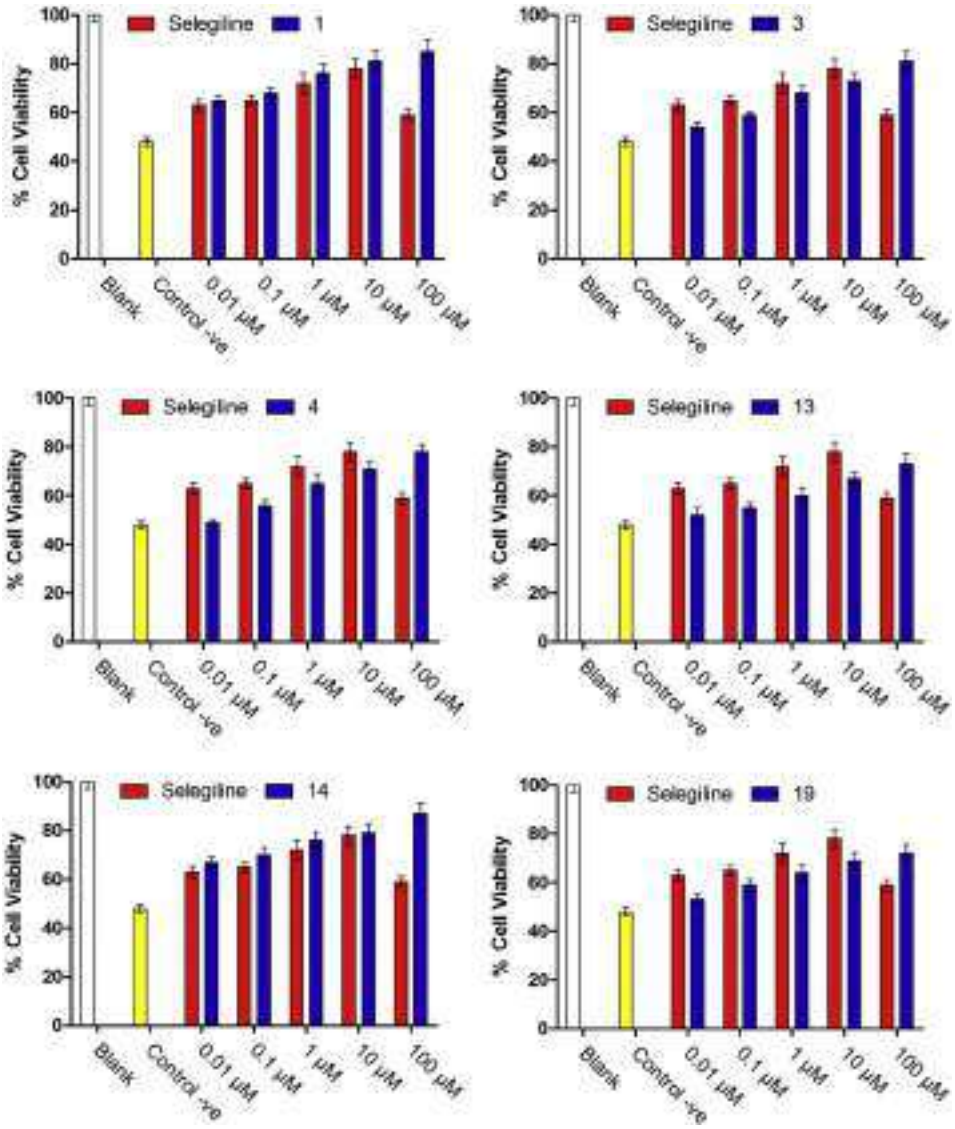


Fig. 1. Protective effects of the most active synthetic compounds against $A\beta_{1-42}$-induced cell damage. Cell viability of compounds was evaluated using the MTT assay. All groups were treated with 25 μM $A\beta_{1-42}$ except for the control group. Selegiline was used as a positive control at the same concentrations. Synthetic compounds and selegiline were pre-incubated at various concentrations (0.01–100 μM) in serum-free media for 24 h before the addition of Aβ peptide. Cell viability is expressed as the mean percentage of viable cells compared with the untreated cells. The data are the mean ± SE ($n = 5$).

and $CDCl_3$ or DMSO-d^6 as the solvent. Electrospray ionization mass spectrometry (ESI-MS) on MicroTOF-Q mass spectrometer (Bruker) was used to obtain high resolution mass spectra (HRMS). Micro-analyses data was obtained using Fison EA 1108 elemental analyzer. Infrared spectra using KBr disc were recorded on a Perkin Elmer 400 (FTIR) spectrometer. Flash column chromatography was carried out with silica gel 60 (230–400 mesh) (Merck) and thin layer chromatography (TLC) was performed on pre-coated silica plates (Kiesel gel 60 F_{254}, BDH). Melting points were determined using an electrothermal instrument and are uncorrected. The compounds were visualized by illumination under ultraviolet (UV) light (254 nm) or by vanillin stain followed by charring on a hotplate.

4.3. Synthesis of α, β-unsaturated carbonyl based compounds

Twenty one α, β-unsaturated carbonyl based compounds (**1**–**7**; **11**–**17**; **21**–**27**) were synthesized by direct coupling of the appropriate aromatic aldehyde with the ten different types of ketones at a molar ratio of 1:2, and the compounds (**8**–**10**; **18**–**20**; **28**–**30**) were synthesized at a molar ratio of 1:1 under base catalyzed Claisen–Schmidt condensation reaction conditions. Scheme 1 demonstrates the general synthesis of α, β-unsaturated carbonyl based compounds d. Concisely, the appropriate aromatic aldehyde (20 mmol, 2 equivalent) and the suitable ketone (10 mmol, 1 equivalent) were mixed and dissolved in 15 ml of ethanol in single necked round bottomed flask, and stirred at 5 °C for a couple of minutes. Afterwards, a 40% NaOH solution in ethanol was then added drop wise for several minutes. The mixture was left stirring at room temperature (27 °C) for 1–24 h. The precipitate formation and color changes of the reaction mixture served as an indication of product formation. The reaction was monitored by TLC and upon completion; the reaction was quenched by the addition of acidified ice to the mixture. The α, β-unsaturated carbonyl based compounds were isolated by column chromatography or by recrystallization.

4.3.1. 2,6-Bis[4-(diethoxymethyl)benzylidene]cyclohexanone (*1*)

Yellow crystals (2.59 g, 54%). mp: 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (s, 2H), 7.29 (d, $J = 8$ Hz, 4H), 6.82 (d,

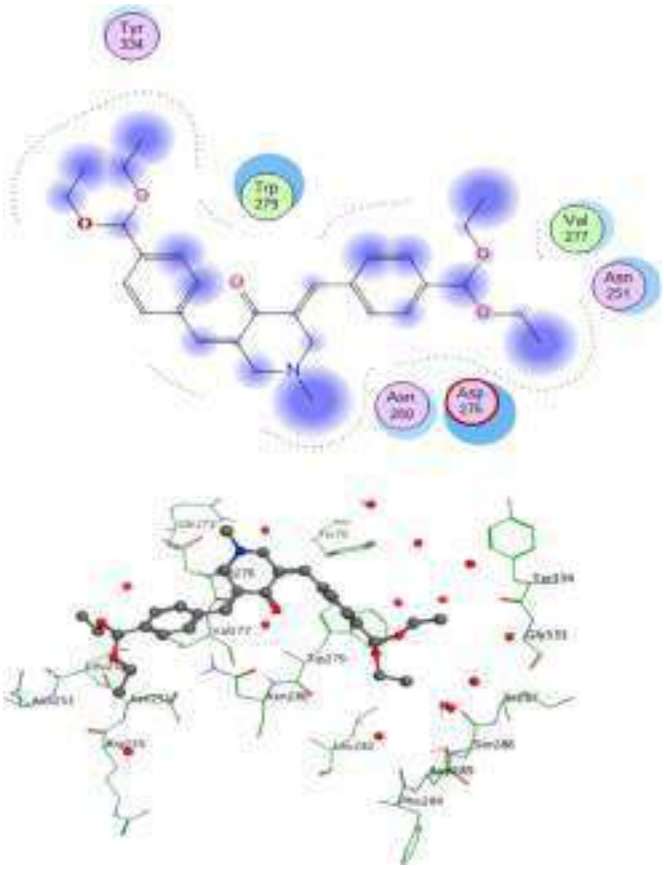


Fig. 2. Docking pose for most active molecule **4** in the active site of AChE.

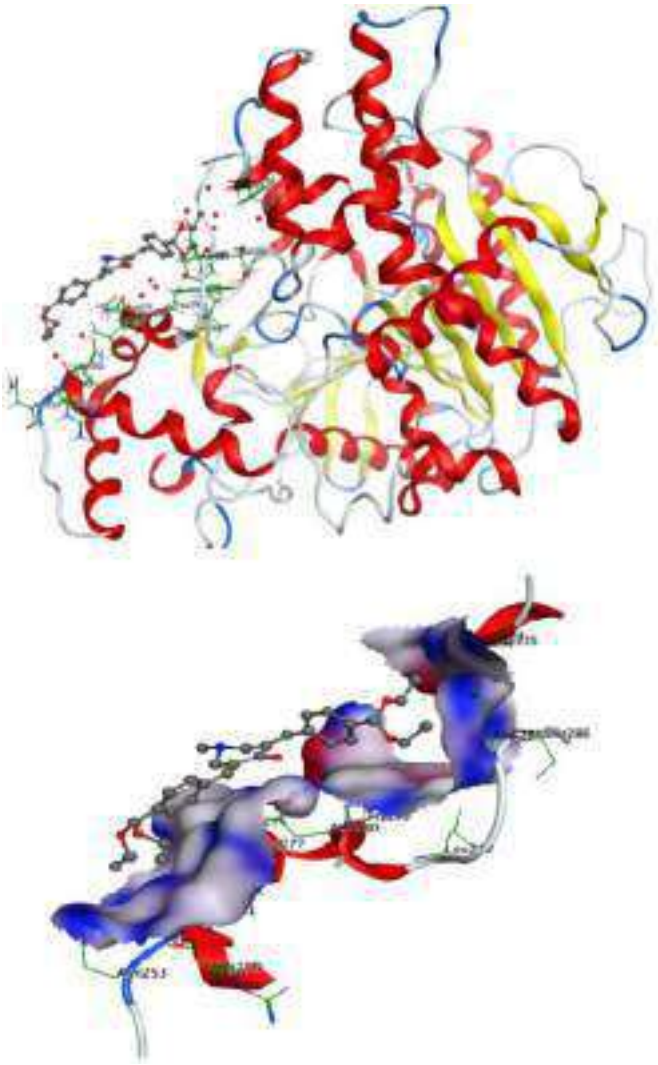


Fig. 3. Docking pose for most active molecule **4** with surface area of active site of AChE (Blue: H-Bonding, White: Hydrophobic and Red: Mild Polar regions). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

J = 8 Hz, 4H), 5.89 (s, 2H), 3.42 (q, J = 7.5, 8H), 2.32 (t, J = 12.0 Hz, 4H), 1.82 (m, 2H), 1.24 (t, J = 7.5, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 186.4, 152.9, 144.4, 136.5, 132.5, 127.3, 126.5, 101.1, 55.0, 28.3, 27.8, 16.2; HRMS (ESI) m/z: 479.68 $[M+H]^+$, Microanalysis calculated for $C_{30}H_{38}O_5$ (478.62), C: 75.28%, H: 8.00%. Found C: 75.42%, H: 8.12%.

*4.3.2. 3,5-Bis-(4-diethoxymethyl-benzylidene)-tetrahydro-pyran-4-one (**2**)*

Pale yellow crystals (3.06 g, 64%). mp: 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (s, 2H), 7.32 (d, J = 8 Hz, 4H), 6.95 (d, J = 8 Hz, 4H), 5.52 (s, 2H), 3.62 (q, J = 7.5, 8H), 2.69 (s, 4H), 1.18 (t, J = 8, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 187.2, 152.7, 143.8, 136.7, 131.9, 126.2, 125.2, 101.5, 62.4, 55.2, 16.1; HRMS (ESI) m/z: 481.65 $[M+H]^+$, Microanalysis calculated for $C_{29}H_{36}O_6$ (480.59), C: 72.48%, H: 7.55%. Found C: 72.62%, H: 7.72%.

*4.3.3. 3,5-Bis[4-(diethoxymethyl)benzylidene]piperidin-4-one (**3**)*

Yellow solid (2.89 g, 60%). mp: 101–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68 (s, 2H), 7.12 (d, J = 7.5 Hz, 4H), 6.93 (d, J = 7.5 Hz, 4H), 5.65 (s, 2H), 3.36 (q, J = 7.5, 8H), 2.65 (s, 4H), 1.27 (t, J = 7.0, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 185.2, 145.1, 144.5, 138.5, 136.2, 128.1, 127.8, 102.1, 55.1, 48.7, 16.4; HRMS (ESI) m/z: 480.71 $[M+H]^+$, Microanalysis calculated for $C_{29}H_{37}NO_5$ (479.61), C: 72.62%, H: 7.78%, N: 2.92%. Found C: 72.71%, H: 7.86%, N: 3.10%.

*4.3.4. 3,5-Bis[4-(diethoxymethyl)benzylidene]-1-methyl-piperidin-4-one (**4**)*

Light yellow solid (2.12 g, 43%). mp: 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (s, 2H), 7.32 (d, J = 8 Hz, 4H), 7.15 (d, J = 8 Hz, 4H), 5.59 (s, 2H), 3.29 (q, J = 7.5, 8H), 2.71 (s, 4H), 2.12 (s, 3H), 1.20 (t, J = 7.0, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 189.7, 148.2, 147.5, 139.8, 135.1, 128.4, 127.1, 101.4, 56.6, 51.2, 40.1, 16.7; HRMS (ESI) m/z: 494.65 $[M+H]^+$, Microanalysis calculated for $C_{30}H_{39}NO_5$ (493.63), C: 72.99%, H: 7.96%, N: 2.84%. Found C: 72.95%, H: 7.99%, N: 2.87%.

*4.3.5. 1-Benzyl-3,5-bis[4-(diethoxymethyl)benzylidene]piperidin-4-one (**5**)*

Brown semisolid (2.76 g, 48%). mp: 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (d, J = 8 Hz, 2H), 7.65 (s, 2H), 7.52 (d, J = 8 Hz, 2H), 7.22 (d, J = 7 Hz, 4H), 7.12 (d, J = 7 Hz, 4H), 6.69 (t, J = 6.5 Hz, H), 5.17 (s, 2H), 4.17 (s, 2H), 3.38 (q, J = 7.5 Hz, 8H), 2.95 (s, 4H), 1.14 (t, J = 7.0, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 191.5, 148.2, 147.9, 139.5, 139.1, 132.5, 128.4, 127.6, 127.0, 125.2, 124.9, 101.8, 64.3, 56.2, 50.92, 17.1; HRMS (ESI) m/z: 570.84 $[M+H]^+$, Microanalysis calculated for $C_{36}H_{43}NO_5$ (569.73), C: 75.89%, H: 7.61%, N: 2.46%. Found C: 75.92%, H: 7.64%, N: 2.44%.

*4.3.6. 1,5-Bis-(4-diethoxymethyl-phenyl)-penta-1,4-dien-3-one (**6**)*

Pale brownish solid (1.96 g, 45%). mp: 98–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (d, J = 6.5 Hz, 4H), 7.71 (d, J = 8 Hz, 2H), 7.49 (d, J = 6.5 Hz, 2H), 7.16 (d, J = 7 Hz, 4H), 5.25 (s, 2H), 3.52 (q, J = 7 Hz, 8H), 1.17 (t, J = 7.0, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ:

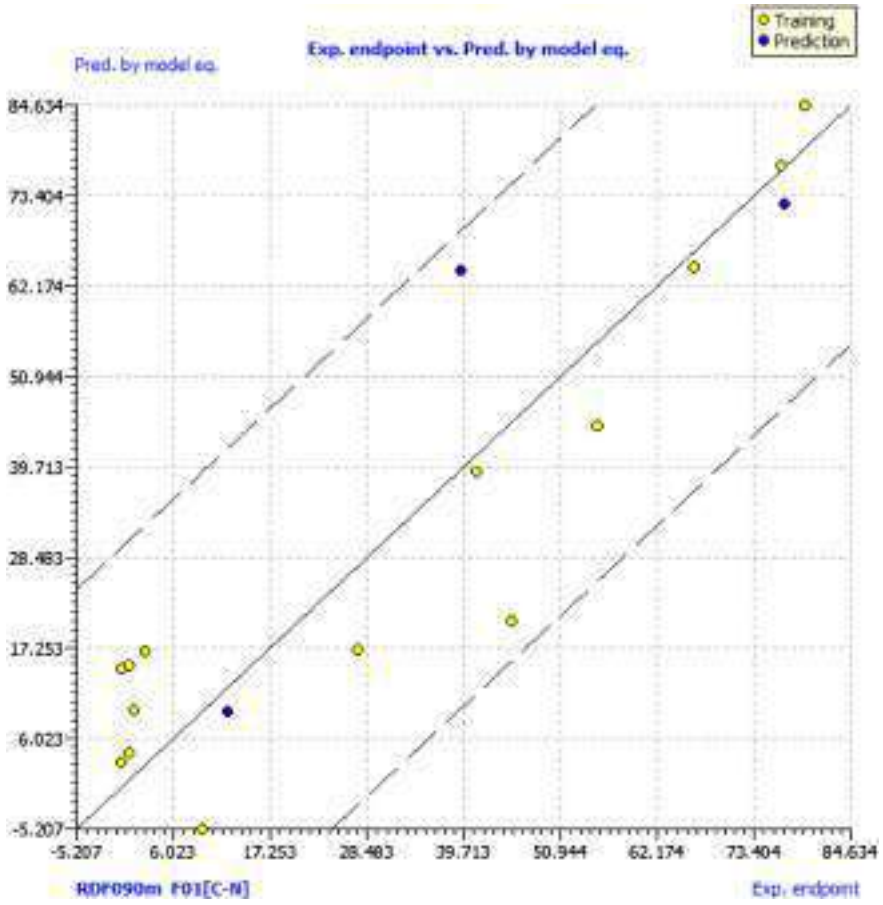


Fig. 4. Correlation between experimental and predicted pIC_{50}.

190.5, 152.2, 148.6, 139.7, 136.4, 135.2, 132.8, 102.2, 55.5, 16.9; HRMS (ESI) *m*/*z*: 439.62 $[M+H]^+$, Microanalysis calculated for $C_{27}H_{34}O_5$ (438.56), C: 73.94%, H: 7.81%. Found C: 74.12%, H: 7.89%.

*4.3.7. 2,5-Bis-(4-diethoxymethyl-benzylidene)-cyclopentanone (**7**)*

Light yellow crystals (3.12 g, 67%). mp: 88–89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (d, J = 6.5 Hz, 4H), 7.42 (s, 2H), 7.21 (d, J = 6.5 Hz, 4H), 5.45 (s, 2H), 3.62 (q, J = 7 Hz, 8H), 2.38 (t, J = 7 Hz, 4H), 1.22 (t, J = 7.0, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 189.7, 149.4, 145.5, 138.7, 136.4, 133.9, 129.1, 100.9, 56.2, 32.5, 16.1; HRMS (ESI) *m*/*z*: 465.72 $[M+H]^+$, Microanalysis calculated for $C_{29}H_{36}O_5$ (464.59), C: 74.97%, H: 7.81%. Found C: 75.18%, H: 7.87%.

*4.3.8. 2-(4-Diethoxymethyl-benzylidene)-indan-1-one (**8**)*

White powder (2.52 g, 78%). mp: 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (d, J = 8 Hz, 2H), 7.69 (s, H), 7.48 (d, J = 8 Hz, 2H), 7.25 (d, J = 7.5 Hz, H), 7.20 (d, J = 7.5 Hz, H), 7.05 (t, J = 7.5 Hz, H), 6.94 (t, J = 7 Hz, H), 5.34 (s, H), 3.49 (q, J = 7 Hz, 4H), 2.75 (s, 2H), 1.29 (t, J = 6 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 193.2, 144.5, 142.2, 140.1, 139.2, 138.8, 136.5, 130.4, 129.6, 128.1, 125.6, 125.1, 124.2, 102.2, 56.3, 29.9, 16.4; HRMS (ESI) *m*/*z*: 323.67 $[M+H]^+$, Microanalysis calculated for $C_{21}H_{22}O_3$ (322.40), C: 78.23%, H: 6.88%. Found C: 78.44%, H: 6.92%.

*4.3.9. 2-(4-Diethoxymethyl-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (**9**)*

Light yellow solid (2.67 g, 80%). mp: 94–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (d, J = 8 Hz, 2H), 7.59 (s, H), 7.47 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, H), 7.22 (d, J = 7.5 Hz, H), 7.12 (t, J = 7.5 Hz, H), 7.02 (t, J = 7 Hz, H), 5.49 (s, H), 3.35 (q, J = 7 Hz, 4H), 2.29 (t, J = 7 Hz, 2H), 2.05 (t, J = 7 Hz, 2H), 1.17 (t, J = 6 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 188.3, 152.2, 150.1, 148.5, 146.2, 143.9, 137.5, 134.4, 129.2, 127.2, 126.2, 124.8, 117.2, 101.7, 56.2, 29.5, 28.2, 16.0; HRMS (ESI) *m*/*z*: 337.51 $[M+H]^+$, Microanalysis calculated for $C_{22}H_{24}O_3$ (336.42), C: 78.54%, H: 7.19%. Found C: 78.33%, H: 7.12%.

*4.3.10. 2-[3-(4-Diethoxymethyl-phenyl)-acryloyl]-3,4-dihydro-2H-naphthalen-1-one (**10**)*

Yellow solid (3.16 g, 83%). mp: 121–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (d, J = 6 Hz, H), 7.52 (d, J = 6 Hz, H), 7.42 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 7.32 (d, J = 7 Hz, H), 7.29 (d, J = 7 Hz, H), 7.17 (t, J = 7 Hz, H), 6.89 (t, J = 7 Hz, H), 5.29 (s, H), 3.47 (q, J = 7 Hz, 4H), 3.29 (t, J = 8.5 Hz, H), 2.12 (t, J = 8 Hz, 2H), 1.95 (t, J = 7 Hz, 2H), 1.24 (t, J = 6.5 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 194.6, 151.1, 148.9, 144.6, 142.3, 139.2, 138.4, 136.2, 135.5, 132.4, 130.6, 129.1, 125.2, 124.2, 103.1, 66.1, 55.7, 30.2, 28.6, 16.7; HRMS (ESI) *m*/*z*: 379.52 $[M+H]^+$, Microanalysis calculated for $C_{24}H_{26}O_4$ (378.46), C: 76.17%, H: 6.92%. Found C: 76.21%, H: 6.91%.

*4.3.11. 2,6-Bis-(4-dimethylamino-2-nitro-benzylidene)-cyclohexanone (**11**)*

White powder (2.78 g, 62%). mp: 139–140 °C; δ: 7.94 (s, 2H), 7.55 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 7.13 (s, 2H), 3.15 (s, 12H), 2.35 (t, J = 12.0 Hz, 4H), 1.87 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 190.7, 149.5, 145.7, 145.6, 140.1, 128.2, 118.6, 117.6, 106.5, 46.8, 29.1, 27.5; HRMS (ESI) *m*/*z*: 451.64 $[M+H]^+$, Microanalysis calculated for $C_{24}H_{26}N_4O_5$ (450.49), C: 63.99%, H: 5.82%, N: 12.44%. Found C: 64.12%, H: 5.72%, N: 12.42%.

*4.3.12. 3,5-Bis[4-(dimethylamino)2-nitro-benzylidene]tetrahydro-pyran-4-one (**12**)*

White powder (2.92 g, 65%). mp: 188–190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (s, 2H), 7.46 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 7.05 (s, 2H), 3.13 (s, 12H), 2.93 (s, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 190.5, 149.2, 146.9, 145.1, 139.9, 128.4, 118.9, 118.1, 107.8, 65.5, 46.2; HRMS (ESI) m/z: 475.52 $[M+Na]^+$, Microanalysis calculated for $C_{23}H_{24}N_4O_6$ (452.46), C: 61.05%, H: 5.35%, N: 12.38%. Found C: 61.24%, H: 5.59%, N: 12.42%.

*4.3.13. 3,5-Bis[4-(dimethylamino)2-nitro-benzylidene]piperidin-4-one (**13**)*

Light yellow solid (2.28 g, 51%). mp: 192–194 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (s, 2H), 7.72 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 6.92 (s, 2H), 3.17 (s, 12H), 3.13 (s, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 189.4, 149.7, 148.6, 142.5, 140.7, 127.3, 118.8, 118.1, 106.5, 49.4, 46.9; HRMS (ESI) m/z: 452.52 $[M+H]^+$, Microanalysis calculated for $C_{23}H_{25}N_5O_5$ (451.48), C: 61.19%, H: 5.58%, N: 15.51%. Found C: 61.42%, H: 5.62%, N: 15.89%.

*4.3.14. 3,5-Bis[4-(dimethylamino)2-nitro-benzylidene]-1-methyl-piperidin-4-one (**14**)*

White powder (2.56 g, 55%). mp: 181–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (s, 2H), 7.45 (d, J = 8 Hz, 2H), 7.23 (d, J = 8 Hz, 2H), 7.13 (s, 2H), 3.21 (s, 12H), 3.03 (s, 4H), 2.19 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 187.5, 148.9, 148.2, 143.2, 141.8, 126.7, 119.6, 118.9, 106.2, 44.5, 46.1, 38.8; HRMS (ESI) m/z: 466.72 $[M+H]^+$, Microanalysis calculated for $C_{24}H_{27}N_5O_5$ (465.50), C: 61.92%, H: 5.85%, N: 15.04%. Found C: 61.99%, H: 5.91%, N: 15.19%.

*4.3.15. 1-Benzyl-3,5-bis-(4-dimethylamino-2-nitro-benzylidene)-piperidin-4-one (**15**)*

White crystals (3.22 g, 60%). mp: 165–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (d, J = 8 Hz, 2H), 7.72 (s, 2H), 7.59 (d, J = 8 Hz, 2H), 7.32 (d, J = 7 Hz, 2H), 7.25 (t, J = 7 Hz, 2H), 7.02 (s, 2H), 6.92 (t, J = 6.5 Hz, H), 4.22 (s, 2H), 3.19 (s, 12H), 2.72 (s, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 189.6, 148.9, 147.2, 139.5, 139.0, 131.9, 128.6, 126.5, 126.0, 125.3, 124.5, 119.2, 104.9, 64.8, 53.8, 45.9; HRMS (ESI) m/z: 542.65 $[M+H]^+$, Microanalysis calculated for $C_{30}H_{31}N_5O_5$ (541.60), C: 66.53%, H: 5.77%, N: 12.93%. Found C: 66.48%, H: 5.79%, N: 12.54%.

*4.3.16. 1,5-Bis-(4-dimethylamino-2-nitro-phenyl)-penta-1,4-dien-3-one (**16**)*

Pale yellow solid (2.97 g, 68%). mp: 177–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (d, J = 6 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 7.44 (d, J = 6 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 7.12 (s, 2H), 3.15 (s, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 187.5, 150.9, 148.6, 144.4, 132.8, 128.1, 117.5, 113.8, 107.9, 46.7; HRMS (ESI) m/z: 409.45 $[M-H]^+$, Microanalysis calculated for $C_{21}H_{22}N_4O_5$ (410.42), C: 61.45%, H: 5.40%, N: 13.65%. Found C: 61.48%, H: 5.62%, N: 13.77%.

*4.3.17. 2,5-Bis-(4-dimethylamino-2-nitro-benzylidene)-cyclopentanone (**17**)*

White powder (2.41 g, 55%). mp: 156–157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, J = 6.5 Hz, 2H), 7.88 (d, J = 6 Hz, 2H), 7.75 (d, J = 6.5 Hz, 2H), 7.44 (s, 2H), 3.10 (s, 12H), 2.45 (t, J = 7 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 188.9, 153.2, 149.9, 144.2, 143.8, 125.8, 118.1, 116.4, 108.3, 46.9, 32.6; HRMS (ESI) m/z: 437.72 $[M+H]^+$, Microanalysis calculated for $C_{23}H_{24}N_4O_5$ (436.46), C: 63.29%, H: 5.54%, N: 12.84%. Found C: 63.42%, H: 5.48%, N: 12.72%.

*4.3.18. 2-(4-Dimethylamino-2-nitro-benzylidene)-indan-1-one (**18**)*

Yellow semisolid (1.95 g, 63%). mp: 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56 (d, J = 8 Hz, H), 7.48 (s, H), 7.32 (d, J = 8 Hz, H), 7.12 (s, H), 6.98 (d, J = 7.5 Hz, H), 6.91 (d, J = 7.5 Hz, H), 6.74 (t, J = 7.5 Hz, H), 6.65 (t, J = 7 Hz, H), 3.22 (s, 6H), 2.81 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 192.8, 145.6, 142.6, 141.3, 139.8, 138.2, 137.4, 130.9, 128.7, 128.0, 125.9, 123.8, 119.5, 117.6, 108.6, 46.8, 28.3; HRMS (ESI) m/z: 309.55 $[M+H]^+$, Microanalysis calculated for $C_{18}H_{16}N_2O_3$ (308.33), C: 70.12%, H: 5.23%, N: 9.09%. Found C: 70.18%, H: 5.59%, N: 9.18%.

*4.3.19. 2-(4-Dimethylamino-2-nitro-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (**19**)*

White powder (2.50 g, 78%). mp: 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (d, J = 6.5 Hz, H), 7.57 (s, H), 7.42 (d, J = 6.5 Hz, H), 7.35 (s, H), 7.28 (d, J = 7 Hz, H), 7.20 (d, J = 7 Hz, H), 7.19 (t, J = 7.5 Hz, H), 6.92 (t, J = 8 Hz, H), 3.14 (s, 6H), 2.47 (t, J = 7 Hz, 2H), 2.14 (t, J = 7 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 188.7, 152.8, 151.3, 148.9, 146.8, 144.2, 136.8, 134.6, 129.9, 127.6, 126.1, 125.3, 124.2, 107.8, 46.2, 29.9, 27.9; HRMS (ESI) m/z: 323.45 $[M+H]^+$, Microanalysis calculated for $C_{19}H_{18}N_2O_3$ (322.36), C: 70.79%, H: 5.63%, N: 8.69%. Found C: 71.12%, H: 5.52%, N: 8.72%.

*4.3.20. 2-[3-(4-Dimethylamino-2-nitro-phenyl)-acryloyl]-3,4-dihydro-2H-naphthalen-1-one (**20**)*

Pale yellow powder (2.93 g, 80%). mp: 102–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (d, J = 6.5 Hz, H), 7.62 (d, J = 6.5 Hz, H), 7.45 (d, J = 7.5 Hz, H), 7.32 (s, H), 7.29 (d, J = 7.5 Hz, H), 7.21 (d, J = 7.5 Hz, H), 7.14 (d, J = 7.5 Hz, H), 7.02 (t, J = 7.5 Hz, H), 6.94 (t, J = 7.5 Hz, H), 3.45 (t, J = 8.5 Hz, H), 3.10 (s, 6H), 2.22 (t, J = 8 Hz, 2H), 2.15 (t, J = 8 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 193.8, 152.2, 148.7, 145.2, 142.8, 139.6, 137.1, 136.8, 135.6, 131.9, 130.5, 129.4, 124.8, 123.5, 116.5, 106.2, 65.8, 46.8, 31.3, 28.7; HRMS (ESI) m/z: 365.55 $[M+H]^+$, Microanalysis calculated for $C_{21}H_{20}N_2O_4$ (364.39), C: 69.22%, H: 5.53%, N: 7.69%. Found C: 69.34%, H: 5.59%, N: 7.81%.

*4.3.21. 2,6-Bis-(4-pyrrolidin-1-yl-benzylidene)-cyclohexanone (**21**)*

Brownish powder (3.12 g, 76%). mp: 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (s, 2H), 7.45 (d, J = 8 Hz, 4H), 6.99 (d, J = 8 Hz, 4H), 2.37 (t, J = 10.0 Hz, 4H), 2.10 (m, J = 6.5 Hz, 8H), 1.84 (m, J = 5.5, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 188.9, 152.2, 145.2, 136.7, 131.9, 127.5, 126.9, 58.1, 28.8, 27.2, 25.6; HRMS (ESI) m/z: 413.62 $[M+H]^+$, Microanalysis calculated for $C_{28}H_{32}N_2O$ (412.57), C: 81.51%, H: 7.82%, N: 6.79%. Found C: 81.67%, H: 7.99%, N: 6.95%.

*4.3.22. 3,5-Bis-(4-pyrrolidin-1-yl-benzylidene)-tetrahydro-pyran-4-one (**22**)*

Light brown solid (2.40 g, 58%). mp: 99–101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81 (s, 2H), 7.37 (d, J = 6.5 Hz, 4H), 7.17 (d, J = 6.5 Hz, 4H), 2.94 (s, 4H), 1.92 (m, J = 6.5 Hz, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 189.0, 150.3, 144.7, 136.8, 130.1, 126.8, 125.6, 62.9, 57.1, 25.5; HRMS (ESI) m/z: 415.49 $[M+H]^+$, Microanalysis calculated for $C_{27}H_{30}N_2O_2$ (414.54), C: 78.23%, H: 7.29%, N: 6.76%. Found C: 78.45%, H: 7.52%, N: 6.72%.

*4.3.23. 3,5-Bis-(4-pyrrolidin-1-yl-benzylidene)-piperidin-4-one (**23**)*

Pale yellow powder (2.83 g, 69%). mp: 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.72 (s, 2H), 7.17 (d, J = 7.5 Hz, 4H), 6.81 (d, J = 7.5 Hz, 4H), 2.88 (s, 4H), 1.74 (m, J = 6 Hz, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 185.7, 145.9, 143.4, 137.1, 136.5, 128.7, 119.9, 56.4, 48.2, 24.9; HRMS (ESI) m/z: 436.62 $[M+Na]^+$, Microanalysis calculated for $C_{27}H_{31}N_3O$ (413.55), C: 78.42%, H: 7.56%, N: 10.16%. Found C: 78.44%, H: 7.60%, N: 10.25%.

*4.3.24. 1-Methyl-3,5-bis[4-(pyrrolidinyl)benzylidene]piperidin-4-one (**24**)*

Yellow powder (1.99 g, 47%). mp: 122–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (d, J = 8.5 Hz, 4H), 7.65 (s, 2H), 7.52 (d, J = 8.5 Hz, 4H), 2.99 (s, 4H), 2.43 (s, 3H), 1.96 (m, J = 6 Hz, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 190.1, 146.4, 144.7, 141.9, 131.8, 128.2, 109.6, 57.4, 56.5, 38.2, 25.5; HRMS (ESI) m/z: 428.71 $[M+H]^+$, Microanalysis calculated for $C_{28}H_{33}N_3O$ (427.58), C: 78.65%, H: 7.78%, N: 9.83%. Found C: 78.82%, H: 7.95%, N: 10.12%.

*4.3.25. 1-Benzyl-3,5-Bis-(4-pyrrolidin-1-yl-benzylidene)-piperidin-4-one (**25**)*

Light yellow crystals (2.16 g, 43%). mp: 88–89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (d, J = 8 Hz, 2H), 7.45 (s, 2H), 7.31 (d, J = 8 Hz, 2H), 7.25 (d, J = 7 Hz, 4H), 7.19 (d, J = 7 Hz, 4H), 6.81 (t, J = 6.5 Hz, H), 4.19 (s, 2H), 2.92 (s, 4H), 1.78 (m, J = 6 Hz, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 192.2, 148.8, 146.3, 138.2, 137.7, 132.7, 128.5, 126.2, 125.4, 124.9, 118.9, 65.1, 58.1, 50.2, 25.7; HRMS (ESI) m/z: 504.69 $[M+H]^+$, Microanalysis calculated for $C_{34}H_{37}N_3O$ (503.68), C: 81.08%, H: 7.40%, N: 8.34%. Found C: 81.25%, H: 7.69%, N: 8.17%.

*4.3.26. 1,5-Bis-(4-pyrrolidin-1-yl-phenyl)-penta-1,4-dien-3-one (**26**)*

Light brownish solid (2.02 g, 54%). mp: 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (d, J = 6 Hz, 4H), 7.52 (d, J = 6 Hz, 2H), 7.12 (d, J = 8 Hz, 2H), 7.05 (d, J = 8 Hz, 4H), 1.85 (m, J = 6 Hz, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 190.0, 151.8, 148.2, 138.2, 136.5, 134.9, 131.2, 56.9, 26.6; HRMS (ESI) m/z: 373.82 $[M+H]^+$, Microanalysis calculated for $C_{25}H_{28}N_2O$ (372.50), C: 80.61%, H: 7.58%, N: 7.52%. Found C: 80.88%, H: 7.74%, N: 7.85%.

*4.3.27. 2,5-Bis-(4-pyrrolidin-1-yl-benzylidene)-cyclopentanone (**27**)*

Yellow powder (2.96 g, 74%). mp: 94–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (d, J = 8 Hz, 4H), 7.59 (s, 2H), 7.12 (d, J = 8 Hz, 4H), 2.42 (t, J = 7 Hz, 4H), 1.91 (m, J = 6 Hz, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 190.1, 149.5, 145.8, 139.1, 136.8, 134.5, 129.8, 58.1, 32.9, 26.2; HRMS (ESI) m/z: 399.51 $[M+H]^+$, Microanalysis calculated for $C_{27}H_{30}N_2O$ (398.54), C: 81.37%, H: 7.59%, N: 7.03%. Found C: 81.42%, H: 7.62%, N: 7.12%.

*4.3.28. 2-(4-Pyrrolidin-1-yl-benzylidene)-indan-1-one (**28**)*

White powder (1.94 g, 67%). mp: 136–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, J = 8 Hz, 2H), 7.81 (s, H), 7.43 (d, J = 8 Hz, 2H), 7.37 (d, J = 7.5 Hz, H), 7.01 (d, J = 7.5 Hz, H), 6.92 (t, J = 7.5 Hz, H), 6.79 (t, J = 7 Hz, H), 2.82 (s, 2H), 1.84 (m, J = 6 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 192.8, 144.7, 142.9, 141.2, 139.5, 137.9, 136.6, 130.8, 129.8, 128.6, 125.2, 124.5, 122.9, 57.7, 28.5, 27.4; HRMS (ESI) m/z: 290.40 $[M+H]^+$, Microanalysis calculated for $C_{20}H_{19}NO$ (289.37), C: 83.01%, H: 6.62%, N: 4.84%. Found C: 83.25%, H: 6.75%, N: 4.82%.

*4.3.29. 2-(4-Pyrrolidin-1-yl-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (**29**)*

Brown solid (2.41 g, 80%). mp: 123–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (d, J = 8 Hz, 2H), 7.52 (s, H), 7.42 (d, J = 8 Hz, 2H), 7.21 (d, J = 7.5 Hz, H), 7.15 (d, J = 7.5 Hz, H), 7.02 (t, J = 7.5 Hz, H), 6.99 (t, J = 7 Hz, H), 2.24 (t, J = 7 Hz, 2H), 1.97 (t, J = 7 Hz, 2H), 1.81 (m, J = 6 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 188.8, 150.5, 149.2, 148.7, 147.4, 142.6, 135.1, 132.4, 129.8, 128.9, 125.5, 124.2, 117.5, 58.9, 29.7, 27.9, 25.9; HRMS (ESI) m/z: 304.56 $[M+H]^+$, Microanalysis calculated for $C_{21}H_{21}NO$ (303.40), C: 83.13%, H: 6.98%, N: 4.62%. Found C: 83.06%, H: 6.91%, N: 4.89%.

*4.3.30. 2-[3-(4-Pyrrolidin-1-yl-phenyl)-acryloyl]-3,4-dihydro-2H-naphthalen-1-one (**30**)*

Pale yellow solid (2.52 g, 73%). mp: 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (d, J = 6 Hz, H), 7.48 (d, J = 6 Hz, H), 7.33 (d, J = 6.5 Hz, 2H), 7.21 (d, J = 6.5 Hz, 2H), 7.17 (d, J = 6.5 Hz, H), 7.02 (d, J = 6.5 Hz, H), 6.98 (t, J = 6.5 Hz, H), 6.81 (t, J = 6 Hz, H), 3.24 (t, J = 6 Hz, H), 2.29 (t, J = 8 Hz, 2H), 1.98 (t, J = 7 Hz, 2H), 1.94 (m, J = 6 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 192.5, 151.8, 149.1, 145.7, 142.5, 140.4, 138.7, 136.9, 135.6, 131.9, 130.8, 129.5, 126.1, 119.1, 65.5, 58.2, 32.5, 28.7, 25.9; HRMS (ESI) m/z: 346.57 $[M+H]^+$, Microanalysis calculated for $C_{23}H_{23}NO_2$ (345.43), C: 79.97%, H: 6.71%, N: 4.05%. Found C: 80.19%, H: 6.55%, N: 4.09%.

4.4. DPPH (1,1-diphenyl-2-picrylhydrazyl) assay

The reported DPPH method was applied to assess the scavenging ability of the compounds [37]. The compounds were tested in the range of 0–25 μg/mL in methanol. To 2.5 ml of compound in 5 different concentrations, 1 ml of 0.3 mM DPPH ethanol solution was added. Then 1 ml of methanol was added to the solution and allowed to react for 30 min in the dark at room temperature. The change in the absorbance was read at 518 nm. The blank was comprised of 2.5 ml of test compound and 1 ml methanol, while the mixture of 1 ml DPPH and 2.5 ml of methanol served as negative control. The percentage antioxidant activity was calculated as follows:

$$\%\ \text{Inhibition} = \frac{A_A - A_B}{A_B} \times 100$$

where: A_B: absorption of blank sample, A_A: absorption of test samples. The IC_{50} value was calculated and compared with that of ascorbic acid as a reference.

4.5. Cell culture

The rat pheochromocytoma (PC12) cell line was purchased from the ATCC. The cells were maintained in RPMI-1640 medium consisting of 10% heat-inactivated FBS and 1% penicillin–streptomycin. The cells were incubated at 37 °C in a 5% CO_2 atmosphere with 95% humidity.

4.6. Cell viability assay

To investigate the cytotoxicity or neuroprotective effects of synthetic compounds in PC12 cells, the MTT assay was performed. The cells (1×10^4 cells/well) were seeded in 96-well cell culture plates and treated with different concentrations of compounds for 24 h. The cell viability was expressed as a relative percentage against control cultures. To assess the Aβ-induced neuroprotective activity, different concentrations of all compounds were individually added to cells for 24 h, before treatment with Aβ. The positive control drug selegiline was also evaluated in the same manner for comparison. 2.0 mg/ml MTT solution was added to each well and incubated for 4 h at 37 °C. The medium was removed and the formazan crystals were solubilized in 100 μL dimethyl sulfoxide (DMSO). A microplate reader was used to determine the optical density (excitation at 570 nm, emission at 630 nm) and data are plotted as percent of control.

4.7. AChE and BuChE inhibition assay

To evaluate the potency of compounds to inhibit AChE and BuChE, all compounds were subjected to a slightly modified method of Ellman's test [38]. The reaction of released thiocholine to

give a colored product with a chromogenic reagent 5,5-dithio-bis (2-nitrobenzoic) acid (DTNB) is the basis of the spectrophotometric method. The measurements were performed on a 1700 Shimadzu UV-1700, UV–Vis spectrophotometer. At a concentration of 2.5 units/mL, the enzyme solutions were prepared in gelatin solution (1%). AChE or BChE solution (50 μL) and compound solution (50 μL), prepared in 2% DMSO at a concentration range of 10^{-1}–10^{-6} mM, were added to 3.0 ml phosphate buffer (pH 8 ± 0.1) and were incubated at 25 °C for 5 min. DTNB (50 μL) and ATC (10 μL) were added to the enzyme-inhibitor mixture to start the reaction. For 10 min, the production of the yellow anion was recorded at 412 nm. Serving as a control, an identical solution of the enzyme without the inhibitor was processed using the same protocol. The blank reading consisted of 3.0 ml buffer, 50 μL 2% DMSO, 50 μL DTNB and 10 μL substrate. All the processes were assayed in triplicate. The percentage inhibition rate was calculated by the following equation:

$$\%\ \text{Inhibition} = \frac{A_C - A_I}{A_C} \times 100$$

where A_I is the absorbance in the presence of the inhibitor, A_C is the absorbance of the control and A_B is the absorbance of blank. Both values were corrected with blank-reading value. The data was expressed as Mean ± SD.

4.8. Molecular docking and QSAR analysis

For docking, the molecules were drawn using ACD Chemsketch 12 freeware followed by energy optimization using MMFF94 force field in TINKER [32]. The protein was first subjected to energy minimization, protonation followed by detection of site detection. The receptor and the drug candidates were optimized before actual docking followed by docking in MOE using the standard procedure found in the manual of software. The molecules were docked in the active site using 'force field' as a refinement technique with default settings in MOE [29]. All of the newly synthesized molecules were docked in the active site of AChE (pdb-1GQR, X-ray resolution = 2.20 A°). For the sake of convenience and comparison, as a representative, we report the docking poses for the most active compound of the series. For QSAR analysis, e-Dragon was used to calculate myriad number of descriptors, followed by random splitting of data set into training set (80%) and test set (20%). QSARINS v1.2 was used to eliminate redundant descriptors and for building GA–MLR (Genetic Algorithm–Multilinear regression) model [31,32].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.06.034.

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Article

Synthesis, X-ray Diffraction, Thermogravimetric and DFT Analyses of Pyrimidine Derivatives

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Abstract: An eco-benign synthesis of pyrimidine derivatives **2a**,**b** containing different functional groups with different electronic character starting from nitroalkenes **1a** and **2b** has been described. The structures for **1a** and **2a**,**b** have been characterized by single crystal X-ray diffraction analysis. The thermal data of the molecules pointed towards important structural aspects of their stability. The mechanism of their thermal decomposition is discussed. The thermodynamic parameters of the dissociation steps were evaluated and discussed. DFT calculations reveal that the compound **1a** possesses a high calculated dipole moment value (8.28 D) which indicates its high reactivity towards its surrounding molecules.

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AMRAVATI

Keywords: pyrimidine; X-ray; DFT; TGA; FT-IR

1. Introduction

Pyrimidine and its derivatives, which are important *N*-heterocyclic molecules, have received the consideration of researchers due to their significant biological and pharmaceutical properties. Pyrimidine and its derivatives have immense importance as antibiotics, and as crucial parts of many vitamins, and coenzymes. Indeed, some of them are the basic constituents of DNA and RNA, and play an important role in the constitutional properties of nucleic acids. Pyrimidine-derived biomolecules have received much attention from spectroscopists, drug, clinical, and industrial researchers because of their therapeutic importance [1–9]. Barbiturates (barbituric acid derivatives) are a class of central nervous system depressants, [10] utilized as sedatives, sleeping agents, hypnotics, anxiolytics, anticonvulsants, and anesthetics [7]. In addition, they have additional pharmacological activities as antioxidant anxiolitics, analeptics, anti-AIDA, immunomodulatory, anticancer agents and in other psychiatric disorders, and possess effects on motor and sensory functions [11–15] For example, phenobarbital, a 5-alkylated barbituric acid, was reported to exhibit sedative and hypnotic properties, and most importantly is an anticonvulsant [16].

In continuation of our research program [17–23], in the present work, the structures of some pyrimidine derivatives were characterized for the first time by single-crystal crystallography and TGA studies. DFT calculations were undertaken to study the optimized molecular structural parameters, vibrational frequencies, thermodynamic parameters, total dipole moment and HOMO-LUMO energy gap for the synthesized molecules using B3LYP/6-311G(d,p) basis set. The findings of these spectroscopic and theoretical studies are reported herein.

2. Results and Discussion

2.1. Synthesis of the Pyrimidine Derivatives

Green chemistry is being increasingly exploited as a powerful tool for the generation of privileged medicinal scaffolds and fine chemicals due to its numerous advantages, such as providing high enantio- and regioselectivity and more environmentally friendliness.

Recently, research groups have become involved in using green chemistry as a synthetic tool for the generation of valuable scaffolds to achieve new biological knowledge. The chemistry used in this paper involves an aqueous diethylamine catalyzed Michael addition of 1,3-dimethylbarbituric acid to nitro-olefins at room temperature for less than 1 h [16] (Scheme 1).

2.2. X-ray Crystal Structures

The structures of **1a** and **2a**,**b** were confirmed by single crystal X-ray analysis (Figure 1). Tables 1–7 display the crystal data and main geometrical parameters of the compounds.

X-ray analysis was performed using a Bruker Apex II D8 Venture diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). The data were processed with SAINT and corrected for absorption using

SADABS [24]. The structure was solved by direct method using the program SHELXTL [25] and were refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters. The non-hydrogen atoms were refined anisotropically. In these compounds, all the H atoms were calculated geometrically with isotropic displacement parameters set to 1.2 times the equivalent isotropic U values of the parent carbon atoms.

Scheme 1. Synthesis of pyrimidine derivatives **2a** and **2b**.

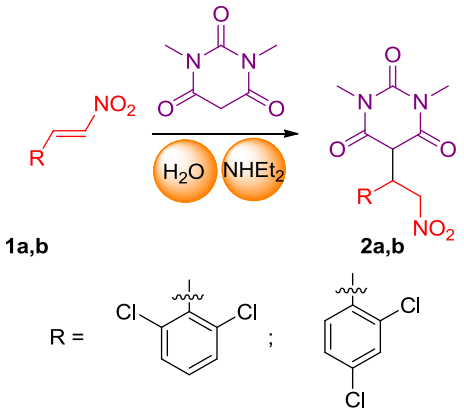
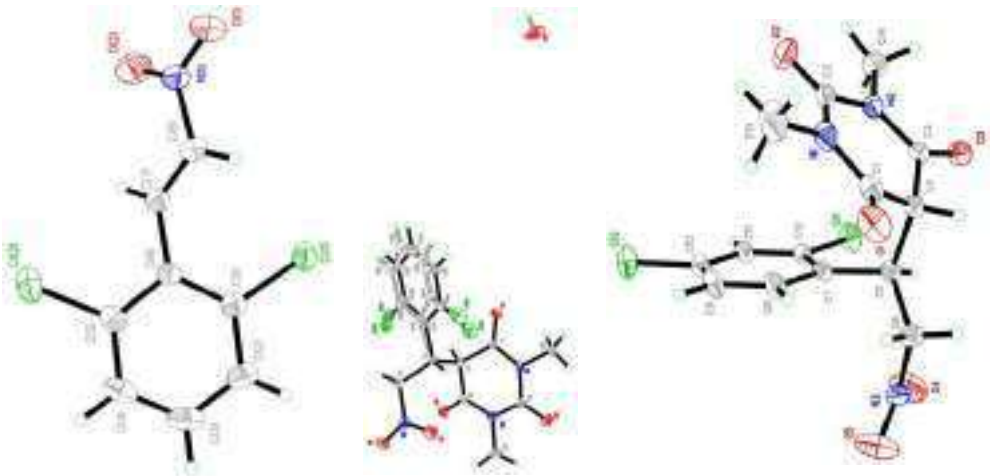


Figure 1. ORTEP diagrams of the structures of **1a** and **2a**,**b**.



(**1a**) (**2a**) (**2b**)

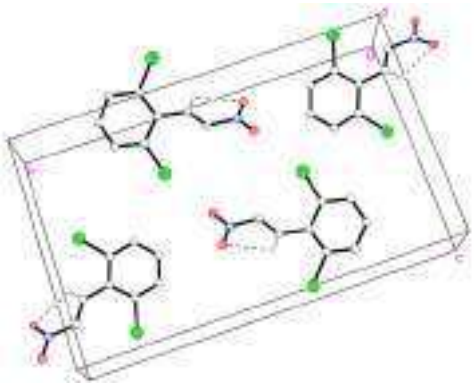
The title compound **1a**, $C_8H_5Cl_2NO_2$, which crystallizes in the monoclinic space group P 21/c comprises one crystallographically independent molecule in its asymmetric unit, as depicted in Figure 1. In the crystal structure (Figure 2A), there is an intramolecular C7-H7A··· O2 hydrogen bond. The crystal is essentially consolidated by Van Der Waals interactions. The crystal data and parameters for structure refinement of the title compound are given in Table 1. Selected geometric parameters are given in Table 2. H-bonding interactions are listed in Table 3.

The title compound **2a**, $C_{14}H_{13}Cl_2N_3O_5 \cdot H_2O$, which crystallizes in the trigonal space group R-3 comprises one crystallographically independent molecule with disorder in the phenyl ring and a water molecule in its asymmetric unitas shown in Figure 1. Figure 2B shows the crystal packing for the major and minor components of **2a** respectively with occupancy ratio 0.755:0.245. There are two intermolecular C6-H6A···O2 and C9 -H9A···O3 hydrogen bonds (Table 5). The crystal structure is

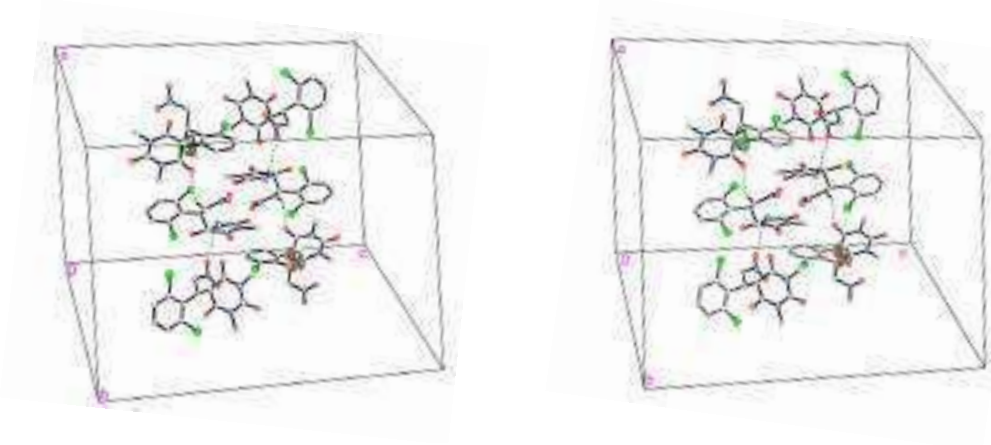
further consolidated by Van Der Waals interactions. The crystal data and parameters for structure refinement of the title compound are given in Table 1. Selected geometric parameters are given in Table 4. H-bonding interactions are listed in Table 5.

Figure 2. Crystal packings of (**A**) **1a**, (**B**) **2a** and (**C**) **2b**.

(**A**)

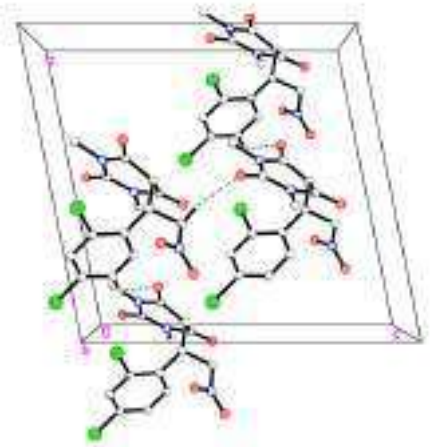


(**B**)



Packing of major component of disorder Packing of minor component of disorder

(**C**)



The title compound **2b**, $C_{14}H_{13}Cl_2N_3O_5$, which crystallizes in the monoclinic space group Cc comprises one crystallographically independent molecule in its asymmetric as shown in Figure 1. In the crystal structure (Figure 2C), there are two intermolecular C6-H6A···O1 and C13-H13C···O5 hydrogen bonds (Table 7). The crystal is further consolidated by Van Der Waals interactions. The crystal data and parameters for structure refinement of the title compound are given in Table 1. Selected geometric parameters are given in Table 6. H-bonding interactions are listed in Table 7.

Table 1. Crystal and experimental data of compounds **1a**, **2a** and **2b**.

Parameters	Compound 1a	Compound 2a	Compound 2b
Empirical formula	$C_8H_5Cl_2NO_2$	$C_{14}H_{13}Cl_2N_3O_5 \cdot H_2O$	$C_{14}H_{13}Cl_2N_3O_5$
Formula weight	218.03	391.02	374.17
Temperature	293(2) K	293(2) K	293(2) K
Wavelength (Mo *K*α radiation, λ)	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	monoclinic	trigonal	Monoclinic
Space group	P 21/c	R-3	Cc
Unit cell dimensions	a = 3.8395 (1) Å, α = 90.00° b = 19.8653 (7) Å β = 90.6258 (10)° c = 11.9619 (4) Å, γ = 90.00°	a = 18.0177(7) Å, α = 90.00° b = 18.0177(7) Å, β = 90.00° c = 26.6558(9) Å, γ = 120.00°	a = 12.9432 (4) Å, α = 90.00° b = 9.3084 (4) Å, β = 101.3572 (16)° c = 13.4650 (5) Å, γ = 90.00°
Volume	912.31 (5)Å^3	7494.1(6) Å^3	1590.51 (11) Å^3
Z	4	6	4
Density (calculated)	1.587 Mg/m^3	1.535 Mg/m^3	1.563 Mg/m^3
Absorption coefficient	0.67 mm^{-1}	0.424 mm^{-1}	0.439 mm^{-1}
F(000)	440	3564	768
Crystal size	0.58 ×0.35 ×0.27 mm	0.33 × 0.21 × 0.09 mm	0.57 ×0.35 ×0.26 mm
Theta range for data collection	2.7 to 30.5°	2.3 to 30.6°	2.7 to 30.6°
Index ranges	$-5 \le h \le 5, -28 \le k \le 28, -17 \le l \le 17$	$-25 \le h \le 25, -25 \le k \le 25, -38 \le l \le 38$	$-18 \le h \le 18, -13 \le k \le 13, -19 \le l \le 19$
Reflections collected/ unique	41303/2404 [R(int) = 0.042]	107278/5130 [R(int) = 0.059]	35961/4754 [R(int) = 0.024]
Completeness to theta = 30.57°	99.8%	99.6%	99.6%
Absorption correction	multi-scan	multi-scan	multi-scan
Refinement	method Full-matrix least-squares on F^2	method Full-matrix least-squares on F^2	method Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.04	1.03	1.27
Largest diff. peak and hole	0.28 and −0.22 e.Å^{-3}	0.72 and −0.26 e.Å^{-3}	0.22 and −0.25 e.Å^{-3}

Table 2. Selected geometric parameters (Å, º) of compound **1a**.

Bond	Experimental	Calculated
Cl1-C1	1.7320 (13)	1.7314
Cl2-C5	1.7295 (14)	1.7405
O1-N1	1.222 (2)	1.2370
O2-N1	1.211 (2)	1.2372
N1-C8	1.4563 (18)	1.4511
Atom Angle	**Experimental**	**Calculated**
O1-N1-O2	124.37 (14)	125.1111
O1-N1-C8	115.73 (14)	115.6492
O2-N1-C8	119.90 (14)	119.2397
Cl1-C1-C2	117.62 (11)	124.7209
Cl1-C1-C6	120.34 (9)	113.6358
Cl2-C5-C4	118.18 (11)	114.3525
Cl2-C5-C6	119.58 (10)	123.4094
N1-C8-C7	120.57 (13)	119.8515

Table 3. Hydrogen-bond geometry (Å, º) of compound **1a**.

D-H···*A*	*D*-H	H···*A*	*D*···*A*	*D*-H···*A*
C7-H7*A*···O2	0.9300	2.4000	2.7323 (18)	101.00

Table 4. Selected geometric parameters (Å, º) of compound **2a**.

Bond	Experimental	Calculated
Cl1A-C8A	1.738 (4)	1.7277
Cl1B-C8B	1.721 (14)	NC
Cl2A-C12A	1.751 (6)	1.7365
Cl2B-C12B	1.715 (14)	NC
O1-C1	1.204 (2)	1.2278
O2-C2	1.205 (2)	1.2325
O3-C3	1.212 (2)	1.2276
O4-N3	1.196 (3)	1.2362
O5-N3	1.215 (3)	1.2378
O1W-O1W ^{i}	0.969 (19)	NC
O1W-O1W ^{ii}	0.97 (2)	NC
N1-C1	1.378 (2)	1.3855
N1-C13	1.473 (3)	1.4513
N1-C2	1.382 (2)	1.3724
N2-C2	1.387 (3)	1.3925
N2-C14	1.463 (3)	1.4515
N2-C3	1.370 (2)	1.3881
N3-C6	1.500 (2)	1.4962
Atom Angle	**Experimental**	**Calculated**
O1W ^{ii}-O1W-O1W ^{i}	60.0 (18)	NC
C1-N1-C2	124.36 (15)	122.9525

Table 4. *Cont.*

Atom Angle	Experimental	Calculated
C2-N1-C13	117.61 (15)	117.6313
C1-N1-C13	117.39 (15)	117.0595
C2-N2-C3	124.74 (15)	123.0628
C3-N2-C14	117.62 (17)	116.9594
C2-N2-C14	117.50 (16)	117.4505
O4-N3-C6	121.03 (18)	117.2445
O4-N3-O5	123.45 (19)	125.7819
O5-N3-C6	115.53 (16)	116.9697
O1-C1-N1	121.69 (16)	123.7575
O1-C1-C4	121.91 (15)	122.9936
N1-C1-C4	116.24 (15)	113.2488
O2-C2-N2	120.68 (18)	123.3871
N1-C2-N2	117.42 (14)	116.2983
O2-C2-N1	121.9 (2)	121.7454
O3-C3-C4	121.55 (15)	123.7560
O3-C3-N2	121.13 (15)	121.7802
N2-C3-C4	117.24 (14)	112.8565
N3-C6-C5	112.43 (14)	111.9825
Cl1A-C8A-C7A	119.7 (3)	124.0885
Cl1A-C8A-C9A	117.4 (3)	114.4806
Cl1B-C8B-C9B	116.7 (10)	NC
Cl1B-C8B-C7B	121.7 (9)	NC
Cl2A-C12A-C7A	120.8 (3)	122.7008
Cl2A-C12A-C11A	114.7 (4)	115.2511
Cl2B-C12B-C7B	122.5 (8)	NC
Cl2B-C12B-C11B	114.4 (10)	NC

Symmetry codes: (i) $-x + y + 1, -x + 1, z$; (ii) $-y + 1, x - y, z$. NC: Not calculated.

Table 5. Hydrogen-bond geometry (Å, °) of compound **2a**.

D-H···*A*		*D*-H	H···*A*	*D*···*A*	*D*-H···*A*
O1W-H2W1···O1W	iii	0.9100	2.1000	2.859 (6)	140.00
O1W-H2W1···O1W	iv	0.9100	1.8500	2.689 (6)	152.00
O1W-H2W1···O1W	v	0.9100	2.0500	2.689 (7)	125.00
C5-H5A···O4		0.9800	2.2700	2.741 (3)	108.00
C6-H6A···O1	vi	0.9700	2.5300	3.337 (3)	141.00
C6-H6B···Cl2A		0.9700	2.6800	3.125 (4)	109.00
C6-H6B···O3		0.9700	2.5800	2.979 (2)	105.00
C13-H13A···O2		0.9600	2.2900	2.716 (3)	106.00
C13-H13C···O5	vii	0.9600	2.5100	3.425 (3)	159.00
C14-H14B···O2		0.9600	2.2400	2.690 (4)	108.00

Symmetry codes: (iii) $-x + 4/3, -y + 2/3, -z + 2/3$; (iv) $y + 1/3, -x + y + 2/3, -z + 2/3$; (v) $x - y + 1/3, x - 1/3, -z + 2/3$; (vi) $y - 1/3, -x + y + 1/3, -z + 4/3$; (vii) $-x + y, -x, z$.

Table 6. Selected geometric parameters (Å, º) of compound **2b**.

Bond	Experimental	Calculated
Cl1-C12	1.7310 (11)	1.7247
Cl2-C10	1.7338 (13)	1.7195
O1-C1	1.2101 (19)	1.2276
O2-C2	1.219 (2)	1.2325
O3-C3	1.2148 (16)	1.2278
O4-N3	1.212 (2)	1.2362
O5-N3	1.204 (3)	1.2378
N1-C1	1.376 (2)	1.3881
N1-C2	1.386 (2)	1.3925
N1-C13	1.469 (2)	1.4515
N2-C2	1.3947 (19)	1.4071
N2-C3	1.3661 (16)	1.3855
N2-C14	1.471 (2)	1.4513
N3-C6	1.496 (2)	1.4962
Atom Angle	**Experimental**	**Calculated**
C1-N1-C2	124.73 (12)	122.7743
C1-N1-C13	117.37 (15)	117.4505
C2-N1-C13	117.89 (15)	117.0006
C2-N2-C3	124.33 (11)	122.9525
C2-N2-C14	117.89 (12)	117.0593
C3-N2-C14	117.64 (12)	117.6313
O4-N3-O5	122.4 (2)	125.7819
O4-N3-C6	118.79 (15)	116.9697
O5-N3-C6	118.86 (17)	117.2445
O1-C1-N1	122.31 (14)	123.3871
O1-C1-C4	120.81 (13)	123.7560
N1-C1-C4	116.80 (12)	112.8565
O2-C2-N1	121.70 (15)	121.7802
O2-C2-N2	120.54 (14)	121.7454
N1-C2-N2	117.74 (12)	116.2983
O3-C3-N2	121.68 (12)	123.7575
O3-C3-C4	121.06 (11)	122.9936
N2-C3-C4	117.18 (10)	113.2488
N3-C6-C5	109.74 (11)	111.9825
Cl2-C10-C9	118.98 (10)	119.8634
Cl2-C10-C11	119.27 (9)	119.9545
Cl1-C12-C7	121.01 (8)	123.6597
Cl1-C12-C11	116.44 (9)	115.4596

Table 7. Hydrogen-bond geometry (Å, °) of compound **2b**.

D-H···*A*		*D*-H	H···*A*	*D*···*A*		*D*-H···*A*
C6-H6A···O2	i	0.9700	2.3900	3.222	(2)	144.00
C6-H6B···O1		0.9700	2.5500	3.118	(2)	117.00
C9-H9A···O3	ii	0.9300	2.5100	3.2290	(18)	134.00
C13-H13B···O2		0.9600	2.3100	2.727	(3)	105.00
C14-H14C···O2		0.9600	2.2700	2.715	(2)	107.00

Symmetry codes: (i) $x, -y + 1, z+1/2$; (ii) $x - 1/2, y + 1/2, z$.

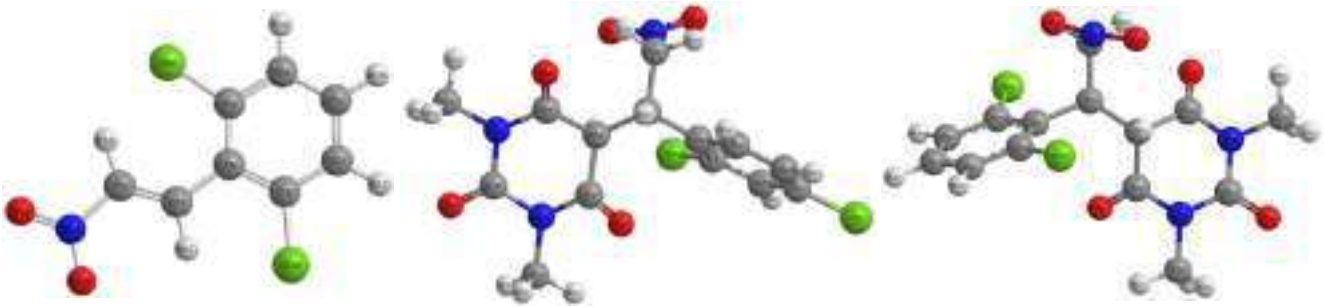
2.3. Optimized Molecular Geometry

From the XRD data, it is clear that the compounds **1a** and **2b** possess monoclinic, whereas, **2a** has trigonal crystal structures. The cell dimensions and other data are tabulated in Table 1. Selected values of experimental and DFT calculated geometric parameters for the compounds are listed in Tables 2, 4, 6 and 8. Figure 3 shows the optimized structures for **1a** and **2a**,**b**.

Table 8. Optimized calculations of various parameters for **1a** and **2a**,**b** using B3LYP/6-311G basis set.

Parameter	1a	2a	2b
Heat of Formation (kcal/mol)	22.075	−100.903	−99.472
Total Energy (kcal/mol)	−896424.216	−1244859.443	−102495.469
Dipole (Debye)	8.281	4.116	3.848
HOMO energy (eV)	−10.019	−10.575	−10.813
LUMO energy (eV)	−4.320	−2.278	−2.383
HOMO–LUMO energy gap (eV)	5.699	8.297	8.430

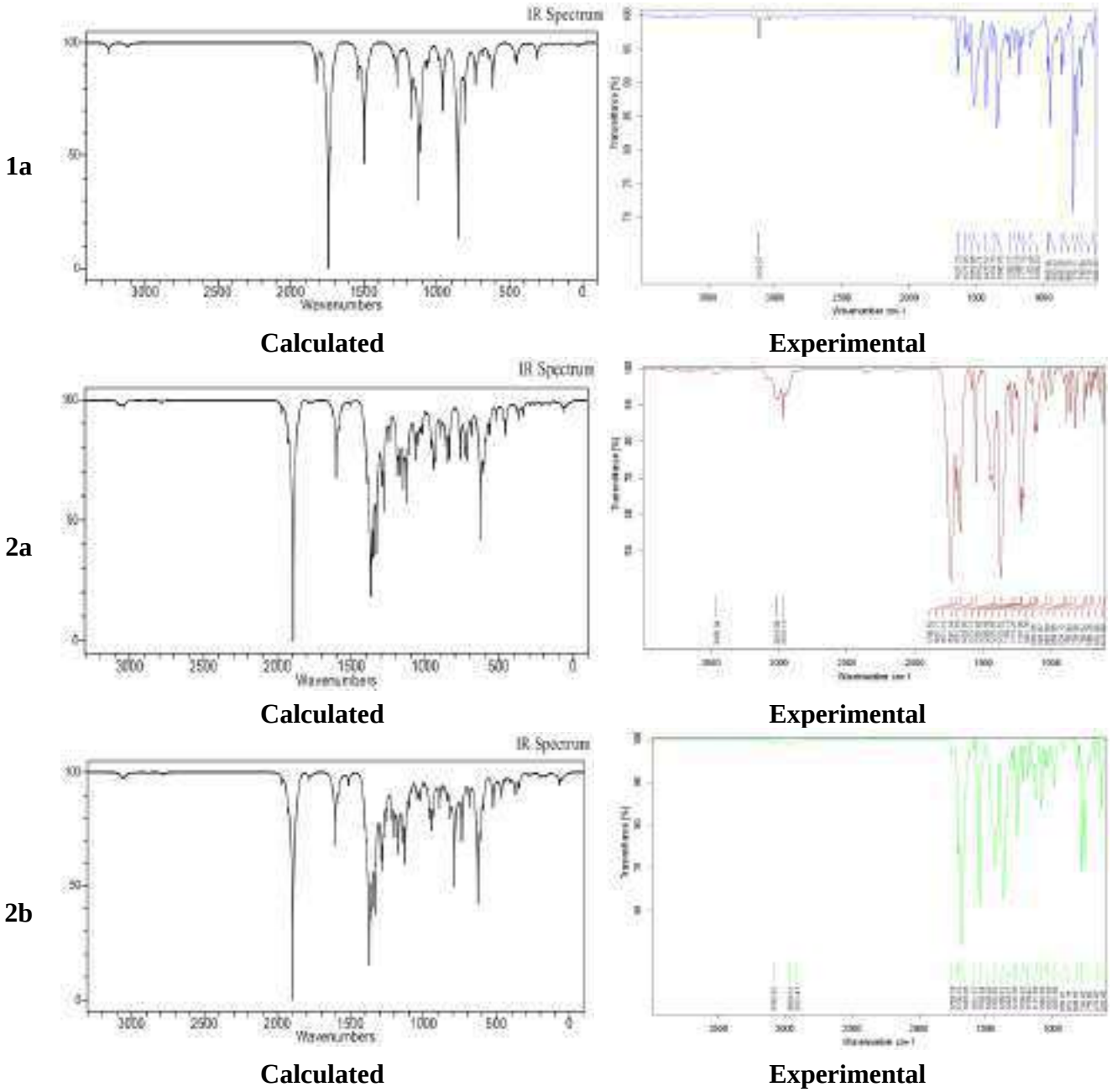
Figure 3. The optimized structures for **1a** and **2a**,**b**.



1a **2a** **2b**

Figure 4 shows the experimental and calculated (B3LYP/6-311G) IR spectrum for **1a** and **2a**,**b**. A comparison of predicted (B3LYP/6-311G) with experimental IR reveals that B3LYP/6-311G basis set gives reasonable deviations from the experimental values. The discrepancies observed between the calculated and the experimental vibrational frequencies may be attributable to the fact that the calculations have been actually performed on a single molecule in the gaseous state contrary to the experimental values recorded in the solid state in the presence of intermolecular interactions.

Figure 4. Experimental and calculated IR spectra for **1a** and **2a**,**b**.



2.4. Experimental and Calculated IR Vibrations

The calculated (B3LYP/6-311G) and experimental C-H, C-Cl, N=O, C=O, and C=C vibration values for all the molecules have good agreement, except for C=O for **2a**. For **2a**, the computed C=O stretching vibrations at 1894 cm^{-1} deviated substantially from the experimental result. A plausible reason for this could be the intermolecular interactions present in solid state whereas during DFT calculations the molecule is assumed to be in isolated gaseous state.

2.5. Geometric Parameters

The solid state X-ray structure analysis revealed disorder in the phenyl moiety for **2a** (see Figure 2). This incongruity noted between the calculated and the experimental vibrational frequencies may be due

to the fact that the calculations have been actually performed on a single molecule in the gaseous state contrary to the experimental values recorded in the solid state. In DFT calculations, bond lengths and angles have been reported only for the major component of the phenyl moiety of **2a** (designated by the suffix "A"). The selected calculated and experimental geometric parameters for **1a** and **2a**,**b** have been tabulated in Tables 2, 4 and 6.

2.6. Thermal Gravimetric Analysis (TGA)

The synthesized novel compounds were subjected to thermogravimetric analysis (TGA) to evaluate their thermal stability and degradation patterns (Table 9) and the TGA and DTG patterns are shown in Figure 5. All samples were subjected to analysis in a nitrogen atmosphere in the temperature range from 30 ℃ to 800 ℃ with a heating ramp rate of 10 ℃ per min. It was observed that the different nitrostyrene derivatives displayed different thermal stabilities and degradation patterns. The pyrolysis processes of the materials are characterized by single-stage degradation, with an exception of **2a**, which displays two-stage degradation. Interestingly, it was detected that upon the incorporation of the barbituric acid ring into the styrene, the resulting molecule was slightly more thermally stable than its precursor. The weight loss pattern of all the compounds was found to be different at different intervals with **1a**,**b** displaying a weight loss of 70% and 98% respectively at 200 ℃, but at the same temperature the weight loss percentage for the barbituric acid derivatives **2a**,**b** were found to be 48% and 18 % respectively. When a comparison of thermal degradation pattern between **1a** and **2a** was made it was found that **1a** undergoes single stage degradation with decomposition range of 100–190 ℃ (90 ℃), while **2a** displays two stage degradation with decomposition taking place in the range of 105–195 ℃ (90 ℃) and 200–275 ℃ (75 ℃). The degradation temperature range of **1b** and **2b** was found to take place at a 162–262 ℃ (100 ℃) and 125–230 ℃ (105 ℃), respective ly. The peak temperature of **2b** (220.02 ℃) was higher than that of **1b** (199.38 ℃), while the decomposition intensity of **1b** was found to be high with 2.35 wt %/℃ compared to 1.99 wt %/℃ **2b**. This behaviour can be attributed to the presence of barbituric acid. However, when the temperature was increased further all the compounds followed similar weight loss patterns with varying percentages of residue at the final temperature of 800 ℃. From the residual weight values obtained at ~800 ℃ it can be concluded that there is no significant thermal stability among any of the four compounds tested, however it can be said that thermal stability of the barbituric acid derivative of the styrene molecule is slightly improved compared to that of its precursor. The weight loss percentage at different temperatures is mentioned in the table below and a comparative graphical representation of the compounds is given in Figure 5. A detailed study into the thermal behaviour of the synthesized compounds shall be carried out the thermal kinetics will be reported separately.

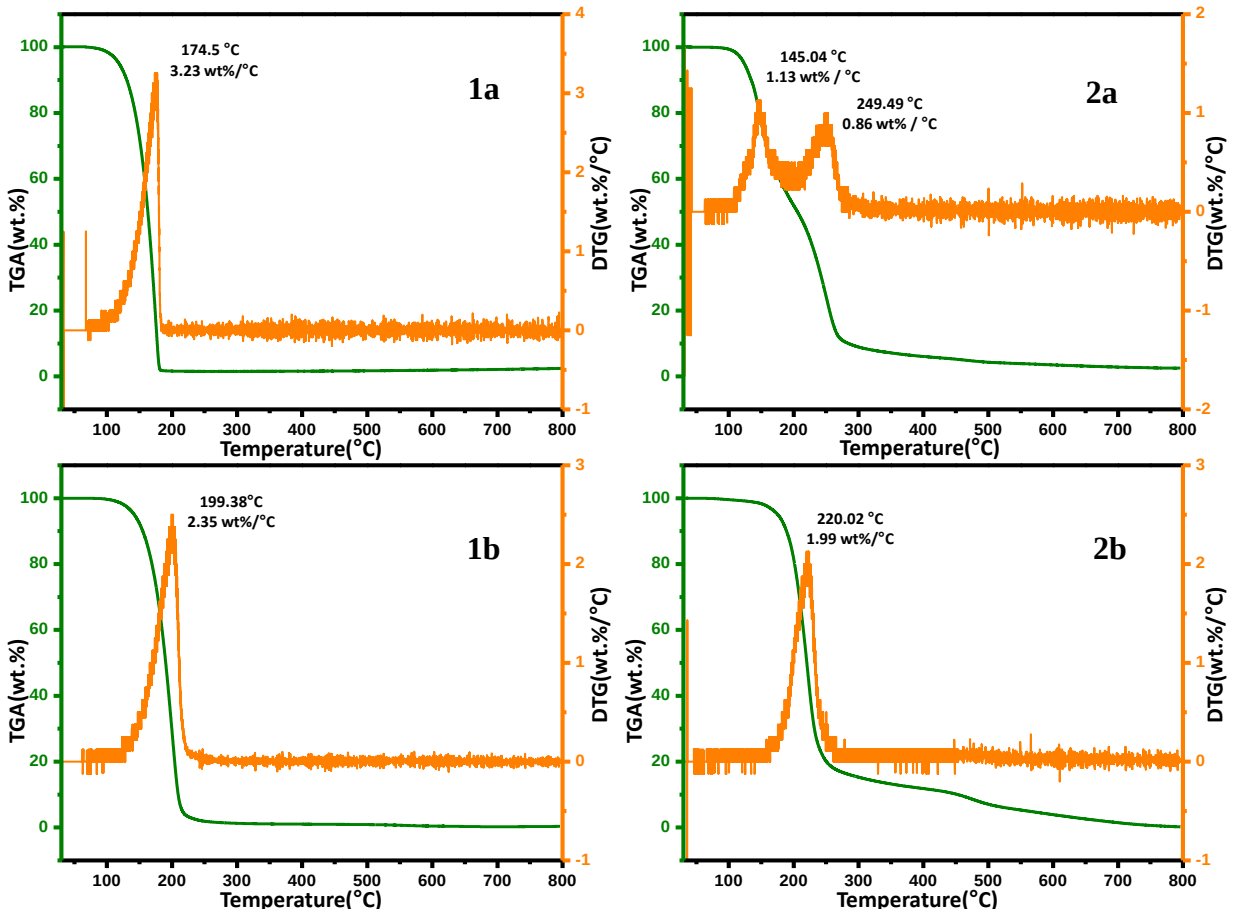
Table 9. Weight loss percentage at different temperatures for **1a**,**b** and **2a**,**b**.

Temperature	Weight Loss (%)			
	1a	**2a**	**1b**	**2b**
100	0.33	0.63	1.42	0.44
200	70.85	48.06	98.37	18.45
300	98.72	91.07	98.46	84.73

Table 9. *Cont.*

Temperature	Weight Loss (%)			
	1a	**2a**	**1b**	**2b**
400	98.98	93.95	98.40	88.19
500	99.11	95.67	98.29	92.93
600	99.56	96.47	98.08	96.10
700	99.77	97.14	97.87	98.52
800	99.66	97.47	97.55	99.81

Figure 5. TGA and DTG curves of the synthesized compounds.



3. Experimental Section

3.1. General

All the chemicals were purchased from Aldrich (Riedstraße, Germany), Sigma-Aldrich (St. Louis, MO, USA), Fluka (Buchs, Switzerland), and used without further purification, unless otherwise stated. The structure of **1a** was confirmed by X-ray crystal structure analysis (Bruker AXS GmbH, Karlsruhe, Germany). The crystallographic data for **1a** (CCDC-992700), **2a** (CCDC-992327) and **2b** (CCDC-992701) have been submitted to the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request/cif). Compound **1a** was prepared from 2,6-dicholorobenzaldehyde and nitromethane as white crystals according to the reported procedure [16]. Colorless block-shaped

crystals of the compound suitable for X-ray analysis were formed in isopropanol/heptane at room temperature after 3 days.

3.2. 5-(1-(2,6-Dichlorophenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**2a**)

According to the reported procedure [16], **2a** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-2,6-dichloro-1-(2-nitrovinyl)benzene (**1a**) as white crystals. Colorless block-shaped crystals of the compound suitable for X-ray analysis were formed in $CHCl_3/Et_2O$ at room temperature after 2 days.

3.3. 5-(1-(2,4-Dichlorophenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**2b**)

According to the reported procedure [16], **2b** was prepared from 1,3-dimethylbarbituric acid and (*E*)-2,4-dichloro-1-(2-nitrovinyl)benzene (**1a**) as yellow crystals. Colorless block-shaped crystals of the compound suitable for X-ray analysis were formed in DCM/Pet. ether at room temperature after 1 day.

3.4. DFT Calculations

The DFT calculations were performed using the GAMESS package. The input geometry of the synthesized molecules were optimized without imposing any external constraint on the potential energy surfaces generated by the B3LYP/6-311G(d,p) basis set for C, O, N and H atoms. The resulting optimized geometry was used as an input for vibrational frequencies calculations, with inclusion of polarization functions to handle the polar bonds such as N=O, C=O, *etc.*

4. Conclusions

In a summary, pyrimidine derivatives **2a**,**b** were prepared starting from nitroalkenes **1a**,**b** using an eco-benign method. The structures for **1a** and **2a**,**b** have been characterized by their single crystal X-ray diffraction analysis. DFT/TGA/IR analyses were performed and discussed.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/19/10/17187/s1.

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Author Contributions

Hany J. Al-Najjar and Mohamed Ali carried out the experimental part; Syed F. Adil carried out thermo-analysis; Vijay H. Masand carried out computational studies; Hazem A Ghabbour and Hoong-Kun Fun carried out X-ray part; Abdullah M. Al-Majid helped in the results and discussion and writing the manuscript; Assem Barakat: proposed the subject and designed the study. All the authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **1a**,**b** and **2a**,**b** are available from the authors.

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PHYSICAL CHEMISTRY OF SOLUTIONS

Molecular Interactions in Substituted Pyrimidines–Acetonitrile Solutions at 298.15–318.15 K[1]

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Abstract—Density, ultrasonic speed in pure solvent acetonitrile (AN) and ligand solution of substituted pyrimidine in pure AN were measured at different temperatures (298.15, 303.15, 308.15, 313.15, and 318.15 K). Acoustical parameters such as adiabatic compressibility, intermolecular free length, acoustical impedance and relative association were determined from the experimental data of density and ultrasonic speed. The effect of temperature variations on the strength of molecular interaction has been studied. An excellent correlation represents in terms of solute–solvent interaction at all temperatures.

Keywords: density, ultrasonic velocity, acoustical parameter, molecular interaction, pyrimidine, acetonitrile.

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INTRODUCTION

Ultrasonic methods have established an important place in science and new applications are found for the solution of many theoretical and practical problems [1]. Most important features of ultrasonic systems are robustness, non-invasiveness, precision, low cost, rapidity, and easy automation. Investigation of changes in thermodynamical properties of mixtures and the degree of their deviations from ideal mixing behavior are an excellent qualitative way to elicit information about molecular structure and intermolecular forces in liquid mixture. This has given impetus to the theoretical and experimental investigation of excess thermodynamic properties of liquid mixtures [2–5].The measurements of physicochemical properties such as density, viscosity, ultrasonic velocity and refractive indices of pure components and their mixtures are being increasingly used as tools for investigations of the properties of pure and the nature intermolecular interaction between components of liquid mixtures [6, 7]. The knowledge of fluid properties is important for many industrial applications. Among these properties density plays an important role in many industrial processes [8].

Ultrasonic studies have found wide applications owing to their ability to characterize the physicochemical behavior of solutions. The measurements of ultrasonic velocity in solutions thus provide useful information regarding the degree of deviation from ideality, molecular association in solution and important correlation with various acoustical parameters [9–11]. Ultrasonic speed measurements are useful when dealing with the problems of structure and molecular interaction in liquids because of their accuracy. The concentration and temperature dependence of acoustic properties has proved to be a significant observation of intermolecular interaction in liquids and liquid mixtures [12, 13].

The thermodynamical functions like adiabatic compressibility, acoustic impedance, intermolecular free length, molar sound velocity have proved to be of immense value in predicting nature and strength of molecular association in liquid medium [14]. Bachu et al. [15] have reported the densities, viscosities and speed of sound of binary mixtures of phenylacetonitrile with some aliphatic alcohols at 308.15 K. This result reveals that the position of hydroxyl group, alkyl chain length and branching of alkyl chain have significant effects on thermodynamic properties of the system investigated. The substantial work also has been reported on the excess properties of acetonitrile + alkanols [16], acrylonitrile + alkanols [17], and benzonitrile + alkanols [18]. Abraham et al. [19] reported densities and sound speeds of AN + toluene mixture and observed negative variations in deviations of isentropic compressibility thereby suggesting strong interactions between AN–toluene molecules. These considerations prompted us to assess the densities, ultrasonic velocities and acoustical parameters of the mixture of AN with L_1, L_2, L_3, and L_4 mixtures at different tem-

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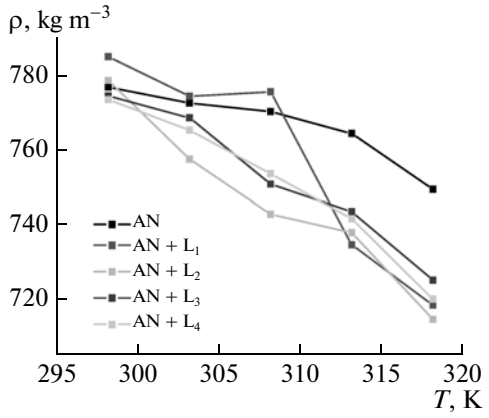


Fig. 1. The temperature dependences of experimental density of solutions of AN, L_1, L_2, L_3, and L_4 in AN with solute concentration of 1×10^{-3} M.

peratures (298.15, 303.15, 308.15, 313.15, and 318.15 K).

Heterocyclic compounds are of a great synthetic and structural versatility because they have a number of potential substitution positions. Furthermore heteroatoms offer the possibility of several modes of coordination. Heterocycle containing pyrimidine moiety possesses pharmaceutical, medicinal, agricultural, industrial and biotechnological significances. AN belong to nitrile series having functional group (–C≡N). It is a part of several biologically important molecules such as proteins, lipids and hormones. AN molecules are highly polar with their dipoles arranged in antiparallal pairs and this strongly ordered structure is stabilized by dipole–dipole interactions. AN is used mainly as a solvent in the purification of butadiene [20] in battery applications and also in the manufacture of DNA oligonucleotides from monomers. Industrially, it is used as a solvent for the manufacture of pharmaceuticals and photographic film. The great potential along with their interesting molecular structure promoted us to study molecular interaction in non aqueous media.

In the view of applications of these solvents and solutes in chemistry and modern technology for four binary mixtures they have been studied at different temperatures (297.15, 303.15, 308.15, 313.15, and 318.15 K).

EXPERIMENTAL

The ligands L_1, L_2, L_3, and L_4 were synthesized in the laboratory by known literature method [21]. The concentrated solutions of ligands were prepared by dissolving an accurate amount in AN solvent in standard flasks with airtight caps and the mass measurements were performed using high precision digital balance (Adair Datta of accuracy ±0.01 mg). The ultrasonic velocity in pure components and their mixtures were measured by ultrasonic interferometer (Mittal enterprises, model F-81s) at 2 MHz with frequency tolerance ±0.03%. It consists of high frequency generator and a measuring cell. The densities of AN and ligands were measured by the specific gravity bottle with capacity 10 mL (Fig. 1). The accuracy of instrument was examined with pure distilled water and AN.

THEORY

Numerous methods are available in the literature for measuring ultrasonic velocity in solids and liquids. The ultrasonic interferometer is considered as more reliable and precise instrument. The expression used to determine ultrasonic velocity using ultrasonic interferometer is;

$$u = \nu\lambda, \quad (1)$$

where u is ultrasonic velocity, and λ is wavelength. The adiabatic compressibility (β_s) was calculated from Newton–Laplace equation. It is extensively applicable in understanding physicochemical behavior of liquid mixtures such as molecular association, dissociation and formation. The adiabatic compressibility is given by equation:

$$\beta_s = 1/\rho_s u^2, \quad (2)$$

where ρ_s is density of solution, and u is speed of ultrasonic velocity. The intermolecular free length between molecules in the liquid state is an essential and characteristic feature for interaction. Intermolecular force is one way or another to determine the properties of liquids of attractive and repulsive forces [22]. The intermolecular free length (L_f) is calculated by using the standard expression;

$$L_f = K\beta_s^{1/2}, \quad (3)$$

where K is a temperature dependent constant known as Jacobson constant. The acoustic impedance (Z) of a wave can be mathematically defined as the product of the wave velocity in the medium and its density. As the waves encounter the interface between the liquid and solid, they sense a change in acoustic impedance and are obtained by equation:

$$Z = u\rho. \quad (4)$$

The relative association (R_A) was calculated by the following equation;

$$R_A = (\rho_s/\rho_0)(u_0/u_s)^{1/3}, \quad (5)$$

where ρ_0 is density of solvent, and u_0 is velocity of solvent.

RESULTS AND DISCUSSION

The calibration of the ultrasonic interferometer and specific gravity bottle were done by measuring the ultrasonic velocities and densities of pure AN and distilled water respectively. The measured values reported in Table 1 are good concordance with literature values. Small difference may result from differences in the

Table 1. Comparison of densities (ρ) and ultrasonic velocities (u) of distilled water and AN along with their literature values at different temperatures

Liquid	T, K	ρ, g cm^{-3}		u, m s^{-1}	
		exptl.	lit.	exptl.	lit.
Water	298.15	0.9962	0.9900 [23], 0.9970 [24]	1497	1480 [23], 1520 [24],
	293.15		0.9982 [26]		1496.9 [25], 1483.1 [26]
AN	298.15	0.7771	0.7765 [27], 0.775 [28]	1268	1271.3 [28]
	303.15	0.7728	0.7699 [27]	1252	1250 [27]
	308.15	0.7705	0.7652 [26]	1234	–
	313.15	0.7646	–	1218	–
	318.15	0.7496	–	1206	–

Table 2. Experimental density and ultrasonic velocity of L_1, L_2, L_3, and L_4 in AN at different temperatures with solute concentration of 1×10^{-3} M

T, K	ρ, kg m^{-3}					u, m s^{-1}				
	AN	AN + L_1	AN + L_2	AN + L_3	AN + L_4	AN	AN + L_1	AN + L_2	AN + L_3	AN + L_4
298.15	777.1	785.3	778.9	774.7	773.7	1268	1288	1296	1292	1289
303.15	772.8	774.6	757.7	768.8	765.5	1252	1260	1260	1262	1262
308.15	770.5	775.8	743.0	751.0	753.8	1234	1248	1245	1247	1253
313.15	764.6	734.8	738.1	743.7	741.8	1218	1232	1224	1220	1232
318.15	749.6	718.6	714.8	725.3	720.2	1206	1212	1184	1192	1208

purity of chemicals, measurements, techniques and calibrations. The values of densities and ultrasonic velocities of L_1, L_2, L_3, and L_4 listed in Table 2 showed that decreases with increase in temperature [29, 30]. As the temperature increased available thermal energy facilitates the breaking of the bonds between the associated molecules into their monomers. Moreover, increases of thermal energy weaken the molecular forces which tend the decrease the ultrasonic velocity. Figure 2 shows the variation of ultrasonic velocity with substituted pyrimidine in AN at different temperatures. The thermodynamic parameters, adiabatic compressibility, free length, acoustic impedance and relative association are presented in Tables 3 and 4. Figure 3, it can be seen that the values of adiabatic compressibility increase by increasing temperature

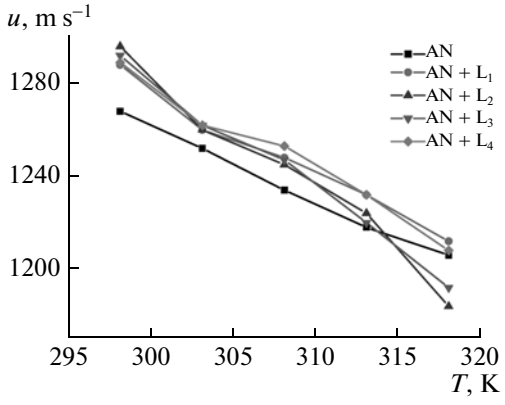


Fig. 2. The temperature dependences of ultrasonic velocity in solutions of AN, L_1, L_2, L_3, and L_4 in AN with solute concentration of 1×10^{-3} M.

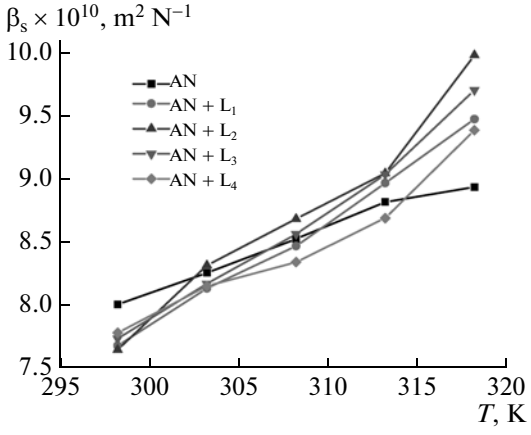


Fig. 3. The temperature dependences of adiabatic compressibility (β_s) of solutions of AN, L_1, L_2, L_3 and L_4 in AN with solute concentration of 1×10^{-3} M.

Table 3. Variation of adiabatic compressibility (β_s) and linear free length (L_f) and acoustic impedance (Z) of L_1, L_2, L_3, and L_4 in AN at different temperatures with solute concentration of 1×10^{-3} M

T, K	AN	AN + L_1	AN + L_2	AN + L_3	AN + L_4
			$\beta_s \times 10^{10}$, m^2 N^{-1}		
298.15	8.0035	7.6759	7.6437	7.7328	7.7789
303.15	8.2551	8.1317	8.3130	8.1671	8.1490
308.15	8.5230	8.4670	8.6830	8.5630	8.3390
313.15	8.8159	8.9662	9.0431	9.0341	8.6883
318.15	8.9338	9.4734	9.9795	9.7035	9.3847
			$L_f \times 10^{10}$, m		
298.15	5.6182	5.4845	5.4730	5.5048	5.5211
303.15	5.7331	5.6901	5.7258	5.7024	5.6961
308.15	5.8715	5.8522	5.8798	5.8853	5.8078
313.15	6.0279	6.0790	6.1051	6.1021	5.9841
318.15	6.1153	6.3168	6.4833	6.3930	6.2871
			Z, N s m^{-5}		
298.15	985.36	1011.46	1009.45	1000.91	997.29
303.15	967.54	975.99	954.70	970.22	972.37
308.15	950.79	946.35	925.03	936.49	957.63
313.15	931.28	905.27	903.43	907.31	934.22
318.15	904.01	870.94	846.32	864.55	882.08

this is because at higher temperature ion–solvent interactions are weakened and therefore the number of AN molecules affected by the ions decreases with increasing temperature [31]. In the system the interaction becomes weak due to the thermal agitation of component molecules and this is indicated by the decrease in velocity values [32].

Figure 4 shows the variation of free length at different temperatures. The adiabatic compressibility and free length show an opposite trend to that of velocity. The decreased compressibility brings the molecules to a closer packing resulting a decrease in intermolecular free length. This may be due to presence of solvent molecules around the ions. According to a model proposed by Erying and Kinkaid [11], ultrasonic velocity decreases with increase in free length and vice versa. Increase in compressibility and free length with temperature for all system suggests breaking of hetero and homo association of molecules at higher temperature [33]. Acoustic impedance (Z) is dependent on both material and its geometry. It is seen from Fig. 5 the acoustic impedance decreases with increasing temperature in all the system [34]. The relative association (R_A) is influenced by two factors (i) the breaking up of

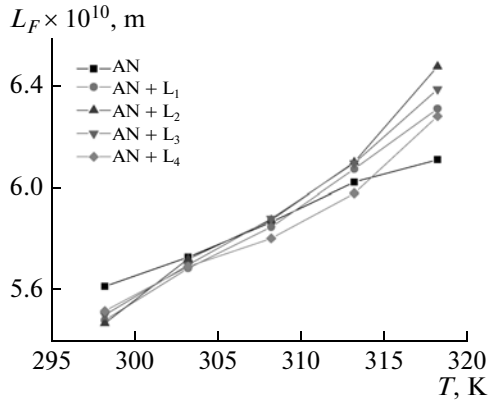


Fig. 4. Variation of linear free length (L_f) of L_1, L_2, L_3, and L_4 in AN at different temperatures T (K) with solute concentration of 1×10^{-3} M.

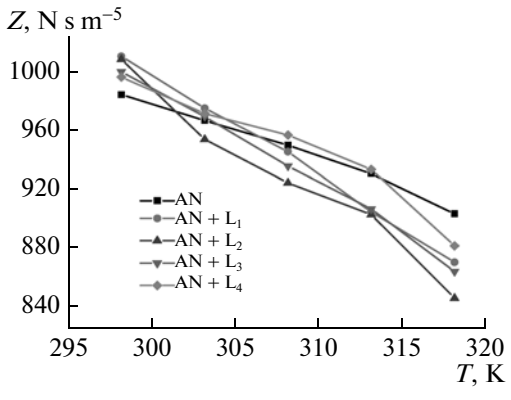


Fig. 5. The temperature dependences of acoustic impedance (Z) of L_1, L_2, L_3, and L_4 in AN different temperatures T (K) with solute concentration of 1×10^{-3} M.

Table 4. Variation of relative association (R_A) of L_1, L_2, L_3, and L_4 in AN at different temperatures with solute concentration of 1×10^{-3} M

T, K	AN + L_1	AN + L_2	AN + L_3	AN + L_4
298.15	1.0052	0.9950	0.9907	0.9901
303.15	1.0002	0.9783	0.9921	0.9943
308.15	0.9804	0.9614	0.9712	0.9862
313.15	0.9573	0.9637	0.9721	0.9879
318.15	0.9570	0.9594	0.9713	0.9735

the solvent molecules on addition of solute to it and (ii) the solvation of solute that are simultaneously present [35].

CONCLUSIONS

Ultrasonic method is a powerful tool for characterizing physicochemical properties and existence of molecular interaction in the mixture. The result reveals that the density and ultrasonic velocity of pure acetonitrile and ligand solutions increases with decreased with temperature. It is also seen that the formation of linear plot between temperature and respective parameters indicated that the stronger solute–solvent interaction. The plot between temperature and relative association are found to be nonlinear showed that the weaker solute–solvent interaction.

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Fabrication of multilayer SnO_2–ZnO–PPy sensor for ammonia gas detection

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ORIGINAL PAPER

Fabrication of multilayer SnO_2–ZnO–PPy sensor for ammonia gas detection

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Abstract: The sensitivity of SnO_2–ZnO composites in multilayer with PPy and Al_2O_3 has been studied. Composites of SnO_2–ZnO have been prepared and multilayer sensor has been fabricated using screen printing technique with Al_2O_3 as substrate on glass plate and PPy in multilayer with SnO_2–ZnO. The morphologies of composites of SnO_2–ZnO and PPy have been studied by scanning electron microscopy and crystallite size by X-ray diffraction. Sensitivity has been found to be more for $70SnO_2$:30ZnO/PPy/Al_2O_3 multilayer sensor, which is supported by scanning electron microscopy and X-ray diffraction studies. It has been found that with the increase in concentration of NH_3 gas, the response of multilayer sensor increases.

Keywords: Multilayer; SnO_2–ZnO; Gas sensor

PACS No.: 07.07.Df

1. Introduction

Gas sensors based on semiconductor metal oxides are the most investigated devices. They have attracted the attention of many researchers due to their low cost, ease of fabrication, simplicity of use and large number of detectable gases [1]. Most of the companies provide metal oxide-based gas sensors due to their applications ranging from detection of combustible or toxic gas to air intake control in automobile and glucose biosensors [2]. Tin oxide (SnO_2) is the most used sensing material among commercially sensor devices for toxic gas detection [3]. It is well known that the sensing properties of SnO_2-based materials depend on their chemical and physical characteristics, which are strongly dependent on the preparation conditions, dopant and grain size. This implies that the synthesis of the sensing materials is a key step in the preparation of high-performance metal oxide semiconductor (MOS) gas sensors. SnO_2 powders and films can be prepared by a variety of methods [4–7]. DC-electrical resistance of SnO_2 doped with ZnO and TiO_2 sensors is measured in the presence of humidity. SnO_2–$5Al_2O_3$ and ZnO–$5Al_2O_3$ sensors are found to be good sensing materials for humidity.

Due to various applications in organic light-emitting diodes (OLEDs) [8], lithography [9], electrode material [10], electromagnetic shielding [11] and sensing [12, 13], conducting polymers have attracted considerable interest. Sensors constructed from conducting polymers such as polypyrrole, polyhexylthiophene, polymethylthiophene, polyethylene and polyaniline have been investigated [14–19] to study their potential applications in detecting gases, like nitrogen dioxide, carbon monoxide, carbon dioxide, ammonia and hydrogen besides moisture and a number of organic volatile compounds [20].

The present paper mainly deals with the preparation of NH_3 gas sensor in multilayer pattern with SnO_2 doped as ZnO and polypyrrole layer. It is found that SnO_2–ZnO system in multilayer with polypyrrole shows sensitivity to 70 ppm of ammonia gas concentration even at room temperature.

2. Experimental details

Powder polypyrrole was prepared from 4.290 (high) weight ratio of pyrrole (Py) monomer and oxidant ($FeCl_3$). During

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the synthesis, concentration of $FeCl_3$ was kept constant and methanol was used as a solvent. The Py-monomer, anhydrous iron(III) chloride ($FeCl_3$) and methanol were used for synthesis of PPy. The solution of 7 ml methanol and 1.892 g $FeCl_3$ was first prepared in round-bottom flask and 8.4 ml Py-monomer was added to ($FeCl_3$ + methanol) solution with constant stirring in absence of light. The amount of Py-monomer was added to the solution (1/2.33 times of $FeCl_3$) in such a way to get maximum yield [21]. The polymerization of Py, which was suppressed in a solution, progressed rapidly due to an increase of oxidation potential caused by evaporation of solvent. In the polymerization reaction of Py, it was observed that as soon as the Py-monomer was added to the solution, the colour changed to dark green/black. There was an increase in temperature of the solution during the start of reaction, indicated that it was an exothermic reaction [22] and it was carried out at room temperature for 4 h. The final precipitated polymer was filtered by a conventional method. The polymer was washed with distilled water several times till the filtrate obtained was colourless. To remove last traces of un-reacted pyrrole and remaining ferric and ferrous chloride formed due to polymerization, it was then washed with methanol. The polymer, obtained in powder forms, was dried first at room temperature for a few hours and then finally dried in an oven (Gallenkamp, British Made) kept at 80 °C for 5–6 h. This polypyrrole was then used for active layers of semiconductor gas sensors.

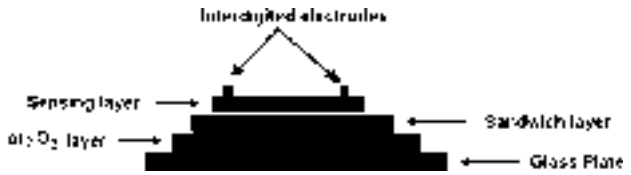


Fig. 1 Design of multilayer sensor

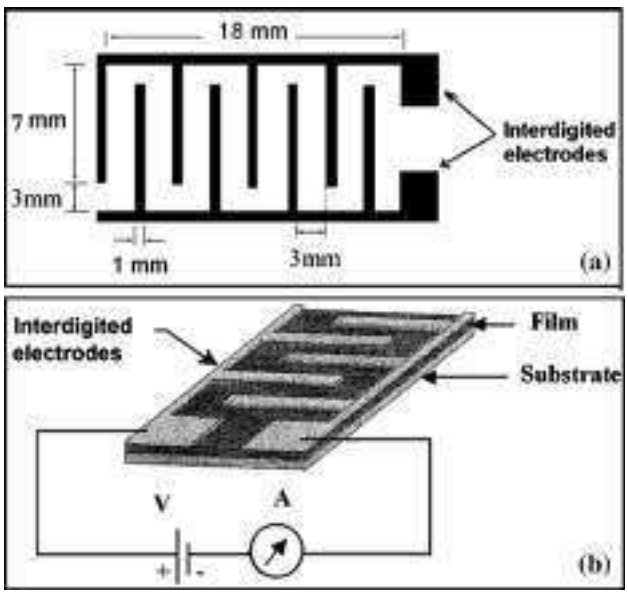


Fig. 2 (**a**) Fabrication of interdigited electrodes, (**b**) circuit of resistance measurement using interdigited electrodes

SnO_2, ZnO and Al_2O_3 powders (AR grade) were calcinated at about 800 °C for 4–5 h and were crushed to get fine powder of the samples. XRD patterns of the samples were obtained using diffractometer system XPERT-PRO (CuKα radiation $\lambda = 1.54$ Å) at continuous scan type at step size $2\theta = 0.017°$.

The ink or paste of the sample was prepared by using screen printing (thick film technique) technique [23, 24]. The binder for screen printing was prepared by thoroughly mixing 8 wt% butyl carbitol with 92 wt% ethyl cellulose. On chemically cleaned glass plate, paste of Al_2O_3 was screen-printed and it was kept for 24 h to dry it at room temperature and then heated at 140 °C for 2.5 h to remove

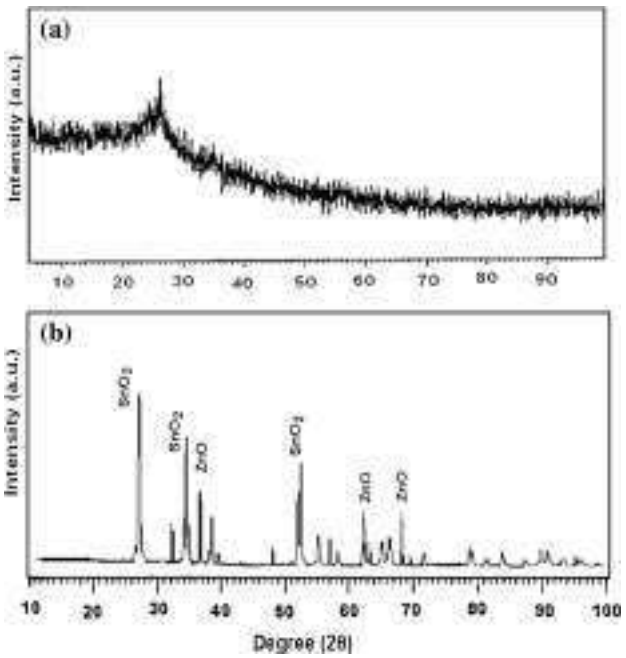


Fig. 3 (**a**) XRD of polypyrrole and (**b**) XRD of $70SnO_2$:30ZnO

Table 1 Crystallite size, sensitivity and response time of sensors

S. no.	Composition (mol%)	Crystallite size (nm)	Sensitivity (S) at 70 ppm at 313 K	Response time (s)	
				On time	Off time
1	$70SnO_2$–30ZnO	96.01	0.67	67	106
2	Pure SnO_2	120.68	0.48	114	145
3	Pure ZnO	162.09	0.35	125	168

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the binder. The Al_2O_3 layer provided mechanical support as well as high thermal conductivity. Paste of SnO_2 and ZnO mixed in proper stoichiometry was then screen-printed on Al_2O_3 layer. Again plate was dried at room temperature for 24 h and binder was removed by heating it at 150 °C for 2.5 h. Finally, polypyrrole layer was deposited on SnO_2 doped with ZnO layer by screen printing, whole plate was dried and again binder was removed as above. Polypyrrole was selected as one of the layers during the fabrication of sensors, but it did not act as interdigited electrodes. Fabrication of multilayer sensor was done, as shown in Fig. 1.

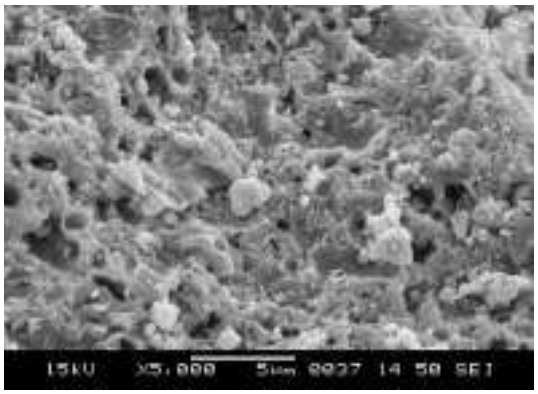


Fig. 4 SEM picture of polypyrrole

Finally on the top surface of the sensor, interdigited electrodes [25–27] were fabricated using conducting silver paste, as shown in Fig. 2(a). Thickness of SnO_2 doped with ZnO layer and PPy layers was recorded with the help of digital micrometre (series 293, Japan) having resolution of ±0.001 mm and was found to be 10 and 7 μm, respectively. To measure the sensitivity, electrical resistance was measured with the help of voltage drop method [28]. The circuit of resistance measurement using interdigited electrodes was shown in Fig. 2(b).

3. Results and discussion

XRD of PPy is shown in Fig. 3(a), which indicates amorphous nature of polypyrrole. Figure 3(b) indicates crystalline nature of ($70SnO_2$:30ZnO) composition sample. The average crystalline size has been calculated by using Scherrer's formula given by Eq. (1),

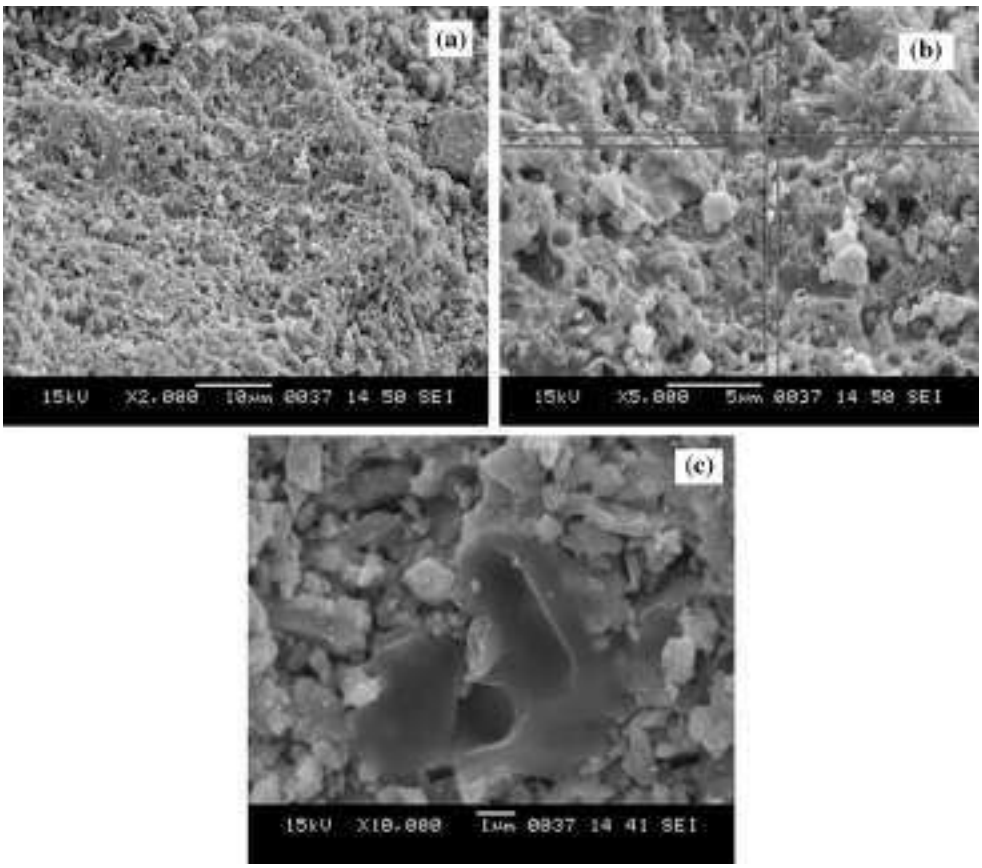


Fig. 5 SEM pictures of $70SnO_2$:30ZnO at magnification (**a**) ×2000, (**b**) ×5000 and (**c**) ×10,000

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$$D = \frac{K\lambda}{\beta\cos\theta} \quad (1)$$

where D is the crystalline size, K is the shape factor and β is the full width at half maximum of diffraction angle in radians. The sensor parameters are listed in the Table 1.

The surface morphology of polypyrrole material has been studied by SEM as shown in Fig. 4.

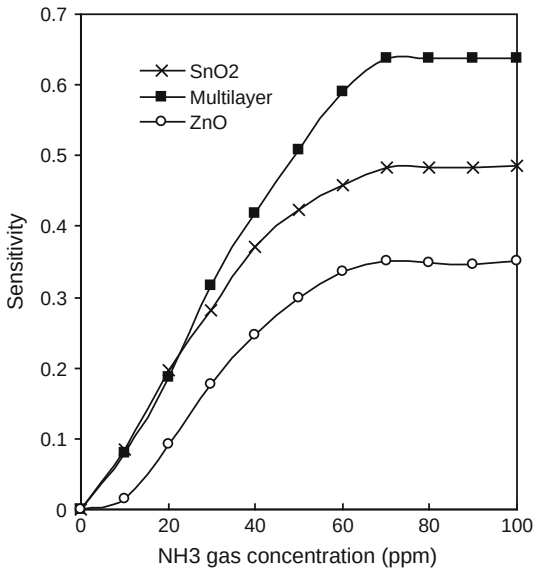


Fig. 6 Variation of sensitivity with of NH_3 gas concentration at room temperature

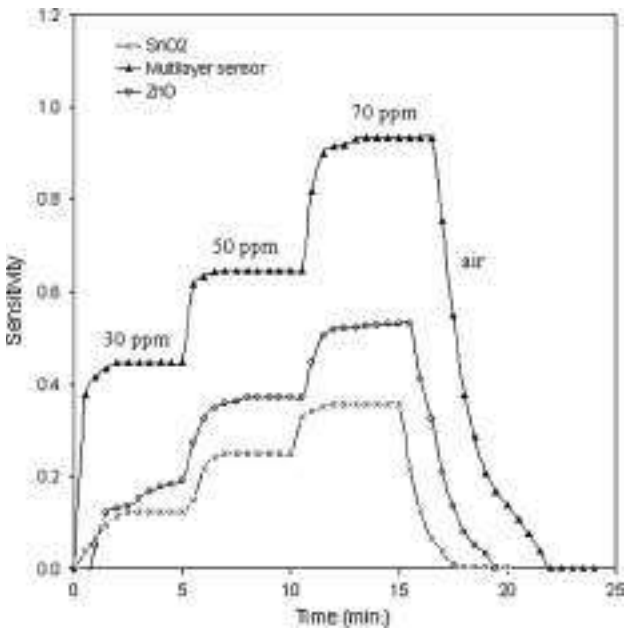


Fig. 7 Dynamic response of pure SnO_2, pure ZnO and multilayer sensor at room temperature

From SEM picture, it is observed that PPY is porous in nature and pore size varies from ~0.5 to 3 μm. The active surface area is found to be large due to their small pores size and hence, it shows more sensitivity. Some portion of SEM picture shows some rods with fine voids over them which helps to increase sensing properties.

SEM pictures of $70SnO_2$:30ZnO at different magnifications are shown in Fig. 5(a)–5(c). It has been found that $70SnO_2$:30ZnO composition has more pores per unit area than SnO_2 and ZnO individual and also the surface is rough because of pores and small granules of SnO_2 and ZnO. The pore size is found to be of the order of 0.8 μm. Thus,

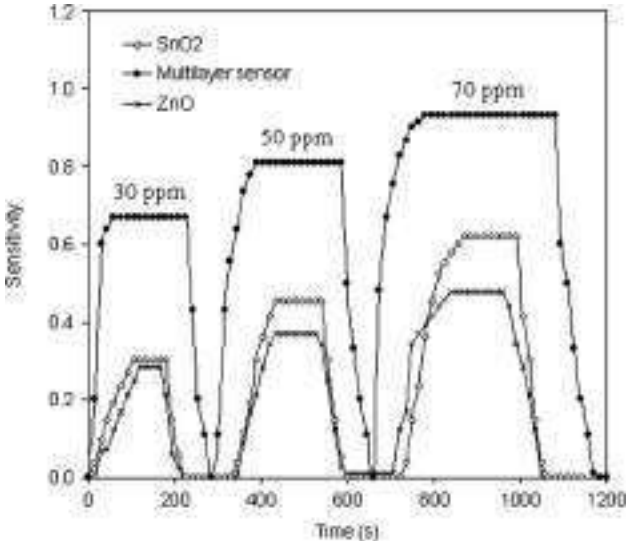


Fig. 8 Static response of pure SnO_2, pure ZnO and multilayer sensor at room temperature

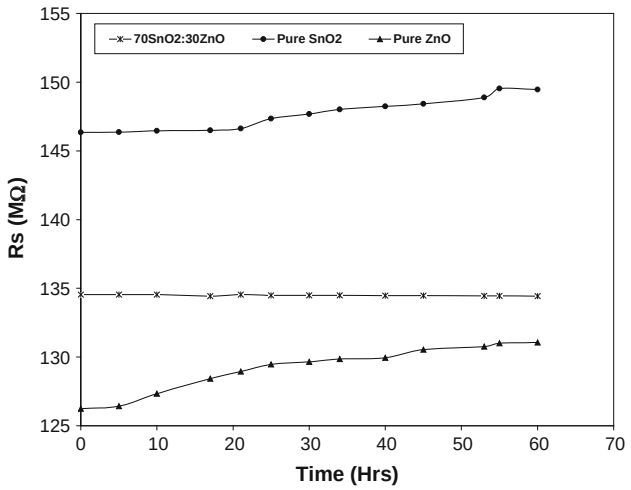


Fig. 9 Dependence of response on time for pure SnO_2, pure ZnO and multilayer sensor

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$70SnO_2$:30ZnO composition has more active surface area and exhibits more sensitivity to NH_3 gas.

The sensitivity of the sensor is given by Eq. (2) shown below,

$$S = \left(\frac{R_{air} - R_{gas}}{R_{air}}\right) = \left(\frac{\Delta R}{R_{air}}\right) \quad (2)$$

where R_{air} and R_{gas} are the resistances of sensors in air and gas, respectively.

From Fig. 6, it is observed that the multilayer structure of the sensor shows more sensitivity to ammonia gas than that for pure ZnO and pure SnO_2. Resistance of multilayer sensor is found to be decreasing with the increase of ammonia gas concentration and thereby sensitivity increases. Maximum sensitivity has been recorded for multilayer sensor at 70 ppm concentration of NH_3. The sensing mechanism is explained on the basis of NH_3 heats of adsorption [29, 30]. Four-coordinate Sn^{2+} cations at bridging oxygen vacancies on the reduced surface appear to be more acidic than five-coordinate Sn^{4+} cations. The stronger interactions with Sn^{2+} cations are attributed to a predominant covalent contribution to the NH_3–Sn bond. The Lewis acidity of the Sn cations based on NH_3 heats of adsorption goes through a maximum for the formation of a reduced surface as the surface becomes more oxygen deficient, and a similar trend is seen in the extent of dissociation of methanol. Four-coordinate Sn^{2+} cations form stronger covalent bonds with NH_3 and methanol due to greater molecular overlap with lone pairs available on both molecules. The introduction of in-plane oxygen vacancies on the defective surface reduces the heats of adsorption of the associated cations possibly due to a higher electronic charge density around the cations associated with in-plane oxygen vacancies.

Dynamic and static responses for pure SnO_2, pure ZnO and multilayer sensor for 30, 50 and 70 ppm are shown in Figs. 7 and 8, respectively. The time taken to reach 90 % of the response when ppm of gas is changed is known as response time and time taken to reach 90 % of recovery when gas is turned off is known as recovery time. The response time (t_{res}) and recovery time (t_{rec}) are the two important parameters of the sensor. It is found that response time is 67.2 s and recovery time is 106.2 s for multilayer sensor at 70 ppm of NH_3. Recovery time is found to be longer than response time, also t_{res} and $t_{rec.}$ for multilayer sensor are found to be smaller than that for pure SnO_2 and pure ZnO, i.e. multilayer sensor is fast. The selected PPy has major component due to his high porosity nature and it has more sensitivity at room temperature with SnO_2 and sensing conditions are improved.

The rate of change of resistance of the sensor with respect to time defines the stability of the sensor. A sensor should be more stable for its better response. The changes in the resistance for multilayer sensor ($70SnO_2$:30ZnO) and pure samples are shown in the Fig. 9. It is observed that resistance of multilayer sensor does not change drastically as that in case of pure samples. This shows that multilayer sensor is more stable than the other. Figure 10 shows the TG–DTA curve of PPy, plotted as a function of temperature. It is observed from Fig. 10 that the weight loss decreases continuously, i.e. PPy goes on decomposition on heating. At about 70 °C, an endothermic peak is observed and it may be due to the combined loss of water and PPy [31]. The total rate of decomposition is found to be 2.9 mg/°C and total loss is nearly 42 % up to 900 °C.

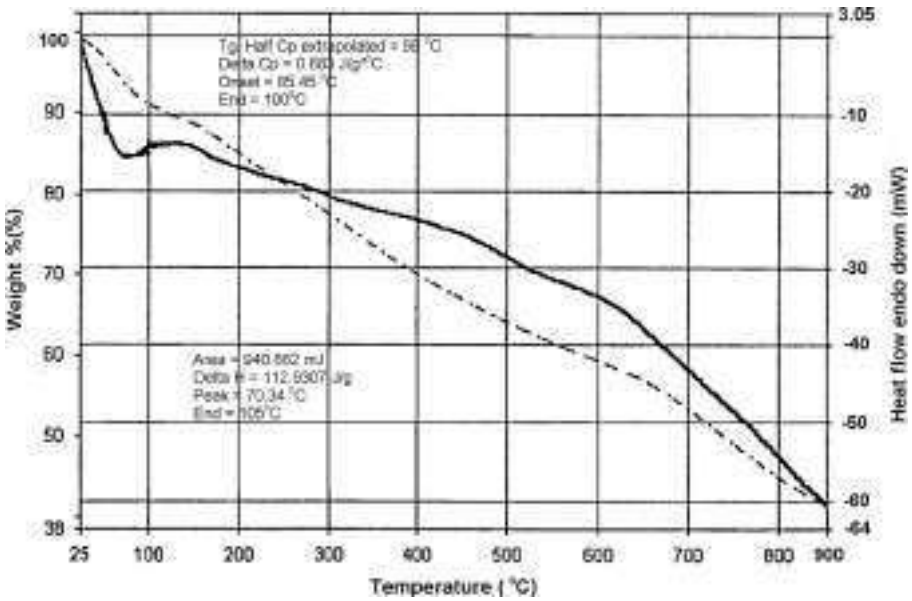


Fig. 10 TG-DTA curve of polypyrrole (PPy)

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4. Conclusions

From XRD and SEM analysis, it is concluded that the crystallite size of $70SnO_2$:30ZnO multilayer is smaller and it is more porus and hence has greater surface area and therefore shows greater response to ammonia gas. $70SnO_2$:30ZnO multilayer sensor shows better stability than pure samples and dynamic response is also fast.

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Preparation and Ethanol Sensing Behavior of Spinel-type Nanosized Mixed Ferrites Containing Zn

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Abstract

Nanocrystalline $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4) mixed ferrite with cubic spinel structure was successfully prepared by the citrated sol-gel method followed by calcinations at 600 ^0C. Characterization of the materials was performed by XRD. Indirect-heating sensors using as-prepared powders of mixed ferrite as sensitive materials were fabricated on an alumina tube with Au electrodes and Platinum wires. The gas response of $Ni_{1-x}Zn_xFe_2O_4$ based thick film sensor to C_2H_5OH, was measured. $Ni_{0.6}Zn_{0.4}Fe_2O_4$ based thick film sensor showed better response to ethanol gas at 300 ^0C as compared with other tested reducing gases. The observed gas sensing potential is explained by using the reducer nature of the gaseous species that react on the surface of the heated semi-conducting mixed oxide. The sensor exhibited a fast response and a good recovery.

Keywords: X-ray diffraction; Mixed ferrites; Gas sensor; Sensor response.

1. Introduction

Metal oxides based semiconductor gas sensors are commonly used in the monitoring of toxic pollutants and can provide the necessary sensitivity, selectivity and stability required by such systems [1]. Gas-sensing properties of semiconducting materials based on SnO_2, ZnO, WO_3, TiO_2, In_2O_3, Fe_2O_3, mixed oxides, ferrites and complex metal oxides have been extensively studied to detect explosive, inflammable, toxic and hazardous gases. In the last decade there is growing interest to investigate the gas sensing properties of ferrites [2-4]. $NiFe_2O_4$ (AB_2O_4) is a well-known inverse spinel with all Ni^{2+} ions on the B-sites and Fe^{3+} ions equally distributed between A and B-sites [5]. $NiFe_2O_4$ exhibit high sensitivity for the reducing gases like chlorine and liquefied petroleum gas [6, 7]. However, to our knowledge the ethanol gas-sensing properties of $NiFe_2O_4$ and Zn doped $NiFe_2O_4$ are still not so widely available.

The gas sensing mechanism involves surface reaction of the oxide surface with the test gas [8]. The ability to control the surface of the nanocrystals by adopting different synthesis routes has opened-up a new dimension to modify material for specific property applications. Also, nano sized materials, which have high surface activity due to their small particle size and enormous surface area, can increase the

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efficiency of the chemical sensor [9, 10]. There are several routes to obtain nanosized ferrites such as hydrothermal synthesis, sol–gel, microemulsion techniques, etc.

The aim of the present investigation is to prepare nanocrystalline Zn modified Ni ferrite by citrated sol-gel method with a low calcination temperature involving low cost metal nitrates as raw materials and characterize them for ethanol gas sensing.

2. Experimental details

The stoichiometric molar amounts of Ferric nitrate [$Fe(NO_3)_3.9H_2O$], Nickel nitrate [$Ni(NO_3)_2.6H_2O$], Zinc nitrate [$Zn(NO_3)_2.6H_2O$] and citric acid monohydrate [$C_6H_8O_7.H_2O$] were weighed and mixed with ethylene glycol. The prepared mixture was stirred magnetically at 80 ^{0}C for 2 h. A transparent solution was obtained after 2 h. Then, this solution was consequently transferred to Teflon-lined stainless steel autoclave. The temperature of the autoclave was raised slowly to 125 ^{0}C and maintained for 10 h to get gel precursor. Afterward, the autoclave was allowed to cool naturally to room temperature and the resulting product further heated for 3 h at 350 ^{0}C in muffle furnace and then milled to a fine powder. The obtained powder was then calcined at 600 for 5 h ^{0}C to improve the crystallinity of the prepared materials. Fig. 1 shows the flowchart to prepare nanosized $Ni_{1-x}Zn_xFe_2O_4$ powder samples.

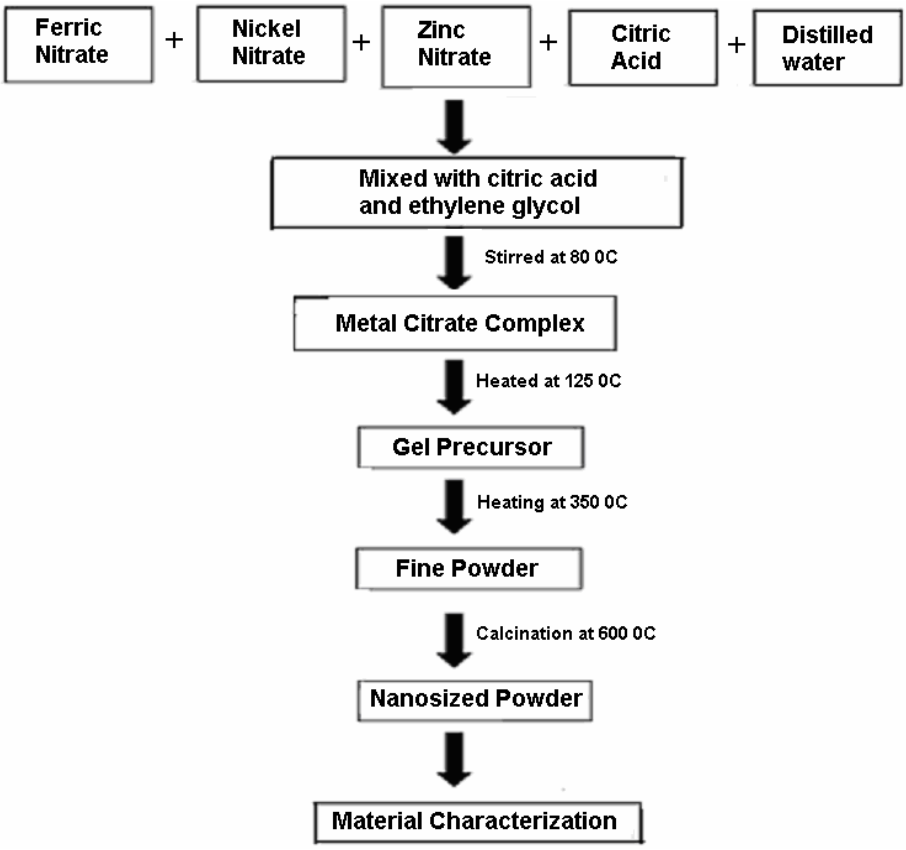


Figure 1. Flow chart for synthesis of $Ni_{1-x}Zn_xFe_2O_4$ powders

The structure and constituents of the products were determined on an X-ray diffractometer (Model: Philips X'pert) with a Cu Kα radiation (λ = 1.5406Å). The crystallite size (D_{hkl}) of the powder sample was calculated using Scherrer relation, which is given by,

$$D = \frac{K\lambda}{B.Cos\theta}$$

Where B is the full width at half-maximum intensity (in radians) of a peak at an angle θ; K is a constant, depending on the line shape profile; λ is the wavelength of the X-ray source. The crystallite size was determined by taking the average of the strongest peaks D_{220}, D_{311}, D_{400}, D_{511} and D_{440}.

The description of the sensor fabrication and gas sensing measurements has been already depicted in one of earlier reports [4]. Gas sensing properties were investigated at various operating temperatures from 50 to 350 ^{0}C. The experiments were performed with four test gases: liquefied petroleum gas (LPG), ammonia (NH_3), hydrogen (H_2), and ethanol gas (C_2H_5OH). The concentration of test gases was 500 ppm for NH_3, H_2 and LPG whereas it is 100 ppm for C_2H_5OH. The sensor response (S) is defined as the ratio $\Delta R/R_a$, i.e. change in resistance of the sensor (R_a) in air and in the gas (R_g), normalized to the sensor resistance in air.

$$S = \frac{\Delta R}{R_a} = \frac{|R_a - R_g|}{R_a}$$

3. Results and Discussion

3.1. Materials characterizations

The X-ray diffraction patterns of $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4) calcinated at 600 ^{0}C are displayed in Fig. 2. The XRD peaks and their positions with the calculated lattice parameters confirm that all the compositions exhibit single-phase cubic spinel structure with Fd3m space group. No peaks corresponding to any additional crystalline component are observed in the obtained patterns. The average crystallite size has been calculated from the XRD peaks using Debye−Scherrer formula and was found in the range of 23-38 nm for all the investigated samples. The lattice parameters estimated from XRD peaks are presented in Table 1. It is observed that the average crystallite size is minimum for $Ni_{0.6}Zn_{0.4}Fe_2O_4$ composition. Also, it is seen that the lattice parameter increases with an increase of Zn content. The increase in the value of the lattice constant with Zn ion substitution can be explained on the basis of ionic radius, where the ionic radius of Zn ion (0.82 Å) is smaller than that of Ni ion (0.78 Å).

3.2. Ethanol sensing characteristics

To reveal the potential use of the nanocrystalline spinel $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4) synthesized in the present investigation to chemical sensors, its ethanol sensing properties were studied. The response of $Ni_{1-x}Zn_xFe_2O_4$ to ethanol was measured at different operating temperatures to find out the optimal operating temperature for ethanol detection. The response of the nanocrystalline spinel Ni_{1-}

$_xZn_xFe_2O_4$ to 100 ppm ethanol as a function of operating temperature is illustrated in Fig. 3. It can be seen that the composition $Ni_{0.6}Zn_{0.4}Fe_2O_4$ exhibited the maximum response to 100 ppm C_2H_5OH at 300 ^{0}C. At lower operating temperatures, the sensor response is relatively low, but it increases gradually with an increase in the operating temperature. The sensor response to ethanol attains a maximum at ~300 ^{0}C and subsequently it decreases with a further increase of the operating temperature. Thus, the optimal operating temperature for the $Ni_{0.6}Zn_{0.4}Fe_2O_4$ spinel to detect ethanol was at 300 ^{0}C, which is the modest from the perspective of semiconducting oxide gas sensors. Hence, the optimal operating temperature of 300 ^{0}C was chosen to investigate further ethanol sensing properties such as response and recovery times, reproducibility and selectivity.

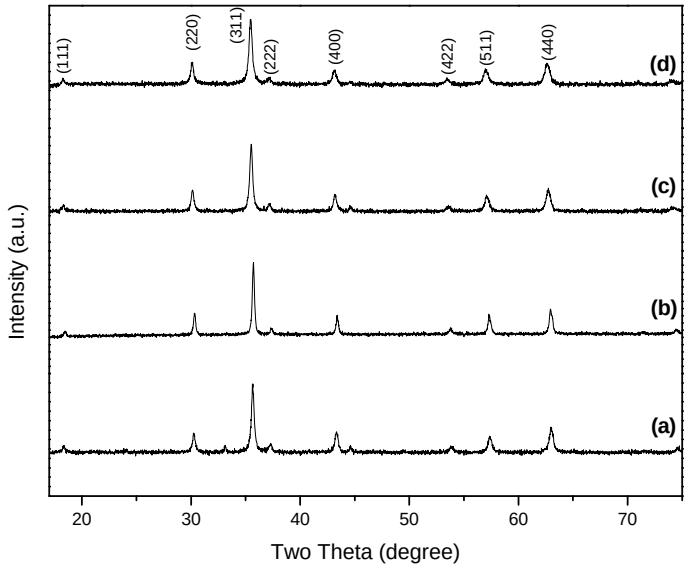


Figure 2. XRD pattern of $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4) powder samples calcinated at 600 ^{0}C.

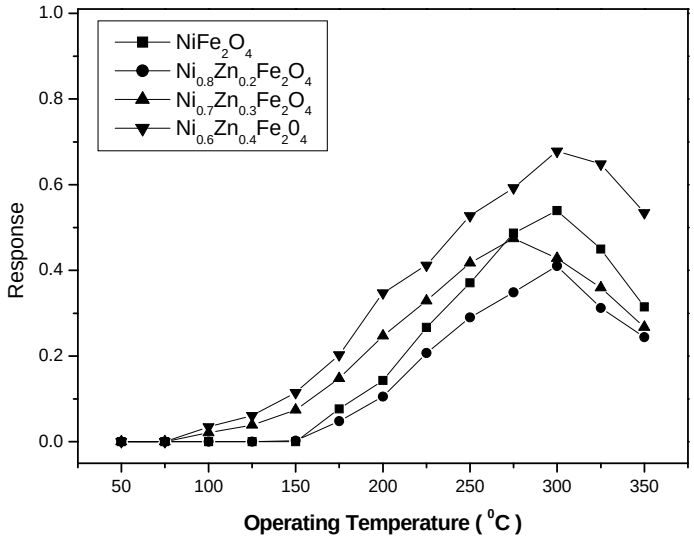


Figure 3. Sensor response of $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4) to 100 ppm ethanol as a function of operating temperature.

Table 1: Calculated lattice parameters of $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4)

Sample $Ni_{1-x}Zn_xFe_2O_4$	Lattice parameters (Å) a=b=c
x = 0	8.343 ± 0.002
x = 0.2	8.348 ± 0.001
x = 0.3	8.379 ± 0.007
x = 0.4	8.393 ± 0.002

For practical application of sensor, not only the sensor response but the response and recovery times are also vital parameters for evaluating the performance of gas sensors. The response and recovery times are defined as the time required for the sensor-resistance to change by 90% of the final resistance. It was found that the nanocrystalline $Ni_{0.6}Zn_{0.4}Fe_2O_4$ based sensor element responds rapidly after introduction of 100 ppm ethanol and recovers immediately when it is exposed to air. The $Ni_{0.6}Zn_{0.4}Fe_2O_4$ has response time of ~70–75 s and the recovery time of ~180–190 s. Furthermore, it was observed that the resistance of the sensing element decreases when exposed to ethanol (reducing gas), which suggests that $Ni_{0.6}Zn_{0.4}Fe_2O_4$ behaves as a n-type semiconductor.

The variation of the response of nanocrystalline $Ni_{0.6}Zn_{0.4}Fe_2O_4$ based sensor element with respect to the ethanol concentration at the optimal operating temperature of 300 ^{0}C is shown in Fig. 4. The $Ni_{0.6}Zn_{0.4}Fe_2O_4$ spinel is able to detect up to 25 ppm for ethanol with good response at the optimal operating temperature of 300 ^{0}C.

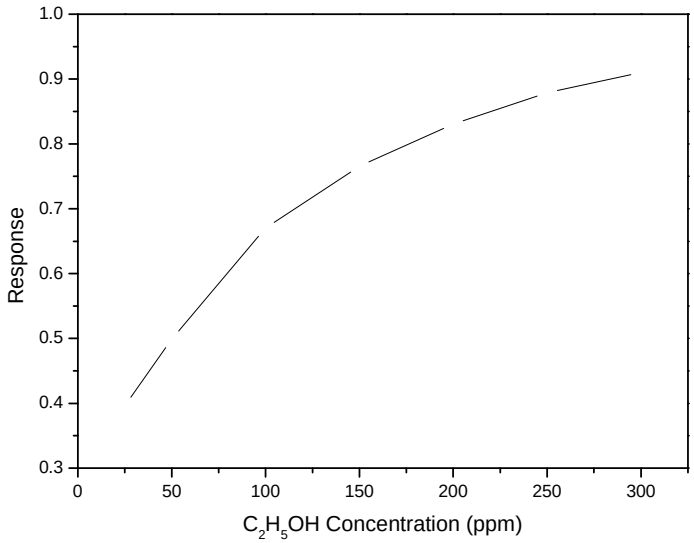


Figure 4. Variation in the response of $Ni_{0.6}Zn_{0.4}Fe_2O_4$ sensor element at 300 ^{0}C against ethanol concentration.

Selectivity is an important parameter of gas sensors and the sensor response toward a specific gas needs to be markedly higher than those to other gases for selective gas detection. To study the selective

behavior of the nanocrystalline $Ni_{0.6}Zn_{0.4}Fe_2O_4$ to ethanol at the optimal operating temperature of 300 ^{0}C, the sensor responses towards H_2, NH_3 and LPG were also measured. The corresponding results are demonstrated in Fig. 5. The $Ni_{0.6}Zn_{0.4}Fe_2O_4$ exhibits higher response to ethanol, whereas it shows a considerably lower response to H_2, NH_3 and LPG. Taking into account the results of gas sensing experiments, it is concluded that the nanocrystalline $Ni_{0.6}Zn_{0.4}Fe_2O_4$ has good ethanol sensing properties such as higher gas response, good selectivity, quick response and recovery, excellent repeatability and relatively lower operating temperature.

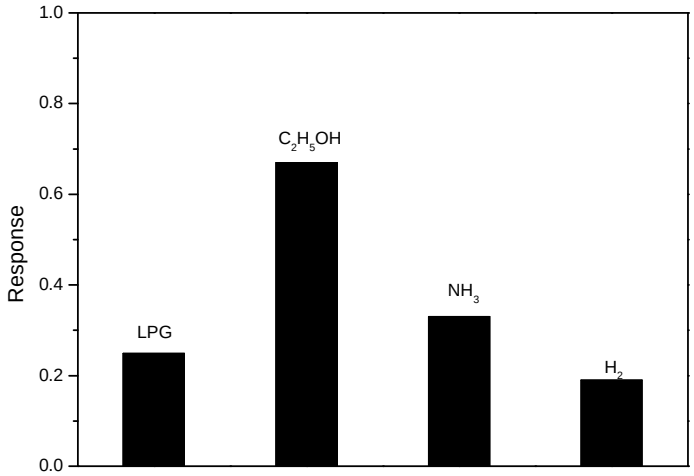


Figure 5. Response of $Ni_{0.6}Zn_{0.4}Fe_2O_4$ towards 100 ppm C_2H_5OH, 500 ppm NH_3, 500 ppm H_2 and 500 ppm LPG at 300 ^{0}C.

3.3. Ethanol sensing mechanism

The oxygen is adsorbed on the surface of the sensor in air and adsorbed oxygen is transformed into chemisorbed oxygen at a definite temperature. The reaction between C_2H_5OH gas and the chemisorbed oxygen ion can take place as [11]:

$C_2H_5OH_{gas} + O_{ad}^{2-} \rightarrow C_2H_5O_{ad}^{-} + OH_{ad}^{-}$

$C_2H_5O_{ad}^{-} \rightarrow (C_2H_5)_2O_{ad} + O_{ad}^{-} + e^{-}$

$C_2H_5OH_{gas} + Oad^{2-} + hole \rightarrow CO_2 + H_2O + V_O^{-}$

Where V_O^{-} is a doubly charged oxygen vacancy. These reactions impart electrons into the sensing material, leading to an increase in electron concentration, and a decrease in resistance of the $Ni_{0.6}Zn_{0.4}Fe_2O_4$-based sensor.

The concentration of chemisorbed oxygen increased and reached optimum value with the increasing operating temperature. When the absorption–desorption of chemisorbed oxygen attained a dynamic equilibrium, the sensor exhibited maximum response towards ethanol gas at 300 ^{0}C. Difference in gas-sensing response to different gases might be due to differences in the adsorption and the reaction processes.

4. Conclusions

In conclusion, $Ni_{1-x}Zn_xFe_2O_4$ (x = 0, 0.2, 0.3 and 0.4) mixed ferrite powder samples with cubic spinel structure were successfully synthesized by citrate sol-gel route. The response of $Ni_{0.6}Zn_{0.4}Fe_2O_4$ based sensor element to 100 ppm ethanol was found maximum at an optimal operating temperature 300 ^{0}C. The response time was ~70–75 s and the recovery time was found to be ~180–190 s. Furthermore, $Ni_{0.6}Zn_{0.4}Fe_2O_4$ sensor exhibited good selectivity to C_2H_5OH when operating at 300 ^{0}C. This means that $Ni_{0.6}Zn_{0.4}Fe_2O_4$ sensor can be a good candidate for practical application in detecting C_2H_5OH because of the good characteristics mentioned.

Acknowledgement

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Synthesis, Charecterisation and Antibacterial Activities of Some New Bromo/Nitro 1,3-Thiazenes

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Abstract

1,3-thiazines were prepared by refluxing the mixture of 2-hydroxy-3-bromo/nitro -5-chlorochalcone and diphenylthiourea in alcohol and aq.KOH medium. The newly synthesized 1,3-thiazenes were characterized on the basis of elemental analysis and spectroscopic data of IR,NMR. The melting points were taken in an open capillary tube. All compounds have been evaluated for their in vitro growth of inhibitory activity against Escherichia coli, Staphylococcus aureas, Bacillus subtilis and Phaseolusargenosa.

Keywords: 1, 3-Thiazines, Antibacterial Activity, pathogenic bacteria.

Introduction

Thiazine is a six membered heterocyclic compound which contains two hetero atoms (N and S) placed at 1,3 positions. 1,3-thiazines have a very broad spectrum of fungicides, insecticides, growth promoting hormonal effect etc. Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities[1-2].The reaction of thiourea with α,β-unsaturated ketones results in 1, 3 thiazines[3-4] .Some chloro-substituted-1, 3-thiazines have been reported for antimicrobial activity[5]

Thiazine reported to exhibit antitubercular, antibacterial used as cannabinoid receptor against[6] 1,3-thiazine derivatives and their evaluation as potential antimycobacterial agents[7].The synthesis of 2,4-dihydro-1H-benzo[d] [1,3] thiazines via silver catalyzed addition-cyclization reactions are reported[8]. Synthesize of new chromene base heterocyclic like thiazine from 2-Amino-5-hydroxy-4-phenyl-7-methyl-4H[1-chromeno-3-carbonitrile which may show a good biological activity[9].Some 1,3-thiazines are reported for its antimicrobial activity.[10]

Experimental

The synthesis of 1,3-thiazines from 3-bromo-5-chlorochalcone and 3-nitro-5-chlorochalcone on treatment with diphenylthiourea in presence of alcoholic KOH. The melting points of these compounds were recorded on ‘Tempo’ melting point apparatus and are uncorrected. The carbon, nitrogen, sulphur and hydrogen analysis was carried out on ‘Carlo Ebra 1106’ analyzer. The IR spectra were recorded on ‘Perkin-Elmer Infra Red spectrophotometer. The PMR spectra were recorded on DRX 300 spectrometer in CDCl3. Purity of the compound was tested by TLC. The study were treated for their antibacterial

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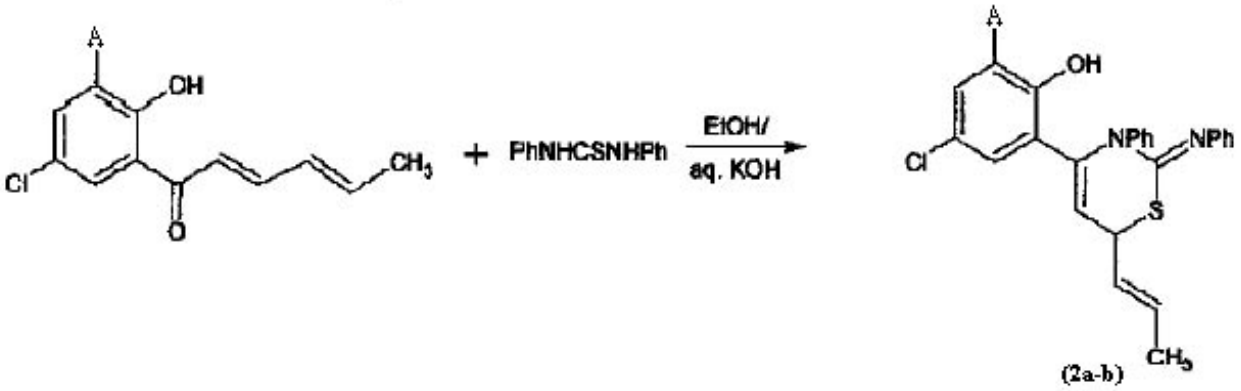
impact against some common pathogenic bacteria viz. *E. Coli, S. aureus, B. Subtilis, P. argenosa.* The solutions of 0.01 mol dilution of test compounds were prepared in dioxane solvent separately. The discs were soaked, assuming that each disc will contain approximately 0.01 ml of test solution. The culture media was prepared by using following composition for one liter distilled water-

Peptone	:	5.0 g./litre
Sodium chloride	:	5.0 g./litre
Beef extract	:	1.5 g./litre
Yeast extract	:	1.5 g./litre
Agar	:	15.0 g./litre
pH (approximately)	:	7.4 ± 0.2.

The culture medium thus prepared was sterilized in autoclave at 15 lbs/inch pressure and 121^{0}C temperature for 15 minutes. After sterilization, it was cooled down to about 50^{0}C and poured into presterilized petriplates of 8.5 cm in diameter each and allowed to solidify the nutrient agar medium of about 14 mm depth. The petriplates were kept with nutrient broth at 37^{0}C for2 4 hr. in an incubator.

(a) Preparation of 4-(2-hydroxy-3-bromo/nitro-5-chlorophenyl)-6-(1'-propene)-2-iminophenyl-3,6- dihydro-1, 3-thiazine (IIa/b)

2-Hydroxy-3-bromo/nitro-5-chlorochalcone and diphenylthiourea were dissolved in ethanol. To this aqueous KOH solution was added and this reaction mixture was refluxed for three hours, after cooling, diluted with water and acidified with 1:1 HCl. The product thus obtained was 4-(2-hydroxy-3-bromo/nitro-5-chlorophenyl)-6-(1'-propene)-2-iminophenyl-3,6-dihydro-1,3-thiazine.



A=Br/NO_2Scheme-1

Compound	Molecular Formula	M.P.	Yield	Rf
1a	$C_{12}H_{10}BrO_2Cl$	85^{0}C	78%	0.76
1b	$C_{12}H_{10}NO_4Cl$	110^{0}C	70%	0.61
2a	$C_{13}H_{10}N_2(Ph)_2BrOCl$	138^{0}C	70%	0.67
2b	$C_{13}H_{10}N_3(PH)_2SO_3Cl$	127^{0}C	70%	0.28

Spectral interpretation of (IIb)

(a) The important frequencies observed in the IR spectrum recorded in KBr are correlated as Follows-IR **(**υmax**)** cm-1:3423**υ** (-OH Stretching); 2320 **υ** (-C=N Stretching); 1444 **υ** (Ar-NO2); 1230 **υ** (C=OStretching); 1313 **υ** (C-N Stretching)

(b) The PMR spectrum of the compound (IIb) was recorded in CDCl3 with TMS as an internal standard. The observed chemical shifts and their correlations are as follows-

NMR :_ 2.5 (d,3H , C=CH-CH3); 4.17 (d,1H , C=C-C-H); 5.5 (d,1H, -CH=CH); 6.5 (d,1H , =C-H); 6.9-7.8 (m,12H ,Ar-H); 11.99 (s, 1H ,Ar-OH);

Results And Discussion

The 1,3-thiazines when screened in vitro against some common bacteria viz. *E. coli,S. aureaus, B. subtilis, P. argenosa* it was noticed that most of all these compounds have shown remarkable inhibitory activity. An assay of newly synthesized 1,3-thiazines revels that, almost all the compounds were strongly active against all the test pathogensE. coli, S. aureaus, B. subtilis, P. argenosa. Their inhibitory impact on the bacterial growth is remarkable.

Table-2: Antibacterial activities of test compounds

S.No.	Test Compound	Zone of inhibition (mm)			
		E. coli	*S. aureus*	*B.subtilis*	*P. argenosa*
1	IIa	27	25	25	26
2	IIb	25	24	25	25

Acknowledgements

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Synthesis and Characterization of Some New Chlorosubstituted Thiazoles and Thiazolo-Imidazoles and their Impact on Pathogens Damaging Oyster Mushroom Cultivation

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Abstract

The mushroom growers in and around Vidarbha region of Central India have been engaged in the cultivation of one of the edible and highly profiTable varieties of mushroom crop ie. Oyster mushroom spp. But now a days farmers of this region facing the most alarming problem related to the susceptibility of this variety that easily falls prey to the pathogenic attack. As a result of this the efforts and investment that farmers put in the cultivation of this crop would not commensurate with the yield. Literature survey reveals that the paucity of data in the field of protection of mushroom cultivation from the attack of causative organism, creates a considerable amount of scope to undertake a systematic research of synthesis of some eco-friendly heterocycles and study of their curative impact on edible mushroom varieties with special reference to Oyster mushroom spp. In this context, in the present study, we have synthesized some new chlorosubstituted thiazoles and thiazolo-imidazole from chlorosubstituted diketones, chromones and chromanones in benign solvents.
The newly synthesized titled compounds were screened for their antipathogenic activities against the causative organisms responsible for the damage of mushroom cultivation in the tropical belt of Vidarbha region. It was encouraging to note that the titled compounds not only inhibit the growth of all the pathogens under examination (C. verticillatum, G. deliquescene, Cladobotryum apiculatum, Velricillium fungicola, Gliocladium vireus, Sibirina fungicola, P. agarici, Arthrobotrys pleuroli and Pseudomonas stulzeri.) to a considerable extent but also exerted a positive impact on the phytotic growth of the test variety of mushroom.

Key words: chlorosubstituted thiazoles, thiazolo-imidazoles, diketones, chromones and chromanones, *Oyster mushroom* crop pathogens like *C. verticillatum, G. deliquescene, C. apiculatum, V. fungicola, G. vireus, S. fungicola, P. agarici. A. pleuroli, P. stulzeri.*

Introduction:

Pleurotus commonly called as *Oyster mushroom* is one of the most widely eaten mushrooms[1] appreciated for its culinary properties[2]. *Oyster spp.* can be successfully cultivated at temperatures of around 30°C and hence it is becoming increasingly popular in both tropical and sub-tropical countries. Being a tropical country, India has been bestowed with bountiful crops. In India, the cultivation of this variety of mushroom is picking up at an alarmingly high rate due to ease of its cultivation.

After *Agaricus spp.* (Button mushrooms), *Pleurotus species* are the second most populer mushrooms growing in India. Though cultivation of *Oyster mushroom* in Vidarbha region is increasing gradualy but the major constraint in its speedy popularization is the susceptibility of this crop towards pathogenic attack. As a consequence, initial investment incurred on the cultivation of *Oyster mushroom* crop could not be recovered. The pathogens inhibit the growth of mushrooms and hinders the production of fruiting bodies. The disease and pasts happen to be devastating and perpeturate easily from one season to another. Shah and Nasreen reported[3] that some growers hardly use the fungicides for the treatment of this havoc of disease. They often found fungicidal treatment as non-economical. Chitra[4] *et al* reported that the 60% concentration of potassium humate influence the mushroom growth as well as nutritional value and recommended to use this for the increase of production.

Literature survey reveals that, nitrogen and oxygen containing chlorosubstituted heterocycles such as pyrazolines, pyrazoles, isoxazolines, and isoxazoles were found to be very useful in controlling the diseases in the field of agriculture. This series of compounds reported to have antibacterial[5], antifungal[6], analgesic[7], anesthetic[8] and antinflammatory activities.

The present study has been carried out to develop ecofriendly and economically viable management of mushroom crop disease by synthesizing some new chlorosubstituted thiazoles and thiazolo-imidazoles from chlorosubstituted diketones, chromones and chromanones and applying them to inhibit the growth of causative organisms.

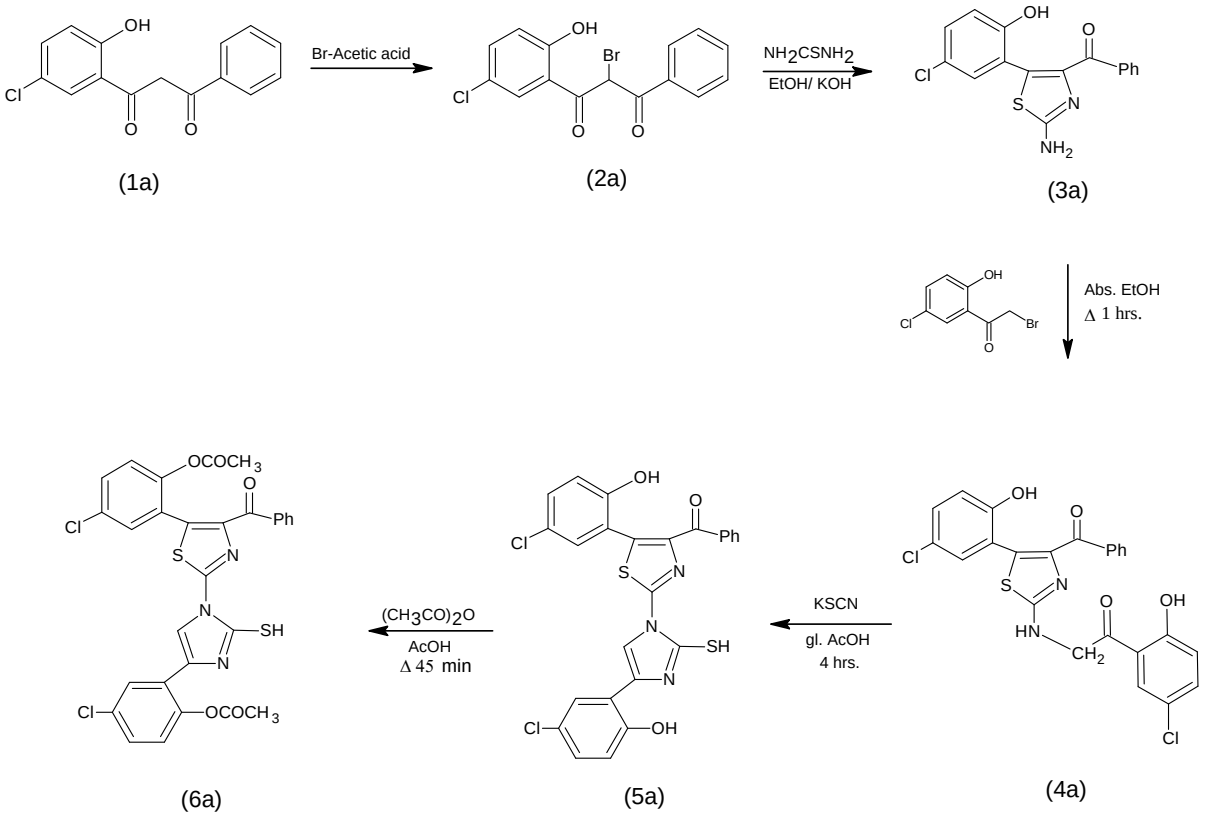
Experimental:

The synthetic route for obtaining the final products is presented in scheme I. 1-(2-Hydroxy-5-chlorophenyl)-3-phenyl-1,3-propanedione (1a) was suspended in bromine-glacial acetic acid reagent to get the compound 1-(2-hydroxy-5-chlorophenyl)-2-bromo-3-phenyl-1,3-propanedione (2a). The bromosubstituted-1,3-propanedione (2a) refluxed with thiourea for about 2.5 hrs. using aqueous KOH solution and ethanol as a solvent. Finally on acidification with conc. HCl yield the product substituted thiazole (3a).

The reaction of substituted thiazole(3a) with 2-bromo-1-(2-chloro-5-hydroxy phenyl) ethanone in absolute ethanol lead to the formation of substituted α- amino ketone (4a) which on treatment with KSCN in glacial acetic acid for 4 hrs. gave substituted thiazolo-imidazole (5a). which on acetylation give its acetyl derivative (6a).

Melting points of all the synthesized compounds were determined in open capillaries and are uncorrected. The homogeneity of all compounds was checked by TLC using benzene-CCl_4 as developing solvent. IR spectra were recorded on Perkin-Elmer 1000 spectrophotometer in KBr. The ^{1}H NMR spectra were recorded on Bruker advance II 400 NMR spectrophotometer using TMS as an internal standard and chemical shifts are expressed in δ (ppm).

Scheme-I:



Antifungal and antibacterial assays of the newly synthesized compounds (3a, 4a, 5a, and 6a):

The titled compounds were assayed for their antifungal and antibacterial activities against the pathogens responsible for *Oyster mushroom* diseases.

DMF was used as a solvent control using agar-agar plate techniques. The zones of inhibition formed were measured in mm and are shown in the following Table:

Entry	***C. verticillatum***	***G. deliquescene***	***C. apiculatum***	***V. fungicola***	***G. vireus***	***S. fungicola***	***P. agarici***	***A. pleuroli***	***P. stulzeri***
3a	10	05	08	07	08	08	08	07	06
4a	10	09	10	09	08	09	10	08	09
5a	11	11	12	10	10	11	12	11	10
6a	12	09	14	12	11	13	13	11	12

The compounds synthesized were found to be detrimental to the growth of the pathogens. From the Table it can be noticed that antifungal and antibacterial properties gradually increase as the complexity of the molecular structures increases.

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Effect of Extracts of Test Plants, Isolated Ingredient and Prepared Analogues on Serum Inorganic Ions (*Sodium, Potassium, Calcium, Magnesium and Phosphorous*) in *Albino Rats*

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Abstract

Medicinal plants are of great value in the field of treatment and cure of diseases. Over the years, scientific research has expanded our knowledge of the chemical effects and composition of the active constituents, which determine the medicinal properties of the plants. It has now been universally accepted fact that the plant drugs and remedies are far safer than that of synthetic medicines for curing the complex diseases like cancer and AIDS. Melghat region is a rich source of medicinal flora. Near about 772 naturalized species found in Melghat region which are used for the cure of various diseases. Butea monosperma, Cassia fistula, Ceasalpinina bonduc, Cassine glauca, and Cassia absus, plants are found in Melghat region. All these plants are frequently used for the eradication of various diseases. In case of serum inorganic ions, the four cations, Na^+, K^+, Mg^{2+} and Ca^{2+}, are widely distributed in all living organisms. These cations play a tremendous variety of roles such as in the transmission of nerves impulses, in muscle contraction, and as enzyme activators and structural factors. In the present study we have undertaken this task to explore the impact of test plants whole extracts; some isolated ingredients and prepared analogues on serum composition of test animals with special reference to inorganic ions.

Keywords: Test plants, isolated ingredient, prepared analogue, serum inorganic ions.

Introduction

Primarily it may be stated that cutaneous lesions are due to influences of source outside the body or which exist or arise within the body. To the former class may be assigned such as depend on temperature and climate, such as are due to traumatism of various kind, such as result from various parasitic invasions, etc. this is in reality but a limited class, on other hand, the etiological factors which arise within the body itself are very numerous. The external causes like excessive heat direct exposure to the Sun may exhibit undue activity of the sudoriferous gland and result in the production of *sudamina* or Sunburn. The excessive cold may result in absolute, congelation of exposed portion of the integument. On the other hand internal causes of skin diseases, however, are far more frequently in operation. In this class we may place those affections of the skin which are due to pre-existing lesions of some part of the nervous system. The nervous system acts as a medium for the transmission of some internal irritation to the surface, thus, the gastric irritation resulting from the ingestion of shell-fish may manifest itself on the skin till another

internal cause of cutaneous lesions is found in ill nutrition or imperfect assimilation. Finally we may have external lesions resulting from the accumulation in the blood of certain infectious material. Sometimes such materials may be generated within the body itself through imperfections in the digestive, assimilative or excretory functions.

In order that nutrition may be healthily carried on in any part there must be a proper state of the blood, a proper condition and behaviour of the tissues to be nourished and a right exercise of the controlling influence exerted by the nerves. These three must work harmoniously together. The theoretical origin, therefore, of diseased changes in the skin may be especially in the blood and here the skin affection is only symptomatic.

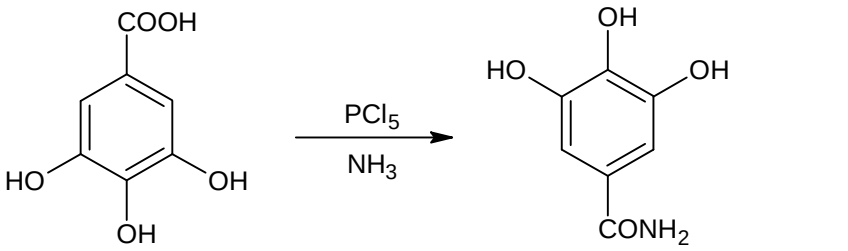
The four cations, Na^+, K^+, Mg^{2+} and Ca^{2+}, are widely distributed in all living organisms These cations play a tremendous variety of roles such as in the transmission of nerves impulses, in muscle contraction, and as enzyme activators and structural factors. The extra- and intracellular concentrations of Na^+, K^+, Mg^{2+} are very different (the values for Ca^{2+} being quite similar). This observation raises the questions about the establishment, maintenance and distribution of dissymmetry[1-4].

In the present study we have undertaken this task to explore the impact of test plants whole extracts, some isolated ingredients and prepared analogues on serum composition of test animals with special reference to inorganic ions.

Materials And Methods

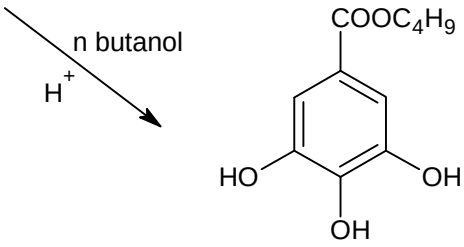
Plant material: The test plant materials of *Butea monosperma, Cassia fistula, Ceasalpinina bonduc, Cassine glauca,* and *Cassia absus,* plants were collected seasonally from the Melghat region of Amravati, District of Maharashtra, India. They were authenticated by the taxonomist Dr. S. P. Rothe with Voucher specimens (ML – 101, ML – 102, ML – 103, ML – 104, ML – 105) and were deposited in the herbarium of Department of Botany, Shri Shivaji College, Akola.

Extraction and Isolation: The test plant materials of *Butea monosperma, Cassia fistula, Ceasalpinina bonduc, Cassine glauca,* and *Cassia absus,* plants were shade dried at room temperature and ground in a manual mill to get coarse powder. The powders were kept in the airtight polythene bags and stored at dry place. These powders were extracted with water as a solvent by using soxhlet apparatus. The extracts were concentrated at 40 ^oC using rotary evaporator. Finally it was dried, crushed and stored in air tight bottle at 4 ^oC for further study. Again by using thin layer and column chromatography techniques, we have isolated the acidic ingredient from Butea monosperma test plant extracts and from the characterization it was found that isolated compound 1 was Gallic acid. The Gallic acid (Compound 1) thus separated from test extracts of Butea monosperma plant was then used for the preparation of its amide analogue (Compound 2) and ester analogue (Compound 3).



3,4,5-trihydroxybenzoic acid
Compound 1

3,4,5-trihydroxybenzamide
Compound 2



butyl 3,4,5-trihydroxybenzoate
Compound 3

Animals: The interdisciplinary part of proposed study was carried out after getting permission from the Institutional Animal Ethical Committee, Pusad (CPCSEA/IAEC/CP_PL/07-2012). The care of laboratory animals was taken according to the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (registration number 729/02/a/ CPCSEA). All the experiments were carried out using adult *albino Wistar male rats* weighing about 130-150 gm. The animals had free access to food and water and they were housed in cages in a natural (12 hrs each) light–dark cycle. The animals were acclimatized to the laboratory conditions for at least 5 days before behavioural experiments which were carried out between 0900 h and 1800 h.

Creation of Burn wound: Dorsal skins of the Wistar rats were shaved at full thickness. The animals were anesthetized by ketamine injection and burn wound of approximate 2 cm in diameter were created (circular area) by the brass probe which was immersed in boiling (100 °C) water until thermal equilibrium was reached. The probe was then placed on the back of the rats for 20 s without applying pressure. They were then housed individually in separate cages after complete recovery from anaesthesia.

Rats were randomly divided into following groups of five animals each:

Control group: Immediately after burning, burn areas were covered with propylene glycol solution once a day for 20 days.

Whole extract of *Butea Monosperma* group: Immediately after burning, burn areas were covered with whole extract of *Butea Monosperma* sample which was prepared in propylene glycol once a day for 20 days.

Whole extract of *Cassia fistula* group: Immediately after burning, burn areas were covered with whole extract of *Cassia fistula* sample which was prepared in propylene glycol once a day for 20 days.

Whole extract of *Ceasalpinina bonduc* group: Immediately after burning, burn areas were covered with whole extract of *Ceasalpinina bonduc* sample which was prepared in propylene glycol once a day for 20 days.

Whole extract of *Cassine glauca* group: Immediately after burning, burn areas were covered with whole extract of *Cassine glauca* sample which was prepared in propylene glycol once a day for 20 days.

Whole extract of *Cassia absus* group: Immediately after burning, burn areas were covered with whole extract of *Cassia absus* sample which was prepared in propylene glycol once a day for 20 days.

Isolated acid group: Immediately after burning, burn areas were covered with isolated acid sample (Gallic acid) prepared in propylene glycol, once a day for 20 days.

Prepared amide analogue group: Immediately after burning, burn areas were covered with the prepared amide analogue sample prepared in propylene glycol once a day for 20 days.

Prepared ester analogue group: Immediately after burning, burn areas were covered with the prepared ester analogue sample also prepared in propylene glycol once a day for 20 days.

Blood samples were collected from control and treated group test animals and left to clot at room temperature for at least 30 minutes. They were centrifuged at 2000rpm for a minute to remove clot and cell debris. Equal amount of serum from Experimental and control animals were pulled in order to have sufficient material to perform the estimations.

The serum samples were analyzed for their *sodium* and *potassium* contents by flam photometric method, *calcium* and *magnesium* by titration method and *phosphorus* by photo colorimetric method the values were expressed as MEq/lit[5-9].

Observation And Results

Data obtain about composition of serum inorganic ions in *control* and *treated* group test animals are shown in the Tables (Table No. 1.1-1.5) along with their graphical presentations (Fig. No. 1.1-1.5).

During cutaneous infection the concentration of *sodium*, *potassium* and *calcium* get significantly increased. It may be due to histopathological changes in kidneys of test animal. Increased potassium concentration may be due to cellular necrosis which has already been reported in many tissues during cutaneous infections. So also dehydration in such cases has been reported. Increased *calcium* in serum could be ascertained due to its release from bones. The level of *calcium* and *phosphorous* in extra cellular

fluids rise markedly because kidney cannot excrete them rapidly. As a consequence of this excessive phosphorous is reabsorbed by bones.

Table 1.1: Serum *sodium ion* change on exposure to burn and exogenous pharmacological drugs in *Albino rats.*

Day	Control	Induced	Treated							
			1	2	3	4	5	6	7	8
2	1.38 ± 0.17	1.41 ± 0.17	1.37 ± 0.17	1.36 ± 0.17	1.34 ± 0.17	1.35 ± 0.17	1.33 ± 0.17	1.37 ± 0.17	1.35 ± 0.17	1.36 ± 0.17
10	1.35 ± 0.17	1.38 ± 0.17	1.32 ± 0.18	1.34 ± 0.18	1.33 ± 0.18	1.34 ± 0.18	1.31 ± 0.18	1.34 ± 0.18	1.35 ± 0.18	1.35 ± 0.18
15	1.33 ± 0.18	1.47 ± 0.18	1.32 ± 0.18	1.30 ± 0.18	1.32 ± 0.18	1.31 ± 0.18	1.29 ± 0.18	1.32 ± 0.18	1.30 ± 0.18	1.31 ± 0.18
20	1.35 ± 0.18	1.56 ± 0.18	1.35 ± 0.18	1.32 ± 0.18	1.34 ± 0.18	1.33 ± 0.18	1.32 ± 0.18	1.33 ± 0.17	1.34 ± 0.17	1.34 ± 0.17

1= *Butea monosperma*, 2= *Cassia fistula*, 3= *Caesalpinia bonduc*, 4= *Cassine glauca*, 5= *Cassia absus*, 6= Gallic acid, 7= Amide and 8= Ester analogues of gallic acid.

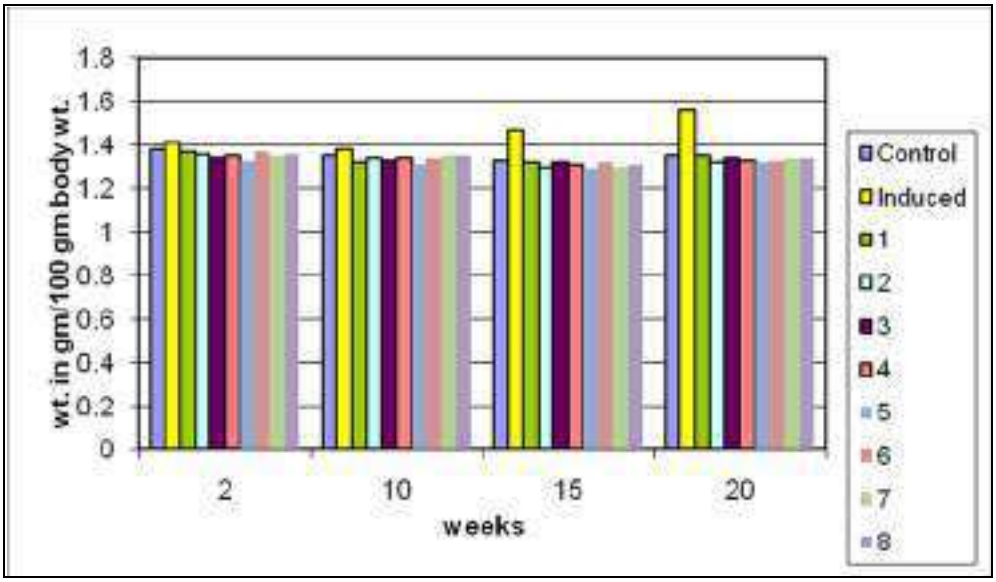


Fig. 1.1: Serum *sodium ion* change: *Wistar Albino rat*

Table 1.2: Serum *potassium ion* change on exposure to burn and exogenous pharmacological drugs in *Albino rats*.

Day	Control	Induced	Treated							
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
2	6.08 ± 0.20	6.07 ± 0.20	6.01 ± 0.20	6.05 ± 0.20	6.03 ± 0.20	6.01 ± 0.20	6.02 ± 0.20	6.05 ± 0.20	6.07 ± 0.20	6.06 ± 0.20
10	5.96 ± 0.17	7.39 ± 0.22	5.88 ± 0.18	5.86 ± 0.17	5.88 ± 0.17	5.89 ± 0.17	5.87 ± 0.17	5.90 ± 0.18	5.92 ± 0.18	5.93 ± 0.18
15	6.18 ± 0.17	8.29 ± 0.23	6.12 ± 0.18	6.09 ± 0.17	6.13 ± 0.17	6.11 ± 0.17	6.14 ± 0.17	6.13 ± 0.18	6.17 ± 0.18	6.17 ± 0.18
20	6.08 ± 0.18	9.39 ± 0.22	6.03 ± 0.18	6.02 ± 0.18	6.04 ± 0.18	6.01 ± 0.18	6.02 ± 0.18	6.08 ± 0.17	6.06 ± 0.17	6.05 ± 0.17

1= *Butea monosperma*, 2= *Cassia fistula*, 3= *Caesalpinia bonduc*, 4= *Cassine glauca*, 5= *Cassia absus*, 6= Gallic acid, 7= Amide and 8= Ester analogues of gallic acid.

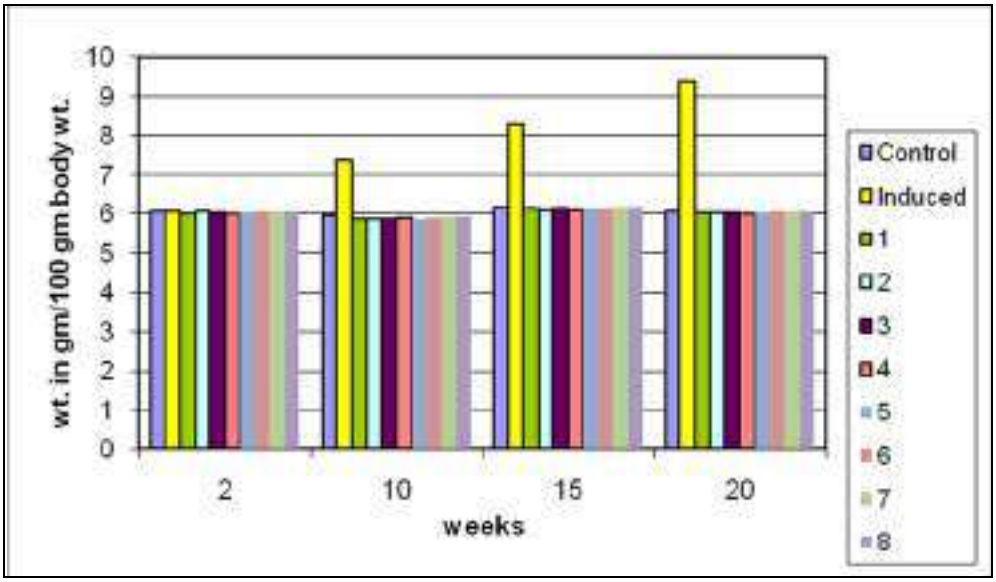


Fig. 1.2: Serum *potassium ion* change: *Wistar Albino rat*

Table 1.3: Serum *calcium ion* change on exposure to burn and exogenous pharmacological drugs in *Albino rats*.

Day	Control	Induced	Treated							
			1	2	3	4	5	6	7	8
2	6.5 ± 0.21	8.9 ± 0.18	6.0 ± 0.21	5.9 ± 0.21	6.3 ± 0.21	6.1 ± 0.21	6.3 ± 0.21	6.4 ± 0.21	6.3 ± 0.21	6.3 ± 0.21
10	6.0 ± 0.21	8.36 ± 0.20	5.8 ± 0.34	5.8 ± 0.34	5.9 ± 0.34	5.7 ± 0.34	5.8 ± 0.34	5.7 ± 0.34	5.9 ± 0.34	5.9 ± 0.34
15	6.4 ± 0.39	9.20 ± 0.37	6.0 ± 0.38	6.2 ± 0.38	6.0 ± 0.38	6.1 ± 0.38	6.1 ± 0.38	6.3 ± 0.34	6.2 ± 0.38	6.2 ± 0.38
20	6.1 ± 0.20	9.42 ± 0.29	5.8 ± 0.34	5.9 ± 0.34	5.8 ± 0.34	6.0 ± 0.34	5.8 ± 0.34	5.9 ± 0.34	6.0 ± 0.34	6.0 ± 0.34

1= *Butea monosperma*, 2= *Cassia fistula*, 3= *Caesalpinia bonduc*, 4= *Cassine glauca*, 5= *Cassia absus*, 6= Gallic acid, 7= Amide and 8= Ester analogues of gallic acid.

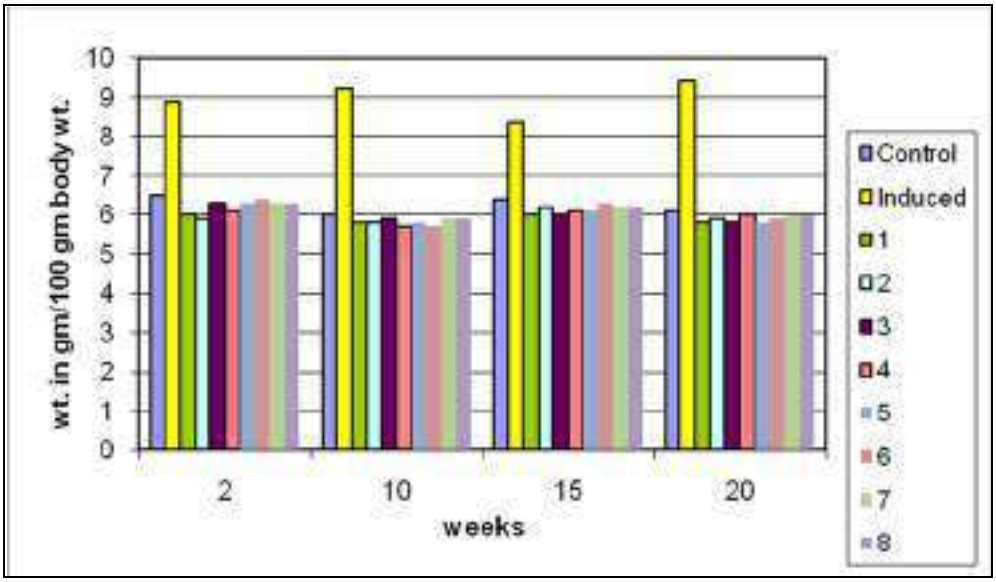


Fig. 1.3: Serum *calcium ion* change: *Wistar Albino rat*

Table 1.4: Serum *magnesium ion* change on exposure to burn and exogenous pharmacological drugs in *Albino rats*.

Day	Control	Induced	Treated							
			1	2	3	4	5	6	7	8
2	3.4 ± 0.18	3.6 ± 0.19	3.0 ± 0.18	3.2 ± 0.18	3.0 ± 0.18	3.1 ± 0.18	3.3 ± 0.18	3.3 ± 0.18	3.2 ± 0.18	3.2 ± 0.18
10	3.4 ± 0.18	4.8 ± 0.18	3.1 ± 0.17	3.1 ± 0.17	3.3 ± 0.17	3.2 ± 0.17	3.0 ± 0.17	3.1 ± 0.17	3.2 ± 0.18	3.3 ± 0.18
15	3.2 ± 0.18	3.7 ± 0.18	3.1 ± 0.18	3.0 ± 0.18	3.0 ± 0.18	2.9 ± 0.18	3.1 ± 0.18	3.0 ± 0.17	3.1 ± 0.17	3.1 ± 0.17
20	3.2 ± 0.18	3.8 ± 0.18	3.0 ± 0.17	3.1 ± 0.17	2.9 ± 0.17	3.2 ± 0.17	3.0 ± 0.17	3.0 ± 0.18	3.1 ± 0.18	3.2 ± 0.18

1= *Butea monosperma*, 2= *Cassia fistula*, 3= *Caesalpinia bonduc*, 4= *Cassine glauca*, 5= *Cassia absus*, 6= Gallic acid, 7= Amide and 8= Ester analogues of gallic acid.

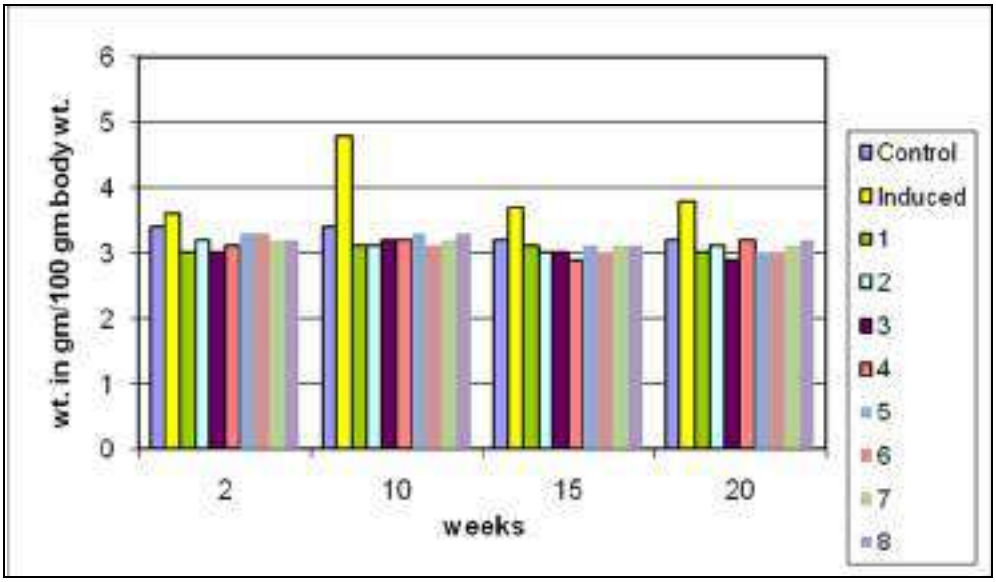


Fig. 1.4: Serum *magnesium ion* change: *Wistar Albino rat*

Table 1.5: Serum *phosphate ion* change on exposure to burn and exogenous pharmacological drugs in *Albino rats*.

Day	Control	Induced	Treated							
			1	2	3	4	5	6	7	8
2	6.0 ± 0.20	4.2 ± 0.18	5.9 ± 0.17	5.7 ± 0.17	5.9 ± 0.17	5.6 ± 0.17	5.6 ± 0.17	5.9 ± 0.18	5.8 ± 0.18	5.8 ± 0.18
10	6.3 ± 0.20	4.8 ± 0.18	6.0 ± 0.18	5.9 ± 0.18	5.8 ± 0.18	6.21 ± 0.18	6.1 ± 0.18	6.2 ± 0.18	6.0 ± 0.18	6.1 ± 0.18
15	6.20 ± 0.20	7.20 ± 0.20	6.15 ± 0.18	6.17 ± 0.18	6.16 ± 0.18	6.18 ± 0.18	6.17 ± 0.18	6.19 ± 0.17	6.17 ± 0.18	6.18 ± 0.18
20	6.5 ± 0.20	8.3 ± 0.20	6.3 ± 0.20	6.0 ± 0.20	6.2 ± 0.20	6.2 ± 0.20	6.3 ± 0.20	6.4 ± 0.20	6.2 ± 0.20	6.3 ± 0.20

1= *Butea monosperma*, 2= *Cassia fistula*, 3= *Caesalpinia bonduc*, 4= *Cassine glauca*, 5= *Cassia absus*, 6= Gallic acid, 7= Amide and 8= Ester analogues of gallic acid.

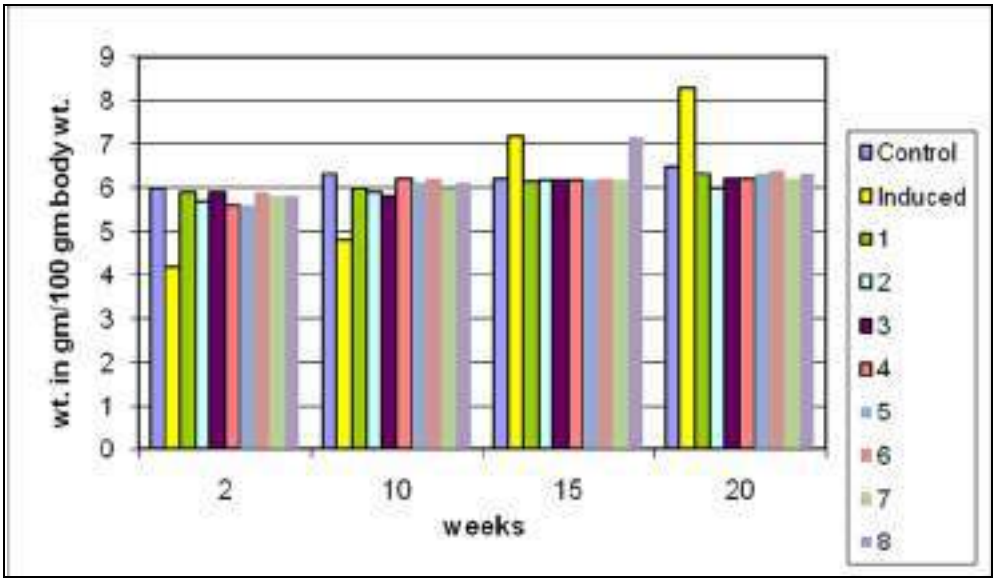


Fig. 1.5: Serum *phosphate ion* change: *Wistar Albino rat*

Conclusion:

Cutaneous infections adversely influence the ion exchange permeability of the skin. This leads to creating barriers in the supply of vital materials (ingredients) to the infected sites resulting into the deterioration of the natural composition and also the texture of the skin. Since the infected part of the skin becomes more susceptible to bacterial infections, the proportion of metal ions present in serum gets abnormally altered. From the above data it was very obvious that the concentration of the *sodium*, *potassium*, *calcium*, *magnesium* and *phosphate* ions for treated animals restored almost to the state of normalcy. It has also been revealed that isolated ingredients of the plant extracts and their chemical analogues are more effective in restoring the normalcy of the skin as compared whole plant extracts. However the author would like to mention that further extensive and systematic study in this field can lead to revealing many more life saving properties and potentials of these herbal preparations.

Acknowledgement

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Study of *Phyllanthus Amarus* Plant Extract and Newly Synthesized Analogue of *Pyllanthin* on Induced Hepatotoxicity in *Albino Rat*

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Abstract

Phyphyllanhtus amarus (Bhuiamala) is medicinally important plant. The literature survey reveals that this plant controls the adverse effect of hepatitis in human being. The extracts isolated from various parts of phyllonthus amarus and newly synthesized analogue of active ingredient i.e. phyllanthin were tested for their curative impact on cythion induced activities in albino rats with special reference to blood serum (VLDL, LDL, and HDL) hepatotoxicity. The effects of intraperitonial administration of test plant extract and snewly synthesized analogue were studied on cythion induced blood serum hepato-toxicity. The blood serum VLDL, LDL and HDL were estimated in order to assess the liver functions by established procedures. Biochemical observations were supplemented with histological examination of liver section. It is evident from the results that levels of various serum lipoproteins were altered in cythion treated animals than control group animals. There was small but significant decrease in the concentration of total serum lipids which may largely due to the reduction of the total lipid concentration in the VLDL, LDL and HDL. However the altered lipoprotein concentration levels were restored almost to the level of their normalcy in Phyphyllanhtus amarus (Bhuiamala) and newly synthesized analogou of active ingredient i.e. phyllanthin treated animals.

Keywords:- Phyphyllanhtus amarus (Bhuiamala), albino rats.

Introduction

Hepatic diseases is a major public health problem in the developed as well as developing countries. This is due to a wide spread use of pesticides in every field of life that become alarmingly hazardous to human health. Most of the pesticides cause metabolic transformations in the body of higher animals and the main site of metabolism is the liver[1,2]. Any metabolic disturbance in the liver produces characteristic hepatic disease.[3-8] These metabolic disturbances are mainly responsible for physiological and chemical alterations in the liver functions. In fact the use of pesticides and their interactions with liver and its most important bio-constituent lipoprotein is the root cause of many diseases and fatty liver. The major form in which triglycerides released by the liver is very low density lipoproteins (VLDL)[9]. In the circulation of low density lipoprotein (LDL), such release was found in a considerable amount.

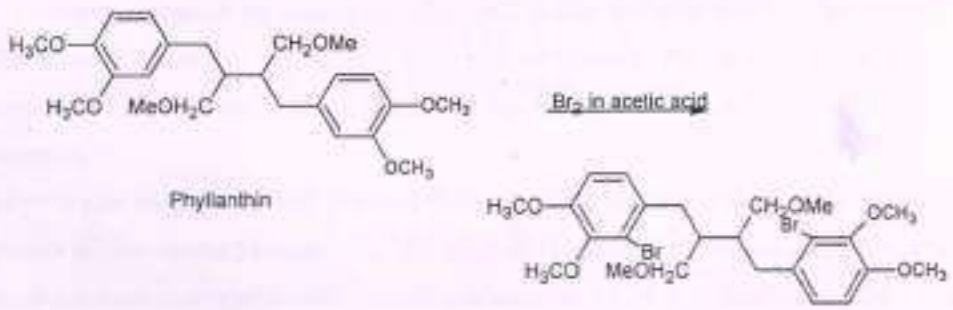
Phyphyllanhtus amarus (Bhuiamala): Phyllanthin is one of the active ingredients of *Phyphyllanhtus amarus spp.* It has been reported that the heterocyclic compounds have a broad spectrum of biological activity with special references to curing impact on hepatotoxicity.[10] The paucity of data in the study of

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hepatoprotective effects of *Phyphyllanhtus* motivated us to undertake the study of test plant extract and analogue prepared on cythion induced hepatic malfunctioning in *albino rats*. We report herewith the synthesis of bromosubstituted phyllanthin as an analogue on its reaction with bromine in acetic acid. The effects of this compound and crude extract of test plant have been studied on cythion induced activities in *albino rats*.

Experimental:-

Phyllanthin (0.01 mol) ingredient extracted from test plant Phyllanthus amarus was dissolved in Glacial acetic acid (2 ml). To this solution bromine in acetic acid reagent was added drop by drop with constant starring. After complete addition of reagent, the reaction mixture was allowed to stand for half an hour. The solid product thus obtained was filtered and washed with a little petroleum ether to get the analogue. It gives yellowish brown layer test with CCl_4 and yellow precipitate with $AgNO_3$ solution thereby confirming the presence of bromine in the product.



Phyllanthin

Bromo derivative of phyllanthin

The spectral analysis of bromo derivative of phyllanthin : **IR (nujol) in cm^{-1}** :- 2916(C-H stre.), 2850.6 (C-H stre.),1168.8 (C-O-C stre.),723.3(C-Br stre.);**UV-VIS ($CHCl_3$)** λ_{max} 370 nm corresponding to $n\rightarrow\pi^*$transition; **PMR($CDCl_3$)**:-δ6.8-7.4(m,4H,Ar-H),δ4.5(s,6H,-OCH_3),δ3.5(s,6H,-OCH_3),δ2.5(s,6H,C-OCH_3),δ2.1(d,4H,-CH_2), δ1.5(s,4H,Ar-CH_2-),δ1.4 (m,2H,-CH-). Melting points recorded are uncorrected and their purity was tested by TLC on microscopic slides with silica gel- G layers in benzene. From elemental analysis, chemical properties and spectral data, the compound (2b) assigned the structure bromo-phyllanthin.

Materials and Methods

The healthy *albino rats* of 6-8 weeks of age and 100-200 gm body weight were obtained from Dr. Punjabrao Deshmukh Medical College, Amravati and maintained in suiTable environment. They were supplied commercial pelleted diet and water ad libitum. The animals were divided into four groups (ABCD). The animals of group A were fed on stock diet and used as control species. Animals of group B

were given cythion pesticide intraperitionially (40SD/Kg body wt/day) for one week. Animals of groups C were given newly synthesised crude extract separately. Animals of group D were given analouge (bromo phyllanthin) in conjugation with cythion. The total period of observation was ten weeks.

The blood samples were collected from animals of group ABCD and left to clot at room temperature for at least 30 minutes to remove the clot and cell debries to perform following analysis.

i) Isolation of LDL and VLDL by precipitation with heparin and $MnCl_2$:

To 5ml of serum were added 0.2ml of 5% heparin solution and 0.25 ml of $MnCl_2$ solution. A ppt. appeared immediately. The reaction mixture was centrifuged for 10 minutes at 600 r.p.m. The precipitated lipoprotein sedimented at the bottom. The supernatant liquid was decanted and precipitate was dissolved in 10% sodium bicarbonate solution. The manganese associated with lipoproteins as bicarbonate salt was removed by concentration. 5 ml of Tris-HCl buffer was added to the clear yellow supernatant and lipoproteins were completely precipitated by the addition of 2ml $MgCl_2$. The ppt was separated by centrifugation and redissolved in 5% NaCl. In order to remove contaminating serum protein, the lipoproteins were precipitated by adding 5ml Tris-HCl buffer and 2ml $MgCl_2$. The solution was then dialysed for 24 hrs. against the tris-HCl buffer to remove heparin. The dialysis bag was transferred to another flask containing 5% $BaCl_2$ solution. After 24 hrs. the insoluble Heparin-Barium salt was removed by centrifugation.

The supernatant was dialysed against Tris-HCl buffer in order to remove $BaCl_2$.This resulted in a clear yellow solution of concentrated lipoprotein. The lipoprotein isolated in this way was the mixture of LDL and VLDL which were separated by ultra centrifugation. After 24 hr. at 1,00,00 r.p.m. the VLDL formed an opalescent band at the top of the tube and the clear yellow LDL sedimented at the bottom.

ii) Isolation of HDL by precipitation with sodium Phosphatungstate and $MgCl_2$:

To 5 ml of serum were added 5ml of 4% sodium phosphotungstate. (NaPhT) and 2 ml $MgCl_2$. The ppt of LDL and VLDL were removed by centrifugation. 4.5 ml of NaPhT was added to the clear supernatant (I). The ppt which appeared immediately was free of lipids and content mostly V-globulins which was removed by centrifugation. To supernatant (II) was added 0.0875 ml of 2ml $MgCl_2$. The precipitation was completed after 2hrs. and the mixture was centrifuged for 30 minutes at 20,000 r.p.m. The clear supernatant (III) (pH 7.1) was decanted and the ppt was dissolved in 2.5 ml of solution of the following composition (1% NaCl + 0.4%, NaPhT + 0.1 M $MgCl_2$). After washing ppt was recovered by centrifugation and was suspended in 1% NaCl, and 10% Na_2CO_3 solution was added dropwise with stirring until redissolution was achieved. This concentrated neutral solution of HDL, contaminated by small amount of serum protein was further purified by ultra centrifugation.

The serum concentration of the VLDL, LDL and HDL were determined by measuring their proteins and total lipid concentrations.

iii) Protein : The protein contents were estimated by Lowry et al. method[11] and values were expressed as mg/100ml of serum.

iv) Total lipids : They were estimated gravimetrically by Folch et al. method.[12]

v) Lipoproteirs :

A suiTable aliquot of the isolated fraction was estimated according to Folch et al.[12] method by using chloroform-methanol (2:1) mixture. These extracts were evaporated and taken in a known valume of chloroform and stored in sealed stopper tubes at 20°C. until required for further estimations.

Observations and Results:

Serum VLDL, LDL and HDL

It is evident from the Tables 1 to 3 and figures 1_f to 3_f the level of serum lipoproteins was altered in animal treated with cythion than controls. There was small but significant decrease in the concentration of serum total lipids which was largely or solely due to a reduction of the total lipid concentration in the VLDL, LDL and HDL.

Tables 1 to 3 and figures 1*f* to 3*f* showed total lipid changes in serum VLDL,LDL and HDL.

Table 1: Serum total lipid changes in very low density lipoprotein (VLDL) on exposure to cythion,plant extrac and analogue of phyllanthin (2b) in *albino rat*.

Weeks	Control	Induced	Plant extract	Analogue
2	61.35 ± 6.25	59.60 ± 5.50	59.82 ± 5.49	59.80 ± 5.39
4	60.95 ± 6.35	58.90 ± 5.80	59.15 ± 5.85	59.35 ± 5.37
6	60.60 ± 6.20	58.65 ± 5.00	58.75 ± 5.33	58.79 ± 5.22
8	61.25 ± 6.35	57.55 ± 5.25	57.90 ± 5.29	57.99 ± 5.32
10	60.90 ± 6.26	57.33 ± 5.4	57.85 ± 5.10	57.90 ± 5.21

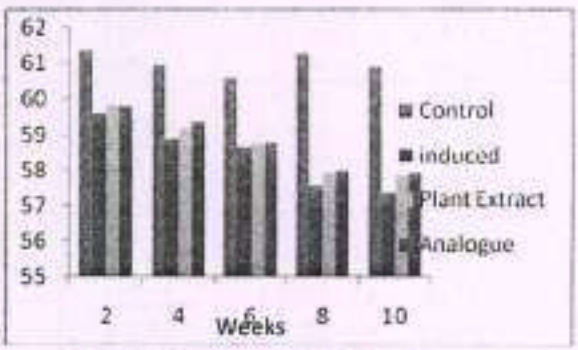


Fig. 1*f*: Serum total lipids : *Albino rat.*

Table 2: Serum total lipid changes in low density lipoprotein (LDL) on exposure to cythion,plant extract and analogue of phyllanthin (2b) in *albino rat.*

Weeks	Control	Induced	Plant Extract	Analogue
2	71.80 ± 10.37	63.27 ± 10.45	64.11 ± 10.39	64.80 ± 10.56
4	70.85 ± 10.69	53.02 ± 10.15	54.25 ± 10.35	54.85 ± 10.38
6	70.95 ± 10.27	41.25 ± 10.90	42.65 ± 10.25	43.85 ± 10.01
8	71.10 ± 10.61	39.05 ± 10.05	40.25 ± 10.05	41.39 ± 10.22
10	71.05 ± 10.26	30.25 ± 10.4	30.75 ± 10.21	31.85 ± 10.11

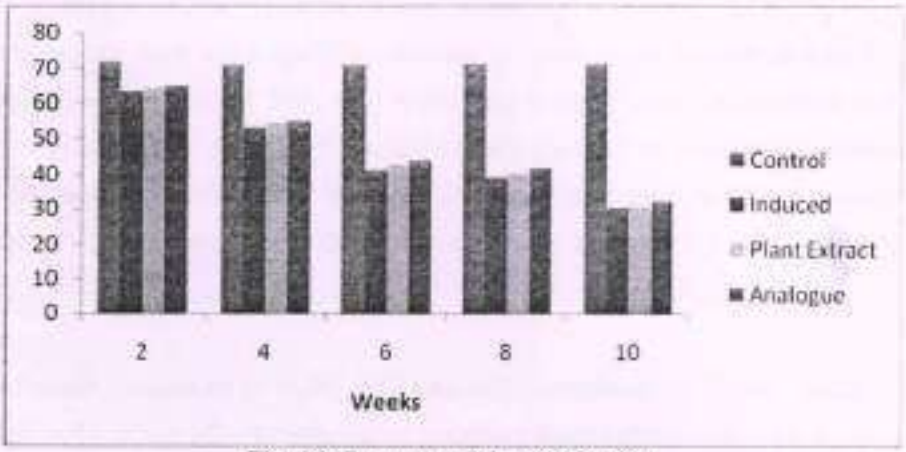


Fig. 2*f* : Serum protein : *Albino rat.*

Table No. 3 : Serum total lipid changes in high density lipoprotein (HDL) on exposure to cythion,plant extract and analogue of phyllanthin (2b) in *albino rat.*

Weeks	Control	Induced	Plant Extract	Analogue
2	113.21 ± 3.00	111.16 ± 7.6	111.79 ± 9.1	112.65 ± 2.5
4	113.22 ± 3.22	110.01 ± 7.23	111.29 ± 9.02	112.10 ± 2.56
6	113.10 ± 3.21	109.00 ± 7.33	110.90 ± 9.10	112.00 ± 2.29
8	121.97 ± 2.99	106.29 ± 6.75	109.29 ± 8.99	111.21 ± 2.10
10	113.29 ± 2.55	105.01 ± 6.59	30.75 ± 8.65	31.85 ± 2.22

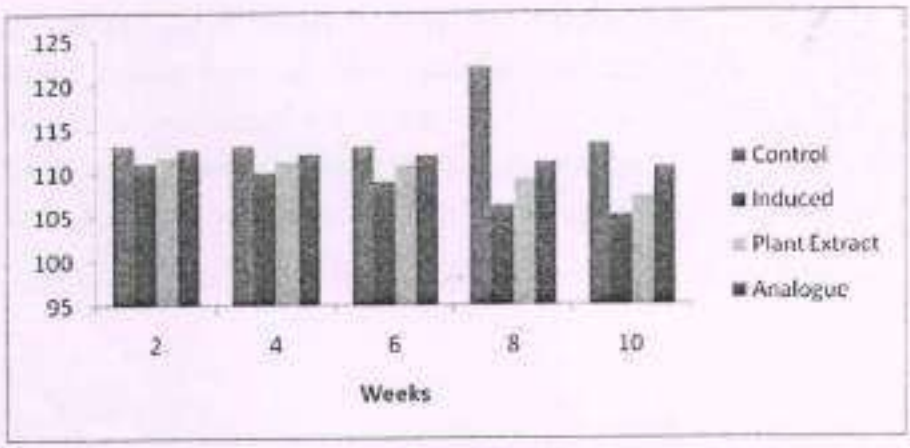


Fig. 3*f*: Serum lipoprotein : *Albino rat*

Result

In cyhtinon treated rats there was a significant decrease in the total lipid concentration i.e.VLDL,LDL and HDL. Whereas a remarkable rie in HDL level is observed in blood serum as compared to that of control group rats.The plant extract and newly synthesised analogues under examination showed significant increase in the levels of VLDL,LDL and HDL.The study also reveled that the newly synthesised analogues have slight curative age over the crude plant extract in HDL level as compared that of VLDL and LDL.

Conclusion

The results of serum estimations in VLDL, LDL and HDL containing total lipids reveals that there is a declining trend in the values of these constituents in cythion treated *albino rats*. And the administration of phyllanthin and analogue of phyllanthin showed remarkable curative effect.

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Synthesis and Antimicrobial Activity of Some Chalcones and Flavones

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Abstract

The chalcones (3a-e) were obtained by Claisen-Schimdt condensation of aromatic aldehydes with o-hydroxy acetophenone. Chalcones (3a-e) on reaction with catalytic amount of I2 in DMSO gave Flavones (4a-e) in high yields. All the synthesized flavones were evaluated in vitro for antifungal screening. It is observed that all flavones showed moderate to good inhibitory activity.

Keywords: 2-Hydroxy acetophenone, 2-Hydroxy chalcones, Flavones, Antifungal activity.

Introduction

Flavones constitute one of the major classes of naturally occurring products. Synthesis of flavones and their derivatives have attracted considerable attention due to their significant biocidal[1-3],pharmaceutical[4-7] and antioxidant[8-10] activities. Chalcones and its derivatives have attracted particular interest during the last few decades . Chalcones are the α,β-unsaturated carbonyl compounds.Chalcones exhibits various biological activities such as antimalerial[11], antiviral[12], anticancer[13] and other activities[14-15]. . In addition to these features chalcones are also acting as anintermediate for the synthesis of various biologically active heterocycles such as pyrimidines[16-17], pyrazolines [18-19], isoxazolines[20-21], flavonoids[22-23], benzodiazepines[24]. Here we describe the syntheses flavones (4a-d) from their corresponding chalcones (3a-d) by usingDMSO/I 2 as an oxidizing agent.

Materials and Methods

General procedure for the preparation of chalcones (3a-e)

To the boiling solution of 2-hydroxy-5-chloro acetophenone (1 mole), aromatic aldehydes(1 mole) and ethanol 20 (ml) were added. Then an aqueous solution of NaOH (40%) was added gradually with constant stirring and the reaction mixture was kept for overnight . It was poured in ice cold water and neutralised with dilute HCl (1:1). Yellow granules thus obtained were filtered, washed with NaHCO3 and finally crystallized from ethanol-acetic mixture..

(3a)-1-(2-Hydroxy-5-chlorophenyl)-3-(4-phenyl)chalcone

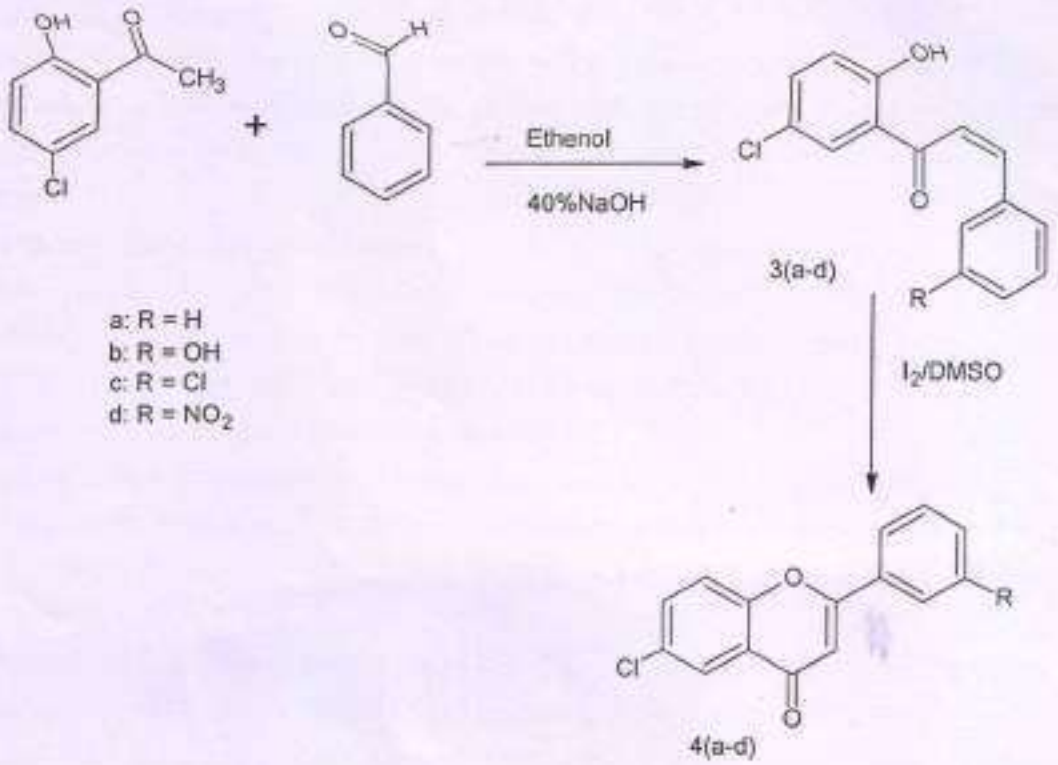
Yellow solid; m.p. =80°C; yield= 78%;Elemental analysis: C 74.00/73.09, O6.11/6.58,

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H 4.01/4.93 **Cl** 14.22/14.60, IR (KBr) in cm^{-1}:-16801.63(C=O stret.), 1635.55 (C=C stret.) 2934.83 (C-H stret.), 3733.17(-OH stret.), 1H NMR-: δ 7.9(m,10H, Ar-H), δ 6..5 (s, 1H, =CH), δ 6..1(d, 1H, =CH),

Scheme 1



(3b)-1-(2-Hydroxy-5-chlorophenyl)-3-(4-hydrooxyphenyl)chalcone

Yellow solid; m.p. =134°C; yield= 72% ;Elemental analysis: **C** 69.11/69.49, **O**12.22/12.35 **H** 4.22/4.63; Cl14.22/14.60 ; IR (KBr): in cm^{-1} 456.59 (C=Cstret.),1766.78(C=O stret.), 2922.48(C-H stret.), 3733.53(-OH stret.), 1H NMR: δ7.9 (m 10 H Ar-H), δ 5.6 (d 1H =CH), δ 6.3 (d,1H =CH) ,δ 11.12 (s,1H,Ar-**OH** (H-bonded),

(3c)-1-(2-Hydroxy-5-chlorophenyl)-3-(4-chlorophenyl)chalcone

Red solid; m.p. =170°C; yield= 70% ;Elemental analysis: **C** 64.44 /64.74, **O**5.61/5.77 **H** 3.5/3.95; **Cl** 25.33/25.53; IR (KBr) in cm^{-1} : 1454.59 (C=C stret.),1511.31(C=O stret.), 2913 (C-H stret.)3439(-OH stret.), 1H NMR: δ 8.1(m, 9 H, Ar-H), δ 5.8 (d, 1H, =CH), δ6.6 (d,1H, =CH) ,

(3d)-1-(2-Hydroxy-5-chlorophenyl)-3-(4nitrophenyl)chalcone

Brown solid; mp=130°C; yield= 71% ;Elemental analysis: **C** 62.12/62.28, **O**16.58/16.60,

H 3.89/3.95**N** 4.94/4.89; **Cl** .09/.12, ; IR(KBr in cm^{-1}) : 1379 (-NO2 stret.); 1445.45 (C=Cstret.), 1691 (C=O stret.), 2944 (C-H stret.), 3479 (-OH stret.), 1H NMR: δ 8.0(m, 9 H, Ar-H), δ 5.6 (d ,1H =CH), δ 6.5(d,1H, =CH) .

General procedure for the preparation of flavones (4a-e):

Chalcones 3a-d (1 mole) were refluxed separately with catalytic amount of I2 (0.1 mole) in DMSO for 20-40 minutes to get flavones (4a-d) .The products thus obtained were filtered, washed with 20% Sodium thiosulphate solution to remove the colour of Iodine and finally crystallized from ehanol-acetic mixture.

(4a)6-chloro-2-phenyl-4Hchromen-4-one

Yellow solid; mp=670C; yield= 63% ; Elemental analysis: **C** 70.21/70.31, **O**11.99/12.55, **H** 3.00/3.51; ,Cl 0.11/0.13 „IR (KBr) in cm^{-1} : 1119 (C-OCstret.); 1609 (C=C stret.), 1639(C=O stret.), 2864(CH stret.),2979 , 1H NMR: δ 8.1 (m,8 H, Ar-**H**), δ 6.5 (s, 1H,=CH),

(4b)6-chloro-2-(2-hydroxypheny)l-4Hchromen-4-one

Yellow solid; mp=95°C; yield= 62% ; Elemental analysis: **C** 62.11/66.17, **O**15.55/17.64, **H** 2.08/3.30; IR (KBr) in cm^{-1}: 784.05 (mono substitutedbenzene), 1132 (C-O-C stret.); 1559.25 (C=C stret.), 1686(C=O stret.), 2914.47(CH)stret.), 1H NMR δ 8.4 (m,8 H, Ar-**H**), δ 6.5(s,1H ,=CH), δ 11.3 (s ,1H ,Ar-O**H**)

(4c)6-chloro-2-(4-chlorophenyl)-4Hchromen-4-one

Brown solid; mp=48°C; yield= 60% ;Elemental analysis: **C** 60.11/61.85, **O**9.04/10.99, **H** 2.06/2.7; Cl .22.1/.24.39 ; IR (KBr) in cm^{-1}: 1118.75 (C-O-C stret.); 1642 (C=C stret.), 1719 (C=O stret.), 2860 (-CH)stret1HNMR: δ 8.6 (m,7 H ,Ar-**H**), δ 6.7(s,1H,=CH),

(4d)6-chloro-2-(4-nitroophenyl)-4Hchromen-4-one

Black solid; mp=92°C; yield= 63% ; Elemental analysis: **C** 65.32/67.66, **O** 22.77/24.06, **H** 2.91/3.09; **N** 4.98/5.26.; Cl 12.55.1/.13.39 IR (KBr) in cm^{-1} : 1181.40 (C-O-C stret.); 1526.60 (-NO2 stret.) . 1644 (C=C stret.),1689 (C=Ostret 2862 (-CH stret.), 1H NMR δ 8.8 (m,7 H, Ar-**H**), δ 6.8(s,1H,=CH),

Table 1 *Antifungal activity of flavones*

S.N	Name of Compound	Zone of inhabitation in mm			
		Curvularia Eryostides	*Drecheslera tetrameda*	*Fusarium cicerg*	*Bipolaris sorokenia*
1	*4a*	*09*	*12*	*14*	*08*
2	*4b*	*08*	*09*	*10*	*06*
3	*4c*	*10*	*12*	*11*	*14*
4	*4d*	*07*	*06*	*09*	*07*

Antimicrobial Screening

The antifungal activities of compounds 4(a-d)have been assayed at the concentration of 200 µg/disc assays against four plants pathogenic and moulds fungi. The inhibitory effects of compounds 4 a-d against these organisms are given in Table 1.The screening results indicate that the compound 4a-e shows good to moderate antifungal activities to the tested fungi against *Curvulariaeryostides, Drecheslera tetrameda, Fusariumcicerg, and Bipolaris sorokenia.*

Results And Discussion

The substituted 2-hydroxy 5-chloro acetophenone was condensed with aromatic aldehydes to obtain corresponding 2-hydroxy5-chloro chalcones (3a-d).the structure of this compound were established from their physical and spectral data. The IR spectrum of 3a-d shows absorption band in the region 1630-1650 cm-1(C=O) and 3295-3480 cm-1 ('-OH).

The flavones (4a-e) were obtained by oxidative cyclization of 2-hydroxy-5-chlorochalcone (3a-d). .All synthesised flavone were evaluated for in vitro antifungal screening. It is observed that the all flavone shows good to moderate antifungal activity. The results are shown in (Table 1).

Conclusion

In summary, we have synthesised some chalcones having 2-hydroxy-5-chloroacetophenone and convert them into flavones. The antifungal screening of flavones (4a-d) were found to be active and due to presence of chlorine on phenyl ring increases the activity of the compound.

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Ecofriendly Synthesis, Characterization and Antibacterial Assay of Some Chlorosubstituted Isoxazoles

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Abstract

The concept of green chemistry is now widely adopted to meet the scientific challenges in order to protect the human health and environment. Nowadays researchers are working extensively to synthesize new compounds using ecofriendly solvents and other conditions. Literature survey reveals that isoxazoles are very useful units in the fields of medicinal, pharmaceutical and agriculture. Isoxazoles have been reported to exhibit a broad spectrum of biological activities. In this regard, in the present study, we have undertaken synthesis and characterization of new chlorosubstitutedisoxazole derivatives by the action of chlorosubstituted flavones, which were prepared from chalcones in a ecofriendly single step, with hydroxylamine hydrochloride in good yields. The newly synthesized compounds are screened against some bacteria with special reference to study antipathogenic activities.

Keywords: *Chlorosubstitutedisoxazoles, flavones, chalcones, antibacterial assay, antipathogenic activities.*

Introduction

Literature survey shows that the chlorosubstituted heterocycles[1] have antifungal[2], antimicrobial[3], antitubercular[4], antiviral[5], and antibacterial[6] activity. Taking into account the widespread applications of chlorosubstituted heterocycles such as pyrazoles, thiazoles, isoxazoles[7] in the fields of pharmaceutical, medicine and agriculture, it was thought interesting to synthesize some new chlrosubstituted isoxazoles and study their impact on plant pathogens especially bacteria. The isoxazoles are the compounds having five membered ring containing both oxygen & nitrogen atoms in the 1,2 positions. It has been observed that flavones are the best starting compounds for the preparation of isoxazole derivatives. These flavones are prepared from chalcones in a ecofriendly single step.

Experimental

Scheme-I

Preparation of 2,4-dichloro phenyl acetate(*1a*): 2,4-dichlorophenol (10gm) was mixed with acetic anhydride (12ml) and anhydrous sodium acetate (1gm). The mixture was refluxed for about an hour. The

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mixture was cooled and poured into cold water. Acetate layer was separated and then washed with water several times. It was finally collected by distillation.

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)ethanone(2a): 2,4-dichlorophenol (10ml) was mixed with anhydrous $AlCl_3$(24gm) and heated at 120^0C for 45 minutes. The reaction mixture was decomposed with ice cold water containing a little HCl. A greenish solid thus separated was recrystallised by ethanol to get compound 2a.

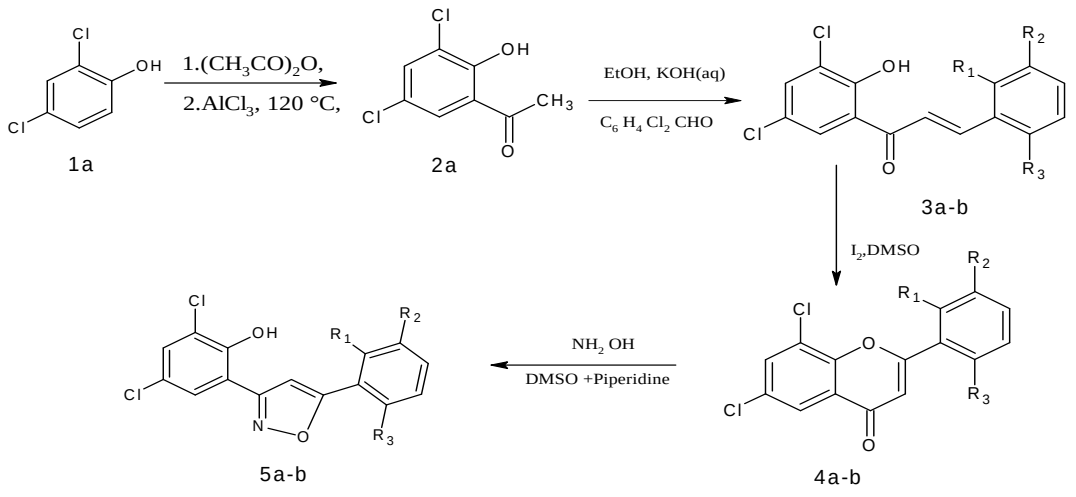
IR(KBr ν_{max})(cm^{-1}) 3050cm^{-1}(-OH phenolic str),1665(C=Ostr), 1300(C-Ostr), 730(C-Clstr)

NMR: δ12.73(s,1H,Ar-H) , δ7.25-7.63(m,2H,Ar-H) , δ2.60,(s,3H,-CH_3).

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)prop-2-en-1-one(3a): 1-(3,5-dichloro-2-hydroxyphenyl) ethanone (0.01M) and 2,3-dichlorobenzaldehyde(0.01M) were added to ethanol(20ml). To this mixture KOH solution(40%,10ml) was added drop wise . The reaction mixture was kept for overnight, then poured on ice containing little HCl. The product was filtered and recyrstallised from ethanol to obtain the compound 3a.

IR(KBr ν_{max})(cm^{-1}) 3417cm^{-1}(O-Hstr),1645(C=Ostr),308cm^{-1}(ArC-Hstr),1648cm^{-1} (C=Cstr),738cm^{-1}(C-Clstr).

NMR: δ8.17(d,1H,CH=CH) , δ7.39(d,1H,CH=CH), δ6.7-7.5(m,5H,Ar-H), δ5.0(s,1H,Ar-OH).



where a; R_1=Cl, R_2=H,R_3=Cl and b ; R_1=Cl, R_2=Cl,R_3=H

Preparation of 6,8-dichloro-2-(2,3-dichlorophenyl)-4*H*-chromen-4-one (4a) -

1-(3,5-dichloro-2-hydroxyphenyl)-3-(2,3-dichlorophenyl)prop-2-en-1-one (0.01M) was dissolved in 20ml DMSO, To this few crystals of Iodine were added. The mixture was refluxed for 10 min. Then the

mixture was poured on the crushed ice. The product was filtered and recrystallised from chloroform to get compound 4a.

IR(KBr ν_{max})(cm^{-1}):3400cm^{-1}(O-Hstr), 1650cm(C=Ostr),1310cm^{-1}(C-Osrt),730cm^{-1}(C-Clstr).

NMR: δ9.1(m,2H,Ar-H) , δ7.9(m,2H,Ar-H),δ7.3(s,1H,Ar-H),δ7.1(m,4H,Ar-H), δ5.1(s,1H,Ar-OH), δ4.8(m,1H,CH), δ2.0(d,1H,-CH_2), δ1.8(d,1H,-CH_2).

Preparation of 2,4-dichloro-6-[5-(2,3-dichlorophenyl)-1,2-oxazol-3-yl]phenol (5a) : 6,8-dichloro-2-(2,3-dichlorophenyl)-4*H*-chromen-4-one (0.01M) and hydroxylamine hydrochloride(0.01) dissolved in 20ml DMSO with a few drops of pipyridine. The mixture was refluxed for 1.5 hrs. The product was filtered and recrystallised from chloroform to get compound 5a.

IR(KBr ν_{max})(cm^{-1}) :3400cm^{-1}(O-Hstr),1584cm^{-1} (C=Nstr),1310cm^{-1}(C-Osrt), ,730cm-1(C-Clstr).

NMR: δ8.3(s,1H,C-H),δ7.1-7.3(m,5H,Ar-H),δ5.2(s,1H,Ar-H).

Antibacterial Study

The newly synthesized compounds(5a and 5b) were screened for their antibacterial activity against some *Gram positive* pathogens viz. *Staphylococcus aureas* and *Streptococcus sp.* and some *Gram negative* pathogens viz. *Pseudomonas sp.* and *Solmonella Typhi.* at conc.of 1000 µm gentamycine as a standard. DMF was used as solvent control using agar plate techniques. The chlorosubstituted isoxazoles synthesized when screened for antibacterial activity, it was noticed that all these compounds had shown remarkable inhibitory activity.

Results And Discution

Physical characterization data of all the compounds are given in Table-1.

TABLE-1

CHARACTERIZATION DATA OF NEWLY SYNTHESIZED COMPOUNDS

Compound	Mol. Formula	M.P.(^{0}C)	Yield(%)	R_f
1a	$C_8 H_6 Cl_2 O_2$	214(B.P.)	85	0.75
2a	$C_8 H_6 Cl_2 O_2$	91-92	70	0.80
3a	$C_{15} H_8 Cl_4 O_2$	84-86	80	0.77
3b	$C_{15} H_8 Cl_4 O_2$	95-97	82	0.73
4a	$C_{15} H_7 Cl_4 O_2$	160-162	59	0.74
4b	$C_{15} H_7 Cl_4 O_2$	183-185	57	0.82
5a	$C_{15} H_7 Cl_4 NO_2$	195-197	63	0.72
5b	$C_{15} H_7 Cl_4 NO_2$	186-188	61	0.81

The synthetic routes which furnished the target compounds are shown below along with their IR and NMR data. The newly synthesized compounds (5a and 5b) were found to be active against test pathogens. A further detailed study in the light of Medical sciences is advised.

Acknowledgements

The authors are thankful to Amolakchand Mahavidyalaya, Yavatmal and Vidyabharati Mahavidyalaya, Amravati for providing all the facilities to carry out synthetic work and Punjab University Chandigarh for providing spectral data, Shri Shankarlal Khandelwal College ,Akola for providing help in carrying out the antibacterial activities.

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Studies in Acoustic Parameters of Promethazine Drug in Dioxane-Water Solvent at Different Temperatures

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Abstract

Measurements of ultrasonic velocity have been carried out for Promethazine hudrochloride (PM) at three different temperatures. Viscosities and densities of present system have been measured at 303K, 308K & 313K. From this data various acoustic parameters such as apparent molar compressibility (ϕ_k), apparent molar volume (ϕ_v), adiabatic compressibility (β_s), specific acoustic impendence (Z), intermolecular free length (L_f), molar compressibility (W) & relative association (R_A) have been determined. From these derived parameters limiting apparent molal volume (ϕ^0_v), limiting apparent molal compressibility (ϕ^0_k) and Experimental slopes (S^0_V&S^0_K) have calculated by using Massons equation. The viscosity data are analysed using Jones – Dole equation. The results are interpreted on the basis of solute-solvent and solute-solute interactions.

Keywords: Promethazine hydrochloride, acoustic parameters.

Introduction

The studies on volumetric, ultrasonic and viscometric properties of liquid mixtures and their dependence on composition and temperature are of importance in many fields of applied research and find applications in many important chemical, textile, leather, industrial and biological process. Ultrasonic waves provide valuable information about the molecular interaction in pure liquids, aqueous solutions, liquid mixtures and also provide valuable information about the structure of solids[1-4].

Ultrasonic velocity measurements have been successfully employed to detect and assess weak and strong molecular interactions, present in binary liquid mixtures [5, 6]. Ultrasonic studies have found wide applications owing to their ability to characterize the physico-chemical behaviour of solutions. The excess properties have been claimed to be an aid in the characterization of the molecular interactions that are present in solutions and liquid mixtures. This is achieved through elevation of ideal quantities. In recent years, considerable efforts have been given for the elevation of ideal and excess thermodynamic quantities of binary and ternary liquid mixtures [7, 8].The study of molecular interaction in the liquid mixtures is of considerable in the elucidation of the structural properties of the molecules.

The nature and degree of molecular interactions in different solutions depend upon the nature of the medium, the structure of the solute molecule and also the extent of solvation taking place in solution.For

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the present study drug *[Dimethy1 (1-(10-H phenothiazin-10-y1) propan-2-y1] amine)* is selected. This drug is used as antihistaminic, sedative. Acoustic parameters provide a better insight into molecular environment to liquid mixtures, it seemed important to study molecular interactions, which motivated theauthors to carry out the present investigation in the binary liquid mixtures of Promethazine hydrochloride (PM) with dioxane-water solvent at different temperatures using ultrasonic technique.

Materials and Methods

Solventdioxane used in the present work was of AR grade, purified and dried by the usual procedure. Densities, viscosities and ultrasonic velocities were measured at different temperatures over a wide range of composition. Densities were determined by using bicapillarypyknometer. The Viscosities (η) of pure compounds and their mixtures were determined using Oswald's Viscometer calibrated with double distilled water [8,9]. Ultrasonic velocity measurements were made by using an ultrasonic interferometer (Mittal Enterprises, New Delhi) at a frequency of 2MHz with a tolerance of ± 0.005%. All the measurements were carried out at different temperatures.

Acoustic parameters such as apparent molar compressibility (ϕ_k), apparent molar volume (ϕ_v), adiabatic compressibility (β_s), specific acoustic impendence (Z), intermolecular free length (L_f),molar compressibility (W) & relative association (R_A)were determined using following relationsLimiting apparent molar volume (ϕ^0_v), limiting apparent molar compressibility(ϕ^0_k)and Experimental slopes (S^0_V&S^0_K) have calculated by using Massons equation.

Ultrasonic velocity	$u = \lambda\upsilon$	1
Adiabatic compressibility	$\beta_s = 1/ u^2_s \rho_s$	2
Apparent molar compressibility	$\phi_k = 10^3(\rho_0\beta_s-\rho_s\beta_0)/m-\rho_s \rho_0 + \beta_s M/\rho_s$	3
Apparent molar volume	$\phi_v = 10^3(\rho_0-\rho_s)/m-\rho_0 \rho_s + M/\rho_0$	4
Specific acoustic impendence	$Z = \rho.u$	5
Intermolecular free length	$L_f = K (\beta_s)^{1/2}$	6
Molar compressibility	$W = M \times (\beta_s)^{-1/7}\rho_s$	7
Relative association	$R_A = (\rho/\rho_0) \times (u_0/u)^{1/3}$	8
Limiting apparent molar volume	$\phi_v = \phi^0_v + S_vC^{1/2}$	9
Limiting apparent molar compressibility	$\phi_k = \phi^0_k + S_k^{1/2}$	10

In the present paper, we report densities (ρ) and Ultrasonic velocities of binary mixtures of Promethazine hydrochloride (PM) withdioxane-water solvent at different temperatures, over the entire composition range.

Table 1: The Experimental values Density, Ultrasonic Velocity and related Parameters at different temperatures System- PM in 20% Dioxane-Water medium

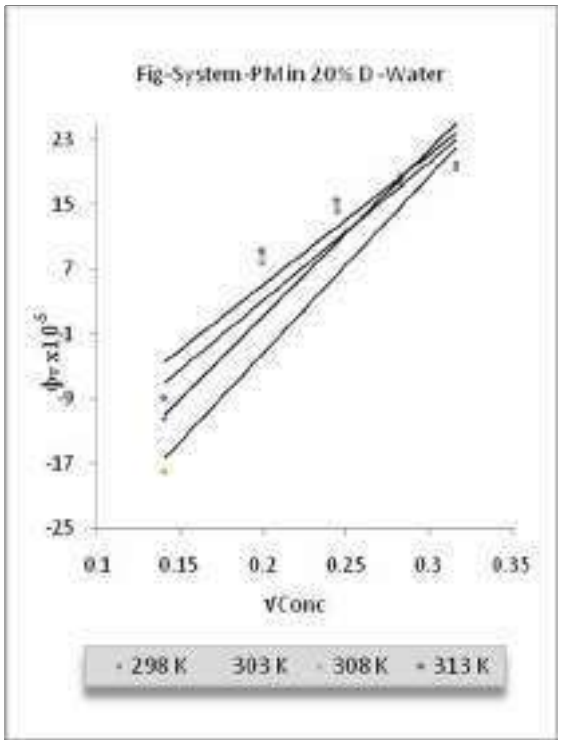
Temp T(K)	Conc. mol. dm^{-3}	Density ρsKgm^{-3}	Ultrasonic Velocity (u) m/s	β_s x10^{-10} Pa^{-1}	Φv x10^{-5} m^3mol^{-1}	Φk x10^{-14} m^3mol^{-1} Pa^{-1}	L_f x10^{-11} (m)	Z x 10^5 Kg m^{-2} sec^{-1}	Relative association R_A X10^{-3}
298K	0.02	1025.45	1621.1	3.7108	-11.454	-152.81	3.9723	16.6235	996.42
	0.04	1025.74	1622.8	3.7020	7.7182	-73.593	3.9675	16.6457	996.36
	0.06	1026.06	1625.4	3.6890	14.506	-47.909	3.9606	16.6775	996.13
	0.08	1026.19	1628.5	3.6745	17.451	-35.190	3.9528	16.7115	995.63
	0.1	1026.41	1631.5	3.6602	19.399	-27.586	3.9451	16.7458	995.23
303K	0.02	1024.45	1625.3	3.6952	-21.937	-176.235	3.9972	16.6503	997.24
	0.04	1024.77	1627.6	3.6836	2.4168	-86.030	3.9909	16.6791	997.08
	0.06	1024.91	1629.9	3.6728	10.820	-55.763	3.9850	16.7050	996.75
	0.08	1025.12	1632.1	3.6621	14.937	-40.646	3.9792	16.7309	996.65
	0.1	1025.31	1634.6	3.6502	17.420	-31.704	3.9728	16.7597	996.18
308K	0.02	1020.96	1629.2	3.6901	-7.9301	-179.43	4.0273	16.6334	993.22
	0.04	1021.12	1631.1	3.6810	9.8516	-86.888	4.0223	16.6554	992.99
	0.06	1021.84	1633.3	3.6685	14.866	-56.945	4.0154	16.6897	993.24
	0.08	1022.06	1635.1	3.6596	17.976	-41.313	4.0106	16.7117	993.09
	0.1	1022.21	1637.5	3.6484	19.909	-32.160	4.0044	16.7386	992.75

Table 2. Limiting values of ϕ_v and ϕ_k along with slope (S_V&S_K) for PM indioxane-water medium at different temperatures

Temp.T (K)	Medium	**Parameters**			
		ϕ_v^0x10^{-5} m^3mol^{-1}	ϕ_k^0 x10^{-14} $m^3mol^{-1}pa^{-1}$	S_vx10^{-5} $m^3mol^{-3/2}dm^{3/2}$	S_k x10^{-14} $m^3mol^{-3/2}dm^{3/2}pa^{-1}$
298K	20%D-W	-31.28	-232.3	171.7	695.7
303K	20%D-W	-40.29	-273.3	194.1	820.8
308K	20%D-W	-40.09	-274.3	205.9	818.5

Results and Discussion

Table 1 shows that density (ρ), ultrasonic velocity (u) and viscosity (η) increases with increase in concentration for all three systems. The increase in ultrasonic velocity is due to decrease in intermolecular free length (L_f) as shown in Table. This suggests that there is a strong interaction between promethazine hydrochloride and solvent molecule. Adiabatic compressibility (β_s) is a measure of intermolecular association or repulsion calculated from the measured ultrasonic velocity (u) and density (ρ). Adiabatic compressibility is found to decrease with increase in concentration[10]. Since adiabatic compressibility is inversely related to the product of density and ultrasonic velocity based on this the compressibility is expected to decrease which has observed in the present case.



When the sound waves travels through the solution, certain part of it travels through the medium and rest gets reflected by the ion[11] i.e. restriction for flow of sound velocity by the ions. The character that determines the restriction movement of sound waves is known as acoustic impendence (Z). It has been found that acoustic impendence increases with increase in concentration. The apparent molar compressibility (ϕ_k) explains the solute-solvent and solute- solute interactions in solution and was calculated by using the equation 3. The apparent molar volume (ϕ_v) is defined as the change in volume of solution for the added one mole of a particular component at constant temperature and pressure. It is thermodynamic property which helps in elucidating solvation behavior of electrolyte in solution. Apparent molar volume was evaluated from the density of solution and solvent. It is evident from the Table 2 that ϕ^0_k values are negative for 20% Dioxane-water. The negative ϕ^0_k values are suggest solute-solvent interaction whereas positive values are due to solute- solute interaction. $S_v$is a measure of solute - solvent interaction. It is observed from the Table 2 that The decreasing values of ϕ^0_v and increasing values of S_v clearly indicates the decrease in solute-solvent and increase in solute-solute interactions with the rise of temperature which indicates the solute-solute interactions are stronger than solute-solvent interactions.

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Microwave Assisted Solvent Free Synthesis of 2,7-(Substituted Phenyl)- 3-Phenyl-5,7,7A-Trihydro-2H-Thiazolo [4,5-D] [1,3] Thiazin-5-Amine Derivatives

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Abstract

Synthesis of Novel 2,7-(substituted phenyl)- -3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5-amine(Va-Vh) by condensation of 2-(substituted phenyl)-3-phenyl thiazolidin-4-one (IVa-IVh) with excess of aromatic aldehyde and thiourea dissolved in polar solvent. In vitro assay of newly synthesized compound were carried out to test antifungal activity by disc diffusion method against Fusarium oxysporum and Rhizoctonia solani. All synthesized compounds were characterized by UV.IR, ^{1}HNMR, ^{13}C NMR, spectral and elemental analysis.

Keywords- Thiazolidione, Thiazolo-Thiazine, Antifungal Activity

Introduction-:

Chemistry nowadays is at fore front of the development of clean production processes and products. Chemistry is no doubt determinant to understand and protect our environment, as the world's future is strongly dependant on the chemical processes adopted. Chemistry plays an integral part of our lives. Sustainability, eco-friendly and green chemistry are new principles that are guiding the development of next generation of products and processes[1,2]. "Green chemistry is considered an essential piece of a comprehensive program to protect human health and the environment." In its essence green chemistry[3-8] is a science based non-regulatory and economically driven approach to achieving the goals of environmental protection and sustainable development. Thiazoles are a familiar group of heterocyclic compounds possessing wide variety of biological activities, and their usefulness as medicines are well established. Thiazole nucleus is also an integral part of all the available penicillin's, which have revolutionized the therapy of bacterial diseases[9] . Thiazoles have attracted continuing interest because of their varied biologicalactivities[10] , which have found applications in the treatment of allergies[11], hypertension[12], inflammation[13], schizophrenia[14]microbial infections[15-16], HIV infections[17], hypnotics [18]and for the treatment of pain[19] . They have been also used asfibrinogen receptor antagonists with antithrombotic activity [20]and as new inhibitors of bacterial DNA gyrase B [21]. Aldo Andreani reported the synthesis and antitubercular activity of imidazo(2,1-b) thiazoles, Raghav Mishra, Synthesized and studied antimicrobial evaluation of some novel thiazole –pyrazoline derivatives. This has been prompted us to synthesize fused thiazo-thiazine derivatives.

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Material and methods-: All chemicals used were of analytical grade. All the synthesized compounds have been characterized on the basis of chemical properties, elemental and spectral analysis. The melting points were measured in a open glass capillary and are uncorrected **.**IR spectra in KBr were recorded on instrument Perkin Elmer - Spectrum RX-IFTIR. ^{1}H-NMR spectra were recorded on FT NMR Spectrometer model Advance-II (Bruker) Its ^{1}H frequency is 400 MHz. ^{13}C the frequency is 100 MHz. ($CDCl_3$ and DMSO-d_6) using TMS as an internal standard All reactions were monitored by TLC using silica gel 60-f-254plates. All reactions were carried out in scientific microwave oven (Scientific microwave system model RG31lL1,700w, 2450MHz).satisfactory C,H,N analysis were carried out for most of the compounds on Thermo Scientific (FLASH 2000) CHN Elemental Analyzer at RSIC, Punjab university, Chandigarh

Synthesis Of 2,7-(Substituted Phenyl)- -3-Phenyl-5,7,7a-Trihydro-2h-Thiazolo [4,5-D] [1,3] Thiazin-5-Amine(Va-h)

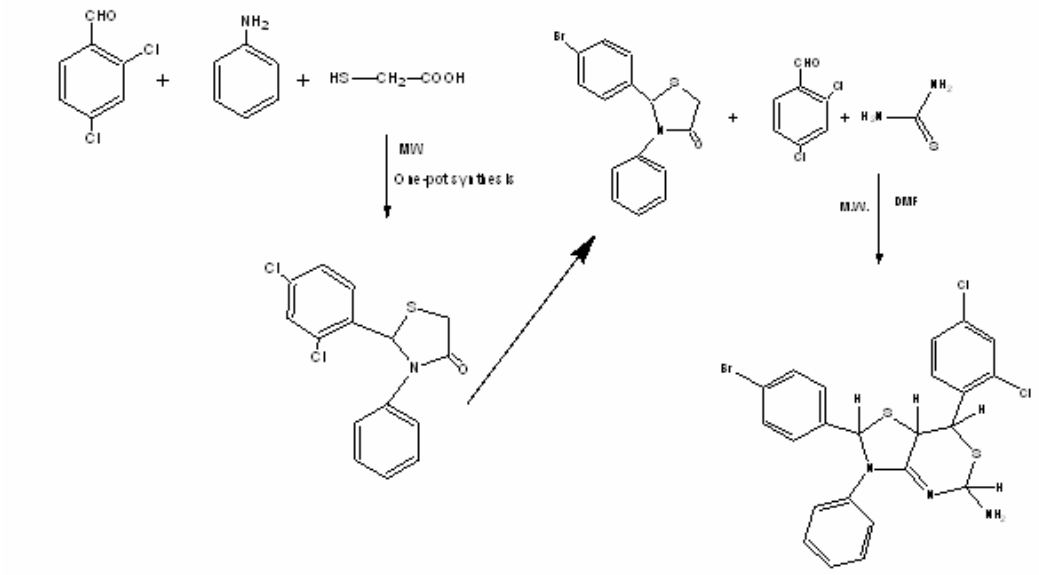
The reaction is completed in following two steps.

1)**Synthesis of 2-(substituted phenyl)-3-phenylthiazolidin-4-one(IVa-IVh)**-:A neat rection technology for one pot synthesis of the starting material 2-(substituted phenyl)-3-phenylthiazolidin)-4-one by condensation of aromatic aldehyde(0.01M), aniline(0.01M), and thioglycolic acid(0.01M). carried out under scientific microwave oven. The irradiation time is 1-1.5 min. The reaction mixture was cooled at room temperature and poured in ice-cold water. The product thus separated out was filtered and crystallized from ethanol to get fine crystals of 2-(substituted phenyl)-3-phenylthiazolidin-4-one . (IVa-IVh).

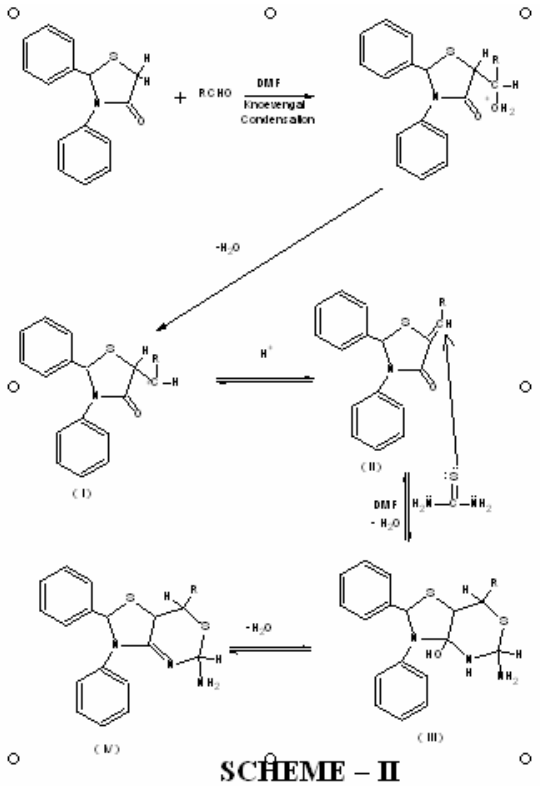
II) Synthesis of 2,7-(substituted phenyl)-3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(Va-Vh)-: The synthesis of Novel 2,7-(substituted phenyl)- -3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5-amine(Va-Vh) by condensation of 2-(substituted phenyl)-3-phenyl thiazolidin-4-one.(0.01M) (IVa-IVh) with excess of aromatic aldehyde and thiourea dissolved in polar solvent under microwave mode (1.5 min) followed by filtration, washing with water and recrystallize from ethanol to get the product

Mechanism

Thiazolidione are the potential synthons in the synthesis of heterocyclic compounds. It is noteworthy that the reactivity of thiazolidione is due to inductive effect of carbonyl group. Thiourea is a weak base ,the reason is that the lone pair of electrons on nitrogen are removed in the formation of ∏- molecular orbital. In this mechanism the first step concern with Knoevengel condensation of thiozalidione and aldehyde through carbonium ion intermediate in situ results in the formation of α-β unsaturated ketone and second step involve nucleophilic addition of thiourea followed by cyclodehydration to lead target molecule.



SCHEME – I Experimental scheme for the synthesis of2,7-(substituted phenyl)-3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(Va-Vh) (IVa-h)



SCHEME – II

Table I: Physical data of of2,7-(substituted phenyl)-3-phenyl-5,7,7a-trihydro -2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(Va-Vh

Compound (Va-Vh)	R	R_1	R_2	*Molecular Formula*	*Melting Point*
a	$-C_6H_5$	$-C_6H_4Cl$	$C_6H_3Cl_2$	$C_{23}H_{18}Cl_3N_3S_2$	265^0C
b	$-C_6H_5$	$-C_6H_4OH$	C_6H_4Br	$C_{23}H_{20}BrN_3OS_2$	270^0C
c	$-C_6H_5$	$-C_6H_4Br$	$C_6H_3Cl_2$	$C_{23}H_{18}BrCl_2N_3S_2$	284^0C
d	$-C_6H_5$	$-C_6H_4$-OCH_3	C_6H_4Br	$C_{24}H_{22}BrN_3OS_2$	264^0C
e	$-C_6H_5$	$-C_6H_4Cl$	$-C_6H_5$	$C_{23}H_{20}ClN_3S_2$	274^0C
f	$-C_6H_5$	$-C_6H_5$	$-C_6H_3Cl_2$	$C_{23}H_{19}Cl_2N_3S_2$	283^0C
g	$-C_6H_5$	$-C_6H_4Br$	$-C_6H_5$	$C_{23}H_{20}BrN_3S_2$	254^0C
h	-C6H5	$-C_6H_5$	$-C_6H_5$	$C_{23}H_{21}N_3S_2$	263^0C

Spectral data

1)2-(4-bromophenyl)- 7-(2,4-dichlorphenyl)3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(V c)

M.wt:-551.35 gm, M.P:-284^0**C,** brownish crystalline solid **IR(cm-1):** 3303(-NH_2) ,3058[C-H st (aromatic)], 2900[C-Hst (aliphatic)], 1693(C=N), 1618 (N-H bend), 1597 [C=C], 1490 [C-N], 1100 [C-Cl(aryl halide)], 692[N-H wagging] ;^{1}**HNMR:**-400 MHz (CDCl3): 3.3[(s,1H,-CH(W-coupling)],3.5(d,2H,NH2) ,3.6[(S,1H, ,-CH(W-coupling)], 3.8(d,1H,-CH ,J^3-15.7Hz) ,3.9(d,1H,-CH ,J^3-15.7Hz)6.4-8.0(m,12H,Ar-H);^{13}CNMR-100 MHz. ($CDCl_3$ and DMSO-d_6) 63.48(C-N,62.79(-CH),32.71(CH)121.07(CNH2),127.97,170.36,130.97,131.35,126.47,137.17,147.7,125.46,128.22,121.37, 139.54,128.67,131.55,137.42,188.74(C=N) calculated %C= 50.10 %N=7.62 %S =11.63 % Br=14.49 % Cl=3.29 % H= 12.86 observed %C= 50.02 %N= 7.12 %S =11.06 % Br= 14.11 % Cl =2.45 % H=12.21

2) **2-(methoxyphenyl)-7-(4-bromophenyl)3-phenyl-5,7,7a-trihydro-2H-thiazolo [4,5-d] [1,3] thiazin-5 –amine(V d)**

M.wt:-511.04 gm, M.P:-264^0**C,** brownish crystalline solid **IR(cm-1):** 3400(-NH assym) ,3258 (NH sym),3058[C-H st (aromatic)], 2940[C-Hst (aliphatic)], 1723(C=N), 1600 (N-H bend), 1625 [C=C], 1444 [C-N], 1067 [C-Br(aryl halide)], 960[N-H wagging] ;^{1}**HNMR:**-400 MHz (CDCl3): 1.28(s,3H,OCH_3), 3.6[(s,1H,-CH(W-coupling)],3.37(Br,2H,NH2) ,3.7[(d,1H, ,-CH(W-coupling)], 4.2(d,1H,-CH ,J^3-7.2Hz) ,4.3(d,1H,-CH ,J^3-7.2Hz),7.0-7.7(m,12H,Ar-H);^{13}CNMR-100 MHz.($CDCl_3$and$DMSOd_6$)63.22(CN),61.29(OCH3),43.14(CH)113.86(CNH2),13.8(CH) ,130.18,128.62,131.99,159.16,138.74,119.23,128.75,123.34,138.83,131.46,131.65,123.52(Ar-CH),167.03(C=N) calculated %C= 56.25 %N=8.20 %S =12.51 % Br=15.59 % O=3.12 % H= 4.33 observed %C= 56.12 %N= 7.98 %S =12.01 % Br= 15.21 % O =2.94 % H=4.33

Antifungal Activity-: All the synthesized compounds were screened for their antifungal activity viz. *fusarium oxysporum*, *Rhizoctonia solani* by using disc diffusion method for their antifungal activity.The punch discs of 6.25 mm diameter of Whatman filter paper no. 1 were prepared and dispensed in the batches of 100 each in screw capped bottles. These were sterilized by dry heat at 140^0C for 60 minutes. The solutions of 1000 ppm and 100 ppm concentrations of test compounds were prepared in dimethyl formamide (DMF) solvent separately. The discs were soaked, assuming that each disc will contain approximately 0.01 ml of test solution

Table 2 - In vitro antifungal screening of above tested compounds

Sr.No.	Tested Compounds	Fungus (zone of inhibition in mm)			
		Fusarium oxysporum		*Rhizoctonia solani*	
		100 ppm	1000 ppm	100ppm	1000ppm
1	Va	6	7	-	12
2	Vb	15	17	14	18
3	**Vc**	**32**	**34**	**31**	**34**
4	Vd	26	28	18	20
5	Ve	20	21	16	18
6	Vf	11	12	9	11
7	Vg	17	18	21	26
8	Vh	9	13	8	10

The observations show that activity of compound Vc is maximum against both the fungi . Almost all the compounds were active against all the test pathogens. The compound 5c is the most dominant among all the test compounds. Their inhibitory impact on the bacterial growth is remarkable.

Conclusion

This was an attempt to synthesize biologically potential heterocyclic moiety in solvent free reaction condition that leads to considerable saving in the reaction time and energetically profiTable. The solvent free condition contributes to saving in cost, time and diminishes the waste disposal problem and environmental pollution this work may bring research fraternity towards sustainable development.

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antimycobacterial activity and in silico study of highly functionalised dispiropyrrolidines

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Abstract Two series of novel and highly functionalised dispiropyrrolidines were synthesized using 1,3-dipolar cycloaddition reaction. The synthesized compounds were screened for their antimycobacterial activity against *M. tuberculosis* H_{37}Rv using the Promega reagent BacTiter-Glo™ Microbial Cell Viability (BTG). Molecular docking analysis was carried out for the active compounds against the target enzyme enoyl-ACP reductase (InhA) to understand the possible binding mode. Of the 24 novel synthesized compounds, seven dispiropyrrolidines revealed inhibition with EC_{50} <25 μM. Compound **5b** 7′-(4-chlorophenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-*c*]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione was found to be the most active with EC_{50} of 10.52 μM, and was 2.2-fold more active than cycloserine. The docking result revealed that **5b** had good affinity with the catalytic residues in InhA, forming hydrophobic and mild polar interactions with the important amino acids in the active site.

Keywords Dispiropyrrolidines · 1,3-Dipolar cycloaddition · Antimycobacterial · Enoyl-ACP-reductase · Molecular docking

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Introduction

Tuberculosis (TB) is an airborne disease caused by various strains of mycobacterium, typically *Mycobacterium tuberculosis*. According to the World Health Organization, one-third of the world's population harbors a latent form of TB which is asymptomatic and 10 % of those infected people will develop active TB in their lifetime (Introduction 2008). Despite half of a century of anti-TB chemotherapy, TB still remains the leading infectious disease, especially in the third world countries (Zhang, 2005; Lawn and Zumla, 2011). In 2012, the total number of TB cases worldwide was approximately 8.6 million, causing 1.3 million deaths. India and China alone had accounted for 26 and 12 % of the global burden, respectively (WHO, 2013). The pandemic of AIDS and the emergence of drug-resistant strains in recent years have further complicated this situation (Chiang *et al.,* 2010; Pawlowski *et al.,* 2012). Therefore, it is of utmost importance to discover a new drug candidate to combat this disease.

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The current front line TB treatment regimen relies mostly on isoniazid (INH), one of the most effective anti-TB agents that was discovered in 1950s (Mitchison, 2000). INH is a prodrug that requires activation step by KatG, the mycobacterial catalase-peroxidase enzyme, to form a tight INH-NAD covalent adduct (Zhang *et al.,* 1992; Timmins and Deretic, 2006). This active adduct inhibits the biosynthesis of mycolic acids by targeting InhA, the enoyl acyl carrier protein (ACP) reductase in type II fatty acid biosynthesis pathway (Banerjee *et al.,* 1994). Recent studies on drug-resistant strains suggest that the predominant mechanism of INH resistance arises from the mutations in KatG (Musser *et al.,* 1996; Cade *et al.,* 2010). Therefore, compounds that can inhibit the ultimate target of INH by by-passing the KatG activation would have great potential for combating ING-resistant as well as other drug-resistant TB (Kuo *et al.,* 2003).

Pyrrolidines have drawn considerable attention lately due to their highly pronounced biological activities (Crooks and Rosenberg, 1978; Bellina and Rossi, 2006; Stylianakis *et al.,* 2003). They make the central skeleton of many natural products, such as Tryprostatin A, (Usui *et al.,* 1998), elacomine (Pellegrini *et al.,* 1996), and broussonetine H (Brimble *et al.,* 2003). Construction of the substituted pyrrolidines with spiro moiety was achieved through 1,3-dipolar cycloaddition. This reaction, also known as the Huisgen cycloaddition, is a classical method to build various highly substituted five-membered heterocycles (Tsuge and Kanemasa, 1989). Our previous studies have utilized the chemistry of this cycloaddition between azomethine ylides with cyclic ketones to form different series of dispiropyrrolidines (Wei *et al.,* 2012b, 2013). Since the previous results shown promising antimycobacterial activity, herein our group further investigated the potential of a new series of dispiropyrrolidines using in vitro and in silico studies.

Materials and methods

Chemistry

All the chemicals and reagents were purchased from Sigma-Aldrich Chemical Co. and E.Merck (Germany). Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). ^{1}H and ^{13}C NMR were performed on Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer in $CDCl_3$, using TMS as internal standard. Mass spectra were recorded on Varian 320-MS TQ LC/MS using ESI. Elemental analyses were performed on Perkin Elmer 2400 Series II CHN Elemental Analyzer. X-ray structural analysis was carried out using *Bruker* SMART APEXII CCD area-detector diffractometer.

General procedure for synthesis of 2-[(*E*)-1-(substituted aryl) methylidene]-1-indanone

An equimolar mixture of 1-indanone and various aromatic aldehydes was dissolved in ethanol (10 mL), and 30 % of sodium hydroxide solution (5 mL) was added and stirred at room temperature for 4 h. The mixture was then poured into crushed ice and neutralized with concentrated HCl. The precipitated solid was filtered, washed with water, and re-crystallized from methanol to reveal the titled compounds.

*Synthesis of substituted dispiropyrrolidine analogs (**5a–5j** and **6a–6j**)*

A mixture of substituted 2-[(*E*)-1-arylmethylidene]-1-indanone (0.001 mol), ninhydrin or acenaphthenequinone (0.001 mol), and thiazolidine-4-carboxylic acid (0.002 mol) (1:1:2) was dissolved in methanol (10 mL) and refluxed for 4–8 h. After completion of the reaction as evident from TLC, the mixture was poured into iced water (50 mL). The precipitated solid was filtered, washed with water, and purified by either recrystallization or silica gel column chromatography to give the desired products.

*7′-Phenyl-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo [1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5a**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.09 (d, 1H, $J = 18.5$ Hz, H-3″), 3.12 (t, $J = 5.5$ Hz, 1H, H-1′), 3.42 (t, $J = 9.5$ Hz, 1H, H-1′), 3.67 (d, $J = 7.0$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.08 (d, $J = 7.0$ Hz, 1H, H-3′), 4.51 (d, $J = 9.0$ Hz, 1H, H-7′), 4.70–4.74 (m, 1H, H-7a′), 7.09–8.02 (m, 13H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 30.9 (CH_2, C-3″), 36.3 (CH_2, C-1′), 50.9 (CH, C-7′), 51.8 (CH_2, C-2″), 71.5 (CH_2, C-3′), 73.2 (CH, C-7a′), 81.5 (C, C-5′), 122.5 (CH, Ar), 123.9 (CH, Ar), 126.1 (CH, Ar), 126.3 (CH, Ar), 126.4 (CH, Ar), 127.5 (CH, Ar), 128.8 (CH, Ar), 129.1 (CH, Ar), 129.2 (CH, Ar), 133.5 (CH, Ar), 133.6 (CH, Ar), 135.6 (CH, Ar), 135.7 (CH, Ar), 135.9 (C, Ar), 140.1 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 152.5 (C, Ar), 197.6 (C, C=O), 199.8 (C, C=O), 201.6 (C, C=O). ESI–MS: *m/z* 452 $(M+H)^+$. Anal. calcd. $C_{28}H_{21}NO_3S$: C, 74.48; H, 4.69; N, 3.10. Found: C, 74.49; H, 4.75; N, 3.06.

*7′-(4-Chlorophenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5b**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.07 (d, 1H, $J = 18.5$ Hz, H-3″), 3.11 (t, $J = 5.0$ Hz, 1H, H-1′), 3.41 (t, $J = 9.5$ Hz, 1H, H-1′), 3.65 (d, $J = 7.5$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.07 (d, $J = 7.5$ Hz, 1H, H-3′), 4.52

(d, $J = 9.0$ Hz, 1H, H-7′), 4.70–4.73 (m, 1H, H-7a′), 7.08–8.01 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 30.9 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.8 (CH, C-7′), 51.8 (C, C-2″), 71.5 (CH_2, C-3′), 73.1 (CH, C-7a′), 81.5 (C, C-5′), 122.5 (CH, Ar), 123.1 (CH, Ar), 123.5 (CH, Ar), 126.5 (CH, Ar), 127.5 (CH, Ar), 128.6 (CH, Ar), 128.8 (CH, Ar), 130.0 (CH, Ar), 130.0 (CH, Ar), 133.5 (CH, Ar), 133.7 (CH, Ar), 135.6 (C, Ar), 135.7 (CH, Ar), 135.7 (C, Ar), 136.7 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 152.5 (C, Ar), 197.6 (C, C=O), 199.8 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 486 $(M+H)^+$. Anal. calcd. $C_{28}H_{20}ClNO_3S$: C, 69.20; H, 4.15; N, 2.88. Found: C, 69.26; H, 4.20; N, 2.79.

*7′-(4-Bromophenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5c**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.06 (d, 1H, $J = 18.5$ Hz, H-3″), 3.11 (t, $J = 5.0$ Hz, 1H, H-1′), 3.42 (t, $J = 9.5$ Hz, 1H, H-1′), 3.60 (d, $J = 7.5$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.06 (d, $J = 7.5$ Hz, 1H, H-3′), 4.52 (d, $J = 9.5$ Hz, 1H, H-7′), 4.69–4.73 (m, 1H, H-7a′), 7.09–8.01 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 30.9 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.8 (CH, C-7′), 51.8 (C, C-2″), 71.6 (CH_2, C-3′), 76.8 (CH, C7a′), 81.5 (C, C-5′), 119.6 (C, Ar), 122.5 (CH, Ar), 126.5 (CH, Ar), 127.5 (CH, Ar), 128.6 (CH, Ar), 128.8 (CH, Ar), 130.3 (CH, Ar), 130.4 (CH, Ar), 130.4 (CH, Ar), 130.6 (CH, Ar), 133.5 (CH, Ar), 133.7 (CH, Ar), 135.7 (CH, Ar), 136.7 (C, Ar), 139.9 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 152.5 (C, Ar), 197.6 (C, C=O), 199.8 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 531 $(M+H)^+$. Anal. calcd. $C_{28}H_{20}BrNO_3S$: C, 63.40; H, 3.80; N, 2.64. Found: C, 63.31; H, 3.82; N, 2.60.

*7′-(4-Trifluoromethylphenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5d**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.05 (d, 1H, $J = 18.0$ Hz, H-3″), 3.12 (t, $J = 5.0$ Hz, 1H, H-1′), 3.42 (t, $J = 9.5$ Hz, 1H, H-1′), 3.60 (d, $J = 7.5$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.06 (d, $J = 7.5$ Hz, 1H, H-3′), 4.52 (d, $J = 9.5$ Hz, 1H, H-7′), 4.69–4.74 (m, 1H, H-7a′), 7.07–8.01 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 30.9 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.8 (CH, C-7′), 51.9 (C, C-2″), 71.5 (CH_2, C-3′), 76.8 (CH, C-7a′), 81.5 (C, C-5′), 122.5 (CH, Ar), 123.2 (CF_3, Ar), 123.7 (CH, Ar), 123.9 (CH, Ar), 125.1 (C, Ar), 126.5 (CH, Ar), 127.5 (CH, Ar), 127.6 (CH, Ar), 128.8 (CH, Ar), 129.1 (CH, Ar), 129.1 (CH, Ar), 133.5 (CH, Ar), 133.6 (CH, Ar), 135.7 (CH, Ar), 136.7 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 144.1 (C, Ar), 152.6 (C, Ar), 197.6 (C, C=O), 199.9 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 520 $(M+H)^+$. Anal. calcd. $C_{29}H_{20}F_3NO_3S$: C, 67.04; H, 3.88; N, 2.70. Found: C, 67.01; H, 3.82; N, 2.66.

*7′-(4-Trifluoromethoxylphenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5e**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.06 (d, 1H, $J = 17.9$ Hz, H-3″), 3.10 (t, $J = 5.2$ Hz, 1H, H-1′), 3.40 (t, $J = 9.8$ Hz, 1H, H-1′), 3.65 (d, $J = 7.6$ Hz, 1H, H-3′), 3.88 (d, $J = 17.5$ Hz, 1H, H-3″), 4.05 (d, $J = 7.6$ Hz, 1H, H-3′), 4.51 (d, $J = 9.0$ Hz, 1H, H-7′), 4.69–4.74 (m, 1H, H-7a′), 7.01–8.00 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 30.9 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.8 (CH, C-7′), 51.9 (C, C-2″), 71.5 (CH_2, C-3′), 76.8 (CH, C-7a′), 81.5 (C, C-5′), 114.2 (CH, Ar), 114.3 (CH, Ar), 122.1 (CH, Ar), 122.1 (CH, Ar), 122.5 (CH, Ar), 126.6 (CH, Ar), 127.5 (OCF_3, Ar), 128.9 (CH, Ar), 129.4 (CH, Ar), 129.5 (CH, Ar), 133.5 (CH, Ar), 133.6 (CH, Ar), 135.2 (C, Ar), 135.7 (CH, Ar), 136.5 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 146.1 (C, Ar), 152.5 (C, Ar), 197.6 (C, C=O), 199.9 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 536 $(M+H)^+$. Anal. calcd. $C_{29}H_{20}F_3NO_4S$: C, 65.04; H, 3.76; N, 2.62. Found: C, 65.07; H, 3.81; N, 2.60.

*7′-(3-Nitrophenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5f**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.07 (d, 1H, $J = 18.5$ Hz, H-3″), 3.11 (t, $J = 5.5$ Hz, 1H, H-1′), 3.41 (t, $J = 9.5$ Hz, 1H, H-1′), 3.65 (d, $J = 7.5$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.07 (d, $J = 7.5$ Hz, 1H, H-3′), 4.52 (d, $J = 9.0$ Hz, 1H, H-7′), 4.70–4.73 (m, 1H, H-7a′), 7.06–8.11 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 30.1 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.9 (CH, C-7′), 51.8 (C, C-2″), 71.5 (CH_2, C-3′), 76.5 (CH, C-7a′), 81.5 (C, C-5′), 117.9 (CH, Ar), 122.5 (CH, Ar), 122.6 (CH, Ar), 123.1 (CH, Ar), 123.2 (CH, Ar), 126.5 (CH, Ar), 127.5 (CH, Ar), 128.8 (CH, Ar), 133.5 (CH, Ar), 133.7 (CH, Ar), 135.7 (CH, Ar), 135.7 (CH, Ar), 136.2 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 141.5 (C, Ar), 146.7 (C, Ar), 152.5 (C, Ar), 197.6 (C, C=O), 199.8 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 497 $(M+H)^+$. Anal. calcd. $C_{28}H_{20}N_2O_5S$: C, 67.73; H, 4.06; N, 5.64. Found: C, 67.76; H, 4.10; N, 5.69.

*7′-(4-Methoxyphenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5g**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.07 (d, 1H, $J = 18.5$ Hz, H-3″), 3.11 (t, $J = 5.5$ Hz, 1H, H-1′), 3.41 (t, $J = 9.5$ Hz, 1H, H-1′), 3.65 (d, $J = 7.5$ Hz, 1H, H-3′), 3.69 (s, 3H, OCH_3), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.07 (d, $J = 7.5$ Hz, 1H, H-3′), 4.52 (d, $J = 9.0$ Hz, 1H, H-7′), 4.70–4.73 (m, 1H, H-7a′), 6.67–8.00 (m, 12H, aromatic); ^{13}C NMR ($CDCl_3$) δ_C: 30.9 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.9 (CH, C-7′), 51.9 (C, C-2″), 54.3 (CH_3, OCH_3), 71.8, (CH_2, C-3′), 73.4 (CH, C-7a′), 81.7 (C, C-5′), 112.2 (CH, Ar), 112.3 (CH, Ar), 122.5 (CH, Ar), 123.7 (CH, Ar), 126.4 (CH, Ar), 127.5 (CH, Ar), 128.9 (CH, Ar), 129.4 (CH, Ar), 129.4 (CH, Ar), 133.5 (CH, Ar), 133.7 (CH, Ar), 135.6 (C, Ar),

135.7 (CH, Ar), 136.0 (C, Ar), 140.4 (C, Ar), 140.7 (C, Ar), 152.5 (C, Ar), 156.7 (C, Ar), 197.6 (C, C=O), 199.8 (C, C=O) 201.5 (C, C=O). ESI–MS: *m/z* 482 $(M+H)^+$. Anal. calcd. $C_{29}H_{23}NO_4S$: C, 72.33; H, 4.81; N, 2.91. Found: C, 72.36; H, 4.81; N, 2.95.

*7′-(4-Benzo[d][1,3]dioxole)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5h**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.04–3.07 (m, 1H, H-1′), 3.09 (d, $J = 18.0$ Hz, 1H, H-3″), 3.43 (t, $J = 9.0$ Hz, 1H, H-1′), 3.67–3.71 (m, 2H, H-3′, H-3″), 4.07 (d, $J = 7.5$ Hz, 1H, H-3′), 4.53 (d, $J = 8.5$ Hz, 1H, H-7′), 4.79–4.84 (m, 1H, H-7a′), 5.95 (s, 2H, CH_2), 7.05–8.00 (m, 11H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 32.1 (CH_2, C-3″), 36.2 (CH_2, C-1′), 50.9 (CH, C-7′), 51.8 (C, C-2″), 71.2 (CH_2, C-3′), 73.6 (CH, C-7a′), 81.5 (C, C-5′), 101.4 (CH_2, OCH_2O), 109.3 (CH, Ar), 119.2 (CH, Ar), 121.2 (CH, Ar), 122.5 (CH, Ar), 123.0 (CH, Ar), 123.1 (CH, Ar), 126.5 (CH, Ar), 127.5 (CH, Ar), 134.9 (C, Ar), 135.2 (CH, Ar), 135.2 (CH, Ar), 135.7 (CH, Ar), 136.7 (C, Ar), 140.5 (C, Ar), 140.7 (C, Ar), 145.7 (C, Ar), 147.0 (C, Ar), 153.1 (C, Ar), 197.9 (C, C=O), 199.2 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 496 $(M+H)^+$. Anal. calcd. $C_{29}H_{21}NO_5S$: C, 70.29; H, 4.27; N, 2.83. Found: C, 70.41; H, 4.31; N, 2.85.

*7′-(4-(Dimethylamino)phenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5i**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.90 (s, 6H), 3.07 (d, 1H, $J = 18.0$ Hz, H-3″), 3.09 (t, $J = 5.5$ Hz, 1H, H-1′), 3.43 (t, $J = 9.5$ Hz, 1H, H-1′), 3.67 (d, $J = 7.5$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3″), 4.07 (d, $J = 7.5$ Hz, 1H, H-3′), 4.53 (d, $J = 8.5$ Hz, 1H, H-7′), 4.84–4.90 (m, 1H, H-7a′), 6.62–8.19 (m, 12H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.9 (CH_2, C-3″), 36.2 (CH_2, C-1′), 40.2 (CH_3, $N(CH_3)_2$), 40.4 (CH_3, $N(CH_3)_2$), 50.9 (CH, C-7′), 51.8 (C, C-2″), 71.2 (CH_2, C-3′), 73.1 (CH, C-7a′), 81.5 (C, C-5′), 111.9 (CH, Ar), 112.1 (CH, Ar), 123.0 (CH, Ar), 123.4 (CH, Ar), 123.6 (CH, Ar), 126.5 (CH, Ar), 127.5 (CH, Ar), 130.2 (CH, Ar), 130.3 (CH, Ar), 131.2 (C, Ar), 135.4 (CH, Ar), 135.5 (CH, Ar), 135.7 (CH, Ar), 136.7 (C, Ar), 140.5 (C, Ar), 140.7 (C, Ar), 147.5 (C, Ar), 152.9 (C, Ar), 197.9 (C, C=O), 199.7 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 495 $(M+H)^+$. Anal. calcd. $C_{30}H_{26}N_2O_3S$: C, 72.85; H, 5.30; N, 5.66. Found: C, 72.97; H, 5.31; N, 5.65.

*7′-(4-(Morpholine-1-yl)phenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5j**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.05 (d, 1H, $J = 17.5$ Hz, H-3″), 3.10 (t, $J = 5.5$ Hz, 1H, H-1′), 3.12 (t, $J = 9.0$ Hz, 4H, CH_2), 3.43 (t, $J = 9.5$ Hz, 1H, H-1′), 3.67 (d, $J = 7.5$ Hz, 1H, H-3′), 3.87 (t, $J = 9.0$ Hz, 4H, CH_2), 3.90 (d, $J = 17.5$ Hz, 1H, H-3″), 4.07 (d, $J = 7.5$ Hz, 1H, H-3′), 4.53 (d, $J = 8.5$ Hz, 1H, H-7′), 4.79–4.82 (m, 1H, H-7a′), 6.69–8.19 (m, 12H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.9 (CH_2, C-3″), 36.3 (CH_2, C-1′), 49.2 (CH_2, NCH_2), 49.3 (CH_2, NCH_2), 50.9 (CH, C-7′), 51.8 (C, C-2″), 69.5 (CH_2, OCH_2), 69.5 (CH_2, OCH_2), 71.2 (CH_2, C-3′), 73.1 (CH, C-7a′), 81.5 (C, C-5′), 116.7 (CH, Ar), 116.9 (CH, Ar), 123.0 (CH, Ar), 123.5 (CH, Ar), 124.1 (CH, Ar), 126.1 (CH, Ar), 127.0 (CH, Ar), 130.0 (CH, Ar), 130.1 (CH, Ar), 131.2 (C, Ar), 135.4 (CH, Ar), 135.5 (CH, Ar), 135.7 (CH, Ar), 136.7 (C, Ar), 140.6 (C, Ar), 140.7 (C, Ar), 146.1 (C, Ar), 152.9 (C, Ar), 197.9 (C, C=O), 199.7 (C, C=O), 201.5 (C, C=O). ESI–MS: *m/z* 537 $(M+H)^+$. Anal. calcd. $C_{32}H_{28}N_2O_4S$: C, 71.62; H, 5.26; N, 5.22. Found: C, 71.70; H, 5.31; N, 5.25.

*7′-(2,5-Dimethoxylphenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5k**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.04–3.07 (m, 1H, H-1′), 3.21 (d, $J = 17.5$ Hz, 1H, H-3″), 3.38 (s, 3H, OCH_3), 3.45 (t, $J = 9.5$ Hz, 1H, H-1′), 3.64–3.70 (m, 2H, H-3′), 3.70 (s, 3H, OCH_3), 4.08 (d, $J = 7.5$ Hz, 1H, H-3″), 4.69 (d, $J = 8.5$ Hz, 1H, H-7′), 4.81–4.86 (m, 1H, H-7a′), 7.00–8.13 (m, 11H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 32.1 (CH_2, C-3″), 36.6 (CH_2, C-1′), 49.4 (CH, C-7′), 50.9 (C, C-2″), 54.5 (CH_3, OCH_3), 55.8 (CH_3, OCH_3), 71.5 (CH_2, C-3′), 73.0 (CH, C-7a′), 80.2 (C, C-5′), 110.1 (CH, Ar), 112.5 (CH, Ar), 115.8 (CH, Ar), 122.9 (CH, Ar), 123.0 (CH, Ar), 123.0 (CH, Ar), 124.2 (CH, Ar), 125.9 (C, Ar), 126.8 (CH, Ar), 134.8 (CH, Ar), 135.2 (CH, Ar), 135.9 (CH, Ar), 136.8 (C, Ar), 140.5 (C, Ar), 142.6 (C, Ar), 151.5 (C, Ar), 152.0 (C, Ar), 153.1 (C, Ar), 197.9 (C, C=O), 199.0 (C, C=O), 200.9 (C, C=O). ESI–MS: *m/z* 512 $(M+H)^+$. Anal. calcd. $C_{30}H_{25}NO_5S$: C, 70.43; H, 4.93; N, 2.74. Found: C, 70.49; H, 5.01; N, 2.77.

*7′-(4-(Piperidin-1-yl)phenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-c]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione (**5l**)* ^{1}H NMR ($CDCl_3$): 1.52–1.63 (m, 6H, CH_2), 2.67 (t, $J = 9.0$ Hz, 4H, CH_2), 3.07 (d, 1H, $J = 18.5$ Hz, H-3″), 3.11 (t, $J = 5.0$ Hz, 1H, H-1′), 3.43 (t, $J = 9.0$ Hz, 1H, H-1′), 3.67 (d, $J = 7.5$ Hz, 1H, H-3′), 3.91 (d, $J = 17.5$ Hz, 1H, H-3′),4.03 (d, $J = 7.5$ Hz, 1H, H-3″), 4.51 (d, $J = 9.5$ Hz, 1H, H-7′), 4.69–4.73 (m, 1H, H-7a′), 7.08–8.01 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$) δ_C: 23.9 (CH_2), 24.4 (CH_2), 24.6 (CH_2), 32.1 (CH_2, C-3″), 36.7 (CH_2, C-1′), 49.3 (CH, C-7′), 50.4 (CH_2, NCH_2), 50.9 (CH_2, NCH_2), 52.9 (C, C-2″), 71.4 (CH_2, C-3′), 73.0 (CH, C-7a′), 80.3 (C, C-5′), 112.7 (CH, Ar), 112.8 (CH, Ar), 122.9 (CH, Ar), 123.0 (CH, Ar), 123.0 (CH, Ar), 124.3 (CH, Ar), 126.5 (CH, Ar), 128.4 (CH, Ar), 129.0 (CH, Ar), 130.7 (C, Ar), 134.1 (CH, Ar), 134.7 (CH, Ar), 135.4 (CH, Ar), 136.8 (C, Ar), 140.5 (C, Ar), 141.7 (C, Ar), 149.1 (C, Ar), 152.9 (C, Ar), 197.9 (C, C=O), 199.0 (C, C=O), 200.9 (C, C=O). ESI–MS: *m/z* 535 $(M+H)^+$. Anal. calcd. $C_{33}H_{30}N_2O_3S$:

C, 74.13; H, 5.66; N, 5.24. Found: C, 74.16; H, 5.72; N, 5.25.

*7′-Phenyl-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6a**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.91 (d, J = 16.5 Hz, 1H, H-3″), 3.13 (dd, J = 11.4, 3.0 Hz, 1H, H-1′), 3.34–3.37 (m, 1H, H-1′), 3.67 (d, J = 10.2 Hz, 1H, H-3′), 4.03 (d, J = 16.6 Hz, 1H, H-3″), 4.06 (d, J = 10.2 Hz, 1H, H-3′), 4.27 (d, J = 10.6 Hz, 1H, H-7′), 4.73–4.76 (m, 1H, H-7a′), 6.75–8.10 (m, 15H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 32.0 (CH_2, C-3″), 36.5 (CH_2, C-1′), 53.0 (CH, C-7′), 53.9 (CH_2, C-3′), 71.4 (CH, C-7a′), 71.9 (C, C-2″), 83.0 (C, C-5′), 120.9 (CH, Ar), 123.1 (CH, Ar), 125.1 (CH, Ar), 125.9 (CH, Ar), 126.3 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.6 (CH, Ar), 127.7 (CH, Ar), 127.9 (CH, Ar), 128.0 (CH, Ar), 128.2 (C, Ar), 128.4 (CH, Ar), 130.6 (CH, Ar), 131.5 (CH, Ar), 132.1 (C, Ar), 134.1 (C, Ar), 134.9 (CH, Ar), 136.7 (C, Ar), 137.9 (C, Ar), 142.0 (C, Ar), 151.2 (C, Ar), 202.4 (C, C=O), 204.3 (C, C=O). ESI–MS: *m/z* 474 $(M+H)^+$. Anal. calcd. $C_{31}H_{23}NO_2S$: C, 78.62; H, 4.90; N, 2.96. Found: C, 78.66; H, 4.89; N, 2.91.

*7′-(4-Chlorophenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6b**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.01 (d, J = 16.5 Hz, 1H, H-3″), 3.08 (dd, J = 11.4, 3.0 Hz, 1H, H-1′), 3.34–3.37 (m, 1H, H-1′), 3.67 (d, J = 10.2 Hz, 1H, H-3′), 4.03 (d, J = 16.6 Hz, 1H, H-3″), 4.06 (d, J = 10.2 Hz, 1H, H-3′), 4.27 (d, J = 10.6 Hz, 1H, H-7′), 4.73–4.76 (m, 1H, H-7a′), 6.84–8.12 (m, 14H, H–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): ^{13}C NMR ($CDCl_3$) δ_C: 31.9 (CH_2, C-3″), 36.1 (CH_2, C-1′), 52.1 (CH, C-7′), 53.9 (CH_2, C-3′), 71.4 (CH, C-7a′), 71.9 (C, C-2″), 83.0 (C, C-5′), 122.5 (CH, Ar), 123.0 (CH, Ar), 123.4 (CH, Ar), 123.5 (CH, Ar), 123.5 (CH, Ar), 123.9 (CH, Ar), 124.9 (CH, Ar), 126.2 (CH, Ar), 127.1 (CH, Ar), 127.7 (CH, Ar), 130.0 (CH, Ar), 130.1 (C, Ar), 130.6 (CH, Ar), 131.3 (CH, Ar), 132.7 (CH, Ar), 133.6 (C, Ar), 135.4 (C, Ar), 135.6 (C, Ar), 135.7 (C, Ar), 136.7 (C, Ar), 141.0 (C, Ar), 152.0 (C, Ar), 202.4 (C, C=O), 204.3 (C, C=O). ESI–MS: *m/z* 508 $(M+H)^+$. Anal. calcd. $C_{31}H_{22}ClNO_2S$: C, 73.29; H, 4.36; N, 2.76. Found: C, 73.26; H, 4.41; N, 2.72.

*7′-(4-Bromophenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6c**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.88 (d, J = 16.5 Hz, 1H, H-3″), 3.08 (dd, J = 11.5, 3.0 Hz, 1H, H-1′), 3.30–3.34 (m, 1H, H-1′), 3.67 (d, J = 9.9 Hz, 1H, H-3′), 4.00 (d, J = 16.7 Hz, 1H, H-3″), 4.05 (d, J = 10.0 Hz, 1H, H-3′), 4.28 (d, J = 10.5 Hz, 1H, H-7′), 4.88–4.90 (m, 1H, H-7a′), 6.79–8.30 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.5 (CH_2, C-3″), 36.2 (CH_2, C-1′), 52.6 (CH, C-7′), 53.6 (CH_2, C-3′), 70.9 (CH, C-7a′), 71.3 (C, C-2″), 82.7 (C, C-5′), 120.5 (CH, Ar), 121.5 (C, Ar), 122.8 (CH, Ar), 123.4 (CH, Ar), 123.9 (C, Ar), 125.7 (CH, Ar), 125.7 (CH, Ar), 126.3 (CH, Ar), 127.3 (CH, Ar), 127.6 (CH, Ar), 128.2 (CH, Ar), 130.4 (C, Ar), 131.0 (CH, Ar), 131.2 (CH, Ar), 131.8 (CH, Ar), 131.9 (CH, Ar), 133.5 (C, Ar), 134.8 (CH, Ar), 135.3 (C, Ar), 136.1 (C, Ar), 140.5 (C, Ar), 151.2 (C, Ar), 202.1 (C, C=O), 204.2 (C, C=O). ESI–MS: *m/z* 553 $(M+H)^+$. Anal. calcd. $C_{31}H_{22}BrNO_2S$: C, 67.39; H, 4.01; N, 2.54. Found: C, 67.36; H, 4.05; N, 2.55.

*7′-(4-Trifluoromethylphenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6d**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.89 (d, 1H, J = 16.6 Hz, H-1′), 3.10 (dd, J = 11.4, 3.0 Hz, 1H, H-3″), 3.31–3.35 (m, 1H, H-1′), 3.67 (d, J = 10.0 Hz, 1H, H-3″), 4.00 (d, J = 16.6 Hz, 1H, H-3′), 4.06 (d, J = 10.0 Hz, 1H, H-3′), 4.33 (d, J = 10.6 Hz, 1H, H-7′), 4.87–4.95 (m, 1H, H-7a′), 7.01–8.30 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 32.0 (CH_2, C-3″), 36.5 (CH_2, C-1′), 53.2 (CH, C-7′), 53.9 (CH_2, C-3′), 71.4 (CH, C-7a′), 71.8 (C, C-2″), 82.7 (C, C-5′), 123.5 (CH, Ar), 123.7 (C, CF_3), 124.1 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 126.7 (CH, Ar), 127.1 (C, Ar), 127.7 (CH, Ar), 127.9 (CH, Ar), 128.1 (CH, Ar), 128.5 (CH, Ar), 128.6 (CH, Ar), 130.6 (C, Ar), 131.0 (C, Ar), 132.3 (CH, Ar), 133.5 (CH, Ar), 133.7 (CH, Ar), 133.9 (C, Ar), 135.4 (CH, Ar), 136.4 (C, Ar), 141.0 (C, Ar), 144.2 (C, Ar), 151.3 (C, Ar), 202.4 (C, C=O), 204.4 (C, C=O). ESI–MS: *m/z* 542 $(M+H)^+$. Anal. calcd. $C_{32}H_{22}F_3NO_2S$: C, 70.97; H, 4.09; N, 2.59. Found: C, 71.00; H, 4.10; N, 2.55.

*7′-(4-Trifluoromethoxyphenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6e**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.88 (d, 1H, J = 16.6 Hz, H-3″), 3.10 (dd, J = 11.4, 3.0 Hz, 1H, H-1′), 3.32–3.35 (m, 1H, H-1′), 3.67 (d, J = 10.0 Hz, 1H, H-3′), 4.00 (d, J = 16.6 Hz, 1H, H-3″), 4.06 (d, J = 10.0 Hz, 1H, H-3′), 4.32 (d, J = 10.4 Hz, 1H, H-7′), 4.87–4.95 (m, 1H, H-7a′), 6.79–8.30 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 32.1 (CH_2, C-3″), 36.6 (CH_2, C-1′), 53.2 (CH, C-7′), 53.9 (CH_2, C-3′), 71.4 (CH, C-7a′), 71.8 (C, C-2″), 82.5 (C, C-5′), 114.2 (CH, Ar). 114.3 (CH, Ar), 123.5 (CH, Ar), 124.1 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 126.7 (CH, Ar), 127.9 (CH, Ar), 127.9 (CH, Ar), 128.5 (CH, Ar), 128.9 (C, OCF_3), 129.4 (CH, Ar), 129.5 (CH, Ar), 130.6 (C, Ar), 131.0 (C, Ar), 132.3 (CH, Ar), 133.5 (C, Ar), 135.4 (C, Ar), 135.7 (CH, Ar), 136.4 (C, Ar), 141.0 (C, Ar), 146.7 (C, Ar), 151.2 (C, Ar), 202.4 (C, C=O), 204.4 (C, C=O). ESI–MS: *m/z* 558 $(M+H)^+$. Anal. calcd. $C_{32}H_{22}F_3NO_3S$: C, 68.93; H, 3.98; N, 2.51. Found: C, 68.91; H, 4.03; N, 2.53.

*7′-(3-Nitrophenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6f**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.83 (d, 1H, J = 16.8 Hz, H-1′), 3.11 (dd, J = 11.4, 3.3 Hz, 1H, H-3″), 3.34–3.40 (m, 1H, H-1′), 3.71 (d, J = 9.6 Hz, 1H, H-3″), 4.01–4.08 (m, 2H, H-3′), 4.43 (d, J = 10.5 Hz, 1H, H-7′), 4.96–5.02 (m, 1H, H-7a′), 6.82–8.31 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 32.1 (CH_2, C-3″), 36.5 (CH_2, C-1′), 53.1 (CH, C-7′), 53.8 (CH_2, C-3′), 71.4 (CH, C-7a′), 71.8 (C, C-2″), 82.8 (C, C-5′), 121.0 (CH, Ar), 123.0 (CH, Ar), 123.4 (CH, Ar), 124.6 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 126.7 (CH, Ar), 127.9 (CH, Ar), 128.0 (CH, Ar), 128.6 (CH, Ar), 130.1 (C, Ar), 130.8 (C, Ar), 131.3 (CH, Ar), 132.4 (CH, Ar), 133.6 (C, Ar), 135.3 (CH, Ar), 136.3 (C, Ar), 136.6 (C, Ar), 139.1 (CH, Ar), 141.0 (C, Ar), 148.8 (C, Ar), 151.2 (C, Ar), 202.4 (C, C=O), 204.4 (C, C=O). ESI–MS: *m/z* 519 $(M+H)^+$. Anal. calcd. $C_{31}H_{22}N_2O_4S$: C, 71.80; H, 4.28; N, 5.40. Found: C, 71.76; H, 4.32; N, 5.41.

*7′-(4-Methoxyphenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6g**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.03 (d, 1H, J = 16.8 Hz, H-1′), 3.11 (dd, J = 11.4, 3.3 Hz, 1H, H-3″), 3.34–3.36 (m, 1H, H-1′), 3.69 (s, 3H, OCH_3), 3.71 (d, J = 9.6 Hz, 1H, H-3″), 4.01–4.08 (m, 2H, H-3′), 4.26 (d, J = 10.5 Hz, 1H, H-7′), 4.86–4.93 (m, 1H, H-7a′), 6.82–8.31 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.9 (CH_2, C-3″), 36.6 (CH_2, C-1′), 51.9 (CH, C-7′), 54.0 (CH_2, C-3′), 55.1 (C, OCH_3) 71.1 (CH, C-7a′), 71.7 (C, C-2″), 83.0 (C, C-5′), 112.2 (CH, Ar), 112.6 (CH, Ar), 120.9 (CH, Ar), 123.0 (CH, Ar), 123.5 (CH, Ar), 125.7 (CH, Ar), 126.0 (CH, Ar), 126.4 (CH, Ar), 126.7 (CH, Ar), 127.9 (CH, Ar), 129.9 (CH, Ar), 130.1 (CH, Ar), 130.7 (CH, Ar), 131.0 (CH, Ar), 131.9 (C, Ar), 132.1 (C, Ar), 133.9 (C, Ar), 135.4 (C, Ar), 136.3 (C, Ar), 140.4 (C, Ar), 151.5 (C, Ar), 151.9 (C, Ar), 202.4 (C, C=O), 204.5 (C, C=O). ESI–MS: *m/z* 504 $(M+H)^+$. Anal. calcd. $C_{32}H_{25}NO_3S$: C, 76.32; H, 5.00; N, 2.78. Found: C, 76.21; H, 5.03; N, 2.79.

*7′-(4-Benzo[d][1,3]dioxole)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6h**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.04 (d, J = 16.8 Hz, 1H, H-3″), 3.13 (dd, J = 11.5, 2.8 Hz, 1H, H-1′), 3.32–3.35 (m, 1H, H-1′), 3.64 (d, J = 10.2 Hz, 1H, H-3′), 4.04 (d, J = 16.6 Hz, 1H, H-3″), 4.09 (d, J = 10.2 Hz, 1H, H-3′), 4.26 (d, J = 10.6 Hz, 1H, H-7′), 4.83–4.87 (m, 1H, H-7a′), 5.95 (s, 2H, CH_2), 6.80–8.29 (m, 13H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.9 (CH_2, C-3″), 36.6 (CH_2, C-1′), 52.6 (CH, C-7′), 54.1 (CH_2, C-3′), 71.4 (CH, C-7a′), 71.7 (C, C-2″), 83.1 (C, C-5′), 101.4 (CH_2, OCH_2O), 109.3 (CH, Ar), 119.2 (CH, Ar), 120.3 (CH, Ar), 121.0 (CH, Ar), 122.6 (CH, Ar), 123.4 (CH, Ar), 125.5 (CH, Ar), 125.9 (CH, Ar), 126.4 (CH, Ar), 128.1 (CH, Ar), 130.2 (CH, Ar), 130.3 (CH, Ar), 131.8 (C, Ar), 132.8 (CH, Ar), 133.7 (C, Ar), 134.5 (C, Ar), 134.9 (C, Ar), 136.3 (C, Ar), 140.4 (C, Ar), 145.7 (C, Ar), 147.0 (C, Ar), 151.8 (C, Ar), 202.4 (C, C=O), 204.5 (C, C=O). ESI–MS: *m/z* 518 $(M+H)^+$. Anal. calcd. $C_{32}H_{23}NO_4S$: C, 74.26; H, 4.48; N, 2.71. Found: C, 74.23; H, 4.53; N, 2.74.

*7′-(4-(Dimethylamino)phenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6i**)* ^{1}H NMR ($CDCl_3$) δ_H: 2.87 (s, 6H), 3.04 (d, J = 16.8 Hz, 1H, H-3″), 3.13 (dd, J = 11.5, 2.8 Hz, 1H, H-1′), 3.32–3.35 (m, 1H, H-1′), 3.64 (d, J = 10.2 Hz, 1H, H-3′), 4.04 (d, J = 16.6 Hz, 1H, H-3″), 4.09 (d, J = 10.2 Hz, 1H, H-3′), 4.26 (d, J = 10.6 Hz, 1H, H-7′), 4.87–4.91 (m, 1H, H-7a′), 6.60–8.36 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.3 (CH_2, C-3″) 36.6 (CH_2, C-1′), 40.1 (CH_3, $N(CH_3)_2$), 40.4 (CH_3, $N(CH_3)_2$), 52.6 (CH, C-7′), 54.1 (CH_2, C-3′), 71.1 (CH, C-7a′), 71.7 (C, C-2″), 83.1 (C, C-5′), 111.9 (CH, Ar), 112.4 (CH, Ar), 120.3 (CH, Ar), 122.6 (CH, Ar), 123.4 (CH, Ar), 125.5 (CH, Ar), 125.9 (CH, Ar), 126.4 (CH, Ar), 127.0 (CH, Ar), 127.4 (CH, Ar), 128.1 (CH, Ar), 130.2 (CH, Ar), 130.3 (CH, Ar), 131.1 (C, Ar), 131.8 (C, Ar), 132.8 (CH, Ar), 133.7 (C, Ar), 134.5 (C, Ar), 136.3 (C, Ar), 140.4 (C, Ar), 149.6 (C, Ar), 151.8 (C, Ar), 202.3 (C, C=O), 204.5 (C, C=O). ESI–MS: *m/z* 517 $(M+H)^+$. Anal. calcd. $C_{33}H_{28}N_2O_2S$: C, 76.72; H, 5.46; N, 5.42. Found: C, 76.66; H, 5.49; N, 5.41.

*7′-(4-(Morpholine-1-yl)phenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6j**)* ^{1}H NMR ($CDCl_3$) δ_H: 3.05 (d, 1H, J = 16.6 Hz, H-3″), 3.10 (dd, J = 11.5, 2.8 Hz, 1H, H-1′), 3.15 (t, J = 9.0 Hz, 4H, CH_2), 3.32–3.35 (m, 1H, H-1′), 3.67 (d, J = 10.5 Hz, 1H, H-3′), 3.87 (t, J = 9.0 Hz, 4H, CH_2), 4.01 (d, J = 16.6 Hz, 1H, H-3″), 4.07 (d, J = 10.0 Hz, 1H, H-3′), 4.26 (d, J = 10.6 Hz, 1H, H-7′), 4.82–4.90 (m, 1H, H-7a′), 6.69–8.21 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.6 (CH_2, C-3″), 36.9 (CH_2, C-1′), 49.7 (CH_2, NCH_2), 49.9 (CH_2, NCH_2), 53.1 (CH, C-7′), 54.4 (CH_2, C-3′), 69.4 (CH_2, OCH_2), 69.6 (CH_2, OCH_2), 71.2 (CH, C-7a′), 72.0 (C, C-2″), 82.9 (C, C-5′), 116.7 (CH, Ar), 116.9 (CH, Ar), 120.7 (CH, Ar), 123.1 (CH, Ar), 125.9 (CH, Ar), 126.3 (CH, Ar), 126.3 (CH, Ar), 126.7 (CH, Ar), 127.3 (CH, Ar), 127.4 (CH, Ar), 127.8 (CH, Ar), 128.5 (CH, Ar), 130.5 (CH, Ar), 130.7 (C, Ar), 131.5 (C, Ar), 132.2 (CH, Ar), 134.1 (C, Ar), 134.9 (C, Ar), 136.7 (C, Ar), 141.9 (C, Ar), 151.5 (C, Ar), 151.9 (C, Ar), 202.4 (C, C=O), 204.4 (C, C=O). ESI–MS: *m/z* 559 $(M+H)^+$. Anal. calcd. $C_{35}H_{30}N_2O_3S$: C, 75.24; H, 5.41; N, 5.01. Found: C, 75.35; H, 5.49; N, 4.97.

7′-(2,5-Dimethoxyphenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6k**) ^{1}H NMR ($CDCl_3$) δ_H: 3.04 (d, J = 16.6 Hz, 1H, H-3″), 3.12 (dd, J = 11.5, 2.8 Hz, 1H, H-1′), 3.33–3.35 (m, 1H, H-1′), 3.38 (s, 3H, OCH_3), 3.65 (d, J = 10.2 Hz, 1H, H-3′), 3.70 (s, 3H, OCH_3), 4.04 (d, J = 16.6 Hz, 1H, H-3″), 4.09 (d, J = 10.2 Hz, 1H, H-3′), 4.26 (d, J = 10.6 Hz, 1H, H-7′), 4.86–4.90 (m, 1H, H-7a′), 6.90–8.20 (m, 13H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 31.4 (CH_2, C-3″), 36.6 (CH_2, C-1′), 51.9 (CH, C-7′), 54.1 (CH_2, C-3′), 54.5 (CH_3, OCH_3), 55.8 (CH_3, OCH_3), 71.1 (CH, C-7a′), 71.7 (C, C-2″), 83.0 (C, C-5′), 110.2 (CH, Ar), 112.6 (CH, Ar), 115.8 (CH, Ar), 120.9 (CH, Ar), 123.0 (CH, Ar), 123.5 (CH, Ar), 125.7 (CH, Ar), 126.0 (CH, Ar), 126.4 (CH, Ar), 126.7 (CH, Ar), 127.9 (CH, Ar), 130.2 (CH, Ar), 130.7 (C, Ar), 131.0 (C, Ar), 131.9 (CH, Ar), 133.9 (C, Ar), 135.4 (C, Ar), 136.3 (C, Ar), 140.4 (C, Ar), 151.5 (C, Ar), 151.9 (C, Ar), 152.0 (C, Ar), 202.3 (C, C=O), 204.5 (C, C=O). ESI–MS: *m/z* 534 $(M+H)^+$. Anal. calcd. $C_{33}H_{27}NO_4S$: C, 74.27; H, 5.10; N, 2.62. Found: C, 74.16; H, 5.13; N, 2.61.

7′-(4-(Piperidin-1-yl)phenyl)-1′,3′,5′,6′,7′,7a′-hexahydrodispiro[acenaphthylene-1,5′-pyrrolo-[1,2-c]thiazole-6′,2″-indane]-2,1″(1H)-dione (**6l**) ^{1}H NMR ($CDCl_3$) δ_H: 1.54–1.66 (m, 6H, CH_2), 2.83–3.16 (m, 6H, H-3″), 3.32–3.39 (m, 1H, H-1′), 3.66 (d, J = 9.9 Hz, 1H, H-3″), 4.08–4.19 (m, 2H, H-3′), 4.28 (d, J = 10.5 Hz, 1H, H-7′), 4.88–4.93 (m, 1H, H-7a′), 6.79–8.38 (m, 14H, H–Ar); ^{13}C NMR ($CDCl_3$) δ_C: 23.9 (CH_2), 24.4 (CH_2), 24.6 (CH_2), 31.7 (CH_2, C-3″), 36.9 (CH_2, C-1′), 50.4 (CH_2, NCH_2), 50.9 (CH_2, NCH_2), 53.1 (CH, C-7′), 54.4 (CH_2, C-3′), 71.4 (CH, C-7a′), 72.0 (C, C-2″), 82.9 (C, C-5′), 116.4 (CH, Ar), 116.7 (CH, Ar), 120.7 (CH, Ar), 123.1 (CH, Ar), 125.9 (CH, Ar), 126.3 (CH, Ar), 126.3 (CH, Ar), 126.7 (CH, Ar), 127.3 (CH, Ar), 127.4 (CH, Ar), 127.8 (CH, Ar), 128.5 (CH, Ar), 130.5 (CH, Ar), 130.7 (C, Ar), 131.5 (C, Ar), 132.2 (CH, Ar), 134.1 (C, Ar), 134.9 (C, Ar), 136.7 (C, Ar), 141.9 (C, Ar), 151.5 (C, Ar), 152.1 (C, Ar), 202.4 (C, C=O), 204.4 (C, C=O). ESI–MS: *m/z* 557 $(M+H)^+$. Anal. calcd. $C_{36}H_{32}N_2O_2S$: C, 77.67; H, 5.79; N, 5.03. Found: C, 77.50; H, 5.83; N, 5.09.

Biological evaluation

All the synthesized compounds **5a**–**5l** and **6a**–**6l** were tested for their antimycobacterial activity in vitro against *M. tuberculosis* $H_{37}R_V$ (MTB-H_{37}Rv) using a modified high throughput screen assay (Collins and Franzblau, 1997), and the end-point detection was assessed by the Promega reagent BacTiter-Glo^{TM} Microbial Cell Viability (BTG). Compounds screened in dose response were tested in ten twofold dilutions from 100 μM to 0.195 μM. Three standard drugs (isoniazid, ethambutol, and cycloserine) were used as references for the assay. Concurrent with the activity screening, cytotoxicity test was also performed in VERO cells at concentrations of 62.5 μg/mL. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega CellTiter 96 nonradioactive cell proliferation assay.

Molecular docking studies

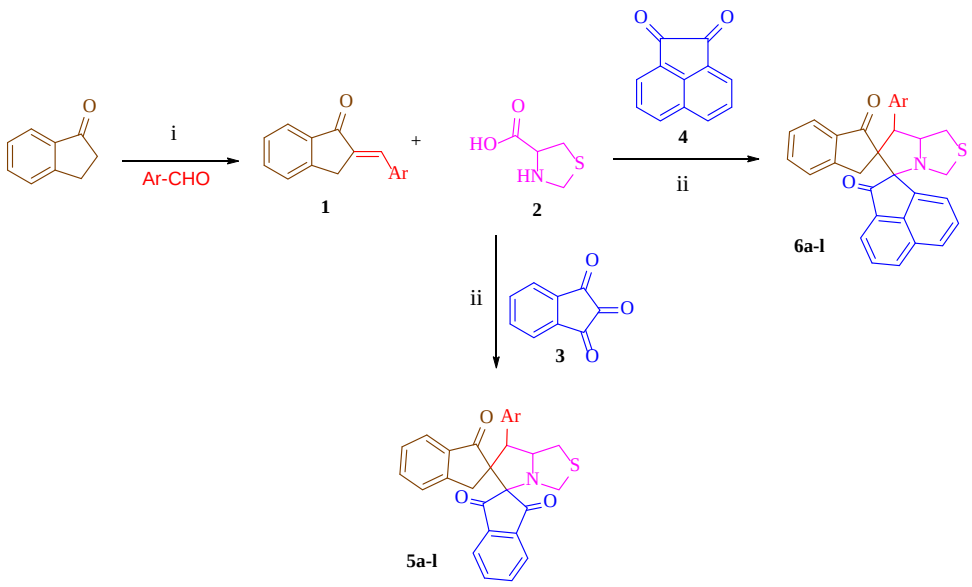
To investigate the binding interactions of the target compounds, docking studies were performed on the lead compound **5b** against *M. tuberculosis* enoyl reductase, InhA (PDB ID: 2H7M, Resolution = 1.62 Å). Two different programs, Autodock 4.2 and Glide 5.7 were used in order to identify the proper docking protocol. The receptor and drug candidates were structurally optimized prior to the actual docking simulation. Control dock of InhA was performed against the bounded ligand, and the root mean square deviation (RMSD) between the crystal geometry and the docked pose was investigated. Since Glide pose showed a lower rmsd value (rmsd = 0.228 Å) compared to Autodock (rmsd = 1.929 Å), Glide XP protocol was used for the rest of the studies to dock the target compounds.

Results and discussion

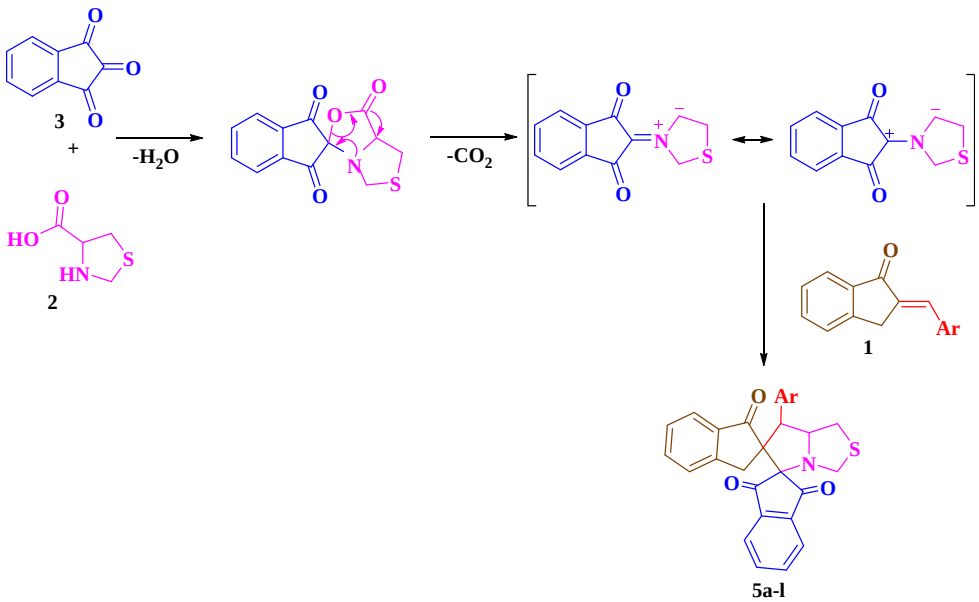
2-[(*E*)-1-(substituted aryl) methylidene]-1-indanones were synthesized by Claisen-Schmidt condensation according to the literature method (Ali *et al.,* 2009), followed by synthesis of dispiropyrrolidines via 1,3-dipolar cycloaddition of azomethine ylides generated in situ from the decarboxylative condensation of ninhydrin or acenaphthenequinone and thiazolidine-4-carboxylic acid with appropriate dipolarophiles, 2-[(*E*)-1-arylmethylidene]-1-indanones (Schemes 1, 2). Purity of the newly synthesized dispiropyrrolidines was checked using NMR, CHN, and mass spectrometry. All the analytical and spectral data showed that the synthesized compounds were in full agreement with the proposed structures. The regio and stereochemical outcome of the cycloaddition reaction of compounds **5a** (Wei *et al.,* 2011) was ascertained by single crystal X-ray analysis (Figs. 1, 2). The molecular structure was stabilized by the intramolecular C–H···O and C–H···N hydrogen bonds.

BacTiter-Glo^{TM} Microbial Cell Viability was used to screen the activity of the newly synthesized compounds. This method was based on the measurement of ATP content as an indicator of the metabolically active cells. The luminescence signal generated by luciferase reaction was proportional to the amount of viable cells present (Yuroff *et al.,* 2008). From the 24 new compounds, six of them showed better activity than cycloserine. Compound **5b** 7′-(4-chlorophenyl)-5′,6′,7′,7a′-tetrahydrodispiro[indan-2,5′-pyrrolo[1,2-*c*]-[1,3]thiazole-6′,2″-indan]-1,3,1″-trione was found to be the most active with EC_{50} of 10.52 μM.

Scheme 1 Protocol for synthesis of titled compounds **5a–5l** and **6a–6l**. (*i*) Ethanol, NaOH, reflux 4 h. (*ii*) Methanol, reflux 4–8 h



Scheme 2 Plausible mechanism for the formation of dispiropyrrolidine



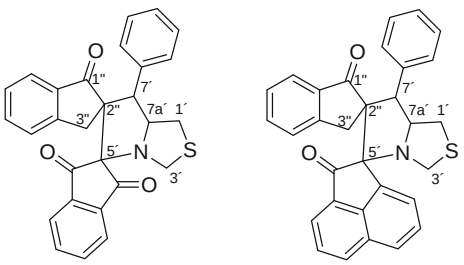


Fig. 1 Structure of compound **5a** and **6a** with atomic numbering

It was followed by compound **5e** (11.07 μM), **6e** (14.76 μM) and **5g** (18.37 μM) that showed EC_{50} of less than 20 μM. By comparing the compounds of two series **5** and **6**, derivatives with ninhydrin showed better activity than derivatives with acenaphthenequinone. Among the twelve compounds from series **5**, eleven showed EC_{50} of less than 100 μM, whereas for series **6**, only two out of twelve showed the similar inhibition. The biological evaluation results also showed that derivatives with electron-withdrawing groups have exhibited comparatively higher antimycobacterial activity. It is noted that the halogen substituent in the phenyl ring enhanced the activity remarkably. However, none of the screened compounds is more potent than ethambutol and isoniazid. Cytotoxicity test was also performed in VERO cells, and all of the compounds were found to be non-toxic up to 62.5 μg/mL. All the data are shown in Table 1.

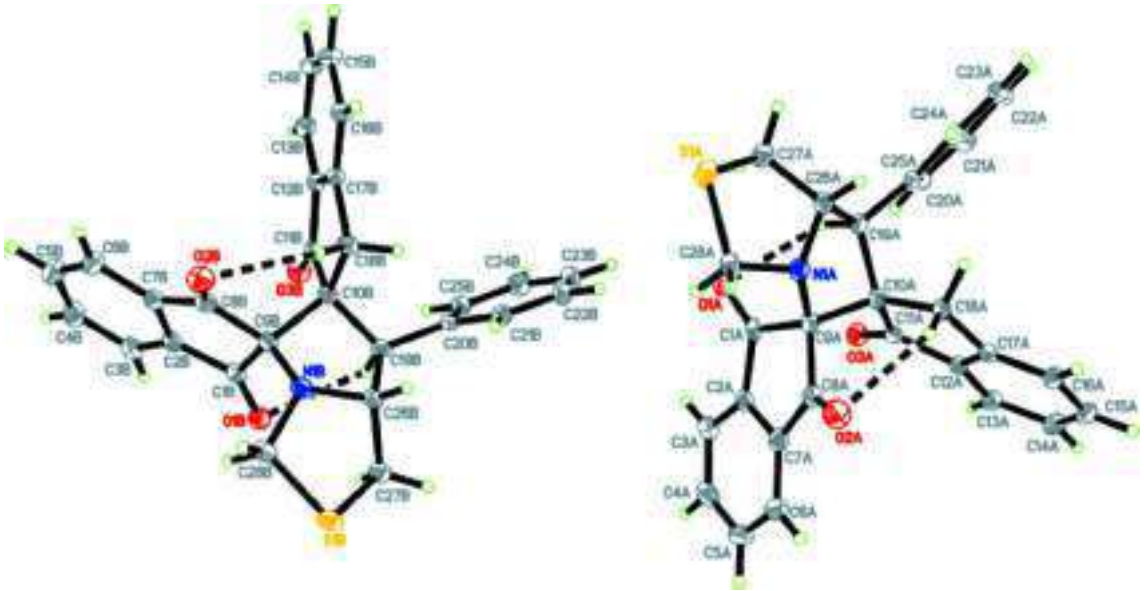


Fig. 2 ORTEP diagram of compound **5a** (from different views). Intramolecular hydrogen bonds are shown in *dashed lines*

Table 1 Antimycobacterial activity of pyrrolidine derivatives **5a–5l** and **6a–6l** against MTB-H_{37}Rv strains

Com	Ar	Entries 5			Entries 6		
		EC_{50} (μM) BTG	MIC (μM) BTG	Cytotoxicity VERO cells (μg/ml)	EC_{50} (μM) BTG	MIC (μM) BTG	Cytotoxicity VERO cells (μg/ml)
a	Phenyl	84.24	NA	>62.5	>100.00	NA	>62.5
b	4-Chlorophenyl	10.52	NA	>62.5	>100.00	NA	>62.5
c	4-Bromophenyl	30.15	NA	>62.5	>100.00	NA	>62.5
d	4-Trifluoromethylphenyl	21.14	NA	>62.5	81.71	NA	>62.5
e	4-Trifluoromethoxyphenyl	11.07	NA	>62.5	14.76	NA	>62.5
f	3-Nitrophenyl	>100.00	NA	>62.5	>100.00	NA	>62.5
g	4-Methoxyphenyl	18.37	NA	>62.5	>100.00	NA	>62.5
h	Benzo[*d*][1,3]dioxole	24.07	NA	>62.5	>100.00	NA	>62.5
i	4-Dimethylaminophenyl	n.d.	NA	>62.5	>100.00	NA	>62.5
j	1-(4-(Morpholine-1-yl)phenyl)	n.d.	NA	>62.5	>100.00	NA	>62.5
k	2,5-Dimethoxyphenyl	63.35	NA	>62.5	>100.00	NA	>62.5
l	1-(4-(Piperidine-1-yl)phenyl)	23.36	NA	>62.5	>100.00	NA	>62.5
	Cycloserine	23.55	100.00	>62.5			
	Ethambutol	1.50	6.25	>62.5			
	Isoniazid	0.18	0.31	>62.5			

Molecular docking analysis was performed to study the possible binding mode between the synthesized compounds and the target protein. The active pocket was determined based on the consideration where the native ligand, 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide was complexed with InhA in 2H7M. It consists of Gly 96, Phe 97, Met 98, Met 103, Phe 149, Met 155, Pro 156, Ala 157, Tyr 158, Met 161, Pro 193, Met 199, Gln 214, Ile 215, Leu 218, Glu 219, and Trp 222 (He *et al.,* 2006). The interaction analysis reveals that the native ligand and synthesized dispiropyrrolidines interact with receptor primarily by hydrophobic and mild polar interactions (He *et al.,* 2007).

From the docking results, compounds **5b** occupied essentially the same pocket as the native ligand (Figs. 3, 4), by retaining some of the interactions mentioned above such as hydrophobic and polar interaction. Besides, some additional interactions were found as well. The two oxygen

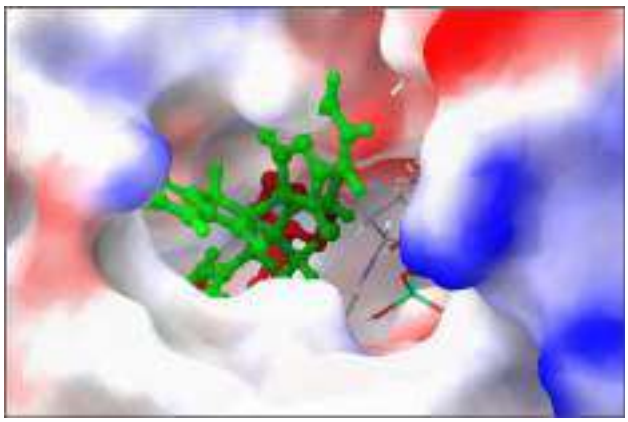


Fig. 3 Overlay of lead compound **5b** (*green*) with the bound ligand (*red*) in crystal geometry at the active site (PDB id: 2H7M) (Color figure online)

atoms of indandione of compound **5b** formed hydrogen bonding with catalytic residue Met 98 backbone amide "NH" (at distance of 1.922 Å) and phosphoryl group of cofactor NADH (at 2.362 Å), respectively. The phenyl moiety of indandione also formed π–π stacking with Phe 97 which further stabilized the conformation of compound **5b** in the active site. Most importantly, **5b** was found to be docked near the substrate-binding loop (residues 195–210) that covered the entrance of active site. It formed hydrophobic interactions with Ala 198, Ile 202, and Leu 207.

Conclusion

Twenty-four of highly functionalised dispiropyrrolidines were designed and synthesized using 1,3-dipolar cycloaddition. This reaction was proved to be highly efficient and selective, affording exclusively one stereoisomer (Wei *et al.*, 2011, 2012a). The synthesized compounds were screened for antimycobacterial activity, and cytotoxicity test was also performed using VERO cells. It is conceivable that derivatives showing more potency and low toxicity make them excellent leads as potential antitubercular agent.

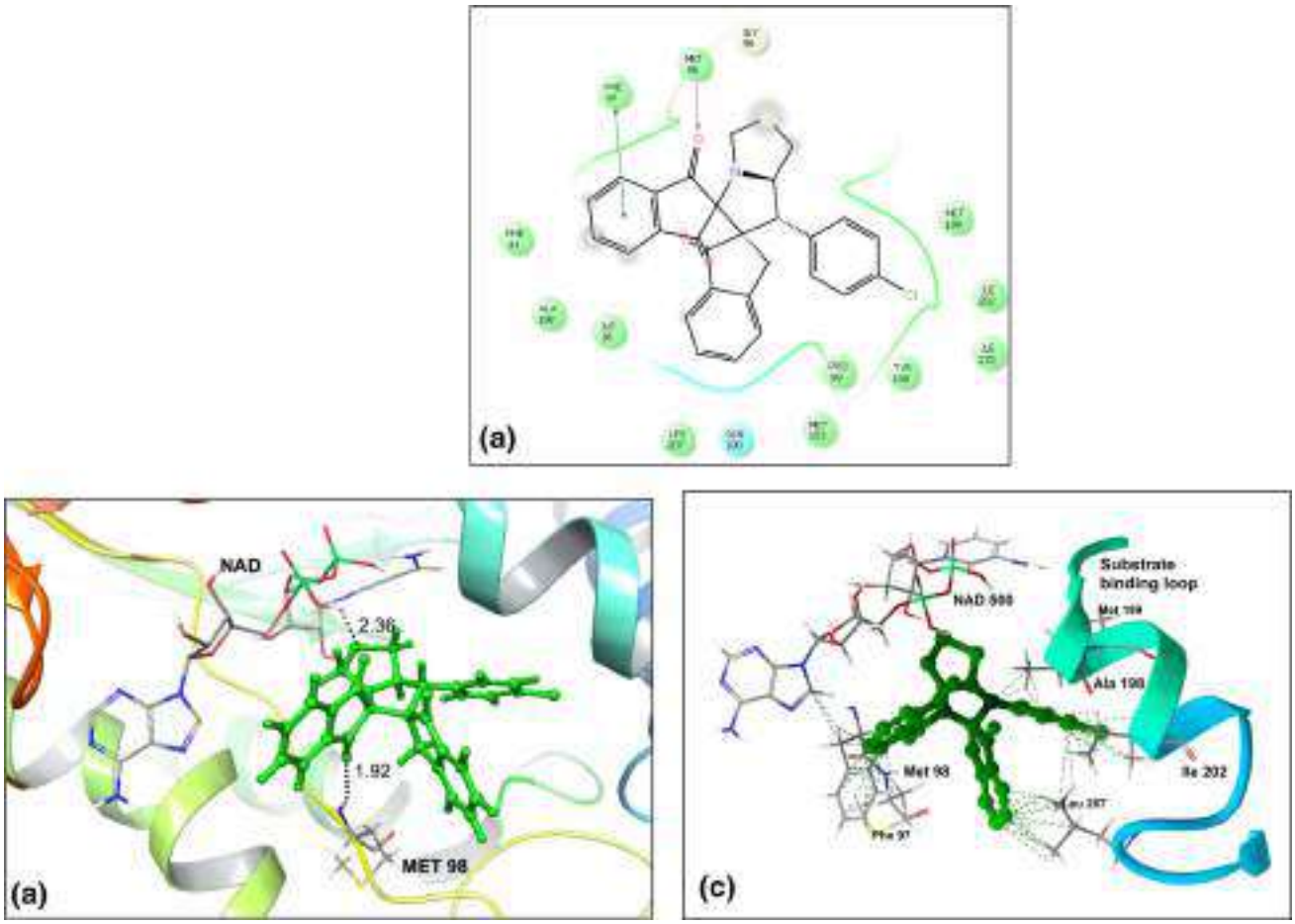


Fig. 4 **a** 2D interaction diagram of lead compound **5b** with the target protein InhA (*Green solid line* represents π–π stacking; *red line* represents hydrogen bonding). *Panel* **b** shows the hydrogen bonding between **5b** (in *green*, *ball* and *stick*) and Met 98 as well as NADH within the active site. *Panel* **c** represents the substrate-binding loop of InhA (in *blue* cartoon) and the hydrophobic contacts of **5b** with residues within 4 Å cut-off distance (Color figure online)

Molecular docking results reveal that the binding mode of the most active compound, **5b** is similar with pyrrolidine carboxamides, the known direct InhA inhibitor. It is encouraging to see that dispiropyrrolidines display potential as direct InhA inhibitor as it is docked near the substrate-binding loop. Further modification on the novel scaffolds is ongoing in our laboratory to exhibit better potency than standard drugs.

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Conflict of interest The authors confirm that this article content has no conflicts of interest.

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Effect of information leakage and method of splitting (rational and random) on external predictive ability and behavior of different statistical parameters of QSAR model

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Effect of information leakage and method of splitting (rational and random) on external predictive ability and behavior of different statistical parameters of QSAR model

Vijay H. Masand · Devidas T. Mahajan · Gulam M. Nazeruddin · Taibi Ben Hadda · Vesna Rastija · Ahmed M. Alfeefy

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Abstract Quantitative Structure–Activity Relationship not only provides guidelines regarding structural features responsible for biological activity but it can be used also for prediction of desired activity prior to synthesis of untested chemicals. Therefore, an appropriate validation of any QSAR is of utmost importance to judge its external predictive ability. Generally, internal and external validations (preferred by many) are used in the absence of a true external dataset. The model developed using external method may not be reliable as it may not capture all essential features required for the particular SAR due to omission of some compounds, especially for small datasets. In external validation, the splitting is done either rationally or in random manner before descriptor selection. In the present study, rational splitting of dataset was performed using a novel method and its effect on statistical parameters was analyzed. The analysis reveals that the predictive ability of a QSAR model is sensitive toward (1) the method of splitting and (2) distribution of the training and the prediction sets. In addition, purposeful selection can be used to influence the statistical parameters; therefore, external validation based on single split is insufficient to guarantee the true predictive ability of a QSAR model. Besides, it appears that the selection of descriptors prior to splitting (information leakage) has little role to play in deciding external predictivity of the model. The present study reveals that as many as possible statistical parameters should be examined along with boot-strapping instead of single external validation.

Keywords QSAR · External validation · Statistical parameters · Splitting methods · Predictivity

Electronic supplementary material The online version of this article (doi:10.1007/s00044-014-1193-8) contains supplementary material, which is available to authorized users.

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Introduction

Under the umbrella of modern drug designing, Computer Assisted Drug Designing (CADD) is the method of choice due to faster, cheaper, and result-oriented analysis (Kubinyi, 2002; Van Drie, 2007; Yuriev *et al*., 2011). Over the years, CADD has matured with the advent of new techniques, algorithms, and software programs. Quantitative Structure–Activity Relationship (QSAR), molecular docking, pharmacophore modeling, etc. are thriving techniques from the tenant of CADD. Of these, QSAR has gained much attention because of its applicability in risk assessment, toxicity prediction, and regulatory decisions apart from drug discovery and lead optimization. Further

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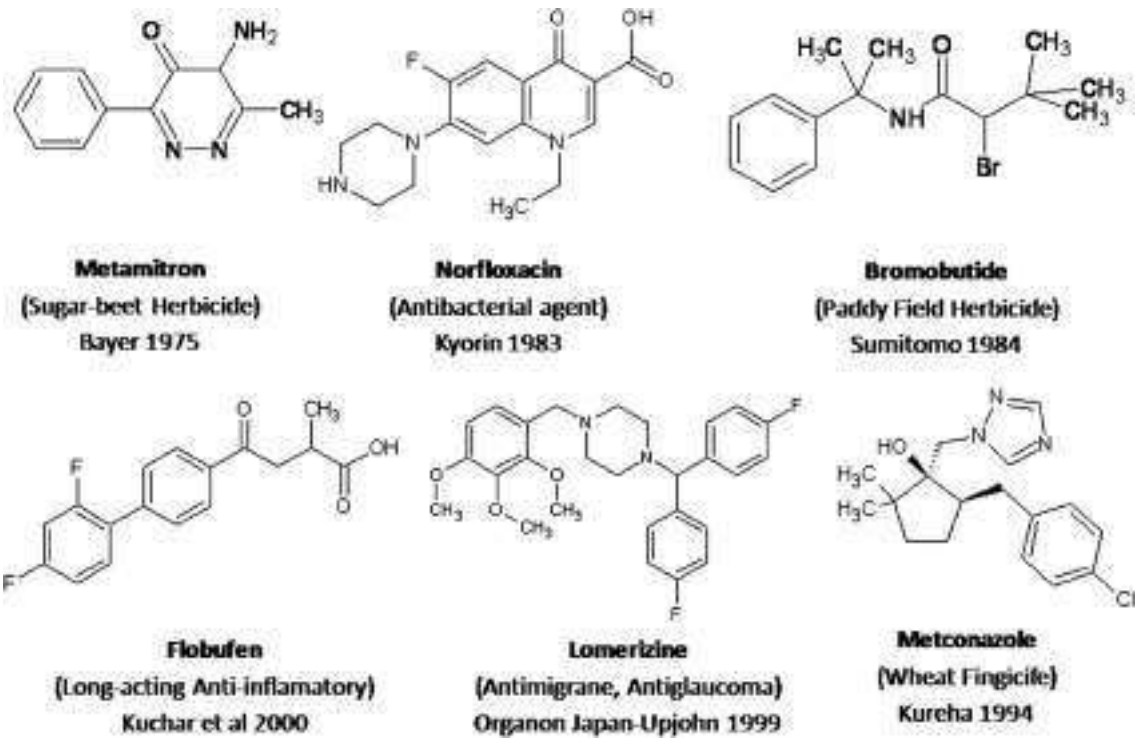


Fig. 1 Some of the commercial drugs developed with the aid of QSAR

application of QSAR models includes prediction of desired activity/property for a molecule before its synthesis and testing (Mahajan *et al*., 2012, 2013; Masand *et al*., 2012, 2010, 2013). In last decades, QSAR has contributed significantly in bringing many successful drugs in the market (see Fig. 1) (Selassie, 2003).

Therefore, QSAR models are routinely built to establish the statistical correlation between structural features (independent or predictor variables) that govern the biological activity or a physico-chemical property (dependent variable) (Scior *et al*., 2009). The four main steps involved in QSAR model building are (1) Structure drawing and geometry optimization, (2) calculation of myriad number of descriptors, (3) generation of model using least (optimal) number of descriptors, and (4) appropriate validation of mathematical model (Tropsha, 2010). The success of any QSAR model depends on various factors like accuracy of the experimental (input) data, selection of appropriate number and type of descriptors, statistical method (or algorithms), and most significantly on apposite validation of the developed model (see Fig. 2) (Huang and Fan, 2011). The utility of a QSAR model depends on its ability to predict accurately for unknown chemicals with some known degree of certainty (Roy *et al*., 2008). The prediction ability is a crucial aspect related to appropriate validation of the QSAR models. A QSAR model is considered appropriately statistically validated if it possesses good internal and external predictive ability, such models are successful in predicting the activity/property of unknown chemical (Scior *et al*., 2009; Tropsha, 2010).

Recently, appropriate validation of QSAR model is under hot debate. For thriving QSAR models, validation must be primarily for statistical robustness, prediction abilities, and applicability domain of the models (Sahigara *et al*., 2012, 2010). There are two standard ways of doing this (1) internal validation (2) external validation (Hawkins *et al*., 2003). These are performed in five different ways: leave-one-out cross-validation, leave-many-out cross-validation, Y-randomization, bootstrapping (least known among the five), and external validation (Hawkins *et al*., 2003; Kiralj and Ferreira, 2009).

The widely accepted parameter Q^2 (also symbolized as R^2_{cv}, r^2_{cv}, q^2, and Q^2_{LOO}) for internal validation is calculated by the formula (Consonni *et al*., 2010; Todeschini *et al*., 2004):

$$Q^2 = 1 - \frac{\sum_{i=1}^{n} (\hat{y}i - yi)^2}{\sum_{i=1}^{n} (yi - \bar{y})^2}.$$

Internal validation, a statistical method regularly performed using leave-one-out or by leave-many-out cross-validation, leads to an overestimation of predictive

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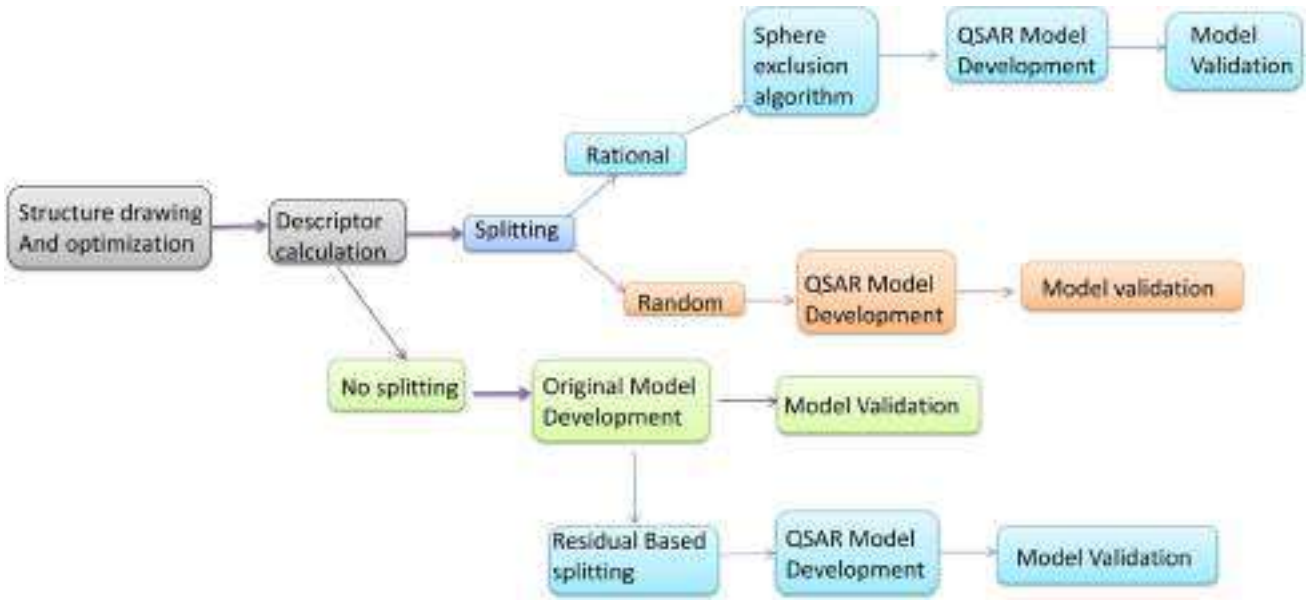


Fig. 2 Flowchart diagram for the methodology used in present study

capacity in many instances. But, it is useful for verification of robustness of the model. Therefore, internal validation may not be sufficient for validation, but it is essential (Consonni *et al*., 2010; Golbraikh and Tropsha, 2002; Gramatica, 2013; Tropsha, 2010). It is still useful, especially, when the dataset is small or of modest size (Hawkins *et al*., 2003).

On the other hand, external validation involves splitting the available data into training (or learning) and test (or prediction) sets. For external validation, selection of proper size of training and prediction sets is very crucial (Kiralj and Ferreira, 2009; Roy *et al*., 2008). Generally, this splitting is performed using random division, but purposeful or rational splitting for selection of compounds whose chemistry covers the whole (or maximum) population, but does not introduce any bias is a good idea (Hawkins *et al*., 2003). Rational or purposeful splitting methods can divide datasets into training and prediction sets in an intelligent fashion (Martin *et al*., 2012). Different algorithms like Kennard-Stone, minimal prediction set dissimilarity, and sphere exclusion algorithms have been developed for smarter way of dividing the datasets into training and prediction sets with the aim of producing more predictive models (Chirico and Gramatica, 2012; Consonni *et al*., 2010; Gramatica 2013; Huang and Fan 2011; Kiralj and Ferreira 2009; Martin *et al*., 2012; Scior *et al*., 2009). Even though, earlier studies have pointed out the superiority of rational division algorithms over the simple random splitting and activity sorting methods. Yet, appropriate selection of rational division method is still unclear because of the conflicting results (Huang and Fan 2011). Recent literature survey indicates that the method/algorithm of choice for splitting has little influence on the statistical performance of a QSAR model. Recently, Martin and co-workers reported the influence of rational selection of training and prediction sets on the model's predictivity (Martin *et al*., 2012). However, if the prediction set is small, unknowingly, the researcher may get a prediction set for which the developed model might show a high predictive ability (Baumann and Stiefl, 2004; Chirico and Gramatica, 2012; Consonni *et al*., 2009; Consonni *et al*., 2010; Hawkins, 2004; Huang and Fan, 2011; Martin *et al*., 2012; Scior *et al*., 2009; Todeschini *et al*., 2004; Tropsha, 2010).

The aim of the present study is to compare the statistical performance of different algorithms of rational selection, and to study the effect of descriptors selection prior to splitting (information leakage) on the external predictive ability of the model. In addition, the aim of the present study is to devise, evaluate, and compare a novel non-algorithmic method for rational splitting that influences the statistical parameters of QSAR model.

Experimental section

Datasets

For the present study, three datasets of varying size are used. The first dataset consists of forty-four N-Phenyl Ureidobenzenesulfonate Derivatives (N-PUSs) with wide variety of substituents present at different positions, as shown in Table 1, was selected from the literature (Turcotte *et al*., 2012). The activities of these compounds

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Table 1 Substituted N-Phenyl Ureidobenzenesulfonate derivatives along with $-\log IC_{50}$ (pIC_{50}) and descriptor values

S. no.	X	R_1	R_2	pIC_{50} (M) (HT-29)	F07 [C–N]	F05 [C–C]	Mor29e	Mor03m	RDF095v
1	O	4-OH	4-CEU	5.824	1	12	0.728	−3.81	1.503
2	O	2-Me	3-CEU	4.481	2	13	0.04	−5.025	5.266
3	O	2-CH_2-CH_3	3-CEU	5.367	2	14	0.283	−5.342	3.314
4	O	2-$(CH_2)_2$-CH_3	3-CEU	4.824	2	16	0.04	−4.293	5.093
5	O	4-OH	3-CEU	3.921	2	12	0.408	−4.627	4.138
6	O	2-CH_2-CH_3	4-CEU	4.770	1	14	0.246	−2.51	1.679
7	O	2-$(CH_2)_2$-CH_3	4-CEU	5.602	1	16	0.249	−4.542	3.791
8	NH	2-Me	3-CEU	4.149	2	13	0.044	−5.776	5.265
9	NH	2-CH_2-CH_3	3-CEU	4.319	2	14	0.003	−4.2	3.792
10	NH	2-$(CH_2)_2$-CH_3	3-CEU	4.824	2	16	−0.015	−5.66	6.562
11	NH	2-Me	4-CEU	4.260	2	13	−0.056	−4.842	4.379
12	NH	2-CH_2-CH_3	4-CEU	4.398	2	14	−0.199	−4.036	3.316
13	NH	2-$(CH_2)_2$-CH_3	4-CEU	4.678	2	16	−0.109	−5.379	4.276
14	O	2-Me	3-CPU	4.678	2	13	−0.099	−4.91	4.18
15	O	2-CH_2-CH_3	3-CPU	4.638	2	14	0.057	−5.709	3.351
16	O	2-$(CH_2)_2$-CH_3	3-CPU	4.854	2	16	0.09	−4.777	5.737
17	O	4-OH	3-CPU	4.292	2	12	0.371	−3.81	3.557
18	O	2-Me	4-CPU	4.585	1	13	0.026	−3.933	2.952
19	O	2-CH_2-CH_3	4-CPU	4.824	1	14	0.1	−4.001	2.835
20	O	2-$(CH_2)_2$-CH_3	4-CPU	4.886	1	16	−0.033	−4.132	4.372
21	O	4-OH	4-CPU	4.301	1	12	0.137	−3.322	2.426
22	NH	2-Me	3-CPU	4.377	2	13	0.144	−4.557	4.698
23	NH	2-CH_2-CH_3	3-CPU	4.018	2	14	−0.233	−5.079	4.639
24	NH	2-$(CH_2)_2$-CH_3	3-CPU	4.824	2	16	−0.265	−5.077	5.298
25	NH	2-Me	4-CPU	4.194	2	13	−0.247	−2.874	2.342
26	NH	2-$(CH_2)_2$-CH_3	4-CPU	4.585	2	16	−0.199	−5.308	4.241
27	O	2-Me	4-CEU	5.328	1	13	0.182	−4.774	3.14
28	O	2-Me	3-EU	4.357	2	13	0.048	−3.826	3.679
29	O	2-CH_2-CH_3	3-EU	4.481	2	14	0.123	−3.92	3.658
30	O	2-$(CH_2)_2$-CH_3	3-EU	4.602	2	16	0.064	−4.152	5.884
31	O	4-OH	3-EU	4.125	2	12	0.245	−3.361	3.747
32	O	2-Me	4-EU	4.921	1	13	0.226	−3.517	2.458
33	O	2-CH_2-CH_3	4-EU	4.921	1	14	0.289	−3.603	2.334
34	O	2-$(CH_2)_2$-CH_3	4-EU	5.620	1	16	0.179	−3.78	3.85
35	O	4-OH	4-EU	4.921	1	12	0.275	−2.822	2.042
36	O	3-Me	4-CEU	5.143	1	12	0.179	−5.158	2.729
37	NH	2-Me	3-EU	3.991	2	13	0.114	−4.003	5.481
38	NH	2-CH_2-CH_3	3-EU	4.824	2	14	−0.077	−3.948	3.99
39	NH	2-$(CH_2)_2$-CH_3	3-EU	4.387	2	16	−0.121	−3.772	4.862
40	NH	2-CH_2-CH_3	4-EU	4.066	2	14	−0.106	−3.638	2.681
41	NH	2-$(CH_2)_2$-CH_3	4-EU	4.495	2	16	−0.179	−3.383	3.517
42	O	4-Me	4-CEU	4.523	1	12	0.411	−2.191	3.995
43	O	4-OMe	4-CEU	4.745	1	13	0.579	−3.646	2.832
44	O	4-$N(Me)_2$	4-CEU	4.409	2	14	0.274	−3.852	5.562

CEU 2-chloroethylurea, *CPU* 3-chloropropylurea, *EU* ethylurea

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reported as IC_{50} (μM) against HT-29 colon carcinoma cells were converted to pIC_{50} (M). These derivatives of N-PUS, their corresponding $-\log IC_{50}$ (pIC_{50}) values along with the values of descriptor are presented in Table 1.

The second data consists of one hundred and twelve 4-aminoquinoline derivatives (Hwang *et al*., 2011) with a variety of substituents at different positions (see Table 2). The anti-malarial activity tested against chloroquine (CQ) sensitive (3D7) strain of *P. falciparum* reported as EC_{50} (μM) values were converted to pEC_{50} (M) for smoother statistical calculations. These derivatives of 4-aminoquinolines, their corresponding $-\log EC_{50}$ (pEC_{50}) values and values of descriptor are presented in Table 2.

The third dataset, which is a subset of the dataset 2, comprises cytotoxicity data of one hundred 4-aminoquinolines (Hwang *et al*., 2011) tested against HepG2 cell lines (see Table 3). For convenience, EC_{50} (μM) values were converted to pEC_{50} (M).

Calculation and selection of descriptors

The structures were drawn using Chemsketch 12 freeware, optimized using MMFF94 force field in TINKER, and then subjected to calculation of a large number of descriptors using e-Dragon, and PowerMV. Objective feature selection was performed to eliminate highly correlated and constant variables using QSARINS v1.2 and RapidMiner 5.0. Redundant descriptors were identified and eliminated using objective feature selection (Chirico and Gramatica, 2012; Gramatica, 2013; Mahajan *et al*., 2013; Masand *et al*., 2012, 2010, 2013). The procedure reported in the literature was employed for objective feature selection (Chirico and Gramatica 2012; Gramatica, 2013; Mahajan *et al*., 2013; Masand *et al*., 2012, 2010, 2013). As a general rule, constant for >80 % molecules, low-variance and correlated ($|R| \geq 0.6$) descriptors were excluded prior to modeling.

Methodology

The general procedure of external validation involves selection of descriptor on the basis of training set after splitting. It is well established that a QSAR model well predicts for a prediction molecule that is structurally very similar to the training set molecules because the descriptor (hence, the model) has captured common features of the training set molecules and is proficient to detect them in the new molecule (Consonni *et al*., 2009, 2010; Huang and Fan, 2011; Schuurmann *et al*., 2008; Todeschini *et al*., 2004), reverse is true for a new molecule which has very little in common with the training set data. That is, the confidence in its prediction should be low. Recently, Roy et al. proposed a new approach to overcome this critical issue, in which they used undivided dataset for selection of variables and performed internal validation (LOO cross-validation) in two different ways to ensure external predictivity of the developed model (Mitra *et al*., 2010). In the present work, descriptor selection was performed for the whole data set prior to splitting (information leakage) to determine the effect of selection of descriptors on external predictivity and behavior of different statistical parameters of the model. Genetic Algorithm (GA) available in QSARINS v1.2 was employed for the selection of optimum number and the set of descriptors applying the default settings (Chirico and Gramatica, 2011, 2012). Though, this step contravenes the basic rule that prediction set compounds should be excluded from the model development procedure, that is, they should be unknown to the developed model. But, this ensures that the selected descriptors capture the essential features that control the biological activity. In addition, it allows determining the effect of early descriptor selection (that is, prior to splitting or information leakage) on external predictivity of the models. Ferreira and Kiralj have termed such models as 'Auxiliary models' (Kiralj and Ferreira, 2009).

In QSARINS (Gramatica *et al*., 2014, 2013), CV (cross-validation) techniques are used as the optimization parameter (fitness function) for GA-based variable selection and also to verify model robustness and to avoid naïve Q^2 (Chirico and Gramatica, 2011, (2012). The novel methodology for splitting (first time reported in this work, termed as residual-based method (RBM)) begins with the creation of an original model on the basis of undivided dataset followed by splitting of dataset into training and prediction sets on the basis of sign of residuals (difference between the actual and predicted value by original model) for each sample. In short, for the whole undivided dataset, a statistically robust GA-MLR model (Original Model) was built. For some molecules, this original model resulted in positive residuals and negative for the rest. Now, for the novel methodology of splitting i.e., RBM, the whole dataset was divided rationally into training and prediction sets on the basis of sign of the residuals (obtained in the original model with the condition that the bigger set as training set). A GA-MLR QSAR model was built for the training and the prediction sets created by RBM method. For comparison purpose, the whole dataset was again divided randomly (random splitting model, termed as RSM) and rationally (using sphere exclusion model, termed a SEM method) into the training and the prediction sets with number of compounds similar to training and prediction sets as in RBM, that is, during these various splitting, the number of molecules in training and prediction set is identical in RBM, RSM, and SEM. A molecule in the training set of one method (RBM or RSM or SEM) may or may not be in the training set of other method (RBM or RSM or SEM). The identical data split with

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Table 2 4-aminoquinolines used in present study along with pEC_{50} and descriptors

Sr. no.	R_1	R_2	pEC_{50} (M)	Mor13e	RDF040v	F06 [N–O]
1	PhO	Furfuryl	5.620	−0.218	7.086	2
2	PhO	2-HO-3-MeO-Bn	5.854	−0.81	7.784	1
3	PhO	Piperonyl	5.921	−1.085	8.62	1
4	PhO	3-F-6-MeO-Bn	5.959	−0.506	7.366	1
5	2-MeO-PhO	Furfuryl	6.143	−0.729	8.331	1
6	2-MeO-PhO	2-HO-3-MeO-Bn	6.152	−1.446	9.537	1
7	2-MeO-PhO	Piperonyl	6.223	−1.455	9.351	1
8	2-MeO-PhO	3-F-6-MeO-Bn	6.236	−0.523	9.875	1
9	3-MeO-PhO	Furfuryl	6.503	−0.319	7.272	1
10	3-MeO-PhO	2-HO-3-MeO-Bn	6.527	−0.748	9.432	1
11	3-MeO-PhO	Piperonyl	6.545	−1.079	9.32	1
12	3-MeO-PhO	3-F-6-MeO-Bn	6.547	−0.64	9.523	1
13	4-MeO-PhO	Furfuryl	6.600	−0.245	7.489	1
14	4-MeO-PhO	2-HO-3-MeO-Bn	6.652	−0.838	9.878	1
15	4-MeO-PhO	Piperonyl	6.682	−1.017	9.645	1
16	4-MeO-PhO	3-F-6-MeO-Bn	6.754	−0.392	9.149	1
17	4-F-PhO	Furfuryl	6.790	−0.428	6.34	1
18	4-F-PhO	2-HO-3-MeO-Bn	6.790	−0.651	8.072	1
19	4-F-PhO	Piperonyl	6.842	−0.842	8.321	1
20	4-F-PhO	3-F-6-MeO-Bn	6.860	−0.691	7.491	1
21	4-Cl-PhO	Furfuryl	6.863	−0.252	8.598	1
22	4-Cl-PhO	Furfuryl	6.879	−0.778	9.636	1
23	4-Cl-PhO	Piperonyl	6.893	−0.749	10.379	1
24	4-Cl-PhO	3-F-6-MeO-Bn	6.896	−0.636	10.35	1
25	3-Me2 N-PhO	Furfuryl	6.928	−0.024	7.162	1
26	3-Me2 N-PhO	2-HO-3-MeO-Bn	6.936	−0.727	8.607	1
27	3-Me2 N-PhO	Piperonyl	6.975	−0.858	8.745	1
28	3-Me2 N-PhO	3-F-6-MeO-Bn	7.018	−0.212	7.919	1
29	4-tertBu-PhO	Furfuryl	7.036	0.559	8.276	1
30	4-tertBu-PhO	2-HO-3-MeO-Bn	7.046	1.005	9.795	1
31	4-tertBu-PhO	Piperonyl	7.051	0.206	9.918	1
32	4-tertBu-PhO	3-F-6-MeO-Bn	7.066	−0.375	10.119	1
33	4-F-Ph	Furfuryl	7.125	−0.585	5.107	0
34	4-F-Ph	2-HO-3-MeO-Bn	7.180	−0.77	6.327	0
35	4-F-Ph	Piperonyl	7.244	−0.931	6.653	0
36	4-F-Ph	3-F-6-MeO-Bn	7.252	−1.058	6.982	0
37	3,5-CF3-Ph	Furfuryl	7.260	−0.722	5.599	0
38	3,5-CF3-Ph	2-HO-3-MeO-Bn	7.268	−0.92	7.079	0
39	3,5-CF3-Ph	Piperonyl	7.268	−1.35	7.336	0
40	3,5-CF3-Ph	3-F-6-MeO-Bn	7.268	−0.935	7.85	0
41	1-Naphtyl	Furfuryl	7.301	−0.703	6.82	0
42	1-Naphtyl	2-HO-3-MeO-Bn	7.337	−0.761	7.719	0
43	1-Naphtyl	Piperonyl	7.337	−1.118	8.451	0
44	1-Naphtyl	3-F-6-MeO-Bn	7.387	−0.556	8.566	0
45	4-CF3-Ph	Furfuryl	7.387	−0.594	5.258	0
46	4-CF3-Ph	2-HO-3-MeO-Bn	7.398	−0.331	6.622	0
47	4-CF3-Ph	Piperonyl	7.398	−0.877	7.122	0
48	4-CF3-Ph	3-F-6-MeO-Bn	7.398	−0.562	7.114	0

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Table 2 continued

Sr. no.	R_1	R_2	pEC_{50} (M)	Mor13e	RDF040v	F06 [N–O]
49	Ph	Furfuryl	7.398	−0.449	5.193	0
50	Ph	2-HO-3-MeO-Bn	7.409	−0.4	6.467	0
51	Ph	Piperonyl	7.409	−0.754	6.74	0
52	Ph	3-F-6-MeO-Bn	7.420	−0.588	6.815	0
53	4-tertBu-Ph	Furfuryl	7.469	−0.104	7.086	0
54	4-tertBu-Ph	2-HO-3-MeO-Bn	7.481	0.348	8.467	0
55	4-tertBu-Ph	Piperonyl	7.495	−0.658	8.7	0
56	4-tertBu-Ph	3-F-6-MeO-Bn	7.509	0.472	9.679	0
57	Piperonyl	Furfuryl	7.509	0.326	4.927	0
58	Piperonyl	2-HO-3-MeO-Bn	7.509	−0.592	7.546	0
59	Piperonyl	Piperonyl	7.538	−0.501	7.801	0
60	Piperonyl	3-F-6-MeO-Bn	7.538	−0.268	8.098	0
61	4-MeO-Ph	Furfuryl	7.553	0.539	6.398	0
62	4-MeO-Ph	2-HO-3-MeO-Bn	7.569	−0.221	8.104	0
63	4-MeO-Ph	Piperonyl	7.569	−0.536	8.312	0
64	4-MeO-Ph	3-F-6-MeO-Bn	7.569	−0.071	7.819	0
65	4-F-Bn	Furfuryl	7.569	0.959	5.326	0
66	4-F-Bn	2-HO-3-MeO-Bn	7.585	−0.233	8.929	0
67	4-F-Bn	Piperonyl	7.585	−0.067	10.705	0
68	4-F-Bn	3-F-6-MeO-Bn	7.602	0.219	8.134	0
69	iso-butyl	Furfuryl	7.602	1.507	6.712	0
70	iso-butyl	2-HO-3-MeO-Bn	7.638	0.808	9.125	0
71	iso-butyl	Piperonyl	7.658	0.497	6.044	0
72	iso-butyl	3-F-6-MeO-Bn	7.658	0.112	10.014	0
73	cHex	Furfuryl	7.699	1.544	7.704	0
74	cHex	2-HO-3-MeO-Bn	7.699	0.438	11.277	0
75	cHex	Piperonyl	7.699	0.752	10.997	0
76	cHex	3-F-6-MeO-Bn	7.699	0.756	9.319	0
77	1-Et-Pr	Furfuryl	7.721	1.399	6.966	0
78	1-Et-Pr	2-HO-3-MeO-Bn	7.721	0.074	9.59	0
79	1-Et-Pr	Piperonyl	7.745	0.193	8.59	0
80	1-Et-Pr	3-F-6-MeO-Bn	7.745	0.864	7.615	0
81	3-CF3-Bn	Furfuryl	7.745	0.117	7.599	0
82	3-CF3-Bn	2-HO-3-MeO-Bn	7.745	−0.196	9.004	0
83	3-CF3-Bn	Piperonyl	7.770	0.261	8.227	0
84	3-CF3-Bn	3-F-6-MeO-Bn	7.770	0.413	8.458	0
85	4-CN-Bn	Furfuryl	7.770	1.409	8.512	0
86	4-CN-Bn	2-HO-3-MeO-Bn	7.824	−0.322	9.482	0
87	4-CN-Bn	Piperonyl	7.824	0.399	9.507	0
88	4-CN-Bn	3-F-6-MeO-Bn	7.824	0.776	9.032	0
89	Bn	Furfuryl	7.854	1.122	8.522	0
90	Bn	2-HO-3-MeO-Bn	7.886	0.25	10.837	0
91	Bn	Piperonyl	7.886	−0.019	6.437	0
92	Bn	3-F-6-MeO-Bn	7.886	0.494	10.293	0
93	3,5-Me-Bn	Furfuryl	7.886	1.444	6.402	0
94	3,5-Me-Bn	2-HO-3-MeO-Bn	7.959	1.194	10.845	0
95	3,5-Me-Bn	Piperonyl	7.959	1.419	11.419	0
96	3,5-Me-Bn	3-F-6-MeO-Bn	7.959	0.887	8.162	0

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Table 2 continued

Sr. no.	R_1	R_2	pEC_{50} (M)	Mor13e	RDF040v	F06 [N–O]
97	2-Cl-4-F-Bn	Furfuryl	7.959	0.839	11.876	0
98	2-Cl-4-F-Bn	2-HO-3-MeO-Bn	7.959	−0.479	9.369	0
99	2-Cl-4-F-Bn	Piperonyl	7.959	−0.34	10.094	0
100	2-Cl-4-F-Bn	3-F-6-MeO-Bn	8.000	0.067	9.652	0
101	iso-pentyl	Furfuryl	8.046	1.491	7.984	0
102	iso-pentyl	2-HO-3-MeO-Bn	8.046	1.243	8.878	0
103	iso-pentyl	Piperonyl	8.046	0.237	9.109	0
104	iso-pentyl	3-F-6-MeO-Bn	8.046	0.566	7.314	0
105	cHexmethyl	Furfuryl	8.046	1.37	8.807	0
106	cHexmethyl	2-HO-3-MeO-Bn	8.046	0.976	10.656	0
107	cHexmethyl	Piperonyl	8.097	0.756	11.296	0
108	cHexmethyl	3-F-6-MeO-Bn	8.155	1.236	8.876	0
109	PhEt	Furfuryl	8.398	0.843	7.842	0
110	PhEt	2-HO-3-MeO-Bn	8.398	0.615	9.586	0
111	PhEt	Piperonyl	8.398	0.336	7.842	0
112	PhEt	3-F-6-MeO-Bn	9.000	0.636	14.152	0

respect to number of compounds in the training and the prediction sets was used in external validation for all models of a dataset to allow better comparison between the respective statistics (Kiralj and Ferreira, 2009). GA-MLR models were built also for the RSM and SEM. Briefly, four models were generated for each dataset.

Results and discussion

For small- and moderate-sized datasets, which is the realistic situation for a QSAR modeler, a very serious problem in developing QSAR models with reduced sets of data (splitting the sets) is the loss of considerable amount of information due to holding out of some compounds for validation purpose (Chirico and Gramatica, 2011, 2012; Consonni *et al*., 2009, 2010; Hawkins, 2004; Hawkins *et al*., 2008; Huang and Fan, 2011; Mitra *et al*., 2010; Roy *et al*., 2008; Schuurmann *et al*., 2008; Scior *et al*., 2009). Other confines associated in using small datasets include fortuitous correlation, poor regression statistics, failure of carrying out various statistical tests, and abnormal behavior in performed tests (Kiralj and Ferreira, 2009). This may lead to spurious conclusions in model interpretation and incorrect proposals for the mechanism of action of the compounds.

In the present study, the main emphasis is on various methods for splitting the dataset. For external validation, random as well as rational splitting methods were adopted to create training and prediction sets. For the rational splitting, a special method RBM was also evaluated. Interestingly, for all the datasets, the residual-based method resulted in radical splitting with ~55–60 % and ~40–45 % compounds in the training and the prediction sets, respectively. GA-MLR models were rebuilt for training and prediction sets using the same descriptors that were used for building the original model. In addition to RBM, sphere exclusion algorithm (SEM) and random (RSM) methods were also used for creating training and prediction sets, keeping the number of compounds the same as in residual-based method in the training and prediction sets. This ensures better comparison of various statistical parameters.

The analysis of Tables S1–S3 and 4, 5, 6 indicates that (i) the training and prediction sets used in RBM, RSM, and SEM models cover the diversity of the datasets and (ii) many compounds in the training and the prediction sets are close to each other (see supplementary figure S1, S2, and S3).

The statistical results for the original model for the three datasets are presented in Table 7. The minimum acceptable statistics (or recommended threshold values of statistical parameters) (Chirico and Gramatica, 2011, 2012; Huang and Fan, 2011; Kiralj and Ferreira, 2009; Martin *et al*., 2012) for regression models in QSAR include following conditions: $R^2 > Q^2$, $Q^2 \geq 0.5$, $R^2_{\text{tr}} \geq 0.6$, $R^2_{\text{ex}} \geq 0.6$, $RMSE_{tr} < RMSE_{cv}$, $\Delta K \geq 0.05$, $CCC \geq 0.85$, Q^2-$F^n \geq 0.70$, and $r^2_m \geq 0.6$ with *RMSE,* and *MAE* should be close to zero. In addition, the chance correlation of a QSAR model is validated on following criteria: $R^2_{Yrand} > Q^2_{Yrand}$,

$Q^2_{Yrand} < 0.2$ and $R^2_{Yrand} < 0.2 \rightarrow$ no chance correlation;

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Table 3 4-aminoquinolines used in present study along with pEC_{50} and descriptors

Sr. no.	R_1	R_2	pEC_{50}	GATS1p	E3u	E1 m	H6u	R2e
1	PhO	2-HO-3-MeO-Bn	5.046	0.959	0.41	0.552	1.306	1.88
2	PhO	Piperonyl	5.886	1.052	0.383	0.578	1.446	2.004
3	PhO	3-F-6-MeO-Bn	6.097	0.907	0.396	0.576	1.404	1.952
4	2-MeO-PhO	Furfuryl	5.538	1.089	0.309	0.483	1.1	1.988
5	2-MeO-PhO	2-HO-3-MeO-Bn	4.812	1.011	0.279	0.572	1.212	2
6	2-MeO-PhO	Piperonyl	5.215	1.085	0.288	0.595	1.355	2.133
7	2-MeO-PhO	3-F-6-MeO-Bn	5.076	0.964	0.353	0.586	1.485	2.008
8	3-MeO-PhO	Furfuryl	5.086	1.089	0.447	0.507	1.073	1.934
9	3-MeO-PhO	3-F-6-MeO-Bn	5.161	0.964	0.316	0.602	1.42	1.983
10	4-MeO-PhO	Furfuryl	5.553	1.089	0.45	0.507	1.07	1.935
11	4-MeO-PhO	2-HO-3-MeO-Bn	5.367	1.011	0.364	0.523	1.445	1.925
12	4-MeO-PhO	Piperonyl	5.066	1.085	0.429	0.607	1.096	2.03
13	4-MeO-PhO	3-F-6-MeO-Bn	5.041	0.964	0.375	0.602	1.402	1.959
14	4-F-PhO	2-HO-3-MeO-Bn	4.857	0.875	0.435	0.657	1.331	1.906
15	4-F-PhO	3-F-6-MeO-Bn	5.066	0.845	0.395	0.683	1.402	1.974
16	4-Cl-PhO	Furfuryl	4.996	0.974	0.471	0.686	1.21	1.89
17	4-Cl-PhO	Furfuryl	5.167	0.901	0.395	0.771	1.293	1.88
18	4-Cl-PhO	Piperonyl	5.056	0.986	0.389	0.786	1.446	1.997
19	4-Cl-PhO	3-F-6-MeO-Bn	5.215	0.858	0.389	0.798	1.264	1.899
20	3-Me2 N-PhO	2-HO-3-MeO-Bn	4.963	1.049	0.361	0.55	1.153	1.948
21	3-Me2 N-PhO	3-F-6-MeO-Bn	5.699	0.993	0.382	0.581	1.17	1.965
22	4-tertBu-PhO	Furfuryl	5.409	1.043	0.446	0.427	1.59	1.972
23	4-tertBu-PhO	2-HO-3-MeO-Bn	5.921	0.949	0.413	0.482	1.646	1.957
24	4-tertBu-PhO	Piperonyl	5.921	1.043	0.404	0.501	1.858	2.096
25	4-tertBu-PhO	3-F-6-MeO-Bn	5.056	0.898	0.389	0.505	1.617	1.977
26	4-F-Ph	Furfuryl	5.013	0.84	0.332	0.592	0.974	1.888
27	4-F-Ph	2-HO-3-MeO-Bn	5.027	0.799	0.393	0.665	1.252	1.91
28	4-F-Ph	Piperonyl	4.921	0.882	0.281	0.706	1.214	2.013
29	4-F-Ph	3-F-6-MeO-Bn	6	0.77	0.424	0.69	1.269	1.955
30	3,5-CF3-Ph	Furfuryl	5.523	0.739	0.262	0.663	0.878	2.48
31	3,5-CF3-Ph	2-HO-3-MeO-Bn	5.921	0.735	0.353	0.759	1.538	2.267
32	3,5-CF3-Ph	Piperonyl	5.854	0.765	0.307	0.762	1.322	2.519
33	3,5-CF3-Ph	3-F-6-MeO-Bn	6	0.73	0.347	0.783	1.441	2.283
34	1-Naphtyl	Furfuryl	5.092	0.98	0.452	0.48	1.156	1.903
35	1-Naphtyl	2-HO-3-MeO-Bn	5.432	0.863	0.367	0.575	1.259	1.918
36	1-Naphtyl	Piperonyl	5.161	0.986	0.4	0.582	1.469	2.008
37	4-CF3-Ph	Furfuryl	5.167	0.749	0.34	0.688	0.919	2.109
38	4-CF3-Ph	2-HO-3-MeO-Bn	5.377	0.74	0.414	0.756	1.279	2.107
39	4-CF3-Ph	Piperonyl	5.481	0.79	0.406	0.77	1.306	2.245
40	4-CF3-Ph	3-F-6-MeO-Bn	5.092	0.728	0.381	0.775	1.169	2.136
41	Ph	Furfuryl	5.092	1.012	0.33	0.51	0.975	1.854
42	Ph	2-HO-3-MeO-Bn	5.409	0.892	0.354	0.566	1.181	1.883
43	Ph	Piperonyl	5.328	1.015	0.279	0.637	1.21	1.979
44	Ph	3-F-6-MeO-Bn	5.456	0.835	0.374	0.603	1.165	1.919
45	4-tertBu-Ph	Furfuryl	5.409	1.009	0.353	0.447	1.453	2.019
46	4-tertBu-Ph	2-HO-3-MeO-Bn	6.155	0.886	0.377	0.497	1.569	2.037
47	4-tertBu-Ph	Piperonyl	5.796	1.011	0.415	0.528	1.756	2.163
48	4-tertBu-Ph	3-F-6-MeO-Bn	6	0.83	0.357	0.528	1.577	2.061

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Table 3 continued

Sr. no.	R_1	R_2	pEC_{50}	GATS1p	E3u	E1 m	H6u	R2e
49	Piperonyl	Furfuryl	5.076	1.057	0.255	0.582	1.033	2.073
50	Piperonyl	2-HO-3-MeO-Bn	5.721	0.985	0.213	0.589	1.608	2.026
51	Piperonyl	Piperonyl	5.119	1.057	0.218	0.604	1.474	2.155
52	Piperonyl	3-F-6-MeO-Bn	5.046	0.939	0.208	0.688	1.718	2.084
53	4-MeO-Ph	Furfuryl	5.119	1.05	0.197	0.532	1.306	1.908
54	4-MeO-Ph	2-HO-3-MeO-Bn	5.602	0.956	0.354	0.504	1.68	1.96
55	4-MeO-Ph	Piperonyl	5.187	1.049	0.225	0.502	1.641	2.051
56	4-MeO-Ph	3-F-6-MeO-Bn	5.041	0.905	0.32	0.497	1.551	1.963
57	4-F-Bn	Furfuryl	5.215	0.838	0.35	0.597	0.765	1.941
58	4-F-Bn	2-HO-3-MeO-Bn	5.027	0.797	0.28	0.605	1.016	1.945
59	4-F-Bn	Piperonyl	5.155	0.88	0.433	0.663	0.961	1.977
60	4-F-Bn	3-F-6-MeO-Bn	5.538	0.768	0.407	0.645	1.403	1.874
61	iso-butyl	2-HO-3-MeO-Bn	5.409	0.925	0.286	0.395	1.138	2.053
62	iso-butyl	Piperonyl	5.569	1.05	0.423	0.438	1.042	2.107
63	iso-butyl	3-F-6-MeO-Bn	5.444	0.865	0.303	0.373	1.305	2.041
64	cHex	Furfuryl	5.18	1.012	0.312	0.476	1.052	2.075
65	cHex	2-HO-3-MeO-Bn	5.77	0.892	0.353	0.464	1.251	2.082
66	cHex	Piperonyl	5.268	1.015	0.256	0.541	1.231	2.129
67	cHex	3-F-6-MeO-Bn	5.495	0.835	0.228	0.517	1.377	2.031
68	1-Et-Pr	Furfuryl	4.987	1.049	0.299	0.484	1.331	1.969
69	1-Et-Pr	2-HO-3-MeO-Bn	6.959	0.925	0.361	0.444	1.619	2.021
70	1-Et-Pr	Piperonyl	5.131	1.05	0.304	0.527	1.334	2.121
71	1-Et-Pr	3-F-6-MeO-Bn	5.032	0.863	0.271	0.584	1.882	1.973
72	3-CF3-Bn	Furfuryl	5.409	0.746	0.369	0.722	1.296	2.168
73	3-CF3-Bn	2-HO-3-MeO-Bn	5.678	0.737	0.356	0.499	1.701	2.132
74	3-CF3-Bn	Piperonyl	5.602	0.787	0.337	0.732	1.565	2.246
75	3-CF3-Bn	3-F-6-MeO-Bn	6.398	0.725	0.311	0.525	1.738	2.205
76	4-CN-Bn	Furfuryl	4.943	0.963	0.23	0.602	0.981	1.931
77	4-CN-Bn	2-HO-3-MeO-Bn	5.066	0.872	0.32	0.566	1.335	1.853
78	4-CN-Bn	Piperonyl	5.066	0.983	0.152	0.578	1.257	1.97
79	4-CN-Bn	3-F-6-MeO-Bn	5.119	0.824	0.157	0.581	1.388	1.802
80	Bn	2-HO-3-MeO-Bn	5.092	0.891	0.14	0.491	1.554	1.792
81	Bn	Piperonyl	5.086	1.014	0.436	0.481	1.119	2.066
82	Bn	3-F-6-MeO-Bn	5.081	0.834	0.211	0.508	1.435	1.787
83	3,5-Me-Bn	Furfuryl	5.143	1.009	0.355	0.494	1.25	1.983
84	3,5-Me-Bn	2-HO-3-MeO-Bn	5.602	0.887	0.176	0.473	1.993	1.875
85	3,5-Me-Bn	Piperonyl	5.523	1.012	0.189	0.49	1.639	1.991
86	3,5-Me-Bn	3-F-6-MeO-Bn	6.046	0.831	0.318	0.499	1.465	2.046
87	2-Cl-4-F-Bn	Furfuryl	5.06	0.789	0.385	0.674	1.245	1.82
88	2-Cl-4-F-Bn	2-HO-3-MeO-Bn	5.538	0.757	0.266	0.597	1.555	1.975
89	2-Cl-4-F-Bn	Piperonyl	5.276	0.834	0.273	0.744	1.297	2.003
90	2-Cl-4-F-Bn	3-F-6-MeO-Bn	5.495	0.733	0.403	0.624	1.312	1.957
91	iso-pentyl	2-HO-3-MeO-Bn	5.194	0.922	0.332	0.625	1.365	2.086
92	iso-pentyl	Piperonyl	5.538	1.047	0.3	0.689	1.134	2.228
93	iso-pentyl	3-F-6-MeO-Bn	6	0.865	0.306	0.451	1.106	2.031
94	cHexmethyl	Furfuryl	5.658	1.011	0.33	0.478	1.266	2.051
95	cHexmethyl	2-HO-3-MeO-Bn	5.921	0.891	0.278	0.473	1.733	2.079
96	cHexmethyl	Piperonyl	5.027	1.014	0.234	0.553	1.335	2.27

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Table 3 continued

Sr. no.	R_1	R_2	pEC_{50}	GATS1p	E3u	E1 m	H6u	R2e
97	cHexmethyl	3-F-6-MeO-Bn	5.553	0.834	0.293	0.476	1.355	2.082
98	PhEt	2-HO-3-MeO-Bn	5.119	0.799	0.278	0.535	1.744	1.963
99	PhEt	Piperonyl	5.229	0.832	0.204	0.554	1.546	1.854
100	PhEt	3-F-6-MeO-Bn	5.252	1.013	0.317	0.542	1.794	1.96

Any Q^2_{Yrand} and $0.2 < R^2_{Yrand} < 0.3 \rightarrow$ negligible chance correlation;
Any Q^2_{Yrand} and $0.3 < R^2_{Yrand} < 0.4 \rightarrow$ tolerable chance correlation;
Any Q^2_{Yrand} and $R^2_{Yrand} > 0.4 \rightarrow$ recognized chance correlation.
$(1\text{-}r^2/r^2_o) < 0.1$, $0.9 \leq k \leq 1.1$ or $(1\text{-}r^2/r'^2_o) < 0.1$, $0.9 \leq k' \leq 1.1$ with $| r^2_o - r'^2_o | < 0.3$

Except for the dataset-3, the statistical parameters point out that the GA-MLR original models for the dataset-1 and 2 are statistically robust with statistically acceptable values of R^2_{tr}, $R^2_{adj.}$, R^2_{cv}, R^2_{LMO}, R^2_{Yrand}, s, Kxx, ΔK, $RMSE_{tr}$, $RMSE_{cv}$, CCC_{tr}, CCC_{cv}, MAE_{tr}, MAE_{cv}, and F. Thus, from the internal validation point of view, the original models for the dataset 1 and 2 are satisfying all the essential conditions and criteria. The positive or negative contribution of a descriptor to activity remains the same during the data split and building original model indicating self-consistency of data(Kiralj and Ferreira, 2009), which is useful for model interpretation and mechanism of action.

Since, for a dataset, the same descriptors that cover the diversity of training and prediction sets are used to build models for different types of training and prediction sets, the statistical performance of residual based, random splitting and sphere exclusion should be comparable with each other for all the datasets. But, the statistical performance of each model is different (see Tables 7, 8, 9, 10). This indicates that the method of splitting has significant effect on the behavior of statistical parameters. Additionally, since the descriptors have been selected prior to splitting, the built models have captured common features of training and prediction set molecules, therefore, the models are capable to detect them in the test molecules, also. Consequently, the external predictivity of models should be high and comparable to each other for a dataset. However, the analysis of Tables 8, 9, and 10 indicates that the external predictivity of different models is different. Thus, it appears that the selection of descriptors prior to splitting has little role to play in deciding external predictivity of model. In fact, it is the diversity of training and prediction set that decides the external predictivity of any QSAR model. In other words, if the compounds in prediction set resemble the training set compounds, high predictive ability is observed for the developed model. Therefore, more number of model based on different training and prediction sets for a dataset must be developed, else, boot-strapping is an attractive option.

Results for the dataset-1

A comparison of various statistical parameters viz. R^2_{tr}, $R^2_{adj.}$, R^2_{cv}, R^2_{LMO}, R^2_{Yrand}, s, R^2_{ex}, Kxx, ΔK, $RMSE_{tr}$, $RMSE_{cv}$, CCC_{tr}, CCC_{cv}, MAE_{tr}, MAE_{cv}, r^2_m av, and F reveals that the performance of RBM model is better than the other models, which suggests that the model is statistically soundful and has good predictive ability. The r^2_m statistic, which penalizes the model profoundly for large difference between predicted and the corresponding experimental response, is higher for residual-based model indicating good external predictivity (Mitra *et al.*, 2010; Roy and Mitra, 2012). A plausible reason for this could be the distribution of the training and the prediction sets in the chemical space because both the sets used in RBM model covers diversity of the dataset. Though RBM model appears statistically robust but apropos of many statistical parameters, everything is not rosy-red for it.

For a good predictive ability $RMSE_{ex}$ and MAE_{ex} should be as low as possible (Chirico and Gramatica, 2011), but for RBM model, the values for these parameters are higher than the rest of the models. The large difference between $RMSE_{tr}$ (=0.118) and $RMSE_{ex}$ (=0.441) as well as between MAE_{tr} (=0.089) and MAE_{ex} (=0.394) raises question on residual-based model's generalizability (Chirico and Gramatica, 2011, 2012). In addition, the lower values of CCC_{ex}, $Q^2{-}F^1$, $Q^2{-}F^2$, and $Q^2{-}F^3$ for RBM model than RSM and SEM models indicate low external predictivity of this model (Chirico and Gramatica 2011, 2012; Consonni *et al.*, 2009, 2010; Schuurmann *et al.*, 2008). Thus, the RBM model is appearing statistically soundful on the basis of many parameters, but some parameters raise doubts on its external predictivity. A possible reason could be the sensitivity of $Q^2{-}F^1$and $Q^2{-}F^2$ toward the presence of outliers in the prediction set (Consonni *et al.*, 2010). That is, the presence of more number of outliers in the prediction set of RBM model than the other models is responsible for its low external predictivity. Therefore, it can be stated

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Table 4 Experimental and predicted pIC_{50} by different models for dataset-1

ID	pIC_{50}	Status	Pred. pIC_{50} (Originalmodel)	Status	Pred. pIC_{50} RBM	Status	Pred. pIC_{50} RSM	Status	Pred. pIC_{50} SEM
1	5.8240	Training	5.2945	Prediction	4.9468	Training	5.5246	Training	5.2338
2	4.4810	Training	4.1434	Prediction	4.0651	Prediction	4.3532	Prediction	4.0669
3	5.3670	Training	5.1114	Prediction	4.6446	Training	5.1312	Prediction	5.0960
4	4.8240	Training	4.6201	Prediction	4.5856	Prediction	4.6241	Training	4.7066
5	3.9210	Training	4.3456	Training	4.2006	Prediction	4.7011	Training	4.2484
6	4.7700	Training	4.9528	Training	4.8453	Training	4.7697	Training	5.0715
7	5.6020	Training	5.4692	Prediction	5.2327	Training	5.4758	Prediction	5.5231
8	4.1490	Training	4.4768	Training	4.1421	Prediction	4.5794	Training	4.3759
9	4.3190	Training	4.4971	Training	4.2888	Training	4.3606	Prediction	4.5313
10	4.8240	Training	4.8351	Prediction	4.5429	Prediction	4.8050	Training	4.8310
11	4.2600	Training	4.2126	Prediction	4.0629	Prediction	4.2534	Prediction	4.1652
12	4.3980	Training	4.3672	Prediction	4.1746	Prediction	4.0790	Prediction	4.4456
13	4.6780	Training	4.8172	Training	4.6643	Prediction	4.8165	Prediction	4.8690
14	4.6780	Training	4.2410	Prediction	4.0579	Training	4.2332	Training	4.2110
15	4.6380	Training	4.8594	Training	4.5173	Training	4.9219	Training	4.8445
16	4.8540	Training	4.7210	Prediction	4.6080	Prediction	4.7724	Prediction	4.7689
17	4.2920	Training	4.3798	Training	4.1487	Training	4.4670	Prediction	4.3226
18	4.5850	Training	4.6987	Training	4.5177	Training	4.6012	Training	4.6975
19	4.8240	Training	4.9861	Training	4.7799	Training	4.8915	Prediction	5.0179
20	4.8860	Training	5.0662	Training	4.9380	Prediction	4.9073	Prediction	5.1382
21	4.3010	Training	4.5949	Training	4.3935	Training	4.4711	Training	4.5774
22	4.3770	Training	4.3227	Prediction	4.1462	Training	4.4158	Prediction	4.2844
23	4.0180	Training	4.2580	Training	4.1286	Training	4.2083	Training	4.2826
24	4.8240	Training	4.5794	Prediction	4.4278	Prediction	4.4112	Training	4.6660
25	4.1940	Training	3.8950	Prediction	3.9259	Prediction	3.6105	Training	3.9953
26	4.5850	Training	4.6599	Training	4.5970	Training	4.6743	Prediction	4.7344
27	5.3280	Training	5.0269	Prediction	4.6933	Prediction	5.0460	Training	4.9675
28	4.3570	Training	4.3042	Prediction	4.1023	Training	4.1680	Training	4.3111
29	4.4810	Training	4.5794	Training	4.3587	Prediction	4.4580	Prediction	4.6178
30	4.6020	Training	4.6885	Training	4.5141	Training	4.5384	Prediction	4.7488
31	4.1250	Training	4.2266	Training	3.9974	Prediction	4.1417	Training	4.1867
32	4.9210	Training	4.9349	Training	4.6648	Training	4.8049	Prediction	4.9387
33	4.9210	Training	5.2090	Training	4.9217	Prediction	5.0860	Training	5.2472
34	5.6200	Training	5.3283	Prediction	5.1025	Prediction	5.1492	Training	5.4025
35	4.9210	Training	4.7116	Prediction	4.4781	Prediction	4.5533	Prediction	4.7109
36	4.9590	Training	4.9578	Prediction	4.5756	Training	5.0387	Prediction	4.8530
37	3.9910	Training	4.1116	Training	3.9965	Training	4.1346	Training	4.0684
38	4.8240	Training	4.3522	Prediction	4.1887	Prediction	4.1562	Training	4.4158
39	4.3870	Training	4.5814	Training	4.4422	Training	4.2705	Prediction	4.7137
40	4.0660	Training	4.3520	Training	4.2611	Training	4.1534	Prediction	4.4426
41	4.4950	Training	4.5532	Training	4.4897	Prediction	4.2078	Training	4.7186
42	4.5230	Training	4.3868	Prediction	4.3279	Training	4.3650	Training	4.3516
43	4.7450	Training	5.1121	Training	4.8920	Training	5.2956	Training	5.0681
44	4.4090	Training	4.3261	Prediction	4.2793	Prediction	4.4605	Prediction	4.3016

RBM Residual-based model, *RBM* Random splitting model, *SEM* Sphere exclusion model

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Table 5 Experimental and predicted pEC_{50} by different models for dataset-2

ID	pEC_{50}(M)	Status	Pred. pEC_{50} (Original model)	Status	Pred. pEC_{50} RBM	Status	Pred. pEC_{50} RSM	Status	Pred. pEC_{50} SEM
1	5.620	Training	5.6830	Training	5.3535	Prediction	5.8460	Training	5.6082
2	5.854	Training	6.5075	Training	6.2924	Prediction	6.5813	Training	6.4897
3	5.921	Training	6.5065	Training	6.2847	Training	6.5663	Prediction	6.4877
4	5.959	Training	6.5481	Training	6.3330	Prediction	6.6285	Training	6.5248
5	6.143	Training	6.5698	Training	6.3449	Prediction	6.6337	Training	6.5420
6	6.152	Training	6.4911	Training	6.2631	Training	6.5357	Prediction	6.4734
7	6.223	Training	6.4744	Training	6.2494	Training	6.5223	Training	6.4594
8	6.236	Training	6.7401	Training	6.4880	Prediction	6.7765	Prediction	6.6853
9	6.503	Training	6.5859	Training	6.3683	Training	6.6674	Prediction	6.5571
10	6.527	Training	6.6512	Training	6.4103	Prediction	6.6959	Prediction	6.6101
11	6.545	Training	6.5626	Training	6.3303	Prediction	6.6101	Prediction	6.5347
12	6.547	Training	6.6844	Training	6.4399	Training	6.7272	Prediction	6.6382
13	6.600	Training	6.6207	Training	6.3983	Training	6.6982	Prediction	6.5865
14	6.652	Training	6.6644	Training	6.4187	Training	6.7015	Prediction	6.6207
15	6.682	Training	6.6030	Prediction	6.3645	Training	6.6446	Prediction	6.5687
16	6.754	Training	6.7149	Prediction	6.4709	Prediction	6.7637	Training	6.6648
17	6.790	Training	6.4868	Prediction	6.2853	Training	6.5849	Training	6.4738
18	6.790	Training	6.5683	Prediction	6.3457	Training	6.6367	Prediction	6.5412
19	6.842	Training	6.5417	Prediction	6.3193	Training	6.6062	Training	6.5182
20	6.860	Training	6.5133	Prediction	6.3001	Training	6.5919	Prediction	6.4950
21	6.863	Training	6.7057	Prediction	6.4669	Prediction	6.7638	Prediction	6.6576
22	6.879	Training	6.6599	Prediction	6.4166	Prediction	6.7011	Prediction	6.6172
23	6.893	Training	6.7250	Prediction	6.4700	Prediction	6.7531	Training	6.6718
24	6.896	Training	6.7500	Prediction	6.4931	Training	6.7783	Training	6.6931
25	6.928	Training	6.6484	Prediction	6.4264	Prediction	6.7312	Prediction	6.6106
26	6.936	Training	6.5918	Prediction	6.3628	Training	6.6509	Training	6.5605
27	6.975	Training	6.5710	Prediction	6.3426	Training	6.6280	Prediction	6.5426
28	7.018	Training	6.6622	Prediction	6.4328	Training	6.7322	Prediction	6.6214
29	7.036	Training	6.8761	Prediction	6.6254	Prediction	6.9378	Training	6.8033
30	7.046	Training	7.1023	Training	6.8198	Prediction	7.1363	Training	6.9942
31	7.051	Training	6.9193	Prediction	6.6514	Training	6.9531	Prediction	6.8380
32	7.066	Training	6.7948	Prediction	6.5360	Training	6.8266	Prediction	6.7317
33	7.125	Training	7.2652	Training	7.1980	Training	7.3070	Prediction	7.3185
34	7.180	Training	7.3159	Training	7.2344	Training	7.3368	Prediction	7.3602
35	7.244	Training	7.3026	Training	7.2195	Prediction	7.3181	Prediction	7.3484
36	7.252	Training	7.2977	Training	7.2123	Prediction	7.3078	Training	7.3438
37	7.260	Training	7.2706	Training	7.1989	Training	7.3042	Training	7.3225
38	7.268	Training	7.3385	Training	7.2489	Training	7.3466	Training	7.3785
39	7.268	Training	7.2549	Prediction	7.1703	Training	7.2595	Prediction	7.3069
40	7.268	Training	7.3952	Training	7.2943	Prediction	7.3897	Prediction	7.4258
41	7.301	Training	7.3706	Training	7.2803	Prediction	7.3827	Training	7.4062
42	7.337	Training	7.4269	Training	7.3244	Training	7.4233	Training	7.4530
43	7.337	Training	7.3980	Training	7.2920	Prediction	7.3824	Prediction	7.4275
44	7.387	Training	7.5425	Training	7.4232	Prediction	7.5236	Prediction	7.5505
45	7.387	Training	7.2748	Prediction	7.2056	Prediction	7.3140	Training	7.3265
46	7.398	Training	7.4449	Training	7.3498	Prediction	7.4595	Prediction	7.4697
47	7.398	Training	7.3523	Prediction	7.2611	Prediction	7.3594	Prediction	7.3902

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Table 5 continued

ID	pEC_{50}(M)	Status	Pred. pEC_{50} (Original model)	Status	Pred. pEC_{50} RBM	Status	Pred. pEC_{50} RSM	Status	Pred. pEC_{50} SEM
48	7.398	Training	7.4276	Training	7.3300	Prediction	7.4341	Training	7.4544
49	7.398	Training	7.3047	Prediction	7.2334	Training	7.3447	Training	7.3521
50	7.409	Training	7.4161	Training	7.3248	Prediction	7.4336	Prediction	7.4454
51	7.409	Training	7.3521	Prediction	7.2640	Training	7.3657	Training	7.3905
52	7.420	Training	7.3980	Prediction	7.3054	Training	7.4098	Prediction	7.4295
53	7.469	Training	7.5359	Training	7.4292	Prediction	7.5418	Training	7.5467
54	7.481	Training	7.7528	Training	7.6162	Training	7.7333	Prediction	7.7299
55	7.495	Training	7.5284	Training	7.4092	Training	7.5073	Prediction	7.5383
56	7.509	Training	7.8774	Training	7.7202	Prediction	7.8364	Training	7.8346
57	7.509	Training	7.4709	Prediction	7.3874	Training	7.5136	Training	7.4941
58	7.509	Training	7.4541	Prediction	7.3507	Training	7.4532	Training	7.4765
59	7.538	Training	7.4960	Prediction	7.3869	Training	7.4903	Prediction	7.5118
60	7.538	Training	7.5754	Training	7.4571	Training	7.5639	Prediction	7.5791
61	7.553	Training	7.6372	Training	7.5275	Prediction	7.6535	Training	7.6340
62	7.569	Training	7.5872	Training	7.4678	Prediction	7.5755	Training	7.5892
63	7.569	Training	7.5275	Prediction	7.4115	Training	7.5129	Prediction	7.5380
64	7.569	Training	7.6011	Training	7.4829	Prediction	7.5941	Prediction	7.6014
65	7.569	Training	7.6547	Training	7.5522	Training	7.6888	Prediction	7.6503
66	7.585	Training	7.6488	Training	7.5174	Training	7.6226	Training	7.6406
67	7.585	Training	7.8276	Training	7.6663	Prediction	7.7699	Training	7.7908
68	7.602	Training	7.6956	Training	7.5667	Training	7.6824	Training	7.6816
69	7.602	Training	7.8951	Training	7.7607	Prediction	7.9036	Training	7.8535
70	7.638	Training	7.9151	Training	7.7593	Prediction	7.8830	Training	7.8675
71	7.658	Training	7.5994	Prediction	7.4958	Prediction	7.6221	Training	7.6022
72	7.658	Training	7.8168	Training	7.6621	Training	7.7707	Prediction	7.7825
73	7.699	Training	7.9816	Training	7.8316	Training	7.9726	Training	7.9259
74	7.699	Training	7.9941	Training	7.8138	Training	7.9251	Training	7.9320
75	7.699	Training	8.0479	Training	7.8653	Prediction	7.9831	Training	7.9783
76	7.699	Training	7.9178	Training	7.7601	Training	7.8823	Training	7.8694
77	7.721	Training	7.8890	Training	7.7530	Training	7.8932	Training	7.8479
78	7.721	Training	7.7745	Training	7.6269	Prediction	7.7360	Training	7.7469
79	7.745	Training	7.7250	Prediction	7.5898	Prediction	7.7038	Training	7.7061
80	7.745	Training	7.8106	Training	7.6761	Prediction	7.8049	Training	7.7803
81	7.745	Training	7.6292	Prediction	7.5104	Training	7.6256	Prediction	7.6257
82	7.745	Training	7.6636	Prediction	7.5303	Training	7.6360	Training	7.6531
83	7.770	Training	7.7130	Prediction	7.5819	Training	7.6980	Prediction	7.6963
84	7.770	Training	7.7678	Prediction	7.6300	Training	7.7483	Prediction	7.7427
85	7.770	Training	8.0122	Training	7.8530	Training	7.9893	Prediction	7.9510
86	7.824	Training	7.6705	Prediction	7.5327	Prediction	7.6349	Training	7.6585
87	7.824	Training	7.8463	Training	7.6933	Training	7.8085	Training	7.8083
88	7.824	Training	7.9001	Training	7.7463	Training	7.8697	Training	7.8548
89	7.854	Training	7.9437	Training	7.7903	Prediction	7.9214	Training	7.8926
90	7.886	Training	7.9143	Training	7.7445	Training	7.8535	Prediction	7.8646
91	7.886	Training	7.5056	Prediction	7.4069	Prediction	7.5227	Training	7.5218
92	7.886	Training	7.9307	Training	7.7639	Training	7.8788	Prediction	7.8792
93	7.886	Training	7.8557	Prediction	7.7272	Training	7.8698	Training	7.8203
94	7.959	Training	8.1426	Training	7.9532	Training	8.0793	Training	8.0592

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Table 5 continued

ID	pEC_{50}(M)	Status	Pred. pEC_{50} (Original model)	Status	Pred. pEC_{50} RBM	Status	Pred. pEC_{50} RSM	Status	Pred. pEC_{50} SEM
95	7.959	Training	8.2417	Training	8.0391	Training	8.1678	Prediction	8.1430
96	7.959	Training	7.8589	Prediction	7.7158	Training	7.8435	Training	7.8208
97	7.959	Training	8.1376	Training	7.9401	Prediction	8.0571	Training	8.0536
98	7.959	Training	7.6238	Prediction	7.4910	Training	7.5906	Training	7.6188
99	7.959	Training	7.7140	Prediction	7.5675	Prediction	7.6677	Prediction	7.6948
100	8.000	Training	7.7776	Prediction	7.6292	Prediction	7.7381	Training	7.7496
101	8.046	Training	7.9907	Prediction	7.8377	Training	7.9769	Training	7.9333
102	8.046	Training	8.0007	Prediction	7.8395	Prediction	7.9719	Training	7.9408
103	8.046	Training	7.7762	Prediction	7.6324	Prediction	7.7457	Training	7.7490
104	8.046	Training	7.7153	Prediction	7.5914	Prediction	7.7155	Training	7.6994
105	8.046	Training	8.0258	Prediction	7.8630	Training	7.9979	Prediction	7.9622
106	8.046	Training	8.0753	Training	7.8931	Training	8.0159	Training	8.0020
107	8.097	Training	8.0722	Prediction	7.8851	Prediction	8.0021	Training	7.9986
108	8.155	Training	7.9989	Prediction	7.8379	Prediction	7.9701	Prediction	7.9392
109	8.398	Training	7.8233	Prediction	7.6858	Training	7.8136	Prediction	7.7908
110	8.398	Training	7.9046	Prediction	7.7459	Training	7.8649	Training	7.8579
111	8.398	Training	7.7010	Prediction	7.5740	Prediction	7.6926	Prediction	7.6866
112	9.000	Training	8.2665	Prediction	8.0393	Prediction	8.1465	Prediction	8.1606

that residual-based model possesses poor external predictivity, hence should not be adopted to create QSAR models. In addition, as many as possible parameters should be reported for a QSAR model developed using single splitting method. Because, the true predictive ability of residual-based model was captured, only when many statistical parameters were calculated.

For some parameters viz. R^2_{tr}, $R^2_{\text{adj.}}$, R^2_{cv}, R^2_{LMO}, R^2_{Yrand}, s, Kxx, ΔK, $RMSE_{tr}$, $RMSE_{cv}$, CCC_{tr}, CCC_{cv}, MAE_{tr}, MAE_{cv}, and F, the performance of random splitting model is either statistically satisfactory or comparable with the other models. But, for some parameters viz. CCC_{ex}, $r^2_m\,av$, and r^2_m, the performance of the model is questionable. A large difference of 0.309 between R^2_{tr} (=0.674), and R^2_{cv} (=0.365) for sphere exclusion model reflects large inaccuracy of the model (Schuurmann *et al*., 2008) or overfitting (Kiralj and Ferreira, 2009). A probable reason could be either the small size of dataset-1 or size of training and prediction sets. But, the problem of large inaccuracy of model or overfitting is not visible for other models. Similarly, the very low value of F (=7.023) indicates low statistical reliability of the sphere exclusion model. A very surprising and rare observation for sphere exclusion model is the higher values of $Q^2{-}F^1$ (=0.706), $Q^2{-}F^2$ (=0.705), and $Q^2{-}F^3$ (=0.828) than R^2 (=0.674), leading to the contrasting conclusion that the model is able to predict new data better than fitting available ones (Chirico and Gramatica, 2011; 2012).

For residual-based and random splitting models, $RMSE_{tr}$ and MAE_{tr} are lower than $RMSE_{ex}$ and MAE_{ex}, respectively. This indicates that the samples for which the models fit very well are present in the training set. Exactly reverse is true for the sphere exclusion model, for which $RMSE_{tr}$ and MAE_{tr} are higher than $RMSE_{ex}$ and MAE_{ex}, respectively. This observation points out one serious drawback of common practice followed in external validation, in which single split is performed to validate the model. If a researcher purposely selects training and prediction sets such that $RMSE_{tr}$ and MAE_{tr} are higher than $RMSE_{ex}$ and MAE_{ex}, respectively then, the model will be with lower internal predictivity but with high external predictivity. In such case, many parameters will give false positive results because of the purposeful selection of training and prediction sets. Therefore, one cannot merely rely on external validation based on single split; instead, boot-strap or multiple modeling (Masand *et al*., 2014) must be followed to develop a good number of statistically robust QSAR models with good external predictive ability.

As the number of compounds is same in the training and the prediction sets for the three models, the difference between R^2 and Q^2 should be comparable for all the models. But, different models have different variation indicating that the method of splitting has good influence on many statistical parameters.

Results for the dataset-2

Similar to the dataset-1, different statistical parameters viz. R^2_{tr}, $R^2_{\text{adj.}}$, R^2_{cv}, R^2_{LMO}, R^2_{Yrand}, s, R^2_{ex}, Kxx, ΔK, $RMSE_{tr}$,

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Table 6 Experimental and predicted pEC_{50} by different models for dataset-3

ID	pEC_{50} (M)	Status	Pred. pEC_{50} (Original model)	Status	Pred. pEC_{50} RBM	Status	Pred. pEC_{50} RSM	Status	Pred. pEC_{50} SEM
1	5.0460	Training	5.2880	Training	5.0711	Prediction	5.2655	Training	5.2987
2	5.8860	Training	5.3162	Prediction	5.1067	Prediction	5.1656	Training	5.3758
3	6.0970	Training	5.4203	Prediction	5.1851	Training	5.4203	Prediction	5.4266
4	5.5380	Training	5.1536	Prediction	5.0015	Prediction	5.0639	Training	5.2397
5	4.8120	Training	5.1292	Training	4.9953	Prediction	5.0477	Prediction	5.1723
6	5.2150	Training	5.2416	Training	5.0927	Prediction	5.0486	Training	5.3319
7	5.0760	Training	5.3873	Training	5.1679	Prediction	5.3175	Training	5.4200
8	5.0860	Training	5.2170	Training	5.0278	Training	5.1048	Prediction	5.2875
9	5.1610	Training	5.2564	Training	5.0749	Training	5.1851	Training	5.2775
10	5.5530	Training	5.2207	Prediction	5.0306	Training	5.1083	Training	5.2915
11	5.3670	Training	5.3308	Prediction	5.1010	Prediction	5.2687	Training	5.3750
12	5.0660	Training	5.1657	Training	5.0194	Prediction	4.9778	Prediction	5.2299
13	5.0410	Training	5.2956	Training	5.0944	Training	5.2224	Training	5.3125
14	4.8570	Training	5.2932	Training	5.0920	Training	5.2728	Training	5.2583
15	5.0660	Training	5.3473	Training	5.1502	Prediction	5.3307	Prediction	5.3120
16	4.9960	Training	5.1086	Training	4.9515	Prediction	4.9761	Training	5.0904
17	5.1670	Training	4.9870	Prediction	4.8743	Prediction	4.8687	Prediction	4.9219
18	5.0560	Training	5.0659	Training	4.9428	Prediction	4.8331	Training	5.0495
19	5.2150	Training	4.9953	Prediction	4.8925	Prediction	4.9007	Training	4.9143
20	4.9630	Training	5.1377	Training	4.9818	Training	5.0357	Prediction	5.1872
21	5.6990	Training	5.2073	Prediction	5.0408	Training	5.1339	Training	5.2368
22	5.4090	Training	5.6696	Training	5.3335	Training	5.6231	Training	5.7631
23	5.9210	Training	5.6557	Prediction	5.3315	Training	5.6635	Training	5.7037
24	5.9210	Training	5.7666	Prediction	5.4245	Training	5.6428	Training	5.8705
25	5.0560	Training	5.6574	Training	5.3471	Training	5.7013	Prediction	5.6881
26	5.0130	Training	5.1211	Training	4.9909	Prediction	5.2146	Prediction	5.0824
27	5.0270	Training	5.2824	Training	5.1005	Training	5.3394	Prediction	5.2222
28	4.9210	Training	5.0851	Training	4.9867	Training	5.0342	Prediction	5.0581
29	6.0000	Training	5.3765	Prediction	5.1800	Training	5.4363	Prediction	5.3123
30	5.5230	Training	5.6885	Training	5.5625	Prediction	5.7878	Training	5.7320
31	5.9210	Training	5.7055	Prediction	5.4872	Prediction	5.7108	Prediction	5.6846
32	5.8540	Training	5.8074	Prediction	5.6322	Training	5.7752	Training	5.8473
33	6.0000	Training	5.6413	Prediction	5.4524	Prediction	5.6397	Training	5.6148
34	5.0920	Training	5.3899	Training	5.1492	Training	5.4014	Training	5.4303
35	5.4320	Training	5.3296	Prediction	5.1263	Prediction	5.3885	Prediction	5.3132
36	5.1610	Training	5.4215	Training	5.1878	Training	5.3298	Prediction	5.4626
37	5.1670	Training	5.3199	Training	5.2029	Prediction	5.4170	Training	5.2786
38	5.3770	Training	5.4780	Training	5.2955	Training	5.5066	Prediction	5.4217
39	5.4810	Training	5.5637	Training	5.3845	Prediction	5.5192	Training	5.5493
40	5.0920	Training	5.4044	Training	5.2601	Prediction	5.4386	Training	5.3439
41	5.0920	Training	5.0119	Prediction	4.8827	Training	4.9975	Training	5.0372
42	5.4090	Training	5.2179	Prediction	5.0396	Training	5.2640	Prediction	5.2032
43	5.3280	Training	4.9977	Prediction	4.8990	Prediction	4.8683	Prediction	5.0198
44	5.4560	Training	5.2855	Prediction	5.1040	Training	5.3574	Prediction	5.2528
45	5.4090	Training	5.5518	Training	5.2783	Training	5.5371	Training	5.6367
46	6.1550	Training	5.7172	Prediction	5.4084	Training	5.7770	Prediction	5.7592
47	5.7960	Training	5.8079	Training	5.4795	Prediction	5.6956	Prediction	5.9094
48	6.0000	Training	5.7385	Prediction	5.4377	Training	5.8305	Training	5.7611

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Table 6 continued

ID	pEC_{50} (M)	Status	Pred. pEC_{50} (Original model)	Status	Pred. pEC_{50} RBM	Status	Pred. pEC_{50} RSM	Status	Pred. pEC_{50} SEM
49	5.0760	Training	5.0362	Prediction	4.9532	Prediction	4.9090	Training	5.1036
50	5.7210	Training	5.2562	Prediction	5.0786	Prediction	5.1665	Prediction	5.2963
51	5.1190	Training	5.2491	Training	5.1047	Training	5.0739	Prediction	5.3336
52	5.0460	Training	5.2651	Training	5.1029	Training	5.1386	Training	5.2798
53	5.1190	Training	4.9765	Prediction	4.8580	Training	4.8949	Prediction	5.0200
54	5.6020	Training	5.5567	Prediction	5.2637	Training	5.5449	Prediction	5.6006
55	5.1870	Training	5.3790	Training	5.1589	Prediction	5.2824	Prediction	5.4672
56	5.0410	Training	5.5276	Training	5.2577	Training	5.5819	Training	5.5568
57	5.2150	Training	5.1070	Prediction	5.0042	Training	5.2056	Training	5.0763
58	5.0270	Training	5.1689	Training	5.0449	Training	5.2921	Training	5.1264
59	5.1550	Training	5.1929	Training	5.0573	Training	5.1803	Training	5.1693
60	5.5380	Training	5.3921	Prediction	5.1635	Prediction	5.4864	Prediction	5.3224
61	5.4090	Training	5.5410	Training	5.3063	Prediction	5.6685	Prediction	5.6176
62	5.5690	Training	5.5278	Prediction	5.2954	Training	5.4907	Training	5.6434
63	5.4440	Training	5.7260	Training	5.4307	Prediction	5.9172	Training	5.7908
64	5.1800	Training	5.3365	Training	5.1632	Training	5.3221	Prediction	5.4211
65	5.7700	Training	5.6413	Prediction	5.3814	Prediction	5.7366	Training	5.6995
66	5.2680	Training	5.3039	Training	5.1497	Training	5.2291	Prediction	5.3851
67	5.4950	Training	5.4599	Prediction	5.2491	Training	5.5817	Training	5.4745
68	4.9870	Training	5.2660	Training	5.0696	Training	5.2030	Prediction	5.3385
69	6.9590	Training	5.7388	Prediction	5.4117	Prediction	5.7975	Training	5.8029
70	5.1310	Training	5.3843	Training	5.1923	Prediction	5.2749	Prediction	5.4800
71	5.0320	Training	5.5372	Training	5.2608	Prediction	5.5536	Training	5.5362
72	5.4090	Training	5.5461	Training	5.3585	Prediction	5.5900	Prediction	5.5134
73	5.6780	Training	6.0272	Training	5.6627	Prediction	6.2168	Prediction	6.0480
74	5.6020	Training	5.6556	Training	5.4393	Training	5.6306	Prediction	5.6522
75	6.3980	Training	6.0451	Prediction	5.6965	Training	6.2229	Training	6.0713
76	4.9430	Training	4.8893	Prediction	4.8292	Training	4.8592	Training	4.8908
77	5.0660	Training	5.2310	Training	5.0376	Prediction	5.2929	Training	5.2048
78	5.0660	Training	4.9741	Prediction	4.8859	Training	4.9271	Training	4.9982
79	5.1190	Training	5.0173	Prediction	4.8858	Training	5.1317	Training	4.9584
80	5.0920	Training	5.1228	Training	4.9395	Prediction	5.2270	Training	5.1068
81	5.0860	Training	5.5045	Training	5.2698	Training	5.4702	Prediction	5.5902
82	5.0810	Training	5.1924	Training	4.9968	Prediction	5.3423	Prediction	5.1544
83	5.1430	Training	5.3475	Training	5.1368	Training	5.3156	Prediction	5.4093
84	5.6020	Training	5.4963	Prediction	5.2000	Training	5.5783	Training	5.5088
85	5.5230	Training	5.3221	Prediction	5.1095	Training	5.2794	Training	5.3884
86	6.0460	Training	5.6648	Prediction	5.3883	Training	5.7883	Prediction	5.6897
87	5.0600	Training	5.1604	Training	4.9940	Prediction	5.2306	Training	5.0745
88	5.5380	Training	5.4862	Prediction	5.2545	Training	5.6187	Training	5.4473
89	5.2760	Training	5.0955	Prediction	4.9946	Prediction	5.0613	Training	5.0430
90	5.4950	Training	5.5162	Training	5.2800	Prediction	5.6582	Training	5.4595
91	5.1940	Training	5.3851	Training	5.1992	Prediction	5.3311	Prediction	5.4108
92	5.5380	Training	5.1659	Prediction	5.0812	Prediction	4.9477	Training	5.2390
93	6.0000	Training	5.5070	Prediction	5.2861	Training	5.6562	Prediction	5.5464
94	5.6580	Training	5.4254	Prediction	5.2085	Prediction	5.3977	Training	5.5069
95	5.9210	Training	5.7454	Prediction	5.4344	Training	5.8117	Training	5.8043
96	5.0270	Training	5.4707	Training	5.2993	Training	5.3705	Training	5.5809

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Table 6 continued

ID	pEC_{50} (M)	Status	Pred. pEC_{50} (Original model)	Status	Pred. pEC_{50} RBM	Status	Pred. pEC_{50} RSM	Status	Pred. pEC_{50} SEM
97	5.5530	Training	5.6583	Training	5.3984	Training	5.8009	Prediction	5.6963
98	5.1190	Training	5.6214	Training	5.3299	Prediction	5.7446	Prediction	5.6112
99	5.2290	Training	5.2426	Training	5.0457	Training	5.3492	Prediction	5.2081
100	5.2520	Training	5.4367	Training	5.1699	Training	5.3379	Training	5.4874

Table 7 Comparison of statistical parameters for original model for dataset-1, 2 and 3

Statistical Parameter	DataSet-1	DataSet-2	DataSet-3
R^2_{tr}	0.709	0.841	0.410
$R^2_{adj.}$	0.670	0.837	0.378
R^2_{cv}	0.597	0.827	0.344
R^2_{LMO}	0.723	0.843	0.419
R^2_{Yrand}	0.120	0.242	0.050
Q^2_{Yrand}	−0.185	−0.488	−0.076
s	0.250	0.242	0.300
Kxx	0.425	0.245	0.208
ΔK	0.025	0.209	0.027
$RMSE_{tr}$	0.233	0.238	0.291
$RMSE_{cv}$	0.274	0.248	0.307
CCC_{tr}	0.830	0.914	0.581
CCC_{cv}	0.763	0.906	0.537
MAE_{tr}	0.193	0.172	0.226
MAE_{cv}	0.226	0.179	0.239
F	18.50	190.388	13.047
r^2	0.601	0.827	0.347
r^2_o	0.429	0.793	−0.574
$1\text{-}(r^2/r^2_o)$	0.285	0.040	2.653
r'^2_o	0.597	0.827	0.344
$1\text{-}(r^2/r'^2_o)$	0.007	0.000	0.009
k	0.996	0.999	0.997
k'	1.001	1.000	0.999

$RMSE_{cv}$, CCC_{tr}, CCC_{cv}, MAE_{tr}, MAE_{cv}, and r^2_m *av* indicate good predictive ability and robust statistical performance of the residual-based model than the other models. The high value of r^2_m (=0.744) for residual model, though lower than sphere exclusion model (=0.804), indicates good external predictivity. A very high F (=328.459) value for residual-based model than the other models (=112.835 for random splitting and 111.362 for sphere exclusion model) indicates very high statistical significance of regression model. Similar to dataset-1, a large difference between $RMSE_{tr}$ (=0.143) and $RMSE_{ex}$ (=0.405) as well as between MAE_{tr} (=0.109) and MAE_{ex} (=0.353) suggests low

Table 8 Comparison of statistical parameters for original, residual-based rational, random splitting, and sphere exclusion models for dataset-1

Statistical Parameter	Original model	Residual-based model	Random splitting Model	Sphere exclusion model
R^2_{tr}	0.709	0.855	0.801	0.674
$R^2_{adj.}$	0.670	0.813	0.743	0.578
R^2_{cv}	0.597	0.732	0.640	0.365
R^2_{LMO}	0.723	0.871	0.815	0.709
s	0.250	0.137	0.241	0.320
R^2_{ex}	–	0.845	0.418	0.722
R^2_{Yrand}	0.120	0.223	0.238	0.231
Q^2_{Yrand}	−0.185	−0.443	−0.421	−0.433
Kxx	0.425	0.457	0.452	0.446
ΔK	0.025	0.036	0.015	0.017
$RMSE_{tr}$	0.233	0.118	0.207	0.275
$RMSE_{cv}$	0.274	0.159	0.279	0.384
$RMSE_{ex}$	–	0.441	0.344	0.200
CCC_{tr}	0.830	0.922	0.890	0.805
CCC_{cv}	0.763	0.859	0.795	0.621
CCC_{ex}	–	0.606	0.611	0.845
MAE_{tr}	0.193	0.089	0.161	0.238
MAE_{cv}	0.226	0.122	0.220	0.325
MAE_{ex}	–	0.394	0.260	0.169
Q^2-F^1	–	0.443	0.266	0.706
Q^2-F^2	–	0.097	0.266	0.705
Q^2-F^3	–	−1.039	0.451	0.828
r^2m	–	0.762	0.290	0.655
r^2m *av*	–	0.678	0.270	0.612
r^2m *de*	–	0.168	0.040	0.085
F	18.50	20.120	13.714	7.023
r^2	0.601	0.845	0.418	0.722
r^2_o	0.429	0.757	0.256	0.677
$1\text{-}(r^2/r^2_o)$	0.285	0.105	0.386	0.062
r'^2_o	0.597	0.836	0.324	0.713
$1\text{-}(r^2/r'^2_o)$	0.007	0.011	0.223	0.012
k	0.996	0.916	0.974	1.005
k'	1.001	1.089	1.021	0.993

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Table 9 Comparison of statistical parameters for original, residual-based rational, random splitting, and sphere exclusion models for dataset-2

Statistical Parameter	Original model	Residual-based model	Random splitting Model	Sphere exclusion model
R^2_{tr}	0.841	0.945	0.856	0.854
$R^2_{adj.}$	0.837	0.942	0.848	0.847
R^2_{cv}	0.827	0.934	0.836	0.834
R^2_{LMO}	0.843	0.947	0.859	0.855
s	0.242	0.148	0.212	0.227
R^2_{ex}	–	0.877	0.842	0.816
R^2_{Yrand}	0.242	0.052	0.053	0.051
Q^2_{Yrand}	−0.488	−0.087	−0.086	−0.089
Kxx	0.245	0.246	0.293	0.220
ΔK	0.209	0.231	0.201	0.219
$RMSE_{tr}$	0.238	0.143	0.205	0.220
$RMSE_{cv}$	0.248	0.157	0.219	0.234
$RMSE_{ex}$	–	0.405	0.287	0.266
CCC_{tr}	0.914	0.972	0.922	0.921
CCC_{cv}	0.906	0.967	0.912	0.911
CCC_{ex}	–	0.777	0.876	0.893
MAE_{tr}	0.172	0.109	0.149	0.166
MAE_{cv}	0.179	0.119	0.160	0.177
MAE_{ex}	–	0.353	0.197	0.187
Q^2-F^1	–	0.553	0.809	0.822
Q^2-F^2	–	0.442	0.809	0.810
Q^2-F^3	–	0.561	0.717	0.788
r^2m	–	0.744	0.689	0.804
r^2m av	–	0.803	0.581	0.720
r^2m de	–	0.118	0.217	0.168
F	190.388	328.459	112.835	111.362
r^2	0.827	0.877	0.842	0.816
r^2_o	0.793	0.877	0.649	0.768
$1-(r^2/r^2_o)$	0.040	0.000	0.229	0.060
r'^2_o	0.827	0.854	0.809	0.816
$1-(r^2/r'^2_o)$	0.000	0.026	0.039	0.000
k	0.999	0.953	1.000	0.992
k'	1.000	1.048	0.998	1.007

Table 10 Comparison of statistical parameters for original, residual-based rational, random splitting, and sphere exclusion models for dataset-3

Statistical parameter	Original model	Residual-based model	Random splitting Model	Sphere exclusion model
R^2_{tr}	0.410	0.621	0.527	0.478
$R^2_{adj.}$	0.378	0.583	0.478	0.426
R^2_{cv}	0.344	0.516	0.430	0.365
R^2_{LMO}	0.419	0.634	0.537	0.495
s	0.300	0.134	0.279	0.305
R^2_{ex}	–	0.662	0.237	0.280
R^2_{Yrand}	0.050	0.093	0.090	0.092
Q^2_{Yrand}	−0.076	−0.144	−0.153	−0.142
Kxx	0.208	0.176	0.232	0.203
ΔK	0.027	0.084	0.028	0.079
$RMSE_{tr}$	0.291	0.127	0.263	0.288
$RMSE_{cv}$	0.307	0.143	0.289	0.318
$RMSE_{ex}$	–	0.524	0.353	0.306
CCC_{tr}	0.581	0.766	0.690	0.647
CCC_{cv}	0.537	0.704	0.625	0.575
CCC_{ex}	–	0.339	0.480	0.488
MAE_{tr}	0.226	0.099	0.203	0.212
MAE_{cv}	0.239	0.112	0.225	0.236
MAE_{ex}	–	0.458	0.280	0.257
Q^2-F^1	–	0.239	0.112	0.246
Q^2-F^2	–	−0.728	0.105	0.238
Q^2-F^3	–	−5.512	0.145	0.414
r^2m	–	0.516	0.151	0.238
r^2m av	–	0.302	0.113	0.127
r^2m de	–	0.430	0.077	0.220
F	13.047	16.382	10.909	9.158
r^2	0.347	0.662	0.237	0.280
r^2_o	−0.574	−0.093	−0.235	−0.602
$1-(r^2/r^2_o)$	2.653	1.141	1.991	3.150
r'^2_o	0.344	0.614	0.106	0.257
$1-(r^2/r'^2_o)$	0.009	0.073	0.554	0.082
k	0.997	0.916	0.995	1.006
k'	0.999	1.089	1.001	0.257

generalizability of the residual-based model. In addition, the lower value of CCC_{ex}, Q^2-F^1, Q^2-F^2, and Q^2-F^3 for residual-based model than random splitting model, and sphere exclusion model points out low true external predictivity of this model.

A conceivable reason for the lower values of Q^2-F^1, Q^2-F^2, and Q^2-F^3 could be the presence of prediction set objects near the boundary of the training set (Chirico and Gramatica, 2011, 2012; Consonni *et al.*, 2009, 2010; Schuurmann *et al.*, 2008). Again, these statistical parameters are sensitive to mean of training and prediction sets, a simple analysis of Table 11 reveals that the mean of the test and the training sets of residual-based model have higher difference than the rest (Chirico and Gramatica 2011, 2012; Consonni *et al.*, 2009, 2010; Schuurmann *et al.*, 2008). This observation once again confirms that the distribution of the test and the training set has important impact on performance of many statistical parameters. Thus, the residual-based model is scoring high for many parameters suggesting statistical robustness of this model,

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Table 11 Mean of experimental pIC_{50} for prediction and training sets of various models for datasets 1–3

DataSet	Set	Original	Residual-based model	Random splitting Model	Sphere exclusion model
1	Prediction	–	4.8308	4.6389	4.6509
	Training	4.6397	4.4652	4.6404	4.6295
2	Prediction	–	7.5342	7.3803	7.3017
	Training	7.3867	7.2633	7.3921	7.4577
3	Prediction	–	5.6296	5.3598	5.3570
	Training	5.3778	5.1799	5.3925	5.3941

but some parameters raise doubts on its external predictivity.

Results for the dataset-3

Various statistical parameters viz. R^2_{tr}, $R^2_{adj.}$, R^2_{cv}, R^2_{LMO}, R^2_{Yrand}, s, R^2_{ex}, Kxx, ΔK, $RMSE_{tr}$, $RMSE_{cv}$, CCC_{tr}, CCC_{cv}, MAE_{tr}, MAE_{cv}, r^2_m av, and F (see Table 10) indicate low predictive ability and poor statistical performance of all the models. But, a closer inspection of various models indicates that the performance of residual-based model is better than the other models. Some of the statistical parameters like R^2_{tr}, R^2_{LMO}, s, R^2_{ex}, $RMSE_{tr}$, $RMSE_{cv}$, MAE_{tr}, and MAE_{cv} are with acceptable values. However, the model possesses low internal and external predictivity. As stated earlier, it is not a useful model at all for the prediction and pattern recognition. The Q^2-F^2 and Q^2-F^3 are negative which indicates that the model is useless for external predictivity.

Comparison of performance of splitting methodologies and statistical behavior of statistical parameters

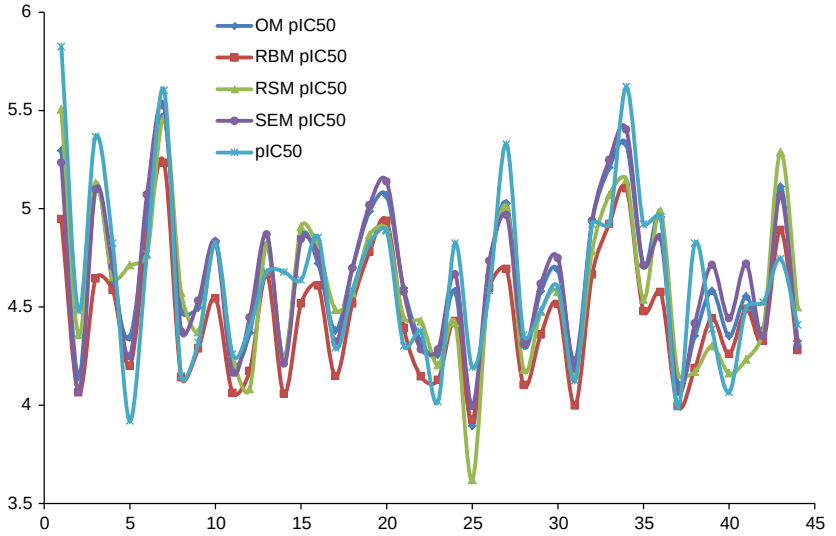
In the present analysis, information leakage was purposely performed for RBM. The descriptors were selected using the whole dataset, therefore, due to the information leakage, the selected descriptors must have captured the common structural features that influence the activity, and consequently, after splitting in any pattern/composition, the performance of RBM model for the all the datasets must be superior than SEM and RSM with respect to internal and external cross-validation parameters, i.e., must show high level of external predictivity with high validation score. Surprisingly, for RBM model, various validation parameters do not show expected behavior and values for all the datasets.

The random splitting models, for all the datasets, have varying performance; this could be due to the fact that during splitting the training or prediction set may not be covering the diversity of the whole dataset or the compounds are not close to each other. Repeating the random splitting several times is a good solution to arrive at best random splitting (Huang and Fan, 2011; Kiralj and Ferreira, 2009). Yet, as pointed out in a recent study, a QSAR model with high external predictivity for one prediction set does not necessarily indicate high accuracy for another external set (Huang and Fan, 2011). Therefore, precautions must be taken in using single random splitting.

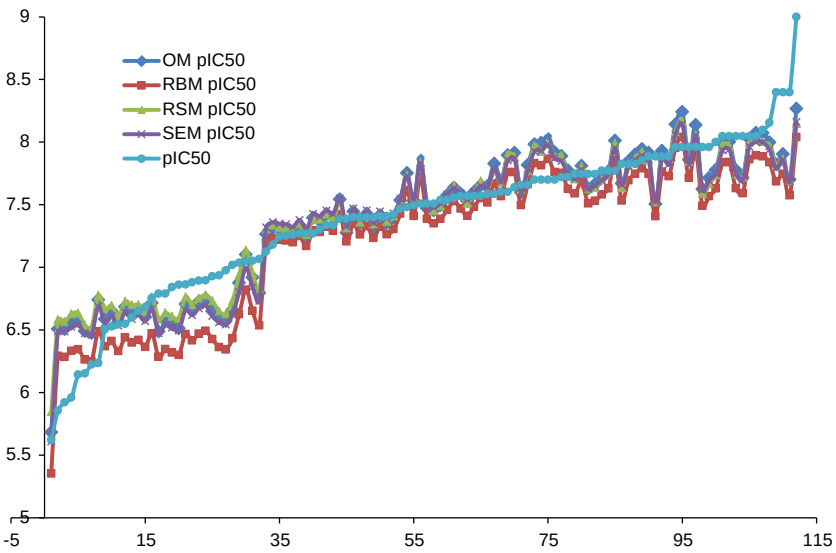
Since, the performance of the RBM, RSM, and SEM models is varying, but by luck or due to rational splitting, the researcher may arrive at the training and prediction sets that indicate high external predictive ability, such situation, though, leads to a statistically robust but a misguiding QSAR model as observed in RBM. An easy and handy solution to this problem is to develop a model using undivided dataset and compare its performance with the other models. Herein, in all the datasets, the performance of original model, though not better than residual based and sphere exclusion models, is still statistically satisfactory. It is expected that a model developed with no prediction set will be most accurate and possess the highest coverage for external evaluation set. But, a recent study reports exactly opposite results in certain situations (Martin *et al*., 2012). Therefore, we recommend and accentuate reporting of a statistically robust QSAR model that is developed using undivided whole dataset and same set of descriptors, which were selected and used in splitting-based model. Then, such a model tells the true effect of inclusion of compounds in the dataset. That is, it is useful in understanding the effect of increase/decrease in size of dataset as well as for capturing less privileged yet useful structural features that govern the activity.

A higher value of R^2_{tr} for residual-based model in all the datasets than the rest of the models indicates a better fitting or explanation of variance (see Tables 8–10). Similar trend for R^2_{ex} for residual-based model for different datasets confers as if the residual based splitting is better method of splitting. Therefore, a QSAR modeler may consider the residual-based model superior than others. This apparent superiority can be attributed to the purposeful selection of the training and the prediction sets, that is, the method of splitting has significant impact on many statistical parameters. Moreover, a careful comparison of residual values for all the models (see Fig. 3) reveals that the difference between the experimental and predicted in many instances is large in case of residual-based model than the others. But, during the calculation of various statistical parameters either sum or average is used. Therefore, the statistical parameters are unable to recognize this serious pitfall. In fact, a QSAR model based on splitting method with an unusually robust training set R^2_{tr} of 0.8 or greater than R^2_{tr} of undivided set

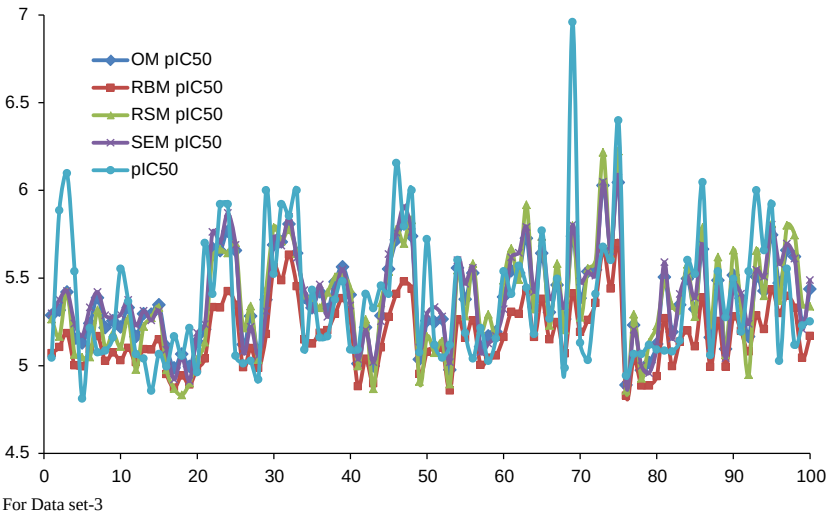
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For Data set-1



For Data set-2



For Data set-3

Fig. 3 Difference between experimental and predicted $p\mathrm{IC}_{50}$ by various models for dataset-1, 2, and 3 (*X-axis*: Compound number and *Y-axis*: $p\mathrm{IC}_{50}/p\mathrm{EC}_{50}$; *X-axis*: Serial number of compound, *Y-axis*: pIC_{50} value)

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should be viewed with suspicion. Some parameters like CCC_{ex}, $Q^2{-}F^1$, $Q^2{-}F^2$, $Q^2{-}F^3$, and r_m^2 are more successful in identifying this crucial aspect. This can be ascribed to the method of calculation of these parameters (Chirico and Gramatica, 2011, 2012); (Consonni *et al.*, 2009, 2010; Schuurmann *et al.*, 2008).

$$Q^2 - F^1 = 1 - \frac{\sum_{i=1}^{n_{ext}} (\hat{y}i - yi)^2}{\sum_{i=1}^{n_{ext}} (yi - \bar{y}_{tr})^2}$$

$$Q^2 - F^3 = 1 - \frac{\sum_{i=1}^{n_{ext}} (\hat{y}i - yi)^2 / n_{ext}}{\sum_{i=1}^{n_{tr}} (yi - \bar{y}_{tr})^2 / n_{tr}} .$$

$$Q^2 - F^2 = 1 - \frac{\sum_{i=1}^{n_{ext}} (\hat{y}i - yi)^2}{\sum_{i=1}^{n_{ext}} (yi - \bar{y}_{ext})^2}$$

$$r_m^2 = r^2\left(1 - \sqrt{r^2 + r_o^2}\right)$$

Thus, r_m^2 considers agreement between the actual and the predicted values as an essential factor to establish the true predictivity (Mitra *et al.*, 2010; Roy and Mitra, 2012). Thence, the statistical parameters viz. CCC_{ex}, $Q^2{-}F^1$, $Q^2{-}F^2$, $Q^2{-}F^3$, and r_m^2 reflect the factual performance of model regarding true external predictivity of a QSAR model. Therefore, these parameters should be used as criteria for selection of a consensus model, as in QSARINS v1.2. In QSARINS v1.2, MAE_{tr}, MAE_{ex}, $RMSE_{tr}$, $RMSE_{ex}$, CCC_{tr}, CCC_{ex}, $Q^2{-}F^1$, $Q^2{-}F^2$, $Q^2{-}F^3$, and some other parameters are used to find a consensus model.

In agreement with the previous reports, the trend of lower CCC with higher RMSE value is true for all the datasets (Chirico and Gramatica, 2011, 2012). However, the claim that the smaller the dataset size, the better the performances of r_m^2-EyPx and CCC compared to the other external validation measures was not observed for any of the dataset (Chirico and Gramatica, 2011, 2012). The similar values of $Q^2{-}F^1$and $Q^2{-}F^2$ for random splitting model for dataset 1 and 2 can be attributed to the fact that these parameters depend on agreement between the mean of the training and the prediction set values (Consonni *et al.*, 2009, 2010). For dataset 1 and 2, the mean of test and training sets values is very close to each other (see Table 11). A good difference between the mean of the undivided set and the training set values of the residual-based model for all the datasets indicates that the prediction set was not selected properly. Such a noticeable difference is absent in case of other models. This again indicates that residual-based method of splitting cannot be functionalised for splitting the dataset for external validation.

Since the whole dataset is involved in descriptor selection and model development, another point view toward the present approach is to consider it as a methodology to develop a model with good external predictivity using advantages of internal validation method. A model with good internal predictivity may or may not be good at external predictivity (Chirico and Gramatica, 2011, 2012; Consonni *et al.*, 2009, 2010; Gramatica 2013, Schuurmann *et al.*, 2008). In the present analysis, sphere exclusion model with higher values of $Q^2{-}F^3$, CCC_{ex}, and lower values of $RMSE_{ex}$, MAE_{ex} indicate good external predictivity of model.

Consonni et al. argued that increasing the mean of training set values increases Q^2 artificially (Consonni *et al.*, 2009). From Table 11, it is observed that the mean of the training set values for the random (for dataset- 1 and 2) and the sphere exclusion models (for dataset-1) is very close to mean of undivided set values; therefore, the value of Q^2 for these models should be close to Q^2 of the original model. However, for random splitting model, $Q^2 = 0.640$ for dataset-1, and $Q^2 = 0.836$ for dataset-2 are higher than that of the original model ($Q^2 = 0.597$). In addition, lower $Q^2 = 0.365$ for sphere exclusion model for dataset-1 than $Q^2 = 0.597$ for original model conflicts the finding of Consonni et al. The mean of the training set for residual model (=4.4652) is lower than mean of training set of undivided set (=4.6397). Therefore, for the sphere exclusion model, Q^2 should be lower than the Q^2 for original model, but the results are exactly opposite. Therefore, further studies are required to understand the effect of mean of training set on Q^2.

Conclusions

In conclusion, external validation based on single splitting is neither perfect nor absolutely accurate method of QSAR model validation as the statistical parameters can be influenced easily due to the biased and purposeful selection of the training and prediction sets. Moreover, the predictive ability of a QSAR model is sensitive toward the method of splitting and its manipulation is feasible. Thus, it is still insufficient to guarantee the true predictability of a QSAR model. The true external predictivity of any QSAR model cannot be decided on the basis of one or two parameters, that is, as many as possible statistical parameters should be calculated to judge the external predictivity. A good number of statistical parameters need to be calculated and presented to identify the true external predictivity of any QSAR model. We

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suggest and emphasize reporting of at least one statistically robust QSAR model that is developed using undivided whole dataset with appropriate cross validation.

In the present study, we presented a novel method for splitting the dataset for external validation. The residual method, though, generates statistically robust model but with low external predictivity. Further studies are in progress for the improvement of this method.

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Molecular docking and QSAR analyses for understanding the antimalarial activity of some 7-substituted-4-aminoquinoline derivatives

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N-(furan-2-ylmethyl)-N′-(7-phenoxyquinolin-4-yl)propane-1,3-diamine (PubChem CID: 56593944)
N-[(5-fluoro-2-methoxy-phenyl)methyl]-N′-[7-(3-methoxyphenoxy)-4-quinolyl]propane-1,3-diamine (PubChem CID: 56595146)
2-[[3-[[7-(4-chlorophenoxy)-4-quinolyl]amino]propylamino]methyl]-6-methoxy-phenol (PubChem CID: 56593662)
N-(1,3-benzodioxol-4-ylmethyl)-N′-[7-(4-tert-butylphenoxy)-4-quinolyl]propane-1,3-diamine (PubChem CID: 56593819)
N-(2-furylmethyl)-N′-(7-isopentyl-4-quinolyl)propane-1,3-diamine (PubChem CID 56593939)
(2H-1,3-benzodioxol-4-ylmethyl)(3-{[7-(2-phenylethyl)quinolin-4-yl]amino}propyl)amine (PubChem CID: 56594874)
N-(1,3-benzodioxol-4-ylmethyl)-N′-(7-phenethyl-4-quinolyl)propane-1,3-diamine (PubChem CID: 56594623)

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ABSTRACT

The quinoline moiety is one of the widely studied scaffolds for generating derivatives with various pharmacophoric groups due to its potential antimalarial activities. In the present study, a series of 7-substituted-4-aminoquinoline derivatives were selected to understand their antimalarial properties computationally by molecular modeling techniques including 2D QSAR, comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA) and molecular docking. The 2D-QSAR model built with four descriptors selected by genetic algorithm technique and CoMFA model showed satisfactory statistical results ($Q^2 = 0.540$, $R^2_{ncv} = 0.881$, F value = 157.09). A reliable CoMSIA model out of the fourteen different combinations has a Q^2 value of 0.638. The molecular docking studies of the compounds for 1CET as the protein target revealed that ten compounds showed maximum interactions with the binding site of the protein. The present study highlights the unique binding signatures of the ligands within the active site groove of the target and it explains the subtle differences in their EC_{50} values and their mechanism of inhibition.

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1. Introduction

Malaria is a severe and infectious disease caused mainly by *Plasmodium falciparum* (*P. falciparum*) (White et al., 2014). About 207 million cases and 627,000 deaths are reported annually, mainly in African sub-Saharan countries (Sonin et al., 2013). Recent reports show that *P. falciparum* has become resistant to all chemotherapeutic agents that are currently in use (O'Brien et al., 2011). Consequently World Health Organization (WHO) has recommended the use of Artemisinin-based combination therapy (ACT) for the treatment of *P. falciparum* related uncomplicated and severe malarial infection. But it has been reported that parasite shows resistance to Artemisinin, compounding an urgent requirement for additional therapeutic agents targeting *Plasmodium* parasites (Kyaw et al., 2013).

The quinoline moiety has attracted much consideration of medicinal chemists, as it is one of the imperative pharmacophores accountable for imparting antimalarial action (Boechat et al., 2014; Videnović et al., 2014; Mishra et al., 2014). Quinoline based drugs exert antimalarial activity by interfering with hemoglobin (Hb) degradation in the parasitic food vacuole. One of the waste products of the parasite's hemoglobin diet is ferriprotoporphyrin IX (FP); a toxic iron-containing molecule (O'Neill et al., 1998). The parasite detoxifies this molecule by means of a crystallization reaction that converts FP into non-toxic hemozoin or malaria pigment while the globin is hydrolyzed into individual amino acids (Ridley, 1996). The most accepted hypothesis is that antimalarial drugs form a complex with FP that inhibits the formation of hemozoin and result in an accumulation of toxic molecules in the parasite, which eventually kills it (Dorn et al., 1998).

In drug discovery process Quantitative Structure–Activity Relationships (QSAR) have great importance (Pourbasheer et al., 2013; Pourbasheer et al., 2010; Riahi et al., 2008, 2009). Molecular descriptors can be 2D as well as 3D. The 3D-QSAR models can be employed for the identification of regions in space which correlate with the biological activities (Du et al., 2012). The 3D QSAR models can be generated using Comparative Molecular Field Analysis (CoMFA) (Cramer et al., 1988) and the Comparative Molecular Similarity Indices Analysis (CoMSIA) (Klebe et al., 1994). CoMFA works out the steric and electrostatic fields surrounding the molecules and correlates the differences in these fields with biological activity. CoMSIA works out three more molecular descriptors than CoMFA: hydrophobic fields, H-bond donor fields and H-bond acceptor fields.

In the present work, the application of CoMFA, CoMSIA methods and molecular docking studies have been employed to generate quantitative models, to predict and determine the pharmacophoric features that govern the activity of 7-substituted 4-aminoquinoline analogs synthesized by Hwang et al. with antimalarial activity against the chloroquine (CQ) – resistant *Plasmodium* strains (Hwang et al., 2011), and to specify regions in space where interactive fields might enhance their activity. QSAR studies of these compounds have already been carried out by Masand et al. (2014). The objective of their study was to determine the factors that influence the activity of the selected compounds and generate QSAR models to predict the activity of molecules prior to actual synthesis and biological screening. They used GA-MLR and optimal SMILES-based descriptors to build QSAR models. The models elucidate that anti-malarial activity has high correlation with the topological distance of six between N and O. Also the models predicted that, the antimalarial activity depends on the presence of heavy atoms in the internal environment of the compounds. We have used *Plasmodium* lactate dehydrogenase (pLDH) in our *in silico* studies as it is an important enzyme of glycolysis and is essential for energy production in the Plasmodia. Moreover, Plasmodia lack functional Krebs cycle during some erythrocytic stages (Lang Unnasch and Murphy, 1998). Lactate dehydrogenase (LDH) is an essential enzyme that catalyses the interconversion of pyruvate and lactate with concomitant conversion of NADH and NAD^+ (Wiwanitkit, 2007). The parasite lactate dehydrogenase is a tetrameric enzyme containing 316 amino acids and present in all four human parasitic *Plasmodium* species. It is known that pLDH has notable structural and kinetic properties making it different from mammalian and bacterial LDH. The predictive ability of the generated model was tested by an external validation technique using 22 test set compounds. The obtained model was further used to generate contour maps for explaining the interaction of the compounds and to study SAR. Molecular docking studies were carried out to understand the important structural features required for binding at the active sites of the protein 1CET (Read et al., 1999).

2. Materials and methods

A series of 112 analogs of 7-substituted-4-aminoquinoline were taken to perform the present study. Table 1 describes the structures and EC_{50} values of the data set. The three-dimensional chemical structures of the compounds were drawn by ChemDraw (version 64-1.5.3). The optimization of the cleaned compounds was done through MOE (MOE Version 2007.09, Chemical Computing Group, Inc.).

2.1. 2D-QSAR modeling and dataset

EC_{50} (μM) data was converted to pEC_{50} (M) for all the QSAR analyses.

$$pEC_{50} = -\log EC_{50} \quad (1)$$

2.1.1. Descriptor calculation

A total of 251 descriptors were calculated which included 2D and 3D molecular descriptors (Lin, 2000). 2D descriptors which describe notation and terminology, physical properties, subdivided surface areas, atom counts and bond counts, Kier & Hall connectivity and Kappa shape indices, adjacency and distance, matrix, pharmacophore features and partial charges. 3D descriptors are classified into internal 3D descriptors (i3D) and external 3D descriptors (×3D) which describe potential energy, surface area, volume and shape and conformation-dependent charge. After objective feature selection filtering, finally a total of 37 descriptors were selected to build the 2D-QSAR model.

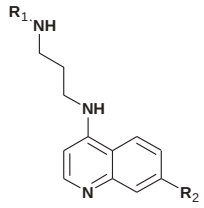
2.2. 3D-QSAR method

For the development of 3D-QSAR models the complete set of these compounds (112 compounds) were divided into a training set (90 compounds) to generate the models and a test set (22 compounds) to evaluate the predictive ability of the resulting models. The steric and electrostatic CoMFA potential fields were performed using Open3DQSAR (Tosco and Balle, 2011). MOE 2007.09 was used to explore the results and graphical visualization. The CoMSIA method was performed with the same parameters used in CoMFA analysis so as to evaluate the similarity indices among the compounds.

2.2.1. Partial least-squares analysis

The predictive ability of the 3D-QSAR models is assessed by applying partial least squares (PLS) analysis (Bush and Nachbar, 1993) as well as the leave-one-out (LOO) (Wold et al., 1984) cross-validation method. In the cross-validation analysis, LOO method was used, in which one compound was removed from

Table 1
Structures and antimalarial activities values of a series of 7-substituted-4-aminoquinline analogs.



Compounds	R_1	R_2	EC_{50} (μM)	pEC_{50} (M)
1	Furfuryl	PhO	0.314	6.5031
2[a]	2-HO-3-MeO-Bn	PhO	0.015	7.8239
3	Piperonyl	PhO	0.018	7.7447
4[a]	3-F-6-MeO-Bn	PhO	0.162	6.7905
5	Furfuryl	2-MeO-PhO	0.092	9.0000
6	2-HO-3-MeO-Bn	2-MeO-PhO	0.001	8.0458
7	Piperonyl	2-MeO-PhO	0.009	7.8539
8	3-F-6-MeO-Bn	2-MeO-PhO	0.009	7.6576
9	Furfuryl	3-MeO-PhO	0.014	8.0458
10	2-HO-3-MeO-Bn	3-MeO-PhO	0.022	7.7447
11	Piperonyl	3-MeO-PhO	0.023	6.7905
12	3-F-6-MeO-Bn	3-MeO-PhO	0.009	5.6198
13	Furfuryl	4-MeO-PhO	0.018	8.3979
14	2-HO-3-MeO-Bn	4-MeO-PhO	0.162	8.3979
15[a]	Piperonyl	4-MeO-PhO	2.400	7.3372
16	3-F-6-MeO-Bn	4-MeO-PhO	0.004	7.2676
17	Furfuryl	4-F-PhO	0.004	7.5850
18	2-HO-3-MeO-Bn	4-F-PhO	0.046	7.9586
19	Piperonyl	4-F-PhO	0.054	7.8239
20	3-F-6-MeO-Bn	4-F-PhO	0.026	6.5272
21	Furfuryl	4-Cl-PhO	0.011	7.3979
22[a]	2-HO-3-MeO-Bn	4-Cl-PhO	0.015	7.9586
23	Piperonyl	4-Cl-PhO	0.297	7.4202
24[a]	3-F-6-MeO-Bn	4-Cl-PhO	0.040	7.5086
25	Furfuryl	3-Me_2N-PhO	0.011	7.5686
26	2-HO-3-MeO-Bn	3-Me_2N-PhO	0.038	8.0000
27	Piperonyl	3-Me_2N-PhO	0.031	5.8539
28[a]	3-F-6-MeO-Bn	3-Me_2N-PhO	0.027	8.1549
29	Furfuryl	4-tertBu-PhO	0.010	5.9586
30	2-HO-3-MeO-Bn	4-tertBu-PhO	1.400	7.2676
31	Piperonyl	4-tertBu-PhO	0.007	6.8633
32	3-F-6-MeO-Bn	4-tertBu-PhO	1.100	6.9747
33	Furfuryl	4-F-Ph	0.054	7.4949
34	2-HO-3-MeO-Bn	4-F-Ph	0.137	8.0458
35	Piperonyl	4-F-Ph	0.106	7.7447
36	3-F-6-MeO-Bn	4-F-Ph	0.032	7.7447
37	Furfuryl	4-F-Bn	0.096	7.2441
38	2-HO-3-MeO-Bn	4-F-Bn	0.057	7.8239
39	Piperonyl	4-F-Bn	0.015	6.8962
40[a]	3-F-6-MeO-Bn	4-F-Bn	0.127	7.1249
41	Furfuryl	iso-pentyl	0.176	6.7545
42	2-HO-3-MeO-Bn	iso-pentyl	0.022	7.6576
43	Piperonyl	iso-pentyl	0.027	7.5686
44	3-F-6-MeO-Bn	iso-pentyl	0.116	6.9355
45	Furfuryl	cHexmethyl	0.055	7.2596
46	2-HO-3-MeO-Bn	cHexmethyl	0.050	7.3010
47	Piperonyl	cHexmethyl	0.041	7.3872
48	3-F-6-MeO-Bn	cHexmethyl	0.138	6.8601
49	Furfuryl	PhEt	0.046	7.3372
50	2-HO-3-MeO-Bn	PhEt	0.017	7.7696
51[a]	Piperonyl	PhEt	0.013	7.8861
52	3-F-6-MeO-Bn	PhEt	0.132	6.8794
53[a]	Furfuryl	iso-butyl	0.075	6.2358
54	2-HO-3-MeO-Bn	iso-butyl	0.581	7.6990
55	Piperonyl	iso-butyl	0.020	7.1805
56	3-F-6-MeO-Bn	iso-butyl	0.066	7.0506
57	Furfuryl	cHex	0.089	6.9281
58[a]	2-HO-3-MeO-Bn	cHex	0.118	7.7212
59[a]	Piperonyl	cHex	0.019	6.8928
60	3-F-6-MeO-Bn	cHex	0.128	7.0458
61	Furfuryl	1-Et-Pr	0.090	7.0655
62	2-HO-3-MeO-Bn	1-Et-Pr	0.086	8.3979
63[a]	Piperonyl	1-Et-Pr	0.004	7.5686

(*continued on next page*)

Table 1 (*continued*)

Compounds	R_1	R_2	EC_{50} (μM)	pEC_{50} (M)
64[a]	3-F-6-MeO-Bn	1-Et-Pr	0.027	7.3979
65	Furfuryl	3,5-CF_3-Ph	0.009	6.5452
66	2-HO-3-MeO-Bn	3,5-CF_3- Ph	0.018	7.5376
67	Piperonyl	3,5-CF_3-Ph	0.018	6.5467
68	3-F-6-MeO-Bn	3,5-CF_3-Ph	0.285	7.0362
69	Furfuryl	1-Naphtyl	0.029	7.5086
70	2-HO-3-MeO-Bn	1-Naphtyl	0.284	7.4815
71	Piperonyl	1-Naphtyl	0.031	6.2233
72[a]	3-F-6-MeO-Bn	1-Naphtyl	0.033	5.9208
73	Furfuryl	4-CF_3-Ph	0.598	7.6990
74	2-HO-3-MeO-Bn	4-CF_3-Ph	1.200	7.8861
75	Piperonyl	4-CF_3-Ph	0.020	7.6021
76[a]	3-F-6-MeO-Bn	4-CF_3-Ph	0.013	7.2676
77	Furfuryl	Ph	0.025	7.6990
78[a]	2-HO-3-MeO-Bn	Ph	0.054	8.0458
79	Piperonyl	Ph	0.020	7.7696
80	3-F-6-MeO-Bn	Ph	0.017	7.9586
81	Furfuryl	4-tertBu-Ph	0.011	6.1524
82[a]	2-HO-3-MeO-Bn	4-tertBu-Ph	0.704	6.6003
83	Piperonyl	4-tertBu-Ph	0.251	6.6517
84	3-F-6-MeO-Bn	4-tertBu-Ph	0.223	6.8416
85	Furfuryl	Piperonyl	0.144	7.7212
86	2-HO-3-MeO-Bn	Piperonyl	0.019	8.0969
87	Piperonyl	Piperonyl	0.008	7.5850
88	3-F-6-MeO-Bn	Piperonyl	0.026	7.5086
89	Furfuryl	4-MeO-Ph	0.031	7.9586
90	2-HO-3-MeO-Bn	4-MeO-Ph	0.011	7.8861
91	Piperonyl	4-MeO-Ph	0.013	7.5376
92[a]	3-F-6-MeO-Bn	4-MeO-Ph	0.029	7.0177
93	Furfuryl	3-CF_3-Bn	0.040	7.2518
94[a]	2-HO-3-MeO-Bn	3-CF_3-Bn	0.056	7.6021
95	Piperonyl	3-CF_3-Bn	0.025	7.4089
96	3-F-6-MeO-Bn	3-CF_3-Bn	0.039	7.3979
97	Furfuryl	4-CN-Bn	0.040	7.4089
98	2-HO-3-MeO-Bn	4-CN-Bn	0.039	7.9586
99	Piperonyl	4-CN-Bn	0.011	7.6383
100	3-F-6-MeO-Bn	4-CN-Bn	0.028	7.5528
101	Furfuryl	Bn	0.040	7.3979
102[a]	2-HO-3-MeO-Bn	Bn	0.017	7.7696
103	Piperonyl	Bn	0.720	6.1427
104	3-F-6-MeO-Bn	Bn	0.011	7.9586
105	Furfuryl	3,5-Me-Bn	0.009	8.0458
106	2-HO-3-MeO-Bn	3,5-Me-Bn	0.009	8.0458
107	Piperonyl	3,5-Me-Bn	0.041	7.3872
108[a]	3-F-6-MeO-Bn	3,5-Me-Bn	0.034	7.4685
109[a]	Furfuryl	2-Cl-4-F-Bn	0.020	7.6990
110	2-HO-3-MeO-Bn	2-Cl-4-F-Bn	0.013	7.8861
111	Piperonyl	2-Cl-4-F-Bn	0.027	7.5686
112	3-F-6-MeO-Bn	2-Cl-4-F-Bn	0.208	6.6819

[a] Test set compounds.

the data set and its activity was predicted using the model derived from the rest of the data set (Podlogar and Ferguson, 2000). The optimum number of components (ONC) and the highest cross-validated coefficient Q^2 were determined using the cross-validation method on the basis of the first minimum cross-validated standard error of prediction. The final non-cross-validated model was developed using ONC by producing the standard error of the estimate (SEE), the non-cross-validated correlation coefficient (R^2_{ncv}) and the *F*-test value.

Also, the CoMFA and CoMSIA models were assessed by predicting the activity of 22 external test set compounds. The predictive R^2 (R^2_{pred}) of test set compounds is computed using the following equation.

$$R^2_{pred} = \frac{(SD - PRESS)}{SD} \quad (2)$$

where SD is the sum of the squared deviations between the biological activity of compounds in the test set and the mean biological activity of the same, and the predictive sum of squares (PRESS) is the sum of the squared deviations between predicted and actual activity values of test set compounds. The model is said to be healthy and predictive if the statistical parameters $R^2_{ncv} > 0.6$, $R^2_{pred} > 0.5$, and $Q^2 > 0.6$. (Afantitis et al., 2009; Golbraikh and Tropsha, 2002).

To further validate the predictive ability of the constructed models, the following equation was used (Rännar et al., 1994):

$$R^2_{m(overall)} = R^2 \times \left(1 - \sqrt{R^2 - R^2_0}\right) \quad (3)$$

where R^2 is squared correlation coefficient between observed and predicted pEC_{50} values of 112 analogs of 7-substituted-4-aminoquinoline and R^2_0 is squared correlation coefficient with intercept set to zero. The parameter determines whether the range of predicted activity values for the whole dataset is really close to the observed activity or not. The value of $R^2_{m(overall)}$ should be greater than 0.5 for a satisfactory model.

2.3. Molecular docking

2.3.1. Target analysis

An X-ray crystallography structure of *P. falciparum* lactate dehydrogenase (PDB ID: 1CET) was obtained from the RCSB Protein Data Bank (Rose et al., 2015). The structure has a resolution of 2.05 Å.

2.3.2. Structure prediction and validation of the target

Primary structure prediction was carried out using the Expasy ProtParam server (Gasteiger et al., 2005). Physiochemical properties like theoretical isoelectric point (pI), molecular weight, total number of positive and negative residues, extinction coefficient, instability index, aliphatic index and Grand Average Value of Hydropathicity (GRAVY) are computed.

Secondary structure prediction has been carried out using Self-Optimized Prediction Method with Alignment (SOPMA) (Geourjon and Deléage, 1995). The protein sequence was submitted to the server and was analyzed for secondary structure.

The stereochemical quality of the protein was evaluated by Ramachandran plot using MOE 2007.09.

2.3.3. Energy minimization and molecular docking

Molecular docking studies are carried out using MOE (MOE Version 2007.09, Chemical Computing Group, Inc.), in order to explore the interaction mechanism and probable binding mode of 7-substituted-4-aminoquinoline derivatives at the active site of the protein 1CET. The energy of the protein molecule is minimized using the Energy minimization algorithm of MOE tool. The initial and final energy of protein are calculated (in kcal/mol) by GizMOE using MMFF94x force field with conjugant gradient method (Gill et al., 1981). In this molecular docking program, the flexibility of ligands is considered while the protein or biomolecule is considered as a rigid structure. A maximum of 30 conformations was allowed to be saved for each ligand using the default parameters of MOE. At the end of molecular docking, the best conformations of the ligands were analyzed for their binding interactions. The resulted binding interactions between these ligands and protein were observed.

3. Results and discussion

3.1. 2D-QSAR

The subjective feature selection was performed using Genetic Algorithm (GA) method in BuildQSAR. 2D-QSAR equation was chosen by optimizing the statistical results generated along with variations of the descriptors in the model.

18 outlier compounds with residuals more than two standard deviations away from the average residual were removed. Thus, the QSAR analysis included 87 compounds, which let us to investigate the model with up to four variables such as *SlogP_VSA9*, *GCUT_SMR_0*, *PEOE_VSA-6* and *opr_nring*.

$$\begin{aligned} pEC_{50} = {} & -0.0027\ (\pm 0.0020)\ SlogP_VSA9 \\ & + 42.1146\ (\pm 15.2143)\ GCUT_SMR_0 \\ & + 0.0480\ (\pm 0.0157)\ PEOE_VSA\text{-}6 \\ & - 0.1613\ (\pm 0.0973)\ opr_nring + 32.4558\ (\pm 10.4617) \end{aligned}$$

$n = 87$; $R = 0.831$; $s = 0.217$; $F = 21.702$; $p < 0.0001$; $Q^2 = 0.619$; SPRESS = 0.241; SDEP = 0.229.

SlogP_VSA9 which signifies sum of van der Waals surface area (in Å^2) calculation for each atom such that contribution to logP(o/w) (Li) > 0.40 is a 3D subdivided surface area descriptor. The Subdivided Surface Areas are descriptors based on an approximate accessible van der Waals surface area (in Å^2) calculation for each atom, v_i along with some other atomic property, p_i. The v_i are calculated using a connection table approximation. In the descriptions to follow, L_i denotes the contribution to logP(o/w) for atom i (Wildman and Crippen, 1999). The ranges were determined by percentile subdivision over a large collection of compounds. The negative coefficient of the descriptor indicates that an increase in the values of this descriptor decreases the antimalarial activity of the compounds. This is the reason for the low biological activity of the compound 32 which showed a high value of *SlogP_VSA9* (151.865).

GCUT_SMR_0 signifies the GCUT descriptors using atomic contribution to molar refractivity. It is an adjacency and distance matrix 2D Descriptor (Wildman and Crippen, 1999). The positive coefficient of *GCUT_SMR_0* shows that increase in the values of this descriptor is beneficial for antimalarial activity.

The next most important factor governing variation in the activity is *PEOE_VSA-6* which is a partial charge 2D descriptor and is directly proportional to the antimalarial activity. The Partial Equalization of Orbital Electronegativities (PEOE) method of calculating atomic partial charges is a method in which charge is transferred between bonded atoms until equilibrium (Gasteiger and Marsili, 1980). To guarantee convergence, the amount of charge transferred at each iteration is damped with an exponentially decreasing scale factor. The amount of charge transferred, dq_{ij}, between atoms i and j when $X_i > X_j$ is

$$dqij = (1/2^k)(X_i - X_j)/X_j^+ \tag{4}$$

where X_j^+ is the electronegativity of the positive ion of atom j; X_i is the electronegativity of atom i (quadratically dependent on partial charge); and k is the iteration number of the algorithm. The PEOE charges depend only on the connectivity of the input structures: elements, formal charges and bond orders. Descriptors using the PEOE charges are prefixed with *PEOE_*. *PEOE_VSA-6* represents the sum of van der Waals surface area (Å^2) of an atom where the partial charge of atom is less than −0.30.

The 2D descriptor *opr_nring* describes the number of rings bonds present in the compound (Oprea, 2000). The negative coefficient of *opr_nring* showed that a decrease in the values of this descriptor is beneficial for antimalarial activity.

Thus, *GCUT_SMR_0* and *PEOE_VSA-6* increases the antimalarial activity while the descriptors *SlogP_VSA9* and *opr_nring* decreases the antimalarial activity.

For the reliability of a 2D-QSAR model both Q^2 and R^2 values should be high. More often, a value of $Q^2 > 0.5$ is considered satisfactory (Ponce et al., 2004; Strazielle and Ghersi-Egea, 2005).

High correlation coefficient ($R = 0.831$) indicates good variance explanation of the model, further supported by low standard deviation ($s = 0.217$). Further, evaluation of the degree of statistical significance was accomplished by the Fischer test (F) and level of confidence ($p < 0.0001$). The validation parameters ($Q^2 = 0.619$ and SPRESS = 0.241), reflects the good predictive power of the model generated. Observed, predicted antimalarial activities and residual values of statistically significantly model obtained are shown in Table 2.

The plot of observed versus predicted activity (Fig. 1) shows a good fit with R^2 value of 0.69 and indicates that the model developed is able to predict the activity of the compounds quite well.

3.2. 3D-QSAR analysis

3.2.1. CoMFA

The predicted pEC_{50} values by CoMFA model are listed in Table 3. Fig. 2 demonstrates the correlation between experimental

Table 2
Observed, predicted and residual values of the compounds with antimalarial activity.

Compounds	Observed pEC_{50}	Predicted pEC_{50}	Residual
2	7.824	7.848	−0.024
3	7.745	7.528	0.216
6	8.046	8.087	−0.041
7	7.854	7.663	0.191
8	7.658	7.572	0.085
9	8.046	7.924	0.122
10	7.745	8.061	−0.316
13	8.398	7.990	0.408
14	8.398	8.101	0.297
15	7.337	7.686	−0.348
16	7.268	7.659	−0.391
17	7.585	7.664	−0.079
18	7.959	7.809	0.150
19	7.824	7.532	0.292
21	7.398	7.627	−0.229
22	7.959	7.911	0.048
23	7.420	7.496	−0.076
24	7.509	7.474	0.034
25	7.569	7.538	0.031
26	8.000	8.021	−0.021
30	7.268	7.480	−0.213
31	6.863	7.115	−0.252
32	6.975	7.071	−0.097
33	7.495	7.603	−0.108
34	8.046	7.919	0.127
35	7.745	7.523	0.222
36	7.745	7.490	0.254
37	7.244	7.506	−0.262
38	7.824	7.803	0.021
40	7.125	7.386	−0.261
41	6.754	6.986	−0.232
42	7.658	7.341	0.317
44	6.936	6.907	0.028
45	7.260	7.154	0.106
46	7.301	7.574	−0.273
47	7.387	7.172	0.215
48	6.860	7.137	−0.277
49	7.337	7.641	−0.304
50	7.770	8.042	−0.272
51	7.886	7.580	0.306
54	7.699	7.360	0.339
55	7.180	6.989	0.191
56	7.051	6.916	0.135
57	6.928	7.218	−0.290
58	7.721	7.632	0.090
59	6.893	7.234	−0.341
60	7.046	7.198	−0.152
61	7.066	7.204	−0.139
63	7.569	7.184	0.385
64	7.398	7.223	0.175
66	7.538	7.723	−0.186
68	7.036	7.013	0.023
69	7.509	7.373	0.135
70	7.481	7.256	0.225
73	7.699	7.448	0.251
74	7.886	7.722	0.164
75	7.602	7.336	0.266
76	7.268	7.296	−0.028
77	7.699	7.559	0.140
78	8.046	7.912	0.134
79	7.770	7.503	0.267
83	6.652	6.997	−0.346
84	6.842	6.990	−0.148
85	7.721	7.748	−0.027
86	8.097	7.977	0.120
87	7.585	7.585	0.000
88	7.509	7.529	−0.020
89	7.959	7.866	0.092
90	7.886	8.090	−0.204
91	7.538	7.702	−0.164
93	7.252	7.492	−0.240
94	7.602	7.867	−0.265
95	7.409	7.452	−0.043
96	7.398	7.422	−0.024
97	7.409	7.636	−0.227
98	7.959	7.999	−0.040
99	7.638	7.581	0.057
100	7.553	7.541	0.012
101	7.398	7.638	−0.240
102	7.770	8.045	−0.275
104	7.959	7.579	0.380
106	8.046	7.851	0.195
107	7.387	7.446	−0.059
108	7.469	7.404	0.065
109	7.699	7.561	0.138
110	7.886	7.894	−0.008
111	7.569	7.476	0.092

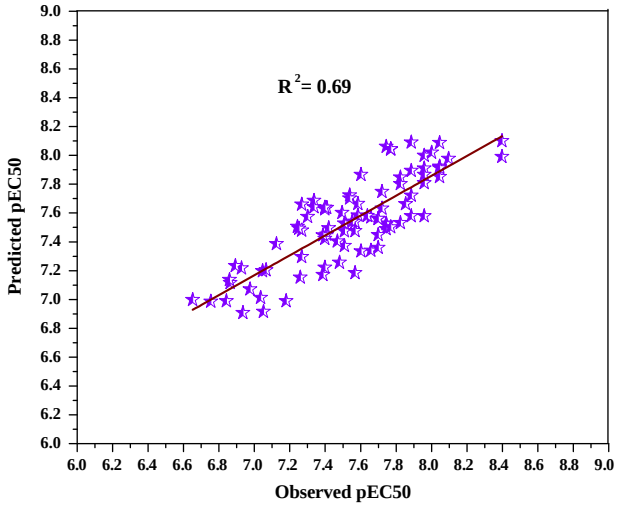


Fig. 1. Plot of actual versus predicted antimalarial activity using 2D-QSAR.

and predicted pEC_{50} values by CoMFA model. It shows a R^2 value of 0.8157.

Statistical parameters derived for CoMFA model are summarized in Table 4. The derived CoMFA model illustrates a cross-validated Q^2 of 0.540 by four components. The optimal number of components (ONC) was calculated by selecting the highest Q^2 value. The non-cross-validated PLS analysis with the four components resulted in a R^2_{ncv} of 0.881, F = 157.090 and SEE of 0.214.

According to Table 4, the contributions of steric and electrostatic fields calculated by the CoMFA model are 46.7% and 53.3%, respectively, suggesting that the steric and electrostatic fields have been found to be almost equally important. The obtained high F, Q^2 and R^2_{ncv} values along with the lower SEE indicate the satisfactory predictive ability of the derived model (Table 4).

To further make sure the predictive ability of the CoMFA model an external test set of 22 compounds, which were not included in the QSAR model generation study was used. The CoMFA model showed an R^2_{pred} value of 0.518. The $R^2_{m(overall)}$ = 0.6604 was calculated and the results shows that the generated model shows a good predictive ability.

3.2.2. CoMFA contour maps

The steric and electrostatic contour maps resulted by CoMFA model based on the reference compound (compound 5) are revealed in Fig. 3. In this figure, the green contours point out the regions where presence of bulkier groups (80% contribution) would donate to enhance the biological activity while the yellow contours (20% contribution) illustrate the regions where such bulkier groups result in reduction of biological activities. Fig. 3A demonstrates the

steric field effects. The CoMFA electrostatic contour maps (Fig. 3B) are represented by red[1] and blue contours. The red contours (20% contribution) demonstrate the regions where electron-rich (electronegative) groups result in increase of biological activity whereas the blue contours (80% contribution) indicate the regions where presence of positive charge (or decreased negative charge) group would result in an increase of biological activity.

The steric contours of the CoMFA display a large green contour near R1 region demonstrating the favorable effect of bulky groups in raising the biological activities of the compounds. According to Table 1, this can be explained by comparing the activities of compounds 61 and 62 where bulk groups (–2-HO-3-MeO-Bn > –Furfuryl) at R1 substituent would result in lower EC_{50} values of 0.004 and 0.086, respectively. Same type of behavior is observed between compounds 25 and 26. The compound 26 has higher inhibitory activity (pEC_{50} = 8.00) and bulky characteristics than compound 25 (pEC_{50} = 7.57). Using the bulky substituents (–2-HO-3-MeO-Bn > –Furfuryl) R1 would lead to increase of pEC_{50} values in the compounds: 86 (having –2-HO-3-MeO-Bn group with pEC_{50} = 8.10) and 85 (having –Furfuryl group with pEC_{50} = 7.72). This effect can also be observed between compounds 34 and 35 where their higher activities can be related to the presence of –Piperonyl and –2-HO-3-MeO-Bn substituents, in which by increasing the bulky behavior of substituent (–Piperonyl < –2-HO-3-MeO-Bn) the inhibitory activities would be increased (7.74 < 8.04). As the bulkiness of the groups decreases in the order 2-HO-3-MeO-Bn > 3-F-6-MeO-Bn > Piperonyl > Furfuryl, the biological activity of the compounds decreases in the order 78 (8.04) > 80 (7.95) > 79 (7.77) > 77 (7.70), respectively. The steric contours of the CoMFA display a tiny green contour near the R2 region. This can be explained by comparing the order of activities of compounds 14 and 78. The compound 14 possesses –4-MeO-PhO substituent in contrast to the compound 78 which has only a Ph substituent at the same position and hence shows higher inhibitory activity (8.40 > 8.04). A comparison between compounds 28 and 80 reveals that compound 28 possesses 3-F-6-MeO-Bn group and displays higher inhibitory activity (pEC_{50} = 8.15) than compound 80 which contains a phenyl substituent as R2 (pEC_{50} = 7.96). As it can be seen from Fig. 3A, the steric contours map shows a small yellow contour at the R1 substituent region which exemplifies the unfavorable effect of bulky groups in some series of compounds. As shown by the pEC_{50} values, using bulky groups such as –3-F-6-MeO-Bn (compound 12 with pEC_{50} = 5.62) in contrast to –Furfuryl (compound 9 with pEC_{50} = 8.04) would result in decrease of activities. This fact can also be described by comparing compounds 72 (having 3-F-6-MeO-Bn as R1) with 69 (having Furfuryl group as R1). Replacing the R1 substituent with a bulkier group would result in decreasing of the pEC_{50} values (5.92 < 7.40).

Fig. 3B which represents the electrostatic contour plot has a blue contour near R2 group and a small blue contour in the bottom of R1 group. The small blue contour at the bottom of R1 group can be explained by comparing compounds 13 and 16 where replacing of 3-F-6-MeO-Bn in place of furfuryl is found to increase the negative charge behavior of this substituent. Consequently, the pEC_{50} values would be decreased (7.26 < 8.40). This blue contour map clearly explains why compound 9 showed higher inhibitory activities (8.04) than compound 10 (7.74). The blue contours at the R2 substituent can be understood by comparing compounds 62 (having –1-Et-Pr group with pEC_{50} = 8.40) and 78 (having –Ph group with pEC_{50} = 8.04) where using the positive charge group as R2 would lead to increasing the inhibitory activities. This fact is also observed among compounds 105, 89 and 73 where increasing the negative charge properties (–4-CF_3-Ph > –4-MeO-Ph > 3,5-Me-Bn) would result in decrease of inhibitory activities (7.70 < 7.96 < 8.05), respectively. The blue contours observed near R2 substituent can be described considering compounds 106 and 94; whereas, positive charge features increased (3,5-Me-Bn > –3-CF_3-Bn), the inhibitory activities (8.05 > 7.60) are also increased. The increasing biological activity can also be observed among compounds 75, 35, 79 and 51 where increasing the positive charge properties (4-CF_3 < –Ph < 4-F-Ph < –Ph < –PhEt) would result in increase of inhibitory activities (7.60 < 7.74 < 7.77 < 7.87), respectively. Fig. 3B demonstrated small red contours near the R2 substituent. The red contours can be explained by comparing compounds 34 and 50 where using the negative charge groups (–4-F-Ph > PhEt) would result in higher biological activities (8.05 > 7.77), respectively. The small red contour at the bottom of R1 group can be explained by comparing compounds 13 and 16 where replacing 3-F-6-MeO-Bn in place of –furfuryl would increase the negative charge behavior of this substituent, and consequently, the pEC_{50} values would be increased (compound 13; pEC_{50} = 7.26 < compound 16; pEC_{50} = 8.40). The red contour map clearly explains that why compound 78 showed higher inhibitory activities (8.05) than compound 77 (7.70).

3.2.3. CoMSIA

In addition to steric (S) and electrostatic (E) fields calculated by the CoMFA approach, hydrophobic (H), hydrogen-bond donor (D) and hydrogen-bond acceptor (A) fields can be derived using the CoMSIA method (Klebe et al., 1994). Different combinations of fields are combined to generate a total of 14 CoMSIA models. The statistical results of the constructed CoMSIA models are summarized in Table 5.

Fig. 4 demonstrates the correlation between experimental and predicted pEC_{50} values by CoMSIA model 12. It shows a R^2 value of 0.8701.

The donor and acceptor fields produced the lowest Q^2 and R^2_{ncv}, whereas the combined steric and electrostatic fields gave good Q^2 and R^2_{ncv} values. Although Q^2 for the CoMSIA model 8 show high R^2_{ncv} value the R^2_{ncv} is slightly lower. The CoMSIA model 4 gave fine Q^2 and R^2_{ncv} values but CoMSIA model 12, however, the combination of hydrophobic field provided more information and better values. Thus according to Table 5, the constructed CoMSIA model 12 with steric, hydrophobic, H-bond donor and H-bond acceptor fields could provide high statistical values for Q^2 (0.638) and R^2_{ncv} (0.946) values with the 10 optimum components. The statistical parameters calculated by CoMSIA model 12 indicate the satisfactory F value of 138.972 with the less SEE value of 0.149. The steric (S), hydrophobic (H) H-bond donor (D) and H-bond acceptor (A) field descriptor contributions were 23.1%, 44.6%, 21.5% and 10.8%, respectively.

The CoMSIA model showed an R^2_{pred} value of 0.521. The $R^2_{m(overall)}$ = 0.760 was calculated and the results shows that the generated model shows a good predictive ability.

3.2.4. CoMSIA contour maps

The contour plots of the CoMSIA model-12 are presented in Fig. 5 which illustrates the steric, hydrophobic, H-bond acceptor and H-bond donor fields using the most active compound 5.

As shown in Fig. 5A, the steric field displayed a large yellow contour in the region of the R2 substituent and a large green contour around the R1 substituent. The yellow contour around the R2 substituent can be understood by comparing the compounds 51 (having PhEt group with pEC_{50} = 7.89) and 107 (having 3,5-Me-Bn group with pEC_{50} = 7.39) where the presence of bulkier size group would result in decrease of pEC_{50} values. This effect can be explained further by considering compounds 77 (having Phenyl group with pEC_{50} = 7.70) and 81 (having 4-tertBu-Ph group with

[1] For interpretation of color in Figs. 3 and 5, the reader is referred to the web version of this article.

Table 3
Experimental activity and predicted activity of the compounds based on 3D-QSAR analysis (CoMFA and CoMSIA).

Compounds	Actual pEC_{50} (M)	Predicted pEC_{50} (M) CoMFA	Residual CoMFA	Predicted pEC_{50} (M) CoMSIA	Residual CoMSIA
1	6.5031	6.681	−0.1779	6.595	−0.2279
2[a]	7.8239	7.376	0.4479	7.393	0.3419
3	7.7447	7.654	0.0907	7.622	0.1197
4[a]	6.7905	7.580	−0.7895	7.242	−0.2805
5	9.0000	8.554	0.4460	8.956	0.1090
6	8.0458	7.884	0.1618	8.155	−0.0032
7	7.8539	7.957	−0.1031	8.084	−0.2721
8	7.6576	7.755	−0.0974	7.651	−0.0384
9	8.0458	7.853	0.1928	7.848	0.1968
10	7.7447	7.954	−0.2093	7.624	0.0747
11	6.7905	7.253	−0.4625	7.041	−0.3775
12	5.6198	5.311	0.3088	5.532	0.0818
13	8.3979	8.272	0.1259	8.429	−0.0151
14	8.3979	8.466	−0.0681	8.373	0.0089
15[a]	7.3372	7.802	−0.4648	7.469	0.0982
16	7.2676	7.278	−0.0104	7.090	0.2396
17	7.5850	7.648	−0.0630	7.757	−0.1020
18	7.9586	7.782	0.1766	7.973	−0.1014
19	7.8239	7.428	0.3959	7.439	0.4699
20	6.5272	6.929	−0.4018	6.993	−0.4558
21	7.3979	7.255	0.1429	7.382	0.0309
22[a]	7.9586	7.802	0.1566	7.966	0.1186
23	7.4202	7.432	−0.0118	7.475	−0.0138
24[a]	7.5086	7.223	0.2856	7.260	0.3286
25	7.5686	7.901	−0.3324	7.511	−0.0074
26	8.0000	8.059	−0.0590	8.036	0.0060
27	5.8539	5.690	0.1639	5.743	0.0899
28[a]	8.1549	7.829	0.3259	7.438	0.7739
29	5.9586	5.825	0.1336	6.059	0.0076
30	7.2676	7.417	−0.1494	7.279	−0.0774
31	6.8633	6.739	0.1243	6.865	−0.0217
32	6.9747	6.698	0.2767	6.910	0.0487
33	7.4949	7.745	−0.2501	7.668	−0.2741
34	8.0458	8.177	−0.1312	8.161	−0.1292
35	7.7447	7.763	−0.0183	7.792	0.0707
36	7.7447	7.460	0.2847	7.496	0.2247
37	7.2441	7.486	−0.2419	7.447	−0.1769
38	7.8239	7.661	0.1629	7.727	0.0179
39	6.8962	7.086	−0.1898	6.803	−0.1098
40[a]	7.1249	7.390	−0.2651	7.113	−0.1781
41	6.7545	7.012	−0.2575	6.749	−0.0025
42	7.6576	7.267	0.3906	7.599	0.0016
43	7.5686	7.176	0.3926	7.436	0.2396
44	6.9355	6.910	0.0255	7.055	−0.1405
45	7.2596	7.091	0.1686	7.184	0.0026
46	7.3010	7.252	0.0490	7.247	−0.0930
47	7.3872	7.345	0.0422	7.353	−0.0218
48	6.8601	6.885	−0.0249	6.903	−0.2199
49	7.3372	7.455	−0.1178	7.237	0.1342
50	7.7696	7.815	−0.0454	7.820	−0.0394
51[a]	7.8861	7.216	0.6701	6.794	0.7831
52	6.8794	7.109	−0.2296	6.809	0.0514
53[a]	6.2358	6.585	−0.3492	6.702	−0.6272
54	7.6990	7.629	0.0700	7.748	−0.1300
55	7.1805	7.291	−0.1105	7.249	−0.0545
56	7.0506	7.394	−0.3434	7.065	0.0046
57	6.9281	7.124	−0.1959	7.016	0.0351
58[a]	7.7212	7.076	0.6452	7.225	0.4872
59[a]	6.8928	7.010	−0.1172	6.995	−0.0332
60	7.0458	6.995	0.0508	7.004	−0.0342
61	7.0655	7.182	−0.1165	7.013	0.1585
62	8.3979	7.998	0.3999	8.340	0.0429
63[a]	7.5686	7.341	0.2276	7.307	0.5766
64[a]	7.3979	7.721	−0.3231	7.786	−0.0651
65	6.5452	6.502	0.0432	6.478	−0.0008
66	7.5376	7.419	0.1186	7.483	0.0086
67	6.5467	6.828	−0.2813	6.628	−0.0353
68	7.0362	7.115	−0.0788	7.077	0.0242
69	7.5086	7.468	0.0406	7.541	0.0226
70	7.4815	7.314	0.1675	7.507	0.0225
71	6.2233	6.329	−0.1057	6.299	0.0343
72[a]	5.9208	5.866	0.0548	6.017	−0.0432
73	7.6990	7.918	−0.2190	7.852	−0.0430

Table 3 (*continued*)

Compounds	Actual pEC_{50} (M)	Predicted pEC_{50} (M) CoMFA	Residual CoMFA	Predicted pEC_{50} (M) CoMSIA	Residual CoMSIA
74	7.8861	8.117	−0.2309	7.880	0.0001
75	7.6021	7.666	−0.0639	7.509	0.0061
76[a]	7.2676	7.504	−0.2364	7.436	−0.3214
77	7.6990	7.620	0.0790	7.673	0.1110
78[a]	8.0458	7.981	0.0648	8.116	−0.0192
79	7.7696	7.623	0.1466	7.760	0.0696
80	7.9586	7.979	−0.0204	7.958	−0.0354
81	6.1524	6.326	−0.1736	6.035	0.2054
82[a]	6.6003	7.311	−0.7107	7.057	−0.4247
83	6.6517	6.822	−0.1703	6.750	−0.0843
84	6.8416	6.801	0.0406	6.835	0.0046
85	7.7212	7.783	−0.0618	7.619	0.1142
86	8.0969	8.220	−0.1231	8.074	0.0279
87	7.5850	7.674	−0.0890	7.575	−0.0160
88	7.5086	7.560	−0.0514	7.430	−0.0524
89	7.9586	7.838	0.1206	7.943	0.2156
90	7.8861	7.832	0.0541	7.886	0.0161
91	7.5376	7.642	−0.1044	7.610	−0.0444
92[a]	7.0177	7.449	−0.4313	7.326	−0.4413
93	7.2518	7.144	0.1078	7.245	−0.0232
94[a]	7.6021	7.330	0.2721	7.328	0.1631
95	7.4089	7.422	−0.0131	7.534	−0.0731
96	7.3979	7.459	−0.0611	7.480	0.0699
97	7.4089	6.993	0.4159	7.360	0.0299
98	7.9586	7.740	0.2186	7.983	−0.1194
99	7.6383	7.557	0.0813	7.633	0.0733
100	7.5528	7.379	0.1738	7.690	0.0228
101	7.3979	7.435	−0.0371	7.533	−0.1231
102[a]	7.7696	7.422	0.3476	7.381	0.1746
103	6.1427	6.760	−0.6173	6.225	−0.1623
104	7.9586	7.427	0.5316	7.685	0.3956
105	8.0458	8.026	0.0198	8.035	−0.0482
106	8.0458	8.179	−0.1332	7.895	0.0948
107	7.3872	7.373	0.0142	7.414	0.0612
108[a]	7.4685	7.517	−0.0485	7.345	0.3295
109[a]	7.6990	7.859	−0.1600	8.227	−0.5010
110	7.8861	7.841	0.0451	7.823	0.0981
111	7.5686	7.442	0.1266	7.515	0.0966
112	6.6819	6.950	−0.2681	6.712	−0.2891

[a] Test set compounds.

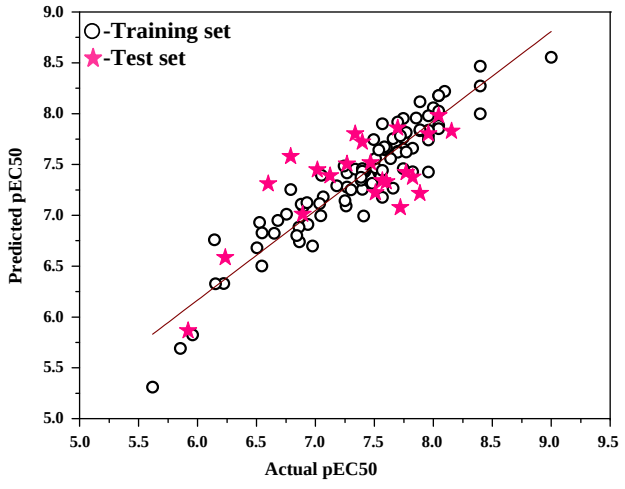


Fig. 2. Plot of actual versus predicted antimalarial activity using CoMFA model.

Table 4
Statistical results of CoMFA and CoMSIA models.

	CoMFA	CoMSIA model 12
Q^2/ONC[a]	0.540/4	0.638/10
R^2_{ncv}[b]	0.881	0.946
SEP[c]	0.437	0.385
SEE[d]	0.214	0.149
R^2_{pred}[e]	0.518	0.521
F value	157.090	138.972
Field distribution percent		
Steric	46.7	23.1
Electrostatic	53.3	–
Hydrophobic	–	44.6
H-bond donor		21.5
H-bond acceptor	–	10.8

[a] Cross-validated correlation coefficient.
[b] Non cross-validated correlation coefficient.
[c] Standard error of prediction.
[d] Standard errors of estimate.
[e] Predicted correlation coefficient for the test set.

pEC_{50} = 6.15) where 4-tertBu-Ph group has bulkier size in contrast to phenyl group and, therefore, showed lower inhibitory activity. As shown by the pEC_{50} values, using bulky groups such as 4-tertBu-PhO (compound 29 with pEC_{50} = 5.96) in contrast to 4-MeO-Ph group (compound 89 with pEC_{50} = 7.96) would result in decrease of activities. The green contour demonstrates the favorable effect of bulky groups in increasing the biological activities of compounds. According to Table 1, this can be explained by comparing the activities of compounds 86 and 85 where using bulk groups (–2-HO-3-MeO-Bn > –Furfuryl) at R1 substituent would result in decrease of EC_{50} values (0.008 < 0.019), respectively. This is also

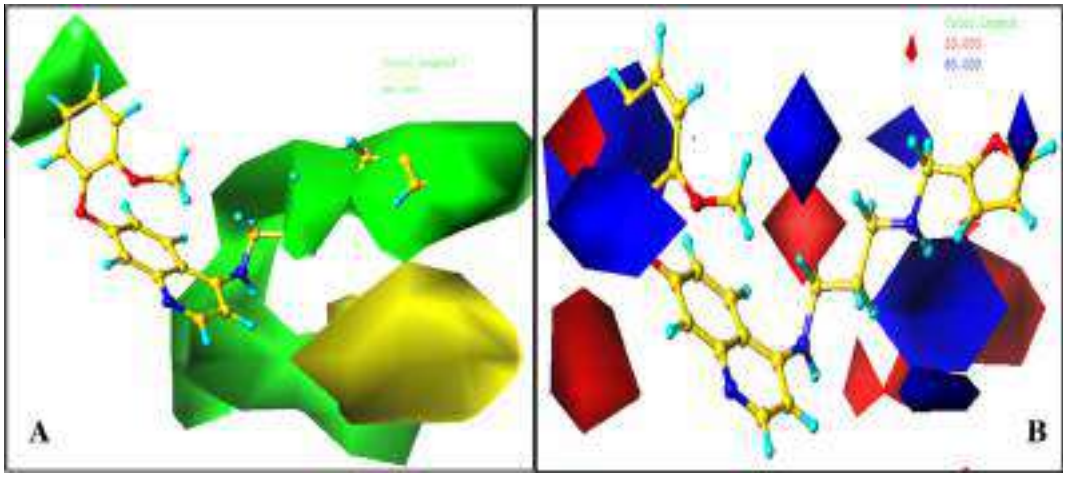


Fig. 3. Contour maps of CoMFA: (A) steric field and (B) electrostatic field based on compound 5.

observed between compounds 90 and 91 where compound 90 shows higher inhibitory activity (pEC_{50} = 7.89) and bulky characteristics than compound 91 (pEC_{50} = 7.54). As can be seen from Table 1, using the bulky substituents (–2-HO-3-MeO-Bn > –Furfuryl) as R1 would lead to increase of pEC_{50} values in the compounds: 46 (having –2-HO-3-MeO-Bn group with pEC_{50} = 7.30) and 45 (having furfuryl group with pEC_{50} = 7.26). This effect can also be observed between compounds 26 and 27 where their higher activities can be related to the presence of 2-HO-3-MeO-Bn and Piperonyl substituents, namely in which by increasing the bulky behavior of substituent (2-HO-3-MeO-Bn > Piperonyl) the inhibitory activities would be increased (8.00 > 5.85).

Fig. 5B demonstrated the hydrophobic contour maps. In a hydrophobic field, orange and blue contours are highlighted areas where the orange contours represents the presence of hydrophobic substituents and using them would be favorable for better activity (favored level 80%), while blue contours indicate regions where hydrophobic groups decrease the biological activity (unflavored level 20%). Fig. 5B displays the large orange contours near R1 region and R2 region, and several small blue contours near R1 and R2 substituents.

Fig. 5C indicates that the presence of H-bond donor group would lead to enhance the inhibitory activity in cyan regions (80% contribution) while the presence of H-bond donor group would lead to decrease the inhibitory activity in purple regions (20% contribution). There is medium purple contours near R1 substituent which can be explained by comparing compounds 78 and 80 where replacing a 2-HO-3-MeO-Bn group in place of 3-F-6-MeO-Bn group would decrease the pEC_{50} value (7.96 < 8.04). The H-bond donor R1 substituents (–2-HO-3-MeO-Bn > –3-F-6-MeO-Bn) would lead to decrease of pEC_{50} values in the compounds: 106 (having –2-HO-3-MeO-Bn group with pEC_{50} = 8.05) and 108 (having 3-F-6-MeO-Bn group with pEC_{50} = 7.47). This effect can also be observed between compounds 46 and 54 where their lower activities can be related to the presence of –2-HO-3-MeO-Bn as R1 substituent, when compared to the compounds 48 and 56, respectively; having 3-F-6-MeO-Bn as R1 substituent. There are no major cyan contours near R1 and R2 substituents.

H-bonds acceptor field was also considered to be important for the activity of the ligands. The H-bonds acceptor contour maps were also provided by the CoMSIA model to facilitate structural optimization. Fig. 5D indicates that the presence of H-bond acceptor group would lead to the decrease of the inhibitory activity in red regions (20% contribution). From the Fig. 5D it is clear that there is no magenta contour which represents the favoured region (80% contribution). There is a large red contour near R1 substituent. The red contour near R1 can be explained by comparing compounds 20 and 18 where replacing a 3-F-6-MeO-Bn group in place of 2-HO-3-MeO-Bn group would decrease the H-bonds acceptor behavior of the substituent, and consequently, the pEC_{50} values would be increased (7.96 > 6.53). It can also be explained by comparing compounds 26 and 28 where replacing a 2-HO-3-MeO-Bn group which has lesser H-bond acceptor tendency in place of 3-F-6-MeO-Bn group which is a H-bond acceptor group would increase the pEC_{50} value (8.05 > 8.00). The H-bond acceptor R1 substituents (–3-F-6-MeO-Bn) would lead to decrease of pEC_{50} value (7.96) in the compound 104 compared with the compound 102 (having –2-HO-3-MeO-Bn group with pEC_{50} = 7.77).

Table 5
Statistical parameters of CoMSIA models.

Model	Descriptors	$R^2_{COO}(Q^2)$/ ONC	R^2_{ncv}/SEE_{ncv}	*F* value	$R^2_{m(overall)}$	R^2_{pred}
1	S and E	0.592/8	0.962/0.124	255.632	0.762	0.391
2	D and A	0.411/4	0.671/0.355	43.351	0.339	0.392
3	S, E and H	0.593/7	0.943/0.151	193.697	0.764	0.516
4	S, E and A	0.613/8	0.962/0.124	256.727	0.766	0.393
5	S, E and D	0.603/9	0.957/0.132	198.397	0.722	0.290
6	D, A and H	0.657/10	0.944/0.152	133.561	0.754	0.493
7	D, A and S	0.453/10	0.883/0.220	59.646	0.639	0.354
8	D, A and E	0.595/9	0.958/0.131	202.186	0.718	0.261
9	S, D and H	0.606/7	0.903/0.196	109.366	0.698	0.527
10	S, E, D and A	0.609/9	0.958/0.132	200.297	0.725	0.307
11	S, E, D and H	0.616/8	0.951/0.140	198.490	0.749	0.431
12	**D, A, H and S**	**0.638/10**	**0.946/0.149**	**138.972**	**0.760**	**0.521**
13	D, A, H and E	0.648/8	0.958/0.131	228.870	0.752	0.399
14	S, E, D, A and H	0.640/9	0.963/0.123	229.875	0.763	0.094

Selected model is given in bold.

3.3. Molecular docking

3.3.1. Structure prediction and validation

Primary structure prediction of the protein 1CET shows that the instability index was found to be 30.26 which classify the protein as stable. The high aliphatic index (110.41) of the protein is evidence for high thermodynamic stability. The positive value of the GRAVY (0.134) supports the protein molecule to be hydrophobic. The estimated half-life is 30 h (mammalian reticulocytes, *in vitro*).

Secondary structure prediction carried out using SOPMA shows that the protein 1CET is structurally stabilized by efficient folding

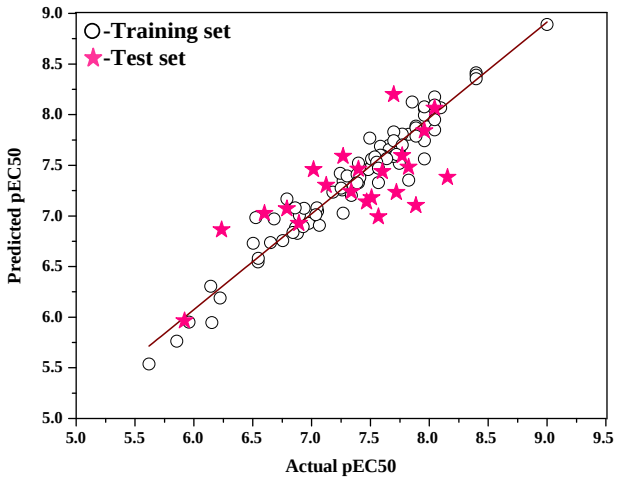


Fig. 4. Plot of actual versus predicted antimalarial activity using CoMSIA model 12.

technique. The low percentage of β-turn (7.91%) and the high percentage of α-Helix (38.29%) hold up the above factor.

Ramachandran plot (Fig. 6) shows that the protein has one outlier amino acid Gly164. The number of residues in the core region is 94.68%. The number of residues in the allowed region is 4.98% and the number of residues in the outlier region is only 0.33%.

3.3.2. Target-ligand interaction

The binding interaction of the 112 ligand molecules with the protein molecule 1CET was analyzed using Dock module in MOE 2007.09. The molecular docking results are summarized in Table 6. The docked conformation of compounds revealed that compounds interacted with the binding pocket residues of targeted protein through several favorable interactions including polar, hydrophobic, hydrogen bonding and the weak van der Waal contacts. Compounds 6, 7, 8, 10, 15, 23, 30, 36, 38 and 39 showed good binding score with the protein 1CET.

The molecular docking interaction of compound 6 with the active site of 1CET shows that the oxygen of the methoxy group interacts (3.26 Å, 1.6 Å and 1.29 Å) indirectly with four amino acids Thr169, Ile270, Lys173 and Val166 in the active site of the enzyme. Arg185, a basic amino acid from the active site of ICET interacts with the nitrogen of the quinoline ring through a side chain hydrogen bonding interaction (3.04 Å). Strength of chemical bond between this active side residue and inhibitor is 30%. Hydrophobic interactions between the quinoline ring and the residues Arg185, Asn188, Pro184, Ala249, Glu256, Ser170, and Val268 appear to constrain the compound in close proximity with the amino acids forming the fore mentioned hydrogen bonding. An arene–cation interaction was observed between the methoxybenzene ring and basic Lys173.

The molecular docking interaction of compound 7 with the active site of 1CET is represented in Fig. 7. The molecular docking score of the compound is −13.7841 kcal/mol. The N atom attached to benzodioxole ring forms hydrogen bonds with 3 water molecules. The water molecules was found to be interacting with several important residues including Thr169, Val166, Lys173, Glu256 and Ile270. A side chain hydrogen bonding interaction was observed between basic Lys173 and O atom (3.47 Å, 10%) present in the five membered ring. An arene–cation interaction was observed between the benzene ring and the residue Lys173. Hydrophobic interactions was observed between quinoline ring

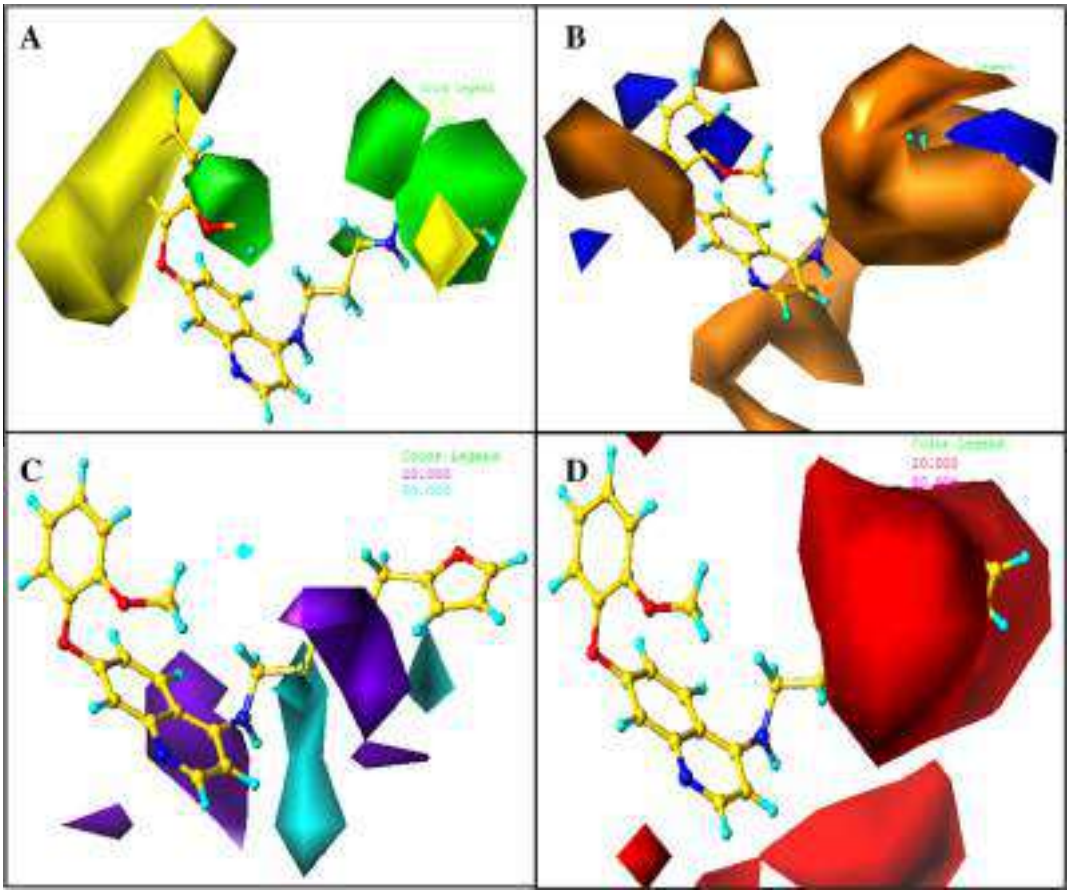


Fig. 5. Contour maps of CoMSIA: (A) steric field, (B) hydrophobic field, (C) H-bond donor field and (D) H-bond acceptor field based on compound 5.

and the sandwich of the backbone atoms of Arg185, Ala252, Tyr174, Ala249 on one side and Ser170 on the other. There are hydrophobic interactions between benzodioxole ring of the ligand and residues Asn188, Val268 and Glu256. A prominent back bone hydrogen bonding interaction was found between Val166 and the NH (2.84 Å, 14%) bonded to benzodioxole ring on one side while basic Lys173 was found to be interacting with the oxygen present in the five membered ring on the other side (3.47 Å), with very low bond strength (10%).

Compound 8 forms arene–cation interaction between basic Lys173 and fluoromethoxy benzene ring. Quinoline ring shows hydrophobic interactions with residues Tyr174, Ser170 and Ala252. The N atom attached to the fluoromethoxy benzene ring forms side chain hydrogen bonding interaction with Lys173 (2.47 Å). The polar bond is having very high bond strength (94%). It also forms interactions with residues Arg185, Val187and Glu256 through bridged water molecules. The top ranking molecular docking score was −13.2418 kcal/mol. The side chain hydrogen bonding interaction of the polar Asn188 with the oxygen of methoxy group bonded to fluoromethoxy benzene ring (2.88 Å) was found with bond strength 45%.

The binding mode observed for the compound 10 shows that the quinoline ring is located in a hydrophobic pocket surrounded by Arg185, Ser170, Lys173, Tyr175, Tyr174, Ala249 and Ala252. An arene–arene interaction was observed involving methoxy benzene ring of the ligand and polar Tyr174. The molecular docking interaction of compound 10 shows basic arene–cation interaction of methoxy phenol ring and Lys173. A side chain hydrogen bonding interaction was observed between the –OH group and Glu256 (1.26 Å) with very low bond strength 12%. Methoxy phenol ring shows hydrophobic interactions with residues Asn188, Val166, Val268, Pro184 and Arg185. The molecular docking score was found to be −13.3169 kcal/mol. Arg185 is a basic amino acid which forms a side chain hydrogen bonding interaction with NH bonded to methoxy phenol moiety with very weak bond strength (2.98 Å, 16%).

Molecular docking of compound l5 with score −13.4950 kcal/-mol showed a basic side chain hydrogen bonding interaction between O atom of the benzodioxole ring and Lys43 (2.67 Å, 77%). Quinoline ring shows arene–cation interaction with the basic residues Lys173 and Arg185 and methoxy benzene ring shows arene–cation interaction with the residue Lys173. Both Quinoline and methoxy benzene rings show hydrophobic interactions with residues Val166, Lys173, Arg185, Asn188, Leu269, Pro184, Val268 and Glu256. The N atom of the Quinoline ring shows hydrogen bond interactions with Lys173, Arg185 and Val187 through bridge water molecules. The O atom of the-methoxy group forms H-bond interactions with Ala189, Asn188 and Pro184. Benzodioxole ring shows hydrophobic interaction with Lys43, acidic Glu256, Pro184 and Val268.

In case of compound 23, a large number of interactions are present (Fig. 7). It was observed that the two oxygen of benzodioxole ring formed H-bond interactions with residues Lys173, Ala189, Ile270, Asn188 and Val268 through bridged water molecules. An arene–cation interaction was observed between quinoline ring and basic Arg185. Hydrophobic interactions between benzodioxole ring and Asn188, Leu269, Val268, Lys173 as well as the quinoline ring with Arg185, Val166 and Glu256 appear to constrain the compound in close proximity with the amino acids forming the fore mentioned hydrogen bonding. Benzodioxole ring forms an arene–cation interaction with basic Lys173. The molecular docking score of the compound 23 was −14.4918 kcal/mol. During interaction basic Lys173 behaves as a side chain acceptor residue that binds to the N atom of benzodioxole ring of inhibitor. The polar bond between the Lys173 and inhibitor is having moderate bond strength (63%). Lys173 was found making interaction with

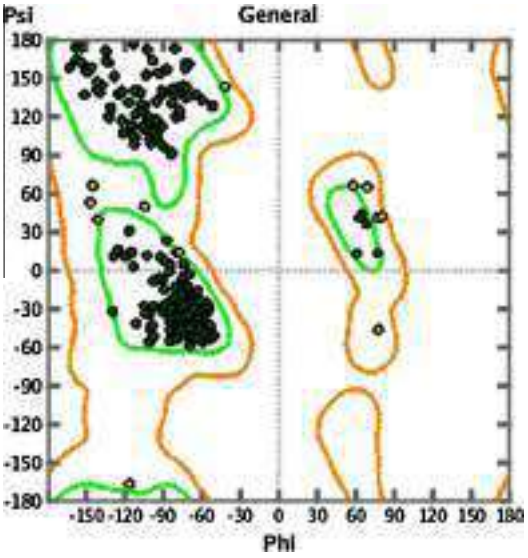


Fig. 6. Ramachandran plot (PDB 1CET) after energy and residue optimization.

Table 6
Docking results of compounds into the protein 1CET.

Compounds	*E* score (kcal/mol)	Amino acid residues in direct interaction	Distance (Å), bond strength (%)	Amino acid residues interaction due to water molecule
6	−13.1957	Arg185, Lys173	3.04, 30	Thr169, Ile270, Val166, Lys173
7	−13.7841	Val166 Lys173 Lys173	2.84, 14 2.56, 53 3.47, 10	Asn188, Ala189, Thr169, Ile270, Val268, Glu256, Val166, Lys173
8	−13.2418	Asn188 Lys173	2.88, 45 2.47, 94	Glu256, Val187, Asn188, Arg185, Val268
10	−13.3169	Arg185 Glu256	2.98, 16 1.26, 12	Ile270, Lys173, Glu256, Ser170, Arg185
15	−13.4950	Lys43 Arg185 Lys173	2.67, 77	Arg185, Lys173, Ala189, Asn188, His190, Val187, Pro184
23	−14.4918	Lys173 Lys173	2.75, 63 3.24, 16	Ile255, Glu256, Ala252, Asn188, Val268, Ala189, Ile270, Lys173, Thr169, Val166
30	−13.0691	Lys173 Lys173	2.92, 53 2.5, 76	Glu256, Tyr174, Asn188, Arg185, Val187, Val268, Ala189, Lys173
36	−13.5305	Lys173 Lys173	2.37, 70 2.87, 61	Ala189, Val268, Ile270, Asn188, Lys173, Val166, Thr166, Glu256
38	−15.1099	Glu256 Glu256	2, 22 1.2, 35	Lys173, Val268, Asn188
39	−13.9625	Asn188 Arg185 Lys173	2.77, 62	Glu256

(2.75 Å, 63%). A direct side chain acceptor interaction was found between basic Lys173 and oxygen atom of the benzodioxole ring (3.24 Å). The polar bond between the Lys173 and compound is having low bond strength (16%) (Fig. 8).

The binding mode observed for compound 30 shows that most of the interactions present are concentrated on the methoxy phenol ring with a molecular docking score −13.0691 kcal/mol. A stacking interaction with varied bond strength was observed between basic Lys173 and inhibitor molecule. Lys173 is interacting as a side chain donor molecule for both OH and NH groups attached to the aryl ring of the inhibitor compound (2.5 Å, 76%; 2.92 Å, 53%). Further stabilization was obtained by hydrophobic interactions with Leu269, Val268, Lys173, Arg185, Asn188, Ser170, Ala249, Ala252, Pro246, Glu256 and Tyr174.

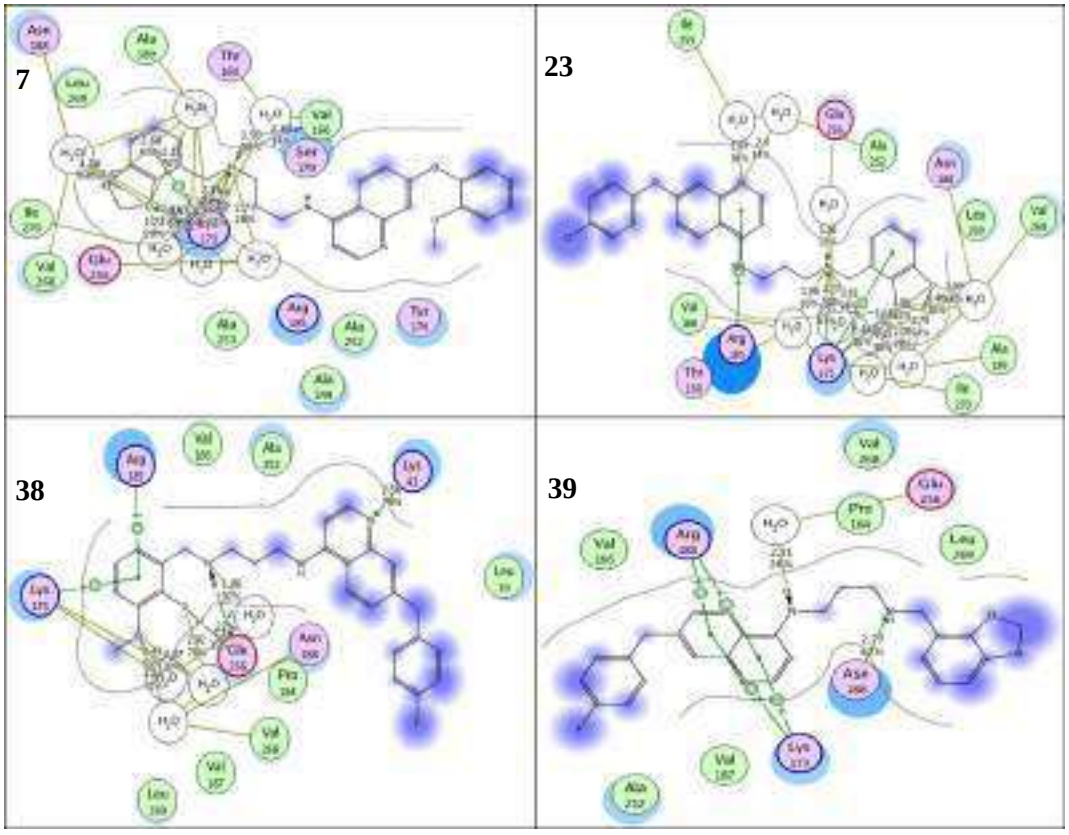


Fig. 7. The 2D interaction of the active compounds 7, 23, 38 and 39 with protein 1CET.

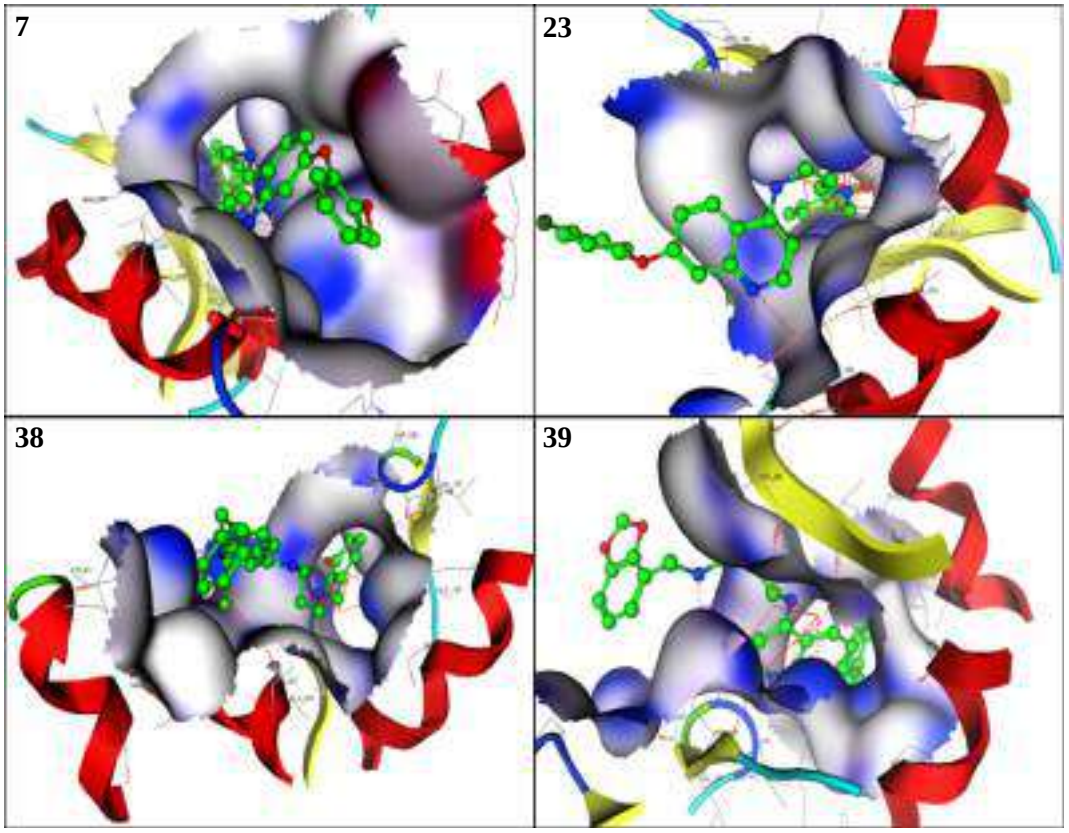


Fig. 8. The docking pose of the active compounds 7, 23, 38 and 39 with protein 1CET.

From the molecular docking analysis it appears that Lys173, Val268, Asn188, Tyr174, Glu256 etc are the residues that make compound 36 a potent inhibitor. Through different kinds of chemical interactions with the above mentioned residues, compound 36 occupies the active site of enzyme and may inhibit or lower its catalytic efficiency. An arene–arene interaction was observed between fluorobenzene ring and polar Tyr 174 amino acid. The oxygen and NH atoms attached to the other fluorobenzene ring shows side chain hydrogen bonding interactions with the basic Lys173 residue (2.92 Å, 2.5 Å). Strength of chemical bonds between this active side residue and inhibitor is 53% and 76% respectively. The molecular docking score observed was −13.5305 kcal/mol.

The binding mode observed for compound 38 (Fig. 7) shows that it binds within the binding pocket with a molecular docking score −15.1099 kcal/mol. This compound has the highest molecular docking scores of the selected compounds. An arene–cation interaction was observed between the methoxy phenol ring and basic residues Lys173 and Arg185. The N atom attached to methoxy phenol ring forms acidic side chain hydrogen bonding interaction with residue Glu256 (2 Å, 22%). A side chain hydrogen bonding interaction was also observed between acidic Glu256 and hydroxyl group of methoxy phenol ring of the compound with very low bond strength (1.2 Å, 35%). Quinoline ring shows hydrophobic interactions with residues Lys43, Leu39, Ala252 and Asn188. The nitrogen atom present in the quinoline ring shows basic side chain hydrogen bonding interaction with Lys43. The polar bond between the Lys173 and compound is having moderate bond strength (79%). The methoxyphenol ring shows hydrophobic interactions with residues Arg185, Lys173, Leu269, Val268, Glu256 and Asn188.

The binding mode observed for the compound 39 shows that the quinoline ring was located in a hydrophobic pocket surrounded by Arg185, Val166, Asn188, Lys173 and Ala252. Quinoline ring shows four arene–cation interactions with basic Arg185 and basic Lys173. The NH group attached to the benzodioxole ring forms side chain acceptor interaction with polar Asn188. (2.77 Å). The polar bond between the Lys173 and compound is having moderate bond strength (62%). Acidic Glu256 shows hydrogen bonding interaction with NH group attached to the quinoline ring (2.31 Å, 26%).

Thus the selected 7-substituted 4-aminoquinoline analogs with maximum molecular docking scores are compounds 6, 7, 8, 10, 15, 23, 30, 36, 38 and 39.

4. Conclusion

The present study on a series of 7-substituted-4-aninoquinoline analogs was carried out using 2D-QSAR, CoMFA/CoMSIA methods and molecular docking analysis. 2D-QSAR final models included *SlogP_VSA9, GCUT_SMR_0, PEOE_VSA-6* and *opr_nring* descriptors and showed a satisfactory statistical quality and predictive abilities as shown by the R^2 and Q^2 values for 2D-QSAR model. The 3D-QSAR models generated indicate that the steric, electrostatic (in CoMFA), H-bond donor, H-bond acceptor and hydrophobic (in CoMSIA) fields have important influences on the ligand–receptor interaction. The predictive ability of the CoMFA (Q^2 = 0.540 and R^2_{ncv} = 0.881) and CoMSIA (Q^2 = 0.638 and R^2_{ncv} = 0.946) models was also as good as the 2D-QSAR models. The CoMFA model and the better CoMSIA model were further validated using an external test set, with the predicted R^2 values of 0.518 and 0.521, respectively. Using molecular docking the appropriate binding conformations of these series of compounds which interact with protein 1CET, were revealed. Thus the present study provides useful guidelines for developing 7-substituted-4-aminoquinoline derivatives as potent antimalarial activity inhibitors.

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ORIGINAL RESEARCH

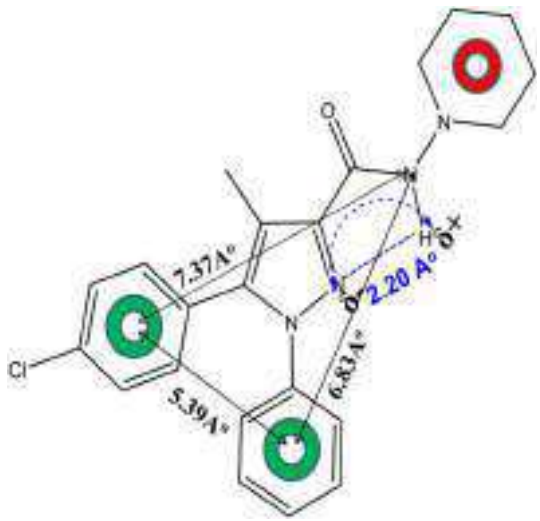
Discovery of Rimonabant and its potential analogues as anti-TB drug candidates

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Abstract Rimonabant and its analogues have been synthesized in moderate to good yields using a simple synthetic route. All the newly synthesized compounds were subjected to in vitro screening against *M. tuberculosis* and *M. smegmatis*. The most potent analogue JMG-14 exhibits MIC value of 3.13 compared to 3.25 and 50 μg/ml for ethambutol and pyrazinamide, respectively. The molecular docking reveals that pyrazole ring, number and position of halogen atoms play a crucial role in deciding interactions with MTCYP-121. These findings open up a new avenue in the search of potent anti-TB drugs with rimonabant and its novel analogue JMG-14 as lead molecules.

Graphical Abstract



Keywords Rimonabant · Diaryl pyrazoles · Tuberculosis · Mycobacterium tuberculosis · H37Rv · MTCYP-121

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Introduction

Tuberculosis (TB) is among the deadly diseases afflicting mankind, and it still remains a major public health burden in many developing countries (Corbett *et al*., 2003). Approximately one-third of the world's population is still under the ill influence of TB. In 2011, nearly 9 million people around the world suffered from TB (WHO 2013), with 1.4 million deaths worldwide. Recent reports reveal that every year 0.2 million from 0.7 million HIV patients die due to TB,

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and thus, TB is a leading killer in HIV-infected patients (Nunn *et al*., 2005; Masand *et al*., 2012; Shukla *et al*., 2014). Emerging resistance to the marketed anti-tuberculosis drugs is a major concern that threatens progress made in TB care and control worldwide (Shukla *et al*., 2014). In most of the cases, drug resistance (Chiang and Schaaf, 2010) arises due to the improper use of antibiotics in chemotherapy, administration of improper treatment regimens and failure to ensure that patient completes the whole course of the treatment (Elzinga *et al*., 2004; Kumar *et al*., 2013). To combat the continuous rise in multidrug-resistant TB, scientific efforts are concentrated on inventing new agents for the treatment of TB. Despite the efforts executed in laboratories and hospitals, TB is nevertheless a major challenge to medicinal chemists.

Developing a new drug is a long, expensive and tedious process, often consuming several years and resources. In addition, the regulatory approval process following the drug discovery/design involves several tests and trials. Even after completing the whole process of drug development, certain drugs such as celecoxib, sibutramine, rimonabant, though approved by the regulatory agencies, were withdrawn from the market due to the appearance of the side effects. At the current stage, it would be a highly beneficial and attractive strategy to identify a drug candidate, which has been approved as a drug by regulatory authorities, effective for the treatment of TB. This would enable a quicker introduction of the drug into the market for TB treatment. In the recent years, azoles viz. pyrazoles, imidazoles and triazoles have attracted the attention of researchers. Some clinically used drugs such as clotrimazole, fluconazole and voriconazole, which contain azole moiety, can be used to treat generalized systemic mycoses. Literature survey reveals that selected azole drugs possess potent anti-mycobacterial activity in the nanomolar range (Kumar *et al*., 2013; Menozzi *et al*., 2004) (Fig. 1).

It has been established (McLean *et al*., 2002; Hudson *et al*., 2012) that many azole compounds possessing potent anti-tubercular activity bind to MT-CYP51 and MT-CYP121, proteins with crucial role in metabolism of *M. tuberculosis*, possessing high affinity and retard the growth of *Mycobacterium bovis* and *Mycobacterium smegmatis*, the two mycobacterial species which closely resemble *M. tuberculosis*. In recent years, cytochrome P450 (CYP121) has gained popularity as an attractive target for designing potent azole-based drugs against *M. tuberculosis*, a plausible reason is that MT-CYP121, which has unique catalytic action, binds commercially available azole drugs with a higher affinity than MT-CYP51 (Menozzi *et al*., 2004). In addition, it has no equivalent enzyme in humans. MT-CYP121 is necessary for bacterial viability since it catalyzes an unusual intramolecular carbon–carbon coupling reaction (Dumas *et al*., 2013). The high affinity of the azole derivatives such as

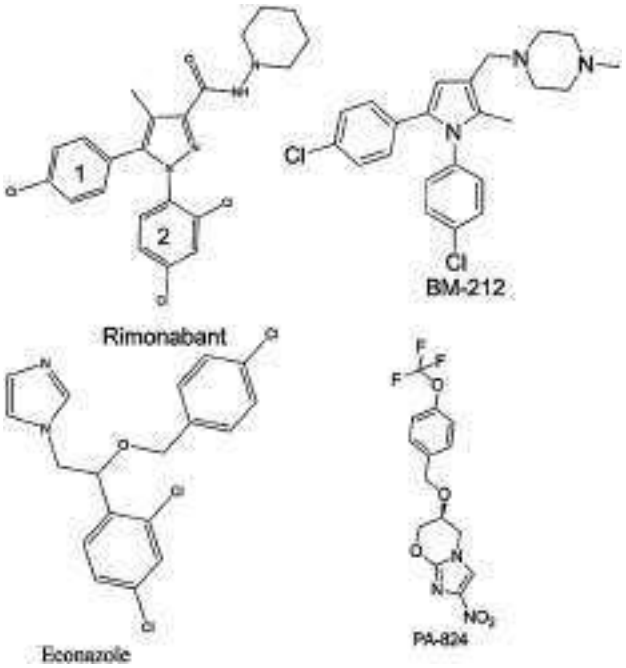


Fig. 1 Azole and pyrazole derivatives possessing anti-tubercular activity

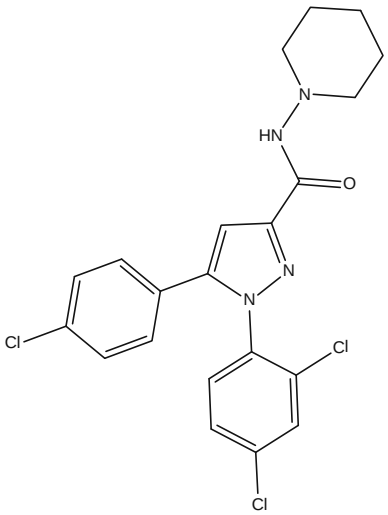


Fig. 2 2D-structure of rimonabant

clotrimazole for MT-CYP121 is attributed to their bulky, polycyclic structure, enhancing favorable interactions with the hydrophobic residues in the largely non-polar active site of the enzyme. Moreover, in many studies, the presence of halogen attached to aromatic moiety has been found to escalate antifungal and anti-mycobacterial activities (Dumas *et al*., 2013; Sundaramurthi *et al*., 2011; Belin *et al*., 2009). Rimonabant (**1**) (Fig. 2), a pyrazole carboxylic acid derivative discovered by Sanofi-Synthelabo in 1994 as the first potent, orally active, selective CB_1 cannabinoid receptor antagonist and sold under several trade names as an anorectic

anti-obesity drug. Rimonabant and its analogues were also shown to have promising activities and also proved safe to human (Lange and Kruse, 2005). It was recently withdrawn (Kang and Park, 2012) from the market following post-marketing surveillance studies, which confirmed a risk of depressive disorders among users. However, modification or elimination of the side chain attached to carboxamide (Jagerovic *et al*., 2008) which is responsible for crossing the blood–brain barrier might reduce the side effects. There are several important anti-TB drug candidates such as PA-824 and BM212, which are structurally reminiscent to rimonabant **1**, and hence, we were curious to study its anti-TB properties. All these observations prompted us to develop new rimonabant analogues that may prove effective against multidrug-resistant strains of the tuberculosis pathogen.

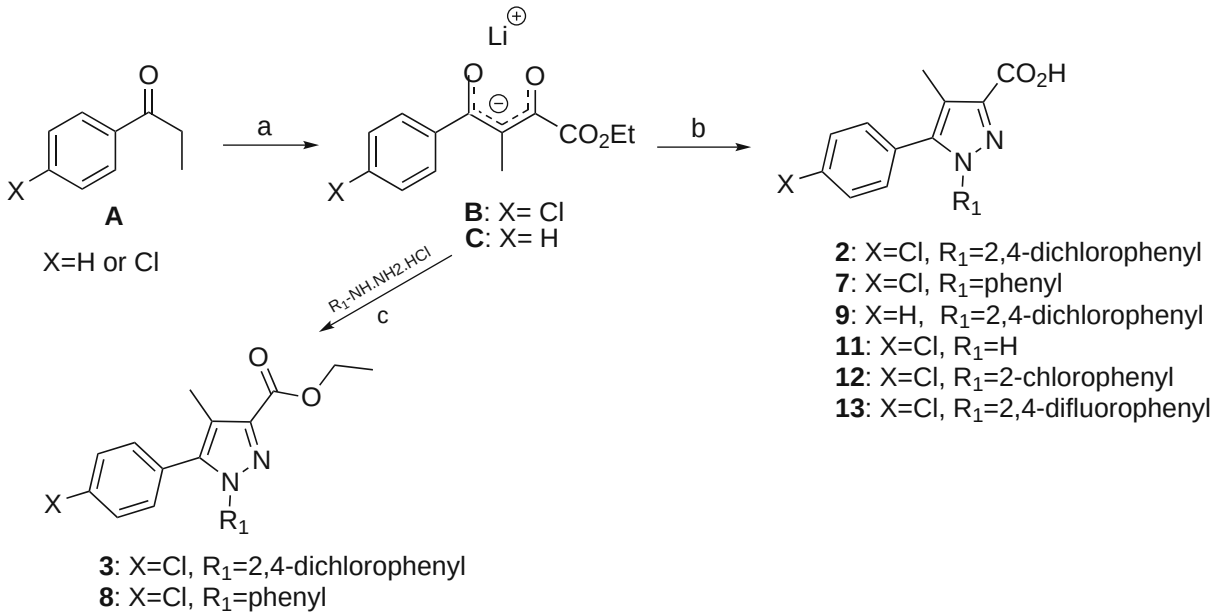
Chemistry

The synthesis of compounds **2**, **3**, **7**, **8**, **9**, **11**, **12**, and **13** was carried out as outlined in the Scheme 1. 4-Chloropropiophenone (A) on condensation with diethyl oxalate in the presence of LiHMDS gave lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate (B). This on condensing with 2, 4-dichlorophenyl hydrazine hydrochloride and phenyl hydrazine hydrochloride in ethanol gave hydrazones, which on refluxing in acetic acid for 24 h yielded esters **3** and **8**, respectively. Subsequent reaction of B with suitable hydrazines in 50 % sulfuric acid and ethanol at 79 °C for 14 h yielded desired acids (**2**, **7**, **9**, **11**, **12** and **13**). These acids on subsequent treatment with thionyl chloride afforded acid chlorides. Finally, the amidation was executed to afford the target compounds **1**, **4**, **5**, **6**, **10**, **14**, **15**, **16**, **17**, **18** and **19** in moderate to good yields (Schemes 2, 3, 4). The structures of newly synthesized compounds were established on the basis of spectral and physicochemical analyses.

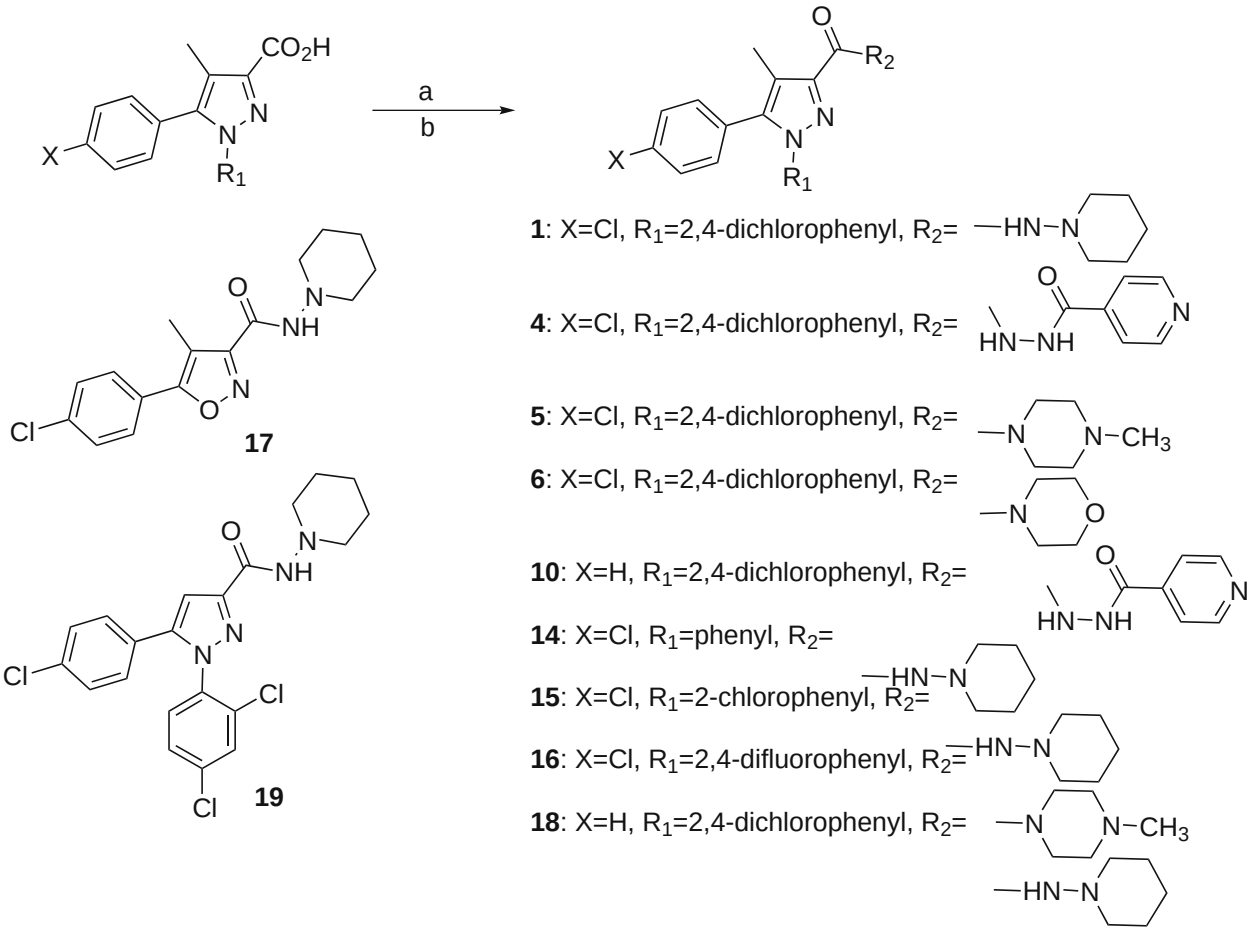
Results and discussion

Our initial study involved screening of rimonabant **1** against *M. smegmatis*. Interestingly, it exhibited a MIC value of 13.56 compared to 16 μg/ml for isoniazid. Therefore, its 18 analogues were synthesized (Lan *et al*., 1999; Kotagiri *et al*., 2007), and few of them were screened against *M. smegmatis*. They showed moderate to high activity (Table 1). Encouraged by the results, rimonabant and all the synthesized analogues were then screened for *Mycobacterium tuberculosis* (virulent strain H37Rv) in vitro (Moore *et al*., 1999). The details of the screening data are shown in Table 1.

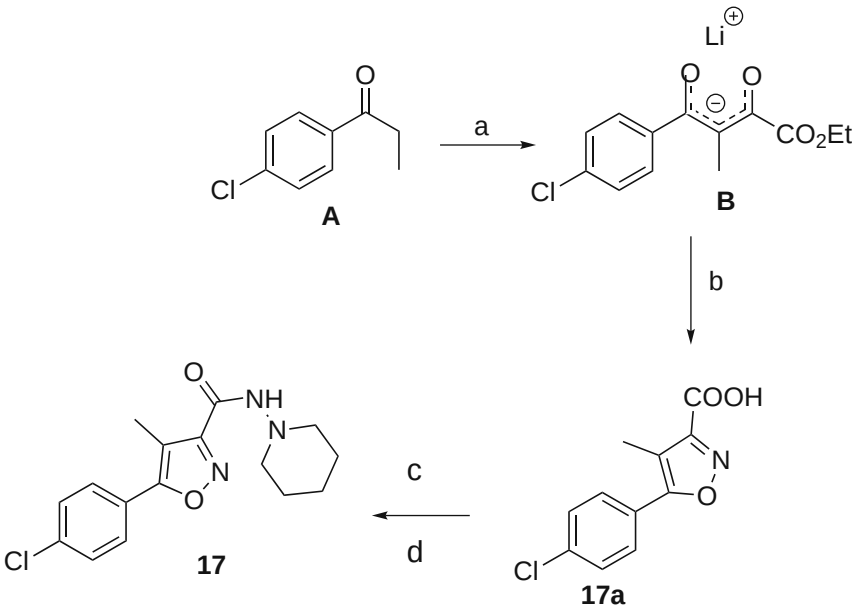
The precursor of rimonabant acid **2** showed improved MTB activity and ester 3 retains the activity as compared to rimonabant. Similarly, the analogues **2**, **4**, **7**, **11** and **15**–**18** exhibited enhanced activity, and the analogues **3**, **5**, **6**, **8**, **10**, **12** & **19** were also found to be active. Most importantly, the analogues **9** and **13** showed very good MTB activity. The analogue JMG-14 came out to be a promising lead with highest activity. Compared with one of the first-line anti-TB drug ethambutol (MIC 3.25 μg/ml), the analogue JMG-14 was found to be equally active. When compared to pyrazinamide (MIC 50.0 μg/ml), all the **18** analogues were found to be more potent. The analogue **13** also emerged as another lead molecule, which can be explored further.



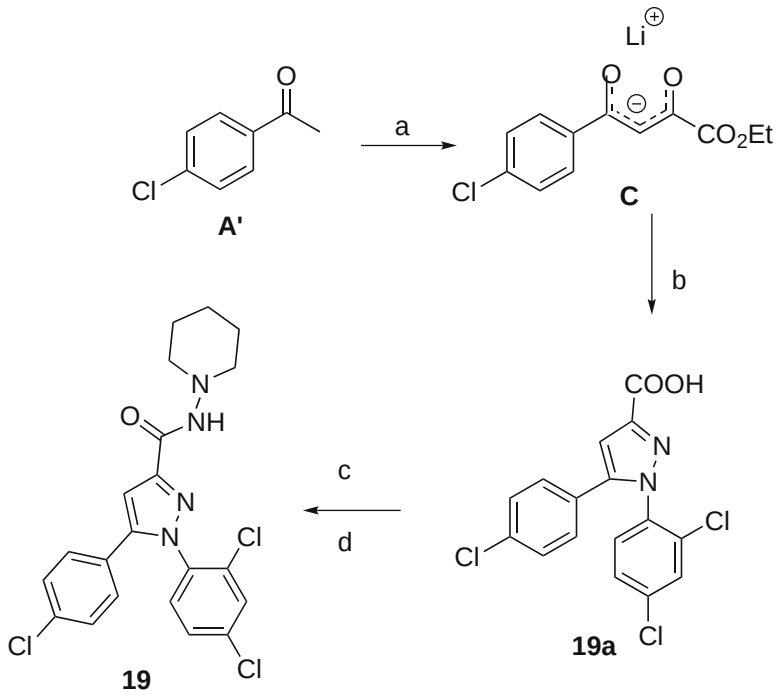
Scheme 1 Reagents and conditions: (a) LiHMDS, diethyl oxalate, methyl cyclohexane, 15–25 °C, 6th; (b) R_1-NH-NH_2·HCl, 50 % aq. H_2SO_4, EtOH, 79 °C, 14th; (c) EtOH, rt, 20 h, then AcOH, reflux, 24 h



Scheme 2 Reagents and conditions: (a) thionyl chloride. DMF (cat.) toluene. 100 °C, 4 h (b) Et_3N sutiable amide. 0°-rt. 12 h



Scheme 3 Reagents and conditions: (a) LiHMDS, diethyl oxalate, methyl cyclohexane, 15–25 °C, 6h; (b) $NH_2OH{\cdot}HCl$, 50% aq. H_2SO_4, EtOH, 79 °C, 14h; (c) thionyl chloride, DMF (cat), toluene, 100 °C, 4th; (d) Et_3N, 1-aminopiperidine, 0°-rt, 12 h



Scheme 4 Reagents and conditions: (a) LiHMDS, diethyl oxalate, methyl cyclohexane, 15–25 °C, 6h; (b) 2,4-dichlorophenylhydrazine. HCl, 50% aq. H_2SO_4, EtOH, 79 °C, 14 h; (c) thionyl chloride, DMF (cat), toluene, 100 °C, 4 h; (d) Et_3N, 1-aminopiperidine, 0°-rt, 12 h

Table 1 In vitro anti-mycobacterial activity of rimonabant (**1**) and synthesized analogues

S. No.	CLog*P*[b]	% inhibition *M. Smegmatis*	MIC (μg/ml) M. TB[a]	S. No.	CLog*P*[b]	% inhibition *M. Smegmatis*	MIC (μg/ml) M. TB
1	6.471	99.33 MIC 13.56 μg/ml	25	13	4.981	NT	6.25
2	6.121	22.84	12.5	14	5.031	99.70	3.13
3	7.083	14.07	25	15	5.754	NT	12.5
4	5.532	19.21	12.5	16	4.526	NT	12.5
5	5.666	14.50	25	17	3.342	NT	12.5
6	5.335	NT	>25	18	5.756	32.37	12.5
7	4.681	17.70	12.5	19	6.841	NT	25
8	5.234	22.70	25	Isoniazid		16 μg/ml	0.05
9	5.407	15.73	6.25	Rifampicin		2 μg/ml	0.1
10	4.818	1.362	25	Ethambutol		NT	3.25
11	3.035	NT	12.5	Pyrazinamide		NT	50.0
12	5.404	NT	25				

NT not tested

[a] *Mycobacterium tuberculosis* H37Rv

[b] Calculated LogP using ChemDraw 12

Based on the analogue **9**, a simple replacement of chlorine by hydrogen might provide a more active analogue of **13**.

The main purpose of this study was to introduce modification on the side chain on carboxamide moiety of rimonabant and its analogues to develop new potential anti-TB agents. In the present work, diverse functional groups were introduced on the side chain of the carboxamide moiety of rimonabant to identify structure–activity relationships. It appears that the piperidinyl side chain is not must for high activity and derivatives with free acids are better candidates for further evaluation. Variation of phenyl ring attached to nitrogen (of pyrazole moiety) shows prominent effect on the activity, and this observation is further vindicated by the docking analysis. The substitution on the ring or its complete removal as well as replacement of that nitrogen with oxygen shows positive effect. Alteration on the *p*-chlorophenyl ring present on central pyrazole also influences the bioactivity. The methyl group seems to be important for the activity, since the analogue without methyl shows diminished activity.

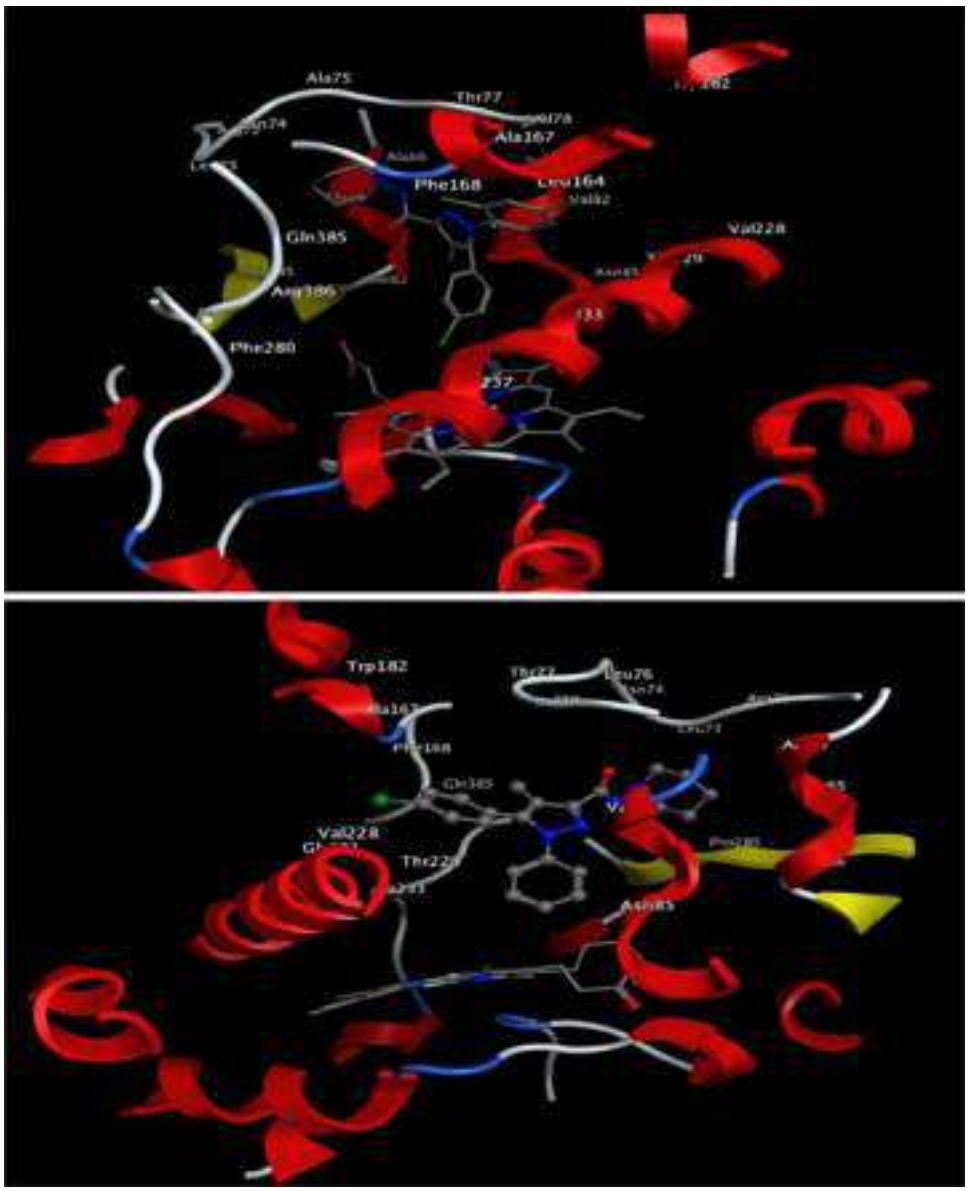


Fig. 3 Docking pose for **a** rimonabant (compound **1**) and **b** most active compound **14**

Docking analysis

Molecular docking analysis was performed to determine the structural features that steer the biological profile of Rimonabant and its novel analogues. As stated earlier (Dumas *et al*., 2013; Sundaramurthi *et al*., 2011; Belin *et al*., 2009), the mechanism of action for anti-TB activity involves interaction of pyrazoles with MTCYP-121; therefore, molecular docking analysis was performed to determine the structural features that govern the anti-TB of present series molecules. The docking analysis was performed for all the compounds, but for the sake of convenience, we represent the docking poses for compounds **1** and **14** as representatives. The active site of MT-CYP121, a heme-based enzyme that transfers a single oxygen atom to the substrate, comprises of Thr-77, Val-82, Val-83, Asn-85, Met-86, Ala-167, Ph-168, Thr-229, Ala-233, Ser-237, Gln-385 and Arg-386. The catalytic site is located on top of the distal side of the heme, where oxygen binds, near to I-helix (Dumas *et al*., 2013; Sundaramurthi *et al*., 2011; Belin *et al*., 2009).

According to the results of our docking experiments (see Fig. 3), the prominent interactions between compound **1** and the receptor are van der Waals, H-bonding and hydrophobic in nature. The compound **1** could adopt bent 'T' shape (or weird propeller shape) while interacting with the cytochrome catalytic site (1350 $Å^3$ in size) orienting chloro atom attached to benzene ring 1 toward the iron atom of the heme group with the heterocyclic rings (pyrazole and piperidine) pointing toward polar residues. Binding of compound **1** involves numerous van der Waals contacts

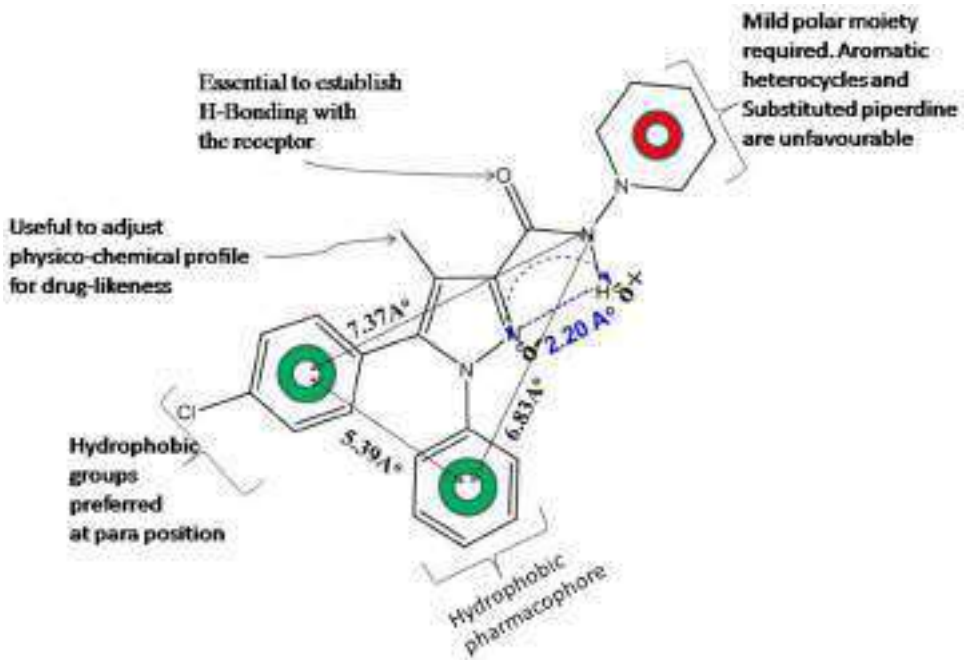


Fig. 4 Summary of SAR and molecular docking analysis for anti-TB activity of rimonabant and its analogues

with the hydrophobic side chains of Leu-76, Val-78, Val-83, Ala-167 and Phe-168. There are water-mediated H-bond network with the N (non-substituted) of pyrazole ring and with N (amide group). Furthermore, a strong H-bond between Arg-72 with N (piperidine ring) enhances the anchoring of compound **1** with CYP-121. The presence of pyrazole moiety in close proximity to Gln-385 indicates that it plays a crucial role in inhibiting the normal functioning of CYP-121.

Compound **14**, like compound **1**, adopts bent 'T' shape while interacting with CYP-121, but interacts with more number of residues of the active site than the compound **1**. The ring 2 is closer to heme moiety with ring 1 pointing toward hydrophobic residues Val-78, Phe-168, Trp- 182 and Val-228. Another remarkable difference in interaction pattern of compounds **1** and **14** is due to the involvement of one and two water molecules, respectively, in enhancing the polar interactions with the receptor. The binding between the receptor and the substrate is enhanced by the water-mediated H-bonding between Thr-77 and the oxygen atom of amide group as well between Arg-72 and N (piperidine moiety).

A plausible reason for bent 'T' shape for compounds **1** and **14** is the presence of bulky Ser-237 in close proximity to phenyl ring attached to N of pyrazole moiety. Another reason could be the presence of unusually close other I-helix residues above the heme. Compounds **1** and **14** have adopted exactly opposite conformations while interacting with the receptor, and this could be attributed to the steric repulsion exerted by bulkier -Cl atoms present as substituents on the phenyl ring. Hudson *et al*. recently reported that the azoles do not coordinate with the heme iron, as is typically observed for the azole antifungal CYP inhibitors (Hudson *et al*., 2012). Our docking experiment also concurs with this. The N (δ−)/N–H (δ+) with a distance of 2.20 Å (depicted in Fig. 3), acting as polar pharmacophore, are responsible for establishing the polar contacts with the receptor.

The molecular docking and structure–activity relationships (SAR) have been summarized in Fig. 4.

Further studies being carried out in our laboratory to explore the mechanism of action of this scaffold and evaluation of these compounds for anti-bactericidal activity as well as activity under alternate growth conditions such as non-replicating growth conditions.

Pharmacology

Anti-mycobacterial activity assay

Anti-mycobacterial activity of the synthesized compounds was performed against *Mycobacterium smegmatis* MC2155 strain using growth inhibition assay by agar dilution followed by turbidimetry method. The assay was semi-throughput and conducted in a 96-well plate (sterile). For *M. tuberculosis*, H37Rv strain was utilized by performing a growth inhibition assay from fresh Middlebrook 7H11 agar slants. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards (NCCLS, 1995) for the determination of minimum inhibitory concentration (MIC) in duplicate.

Conclusion

For the first time, it has been shown that rimonabant could be a lead molecule for finding more potent anti-TB drug candidates. In the present work, JMG-14 is the most potent analogue of rimonabant, emerging as a suitable lead molecule, which can be further optimized using the SAR and molecular docking analyses. Currently, research work is in progress on the development of more rational analogues and their anti-TB.

Experimental

Chemistry

All the reagents and the solvents were used as received from commercial sources unless and otherwise stated. All the experiments were carried out under an atmosphere of nitrogen in round-bottom flask. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin-layer chromatography (TLC). Column chromatographic purifications were carried out on flash silica gel (100–200 mesh) using either petroleum ether and ethyl acetate or dichloromethane and methanol as eluents. Melting points (mp) are uncorrected and were measured on an electrothermal melting point apparatus. The IR spectra were recorded on an FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on 200/400/500 MHz and 50/100/125 MHz NMR spectrometer, respectively, in $CDCl_3$/DMSO-d_6. Mass spectra were taken on LC–MS (ESI) mass spectrometer. HRMS were scanned at NCL, Pune.

Preparation of Lithium salt of Ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate (**B**) Methylcyclohexane (30 ml) and lithium hexamethyldisilazane (30 ml, 31.7 mmol) were introduced in a round-bottom flask under nitrogen atmosphere and cooled to 15–25 °C. A solution of 4-chloropropiophenone (A, 5.0 g, 29.65 mmol) in methylcyclohexane (12.5 ml) was slowly added with continuous stirring for 2.5 h. To this reaction mixture, diethyl oxalate (4.78 g, 32.6 mmol) was added with stirring. The reaction progress was monitored by TLC; the solid obtained was filtered, washed with methylcyclohexane (30 ml) and dried under vacuum (30 min) to afford the lithium salt (Kotagiri *et al*., 2007) (Cream yellow solid, 5.7 g, 71.9 %).

Preparation of ethyl 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate (**3**) To a continuously stirring solution of lithium salt B (1.0 g, 3.64 mmol) in 15 ml of ethanol was added 2,4-dichlorophenyl hydrazine hydrochloride (0.777 g, 3.64 mmol) at room temperature. The shaking was carried for 20 h till precipitate was obtained. The precipitate so obtained was filtered and washed with ethanol (10 ml) and dried under vacuum to give a pale yellow solid (1.1 g), which was dissolved in acetic acid (10 ml) and refluxed for 24 h. On completion of the reaction (TLC), the reaction mixture was poured into cold water (20 ml) and then extracted with ethyl acetate (3 × 15 ml). The combined extracts were washed with water, saturated sodium bicarbonate solution, brine and then dried under vacuum to give the crude product. It was then purified by column chromatography on silica gel using ethyl acetate/petroleum ether (1:9) as elution system to give the ester 3 (Kotagiri *et al*., 2007), (670 mg, 45 %,) pale yellow solid.mp 128–129 °C;^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39 (d, $J = 2.02$ Hz, 1H), 7.34 (d, $J = 1.37$ Hz, 1H), 7.33–7.28 (m, 3H), 7.08 (d, $J = 8.59$ Hz, 2H), 4.51–4.41 (q, $J = 7.08$ Hz, 2H), 2.34 (s, 3H), 1.43 (t, $J = 7.08$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 142.9, 136.0, 135.9, 135.0, 133.0, 130.9, 130.7, 130.1, 128.9, 127.7, 127.0, 119.1, 60.9, 14.4, and 9.6.HRMS-ESI (m/z) Calcd. $C_{19}H_{15}O_2N_2Cl_3$ + H)+: 409.0272 found: 409.0265.

Preparation of 1-(5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one (**8**) Synthesis of **8** was accomplished according to the procedure applied for **3**. Pale orange solid; 595 mg, 48 %; mp 121–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.36 (m, 5H), 7.24–7.27 (m, 2H), 7.10 (d, $J = 8.6$ Hz, 2H), 4.48 (q, $J = 14.14$ Hz, 2H), 2.33 (s, 3H), 1.46 (t, $J = 7.07$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 142.3, 140.9, 139.3, 134.7, 131.3, 128.9, 128.0, 127.9, 127.0, 125.4, 120.0, 60.8, 14.4, 9.7; HRMS-ESI (m/z) Calcd. $C_{19}H_{17}O_2N_2ClNa$: 363.0871 found: 363.0868.

Preparation of 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid (**2**) A mixture of lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate (B, 1.0 g, 3.6 mmol), ethanol (25 ml), 2,4-dichlorophenyl hydrazine hydrochloride (0.777 g, 3.6 mmol), and 50 % sulfuric acid (10 ml) was refluxed for 6 h. After the reaction was complete (TLC), ethanol was removed under reduced pressure, and again, a second installment of 50 % sulfuric acid (20 ml) was added, followed by refluxing for 8 h. The reaction mixture was cooled to room temperature (35 °C) and was poured onto crushed ice, stirred for 15 min, filtered and washed with water (20 ml). The wet solid so obtained was stirred with water (30 ml), and the pH was adjusted to >10 with 20 % dil. NaOH. This aqueous layer was washed with petroleum ether. The aqueous layer was separated, cooled to 0 °C, and pH was adjusted to 2.0 by concentrated hydrochloric acid. Solid so obtained was filtered, washed with water (100 ml) and dried to afford 2 (Kotagiri *et al*., 2007), (0.923 mg, 65 %), Off white solid, mp 208–209 °C; ^{1}H NMR ($CDCl_3$,

400 MHz): δ 7.44–7.41 (m, 1H), 7.35 (d, $J = 1.89$ Hz, 1H), 7.33–7.28 (m, 3H), 7.09 (d, $J = 8.47$ Hz, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 143.3, 136.2, 135.6, 135.1, 133.5, 130.8, 130.5, 129.8, 128.9, 127.8, 127.7, 126.7, 119.6, 9.6; HRMS-ESI (m/z) Calcd. $C_{17}H_{11}O_2N_2Cl_3Na$: 402.9778 found: 402.9781.

Preparation of 5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (**7**) Compound **7** was synthesized by the procedure applied for **2**. Pale brown solid: 719 mg, 58 %; mp 203–204 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.46 (s, 1H), 7.32–7.38 (m, 5H), 7.30–7.20 (m, 2H), 7.13 (d, $J = 6.36$ Hz, 2H), 2.35 (s,3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 165.9, 141.3, 140.9, 139.0, 134.9, 131.3, 129.0, 128.2, 127.6, 125.4, 125.1, 120.5, 9.6; HRMS-ESI (m/z) Calcd. $C_{17}H_{13}O_2N_2ClNa$: 335.0571 found: 335.0566.

Preparation of 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid (**9**) Compound **9** was synthesized by the procedure applied to **2**. Cream solid: 865 mg, 59 %; mp 188–189 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (s, 1H), 7.16–7.27 (m, 5H), 7.08 (s, 2H), 6.02 (s, 1H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 145.6, 136.0, 135.1, 132.2, 131.2, 130.8, 129.6, 129.1, 128.5, 128.3, 128.2, 127.8, 118.0, 9.7; HRMS-ESI (m/z) Calcd. $C_{17}H_{12}O_2N_2Cl_2Na$: 369.0168 found: 369.0164.

Preparation of 5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid (**11**) Compound **11** was synthesized by the procedure applied to **2**. Cream solid; 387 mg, 45 %; mp 288–290 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 13.54 (s, 1H), 7.89, (d, $J = 8.24$ Hz, 2H), 7.77 (d, $J = 8.24$ Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 162.4, 132.7, 130.9, 129.4, 128.9, 128.5, 117.0, 60.5, 9.9; HRMS-ESI (m/z) Calcd. $C_{11}H_9O_2N_2ClNa$: 259.0245 found: 259.0243.

Preparation of 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid (**12**) Compound **12** was synthesized by the procedure applied to **2**. Pale yellow solid: 656 mg, 52 %; mp 204–206 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33–7.42 (m, 4H), 7.26 (d, $J = 6.41$ Hz, 2H), 7.04 (d, $J = 7.79$ Hz, 2 H), 2.32 (s, 3H);^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 143.3, 141.7, 136.9, 134.9, 131.9, 130.9, 130.3, 130.0, 129.8, 128.8 127.5, 126.9, 119.4, 9.6; HRMS-ESI (m/z) Calcd. $C_{17}H_{12}O_2N_2Cl_2Na$: 369.0168 found: 369.0168.

Preparation of 5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid (**13**) Compound **13** was synthesized by the procedure applied to **2**. Pale brown solid; 781 mg, 62 %; mp 196–198 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.31 (bs, 1H), 7.44 (s, 1H), 7.27 (d, $J = 8.46$ Hz, 2H), 7.03 (d, $J = 8.46$ Hz, 2H), 6.87 (s, 1H), 6.72 (s, 1H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.7, 157.5, 155.5, 143.1, 135.0, 130.7, 130.0, 128.9, 127.0, 123.7, 119.5, 112.1, 111.9, 104.8, 9.6; HRMS-ESI (m/z) Calcd. $C_{17}H_{11}O_2N_2ClF_2Na$: 371.0369 found: 371.0369.

Procedure for the synthesis of 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **1** To a stirred solution of 2 (382 mg; 1.0 mmol) in toluene (10 ml), one drop of dimethyl formamide was added. The reaction mixture was cooled to 0 °C and thionyl chloride (140 mg: 1.2 mmol) in 2 ml toluene was added dropwise for the period of 2 min at the same temperature. The reaction mixture was allowed to attain room temperature and heated at 100 °C for 4 h. Excess of thionyl chloride and toluene was distilled off under reduced pressure. In another flask under nitrogen atmosphere was introduced 1-aminopiperidine (100 mg; 1.0 mmol) and triethyl amine (101 mg; 1.0 mmol) in 5.0 ml dichloromethane. The flask was cooled to 0 °C. To this was added a cooled solution of acid chloride dropwise at the same temperature. The resulting reaction mixture was allowed to attain room temperature, and then, it was stirred for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (10 ml) and organic layer was separated, washed with water (2 × 5 ml) and brine solution (5 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (ethyl acetate/petroleum ether 1:9 (v/v)) afforded pure product.

White solid: 292 mg, 63 %; mp 182–183 °C;^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s,1H), 7.41–7.36 (m, 1H), 7.30–7.26 (m, 3H), 7.04 (d, $J = 8.28$ Hz, 2H), 2.93–2.78 (m, 4H), 2.35 (s, 3H), 1.78–1.70 (m, 4H), 1.48–1.37 (m, 2H);^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 144.4, 142.9, 136.0, 135.9, 134.9, 132.9, 130.8, 130.6, 130.3, 128.9, 127.9, 127.2, 118.2, 57.0, 25.4, 23.3, 9.3; HRMS-ESI (m/z) Calcd. $C_{22}H_{22}ON_3Cl_3$ + H)+: 463.0854 found:463.0853.

N′-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide (**4**) Compound **4** was synthesized according to the procedure applied to **1**. Off white solid: 499 mg, 59 %; mp 237–239 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.33 (s,1H), 9.44 (s, 1H), 8.71 (s, 1H), 7.74 (s, 2H), 7.41 (s, 1H), 7.30–7.32 (m, 5H), 7.05 (d, $J = 8.53$ Hz, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 161.2, 150.2, 143.3, 142.4, 136.2, 135.6, 135.2, 132.7, 130.7, 130.5, 130.3, 128.9, 128.8, 127.9, 126.7, 118.4, 30.9, 9.2; HRMS-ESI (m/z) $C_{23}H_{16}O_2N_5Cl_3$ + H)+: Calcd. 500.0442 found: 500.0443.

(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone (**5**) Compound **5** was synthesized according to the procedure applied to **1**. Brown solid; 306 mg, 50 %; mp 111–113 °C;

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (s, 1H), 7.31–7.34 (m, 3H), 7.20 (d, J = 8.54 Hz, 1H), 7.10 (d, J = 8.28 Hz, 2H), 3.99–3.80 (m, 4H), 2.61–2.45 (m, 4H), 2.37 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 146.4, 141.9, 135.9, 135.7, 134.8, 133.0, 130.6, 128.9, 127.8, 127.3, 116.8, 55.5, 54.7, 47.1, 45.9, 41.9, 9.0; HRMS-ESI (m/z) $C_{22}H_{21}ON_4Cl_3$ + H) + :Calcd. 463.0854 found: 463.0862.

(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone (**6**) Compound **6** was synthesized according to the procedure applied to **1**. Cream yellow solid: 590 mg, 63 %; mp 170–172 °C;^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (d, J = 2 Hz, 1H), 7.33 (d, J = 8.54 Hz, 2H), 7.27–7.30 (m, 1H), 7.19 (d, J = 8.55 Hz, 1H), 7.09 (d, J = 8.54 Hz, 2H), 3.85–3.92 (m, 4H), 3.75–3.83 (m, 4H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.2, 146.0, 142.1, 135.9, 135.8, 134.9, 133.0, 130.6, 130.5, 130.3, 128.9, 127.8, 127.3, 117.2, 67.3, 66.9, 47.8, 42.6, 9.1; HRMS-ESI (m/z) $C_{21}H_{18}O_2N_3Cl_3Na$:Calcd. 472.0357 found: 472.0355.

N′-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl)isonicotinohydrazide (**10**) Compound **10** was synthesized according to the procedure applied to **1**. White solid: 273 mg, 68 %; mp 167–168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.28 (bs, 1H), 9.43 (s, 1H), 8.71 (bs, 1H), 7.75 (s, 1H), 7.41 (d, J = 1.47, 2H), 7.28–7.34 (m, 5H), 7.14 (d, J = 4.40, 2H), 7.01–7.04 (m, 1H) 2.33 (s,3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 161.2, 150.3, 144.4, 142.3, 138.8, 135.9, 135.8, 132.8, 130.5, 130.2, 129.5, 128.9, 128.6, 128.2, 127.8, 121.2, 118.3, 9.3; HRMS-ESI (m/z) $C_{23}H_{17}O_2N_5Cl_2$ + H)+: Calcd. 466.0832 found: 463.0830.

5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (**14**) Compound **14** was synthesized according to the procedure applied to **1**. White solid; 580 mg, 65 %; mp 201–202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (bs, 1H), 7.33 (d, J = 7.27 Hz, 5H), 7.21 (d, J = 7.78 Hz, 2H), 7.08 (d, J = 8.28 Hz, 2H), 2.98–2.79 (m, 4H), 2.35 (s, 3H), 1.85–1.68 (m, 4H), 1.52–1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 143.5, 140.9, 139.3, 134.6, 131.2, 129.0, 128.9, 128.0, 127.9, 125.0, 119.1, 57.1, 25.4, 23.3, 9.3; HRMS-ESI (m/z) $C_{22}H_{23}ON_4Cl$ + H)$^+$: Calcd. 395.1633 found: 395.1631.

1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (**15**) Compound **15** was synthesized according to the procedure applied to **1**. Yellow solid: 207 mg, 42 %; mp 248–250 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.69 (bs, 1H), 7.37–7.30 (m, 1H),7.29–7.24 (m, 2H), 7.23–7.15 (m, 3H), 6.98 (d, J = 8.71 Hz, 2H), 2.95–2.72 (m, 4H), 2.30 (s,3H), 1.78–1.61 (m, 4H), 1.45–1.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 143.4, 141.1, 136.5, 135.0, 131.5, 130.9, 130.8, 130.3, 129.8, 128.8, 127.7, 126.6, 118.3, 55.7, 23.8, 21.1, 9.2; HRMS-ESI (m/z) $C_{22}H_{22}ON_4Cl_2$ + H)$^+$: Calcd. 429.1243 found: 429.1246.

(5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone (**16**) Compound **16** was synthesized according to the procedure applied to **1**. White solid; 518 mg, 84 %; mp 174–176 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30–7.24 (m, 1H), 7.24–7.20 (m, 2H), 7.06–6.96 (m, 2H), 6.91–6.69 (m, 2H), 3.91–3.63 (m, 4H), 2.56–2.34 (m, 4H), 2.29 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.2, 146.6, 141.9, 134.8, 130.5, 129.7, 128.8, 127.4, 124.1, 116.8, 112.1, 111.6, 105.0, 104.5, 55.5, 54.7, 47.0, 45.9, 41.8, 8.9; HRMS-ESI (m/z) $C_{22}H_{21}ON_4ClF_2$ + H)$^+$: Calcd. 431.1445 found: 431.1447.

5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl) isoxazole-3-carboxamide (**17**) Compound **17** was synthesized according to the procedure applied to 1. White solid: 240 mg, 45 %; mp 103–104 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63–7.64 (d, J = 8.24 Hz, 1H), 7.57–7.58 (d, J = 8.24 Hz, 1H), 7.47–7.49 (d, J = 8.24 Hz, 2H), 2.99–2.81 (m, 4H), 2.45 (s, 3H), 1.85–1.71 (m, 4H), 1.53–1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.8, 163.0, 157.3, 156.4, 136.1, 129.2, 126.0, 111.7, 56.9, 25.2, 23.1, 8.3; HRMS-ESI (m/z) $C_{16}H_{18}O_2N_3Cl$ + H)$^+$: Calcd. 320.1160 found: 320.1161.

1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (**18**) Compound **18** was synthesized according to the procedure applied to **1**. Pale brown solid: 288 mg, 61 %; mp 172–173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (s, 1H), 7.41 (s, 1H), 7.27–7.32 (m, 5H), 7.11 (s, 2H), 3.05–2.75 (m, 4H), 2.38 (s, 3H), 1.91–1.65 (m, 4H), 1.54–1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 144.2, 144.0, 136.1, 135.7, 133.0, 130.6, 130.2, 129.5, 128.6, 128.6, 128.4, 127.7, 117.9, 57.0, 25.3, 23.2, 9.3; HRMS-ESI (m/z) $C_{22}H_{22}ON_4Cl_2$ + H)$^+$: Calcd. 429.1243 found: 429.1244.

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (**19**) Compound **19** was synthesized from the corresponding acid according to the procedure applied to **1**. Cream solid: 199 mg, 53 %; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J = 2.29 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J = 2.29 Hz, 1H), 7.53 (d, J = 1.83 Hz, 1H), 7.42 (d, J = 9.15 Hz, 2H), 7.26 (d, 2H), 7.23 (s, 1H), 3.35–3.19 (m, 4H), 2.01–1.95 (m, 4H), 1.70–1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.8, 146.8, 145.6, 136.3, 135.7, 135.1, 132.8, 130.5, 130.4, 129.1, 129.0, 128.2, 127.3, 107.5, 56.8, 24.9, 22.7; HRMS-ESI (m/z) $C_{21}H_{19}ON_4Cl_3$ + H)$^+$: Calcd. 449.0697 found: 449.0701.

Anti-mycobacterial activity assay (Abreu *et al*., 2012; Stigliani *et al*., 2012; Handoko *et al*., 2012; Tiwari *et al*., 2012; NCCLS, 1995)

Isolated single colonies of *M. smegmatis* MC2155 (ATCC 14468) grown on 7H10 agar plate were developed overnight in Middlebrook 7H9 medium (0.47 % Middlebrook 7H9 broth base, 10 % ADS, 0.2 % glycerol and 0.1 % Tween 80) to mid-exponential phase at 37 °C. When the OD of this culture reached approximately 0.8, a secondary culture was inoculated in 5 ml Middlebrook 7H9 medium. The secondary culture was incubated overnight and allowed to grow at 37 °C to early log phase (OD600 $\approx$ 0.3). For the anti-mycobacterial assay, 98 µl of 1:1000-folds dilution of the secondary culture was dispensed into 96-well microtiter plate per well along with 2 µl of test compound in triplicate, and 240 µl of sterile water was added to each well of the peripheral rows of 96-well plate to minimize media evaporation during assay incubation. The final concentration of the test compound in each well was 30 µM. Bacterial growth was assessed after 32 h of incubation by measuring turbidity at 600 nm OD600 values using TECAN Infinite 200 PRO^{TM} (Tecan Instruments, Switzerland). Depending upon the percentage of growth, the percentage of inhibition was calculated at a standard concentration of 30 µM. Isoniazid and rifampicin were included in every assay plate as positive controls of growth inhibition using stock solutions of INH (10 mg/ml, HiMedia) and rifampicin (10 mg/ml, HiMedia) to achieve the final concentration of 16 µg/ml for INH and 2 µg/ml for rifampicin. Additional controls DMSO (solvent without compound) and medium without inoculums were included in all the assay plates avoiding intra-assay variability. The results were analyzed as the percentage of growth inhibition.

MIC Assay (Abreu *et al*., 2012; Stigliani *et al*., 2012; Handoko *et al*., 2012; Tiwari *et al*., 2012; NCCLS, 1995)

After the compounds were screened for percentage inhibition, the promising compounds were further screened to obtain the MIC values. Minimum inhibitory concentration (MIC) is the concentration of compound which inhibits the 90 % growth of bacteria under optimum conditions. The growth inhibition assays were carried out in the same analogy as explained above using various concentrations of the test compounds prepared by serial dilutions 100, 50, 25, 12.5 and 6.25 µM to obtain the final concentrations of 46.37, 23.18, 11.59, 5.79 and 2.89 µg/ml, respectively. From the rate of inhibition bacterial growth, the ascertained MIC of the compound was calculated. The MIC value of the test compound 1 (rimonabant) is 13.56 µg/ml (29.24 µM $\pm$ 1.47).

In vitro anti-mycobacterial activity against *M. tuberculosis* H37Rv (MTB) (Abreu *et al*., 2012; Stigliani *et al*., 2012; Handoko *et al*., 2012; Tiwari *et al*., 2012; NCCLS, 1995).

MTB H37Rv strain was obtained from National Institute for Research in Tuberculosis (NIRT), Chennai. Tenfold serial dilutions of each test compound were prepared and incorporated into Middlebrook 7H11 agar medium with OADC growth supplement. Inoculation of *M. tuberculosis* H37Rv ATCC 27294 (MTB) was prepared from fresh Middlebrook 7H11 slants with OADC growth supplement and was adjusted to 1 mg/ml (wet weight) in Tween 80 (0.05 %) saline diluted to 10–2 to achieve a concentration of $\sim$107 cfu/ml (culture forming units). Then, a bacterial suspension of 5 µl was spotted in 7H11 agar tubes having tenfold serial dilutions of compounds per ml. Cultures were then incubated at 37 °C for 4 weeks. The MIC values of the synthesized compounds along with the standard drugs for comparison are tabulated in Table 1.

Experimental methodology for molecular docking analysis

For molecular docking, the structures were drawn using ChemDraw 12 followed by MMFF94 optimization using the default settings. The crystallographic coordinates of CYP121 (pdb id: 2IJ7) from *M. tuberculosis* were obtained from protein data bank (www.rcsb.org). For CYP121 of *M. tuberculosis*, we opted for pdb-2IJ7 for docking, because it has been crystallized with fairly good resolution (1.90 Å) with fluconazole as a ligand. For docking analysis, the standard procedure mentioned in literature (Abreu *et al*., 2012; Stigliani *et al*., 2012; Handoko *et al*., 2012; Tiwari *et al*., 2012; Masand *et al*., 2013) was followed using AutoDock 4.2, running under Linux Ubuntu 12.04.

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Scientific paper

Computational POM and DFT Evaluation of Experimental *in-vitro* Cancer Inhibition of Staurosporine-Ruthenium(II) Complexes: the Power Force of Organometallics in Drug Design

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Abstract

A computational Petra/Osiris/Molinspiration/DFT(POM/DFT) based model has been developed for the identification of physico-chemical parameters governing the bioactivity of ruthenium-staurosporine complexes **2**–**4** containing an antitumoral-kinase (TK) pharmacophore sites. The four compounds **1**–**4** analyzed here were previously screened for their antitumor activity, compounds **2** and **4** are neutral, whereas analogue compound **3** is a monocation with ruthenium(II) centre. The highest anti- antitumor activity was obtained for compounds **3** and **4**, which exhibited low IC_{50} values (0.45 and 8 nM, respectively), superior to staurosporine derivative (pyridocarbazole ligand **1,** $150 \cdot 10^3$ nM). The IC_{50} of **3** (0.45 nM), represents 20,000 fold increased activity as compared to staurosporine derivative **1.** The increase of bioactivity could be attributed to the existence of pi-charge transfer from metal-staurosporine to its ($CO^{\delta-}$–$NH^{\delta+}$) antitumor pharmacophore site.

Keywords: *Cancer-Kinase* (CK), antitumor agents, ruthenium-staurosporine complexes, DFT, Petra/Osiris/Molinspiration (POM) analyses.

1. Introduction

Staurosporine derivatives (Figure 1) have been thoroughly studied in organic and inorganic chemistry. Some of these compounds have been semi-synthesized for industrial, biological, and medicinal aims. Moreover, the staurosporine derivatives are regarded as excellent agents not only for their affinity to complex the kinase enzymes[1] but also to form stable bioactive and selective complexes with

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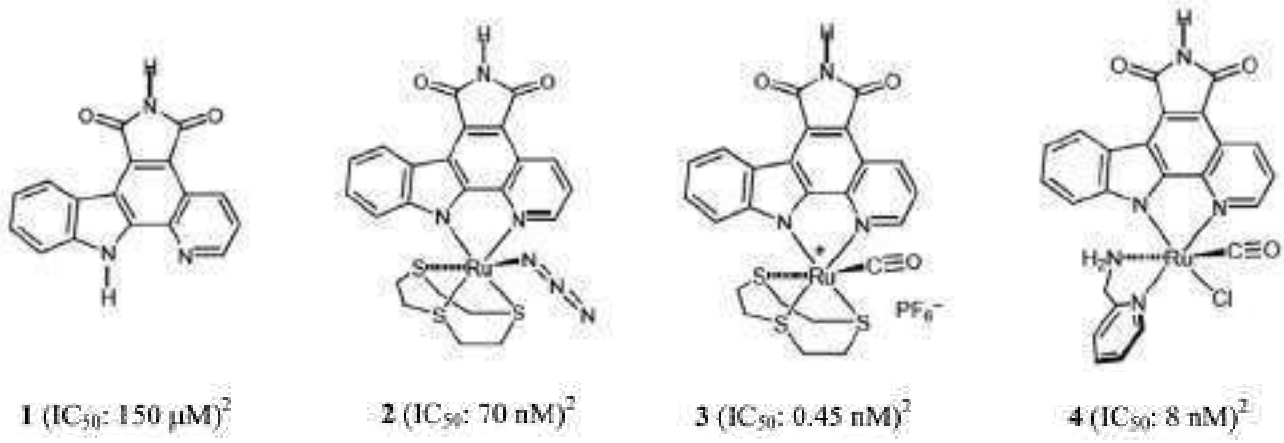


Figure 1. Molecular structure of the ruthenium-staurosporine compounds[2] studied.

plexes are so efficient that it is often projected to use them in clinics.[2,3] The protein kinase inhibition for the treatment of cancer via staurosporine and their ruthenium(II) complexes, rank as an attractive and extensively researched topic.[3–6]

Other studies on the interaction between Pd(II) and Pt(II) complexes of small molecules and DNA has been the focus of similar recent research in the scope of life science, chemistry, clinical medicine and genetics.[7,8] These studies are very useful for investigating the structure and biological function of DNA, kinases and elucidating the damage mechanism of DNA but Ru(II) complexes are less toxic than other transition metal complexes. For this reason we focalize all our attention on Ru-staurosporine complexes.

The inhibition efficiency of such drugs depends essentially on the structure of the inhibitor itself, which includes the number of active functional group centers (NH–C=O) in the molecule, the nature of the metal, and the kinase structure. The structure and the lone electron pairs in the O, N heteroatoms are important features that determine the chelation/interaction of these compounds with the metallic ion and biotargets.

The inhibition efficiency of bacteria, virus, parasite, and fungus, has been found to be closely related to drug bioavailability and molecular physico-chemical-geometric-tautomeric properties for different kinds of organic drugs.[9–22] Recently, it has been shown that the kinase inhibition by an organometallic systems under biological condition may be significantly facilitated if a ligand containing an anti-kinase pharmacophore (NH–C=O), a bidentate N,N coordinative site (staurosporine derivatives) and non-toxic metal (ruthenium) are available.[2–6]

The cancer inhibition of kinase enzymes through organic drugs has been the subject of different theoretical investigations. However, to our knowledge no group has carried out a rational correlation between experimental screenings efficiencies of anti-kinase drugs and the results of Petra/Osiris/Molinspiration (POM) analyses.

The utility of analysis of impact of coordination of drugs to transition metals on their bioactivity is of great importance in answering some fundamental questions in medicinal chemistry and biological chemistry, such as selectivity control (whether or not a given complex will be toxic). An excellent source that illustrates this concept well is the interesting work published by Eric Meggers *et al.*[2–6]

The development of theoretical scales of electrophilicity and nucleophilicity of pharmacophore site is also desirable and crucial, as a validated theoretical scale may be further used to project the global reactivity onto particular regions on the complexed drug.

There are different ways to increase the bioactivity of drugs; by modeling their bioavailability and controlling their electronic structure. A suitable theoretical concept is that proposed by Ben Hadda *et al.*[9–25] apropos of definition of pharmacophore site. The best descriptors for studying and identifying the type of pharmacophore site (antibacterial, antiviral or antitumor) are the description in detail of local electrophilicity and the nucleophilicity of each functionalized group and their spatial arrangement.

Recently, Ben Hadda *et al.* introduced some geometrical parameters, bioavailability, structural complementarily global and local (regional) nucleophilicity to establish modern definition of different pharmacophore sites.[9–25]

For these reasons, we constructed a platform of some of the key bioinformatic model in order to predict and characterize the antitumor drugs performance of the tested series of staurosporine-ruthenium(II) complexes. Our aim in this work is to give a deeper insight into the coordination effect of transition metal (ruthenium) to bioactive drug (staurosporine), on the inhibition efficiency of ruthenium-staurosporine complexes (Figure 1) using POM and DFT analyses.

2. Experimental

2. 1. DFT Method

The molecular modeling was performed using Gaussian 09 program package for calculations. In the present work, the calculations have been carried out at (DFT/B3LYP) method with 6-31+G(d,p) basis set. Electron correlations were included using Becke3-Lee-Yang-Parr (B3LYP) procedure.[26] This contains Becke's gradient exchange corrections, Lee, Yang and Parr correlation functional and/or Vosko, Wilk and Nusair correlation functional.[27]

2. 2. POM Analyses

One of the practical problems associated to the synthetic drugs is the existence of various side effects. For a molecule to be a potential drug, besides having a good biological activity, it must have good pharmacokinetic properties in biological systems. To access the pharmacokinetic profile of the synthesized molecules, we used well established *in silico* tools such as Osiris, Petra and Molinspiration, which have been validated with almost 7000 drug molecules available on the market.

3. Results and Discussion

3. 1. POM Analyses of Compounds 1–5

The analysis of theoretical toxicity risks for the staurosporine (STR) and its organic derivative **1** using the Osiris program showed that compound **1** and probably the rest of series **2**–**4** (Figure 2) are less toxic than standard clinical drugs (camptothecins) and can be used as therapeutic agents. From the data evaluated in Table 1, all structures are supposed to be non-mutagenic when run through the mutagenicity assessment of coordinated system and, as far as irritating and reproductive effects are concerned, all the compounds are at low risk comparable with standard drugs used. The hydrophilicity character of each compound has been expressed in terms of the cLog*P* value. It has been established that the absorption or permeation is greatly affected by the hydrophilicity (value of cLog*P*). Accordingly, when cLog*P* is higher than 5, the absorption or permeation decreases. On this basis, most of compounds **1**–**4** have cLog*P* values within the acceptable criteria and are active at different IC_{50} because another crucial parameter should be taken in consideration. This does not concern the geometrical conformation of phar-

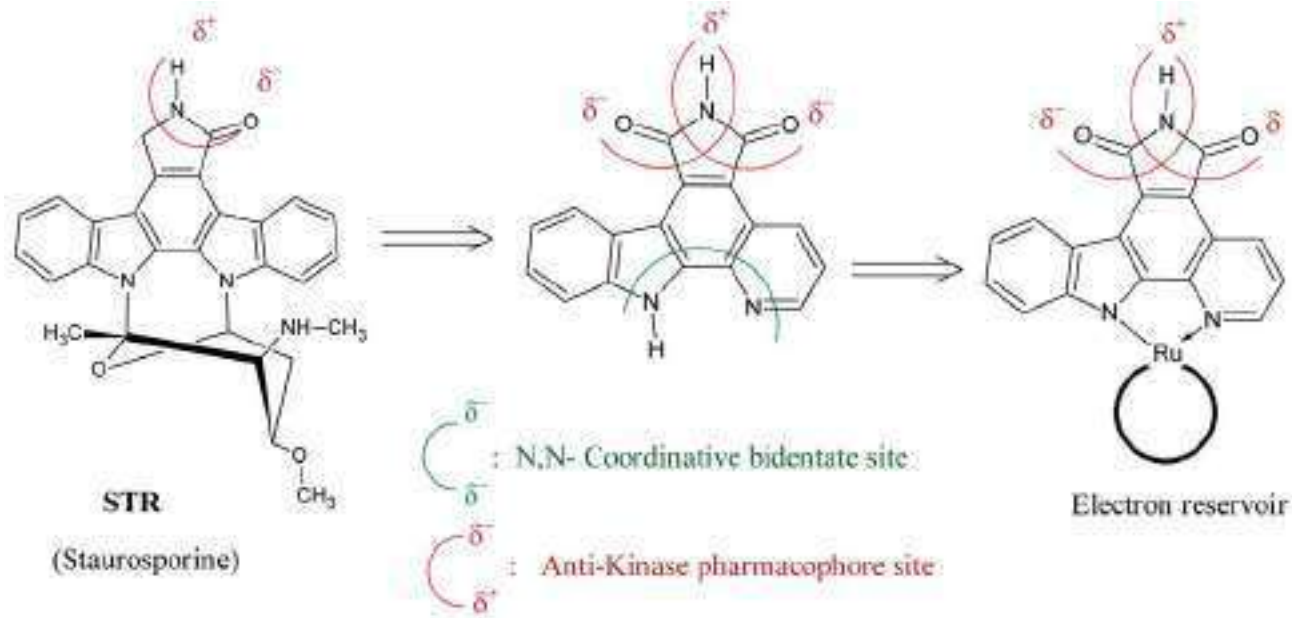


Figure 2. Series of Ru-staurosporine complexes with anti-tumoral pharmacophore site.

Table 1. Osiris calculations of toxicity risks of staurosporine (**STR**) and its derivative (**1**).

Compd.	MW	Toxicity Risks[a]				Osiris calculations[b]			
		MUT	TUM	IRRI	REP	cLog*P*	Sol	DL	DS
1	287	+++	---	+++	+++	2.41	–4.72	2.28	0.42
STR	466	+++	+++	+++	+++	4.44	–6.77	5.28	0.37

Higly toxic: (---), Slightly toxic: (+), Not toxic (+++). [a] MUT: Mutagenic, TUM: Tumorigenic, IRRIT: Irritant, RE: Reproductive effective.
[b] Sol: Solubility, DL: Druglikness, DS: Drug-Score. **STR** : Staurosporine.

Table 2. Molinspiration calculations of staurosporine derivative (**1**) and its complexes (**2**–**4**).

Compd.	Molinspiration calculations [a]				Drug-likeness [b]					
	TPSA	NONH	NV	VOL	GPCRL	ICM	KI	NRL	PI	EI
1	79	2	0	236	0.01	0.02	0.96	.48	0.21	0.56
2	109	1	1	428	0.12	0.15	0.33	–0.56	–0.02	0.42
3	76	1	1	480	0.00	0.28	0.11	0.64	0.08	0.14
4	96	3	1	394	0.04	0.18	0.25	0.70	0.25	0.28
STR	69	2	0	410	0.37	0.23	1.50	–0.18	0.35	0.86

[a] TPSA: Total molecular polar surface area; NONH: number of OH---N or O---NH interaction, NV: number of violation of five Lipinsky rules [50, 51]; VOL: volume. [b] GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor. **STR** : Staurosporine.

macophore because it is fixed for all compounds **1**–**4**. The absorption, distribution characteristics and bioactivity were proved to be dependent on the geometrical parameter and the aqueous solubility of each compound. Consequently, the bad absorption of tested staurosporine-ruthenium(II) complexes **2**–**4** could presumably be due to their low solubility.[28,29] Further, Table 2 shows drug-likeness of compounds **1**–**4,** not in the comparable zone with standard drugs used. We have calculated overall drug-score (DS) for compounds **1**–**4** and compared with that of standard

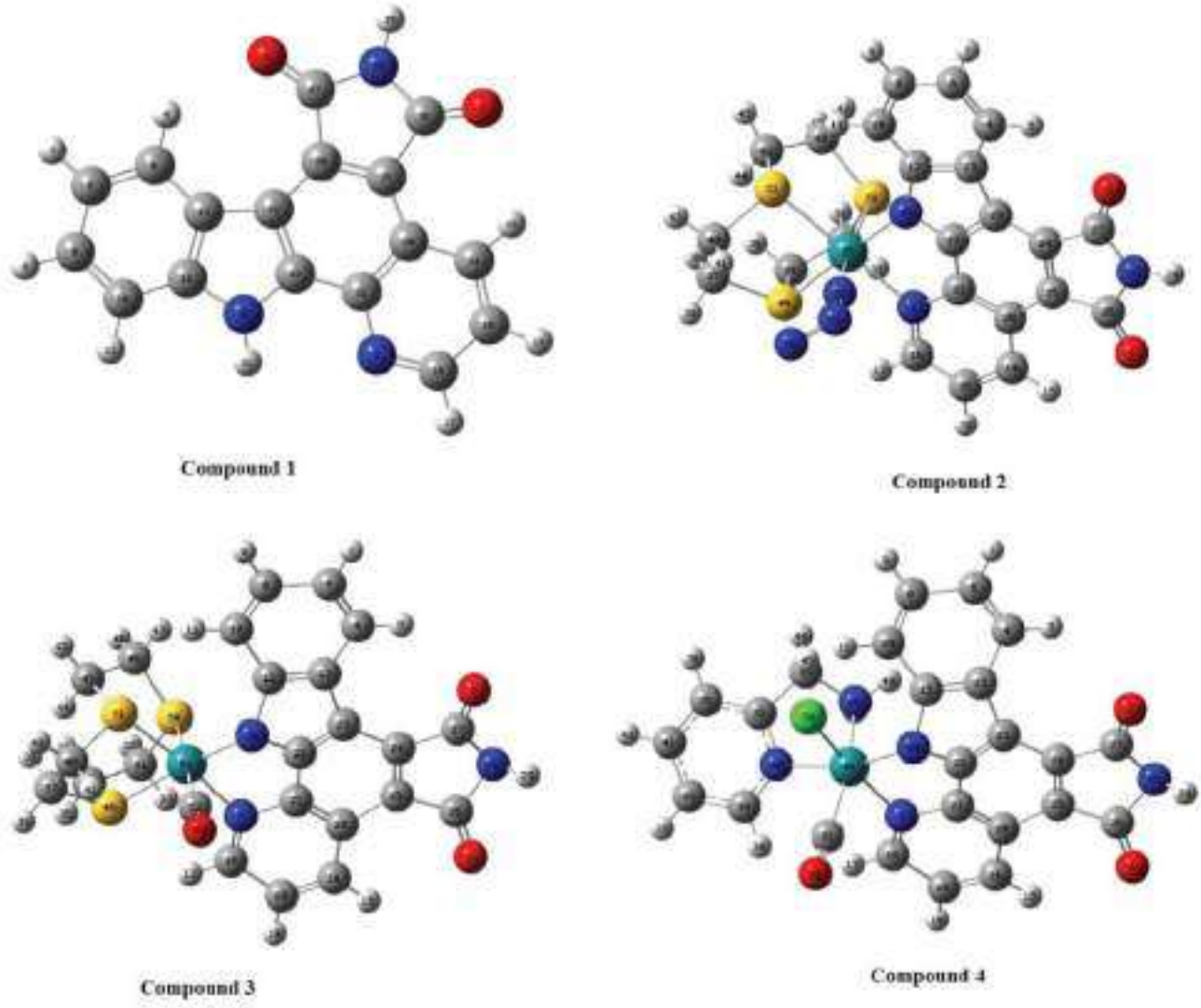


Figure 3. Optimized geometrical structure of compounds **1**–**4**.

drug (STR). The DS combines drug-likeness, cLog*P*, log *S*, molecular weight, and toxicity risks, in one handy value that may be used to judge the compound's overall potential to qualify for a drug. The reported compounds **2**–**4** showed low to moderate DS as compared with standard drug used STR (Table 1).

Incidentally, it is our opinion that DS and DL are not quite reliable since the values depend upon the program used. For this reason, supplementary DFT calculations will clarify this query.

3. 2. Frontier Molecular Orbitals

Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are the most important orbitals to characterize the chemical reactivity,[30,31] optical properties[32] and biological activity.[33] The energy gap between HOMO and LUMO is obtained by first optimization of structures **1**–**4** (Figure 3) as illustrated in Figure 4.

HOMO, HOMO–1, LUMO and LUMO+1 energies were calculated at B3LYP/6-311+G(d,p) and LANL2DZ theory level in order to understand influence of the structural properties of the Staurosporine and its complexes that are summarized in Table 3. As can be seen from Figures 4–7, for compound **1**, HOMO is mainly delocalized on the aromatic ring and heteroatoms except pyrrole carbonyl oxygen; however LUMO is mainly delocalized on the indole ring and heteroatoms. For compound **2**; the HOMO electrons are mainly delocalized on the Ru(II) and azido group, LUMO electrons are delocalized on the Staurosporine ring. For

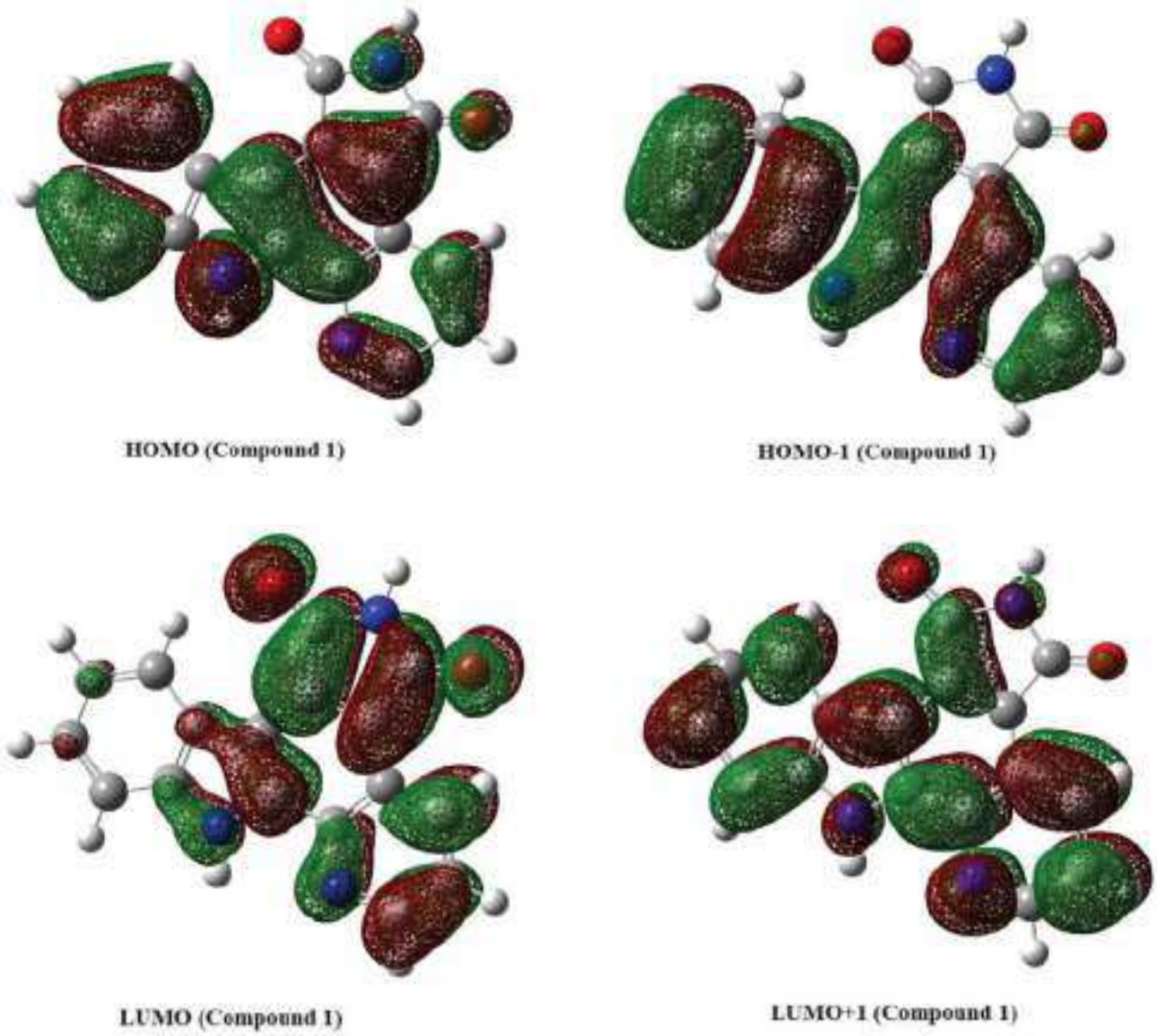


Figure 4. HOMO and LUMO molecular orbitals of the staurosporine derivative N,N-ligand (**1**) using the 6-311+G(d,p) method.

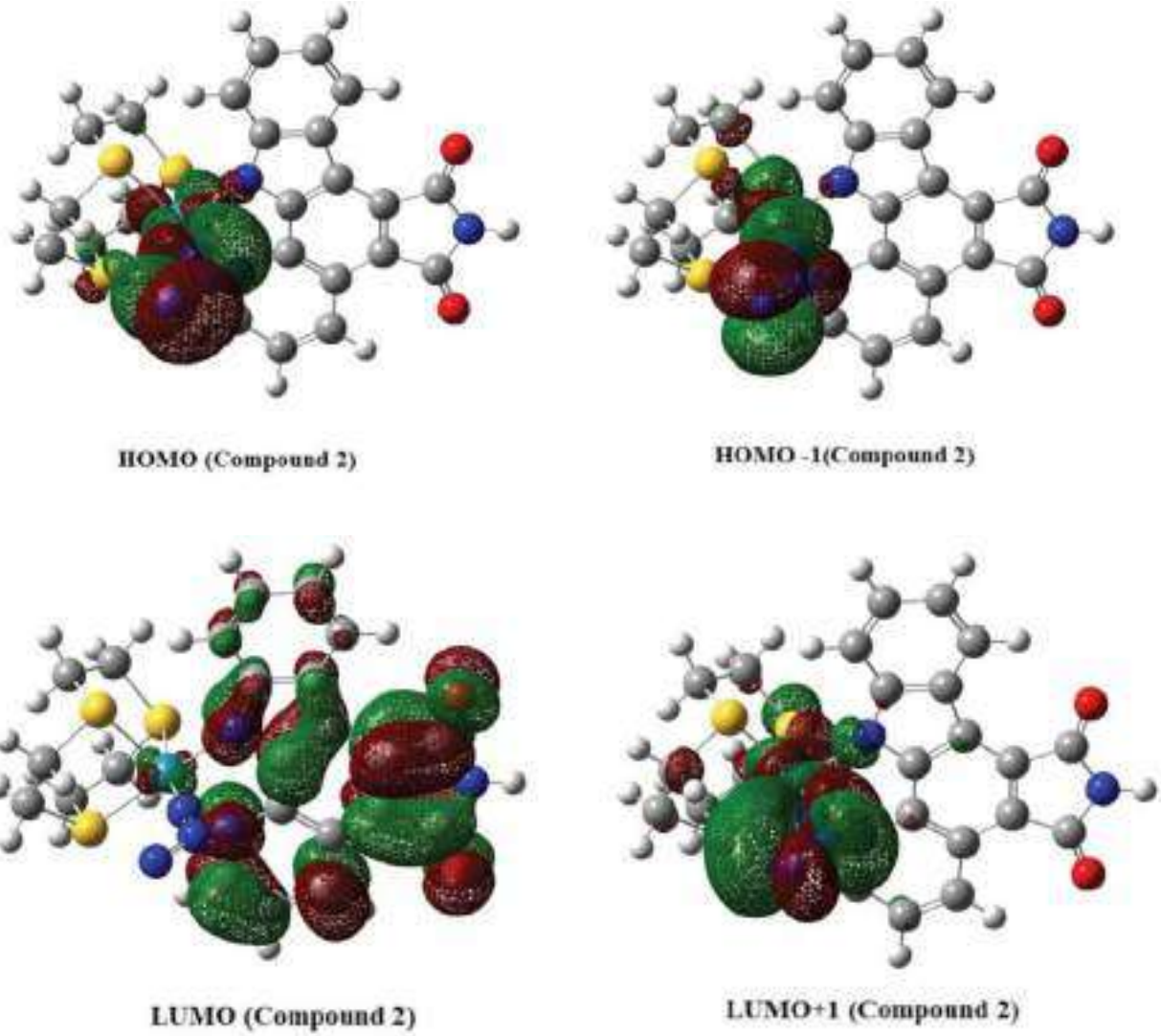


Figure 5. HOMO and LUMO molecular orbitals of the Staurosporine complex (**2**) using the LANL2DZ method.

compound **3**; the HOMO electrons are mainly delocalized on the Ru(II), oxygen atoms and pyrrole ring, while LUMO electrons are delocalized on the 1,4,7-trithiocyclononan ring. For complex **4**; the HOMO electrons are mainly delocalized on the Ru(II), $–NH_2$, indole ring, LUMO electrons are delocalized on the indole and pyridine ring. According to these results; generally HOMO and LUMO orbitals are mainly delocalized on the rings that mean p-antibonding type orbitals.

Various functional groups are the major active centers of the interraction. Indeed, the HOMO of these compounds does not contribute to an explanation of their inhibitory efficiency, but the HOMO-1 can carry out this role. In these cases, analysis of the effectiveness of kinase inhibition is based on the energy gaps (HOMO–1-LUMO+1). The chemical potential and nucleophilicity were estimated using the HOMO–1 and the LUMO (Figures 4–7; Table 3). However, the gap between the HOMO–1 and LUMO orbitals is an important factor that should be considered. The excellent enzyme kinase inhibitors are generally organic compounds that not only donate electrons to the positive charged amino acids of the enzyme but also accept free electrons of the imine groups of kinase enzymes.

By analyzing the HOMO–1-LUMO+1 energy gap values for these complexes (Table 3), it can be noted that for complexes **2–4**, the HOMO–1-LUMO+1 energy gaps values are lower than those obtained for ligand free (**1**). Therefore, complexes **2–4** (containing electron rich organometallic moiety) are predicted to be better kinase enzyme inhibitors with gaps HOMO-LUMO (**2**: 0.03842, **3**: 0.05054, **4**: 0.08147 a.u.) than ligand free compound **1** (containing free bidentate electron-withdrawing group) (**1**: 0.12336 a.u.) as shown in Table 3.

These results are in total agreement with the experimental results (Table 4). The HOMO-LUMO energy gaps of these complexes are consistent with the experimental

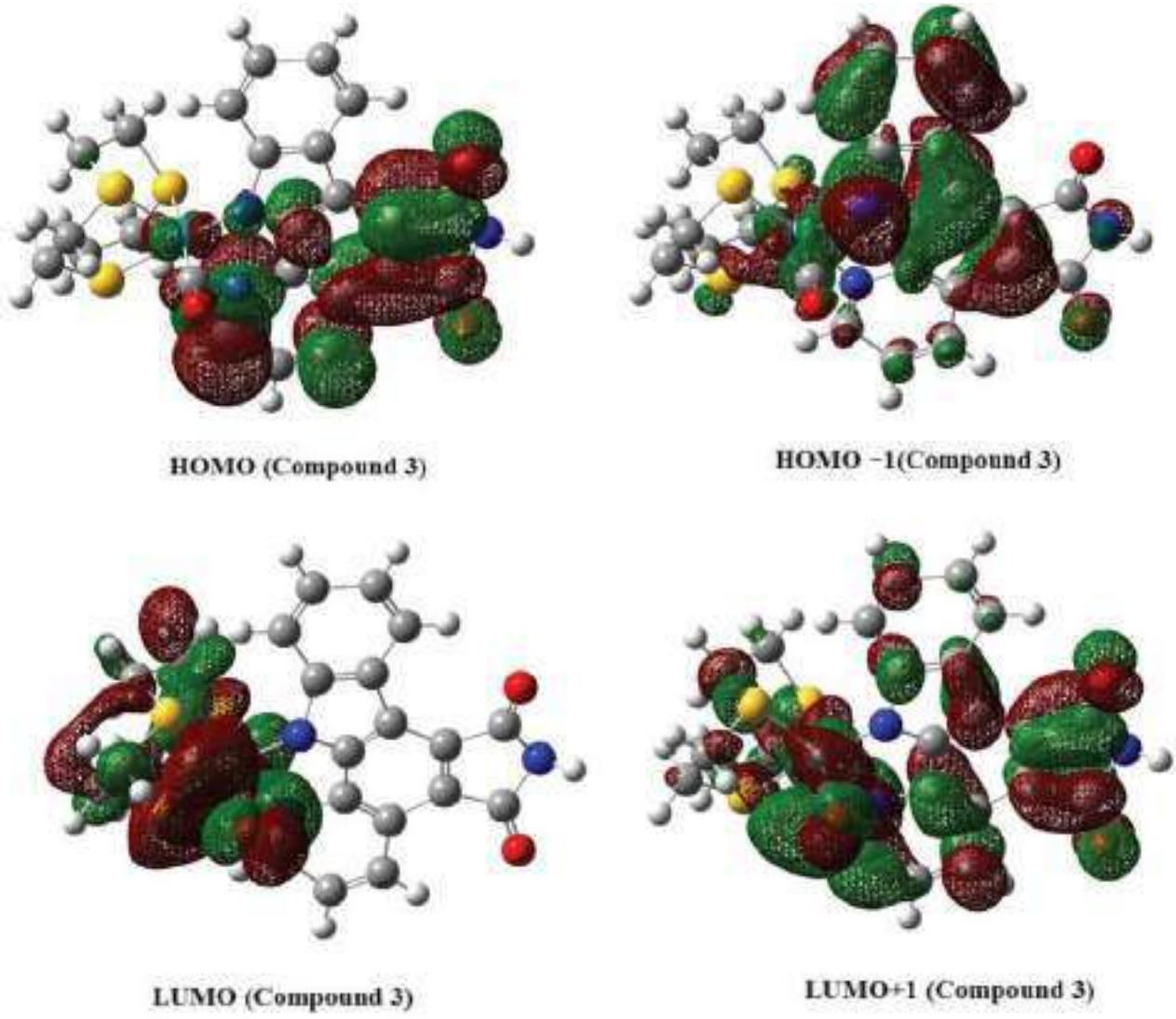


Figure 6. HOMO and LUMO molecular orbitals of the staurosporine complex (**3**) using the LANL2DZ method.

IC_{50} values given in literature[2–6] and the partial atomic charge obtained by calculations (Table 4). Furthermore, the two Oxygen atoms of the OCNHCO pharmacophore site are negatively charged, and the IC_{50} is low (more efficiency in bioactivity). The order obtained was **3** > **4** > **2** > **1** with O-charge: –0.6349, –0.56, –0.6349, –0.5383, respectively.

The structure of complex can affect the bioactivity by influencing not only the electron density of the functional pharmacophore site but also its proper bioavailability. In order to rationalize the local bioactivity, we have calculated the local charge of each heteroatom. The results are summarized in Table 4. The local atomic charges were obtained using DFT calculations

The distribution of the electron density shows that the compounds studied **1**–**4** have many active centers in nucleophilicity. The areas containing the nitrogen and oxygen atoms have more opportunity to form bonds with the metallic ruthenium(II) ions, by donating electrons of the heteroatoms to the metallic ions (Table 4). However,

Table 3. HOMO, HOMO–1, LUMO, LUMO+1 and ΔE energies (a.u.)

Compd.	HOMO	LUMO	HOMO–1	LUMO+1	HOMO-LUMO	HOMO–1-LUMO+1
1	–0.22915	0.10579	–0.24174	–0.07088	0.12336	0.17086
2	–0.12373	–0.09431	–0.14660	–0.06253	0.03842	0.08407
3	–0.09299	–0.04245	–0.19200	–0.03928	0.05054	0.15272
4	–0.18283	–0.10136	–0.19945	–0.07086	0.08147	0.12859

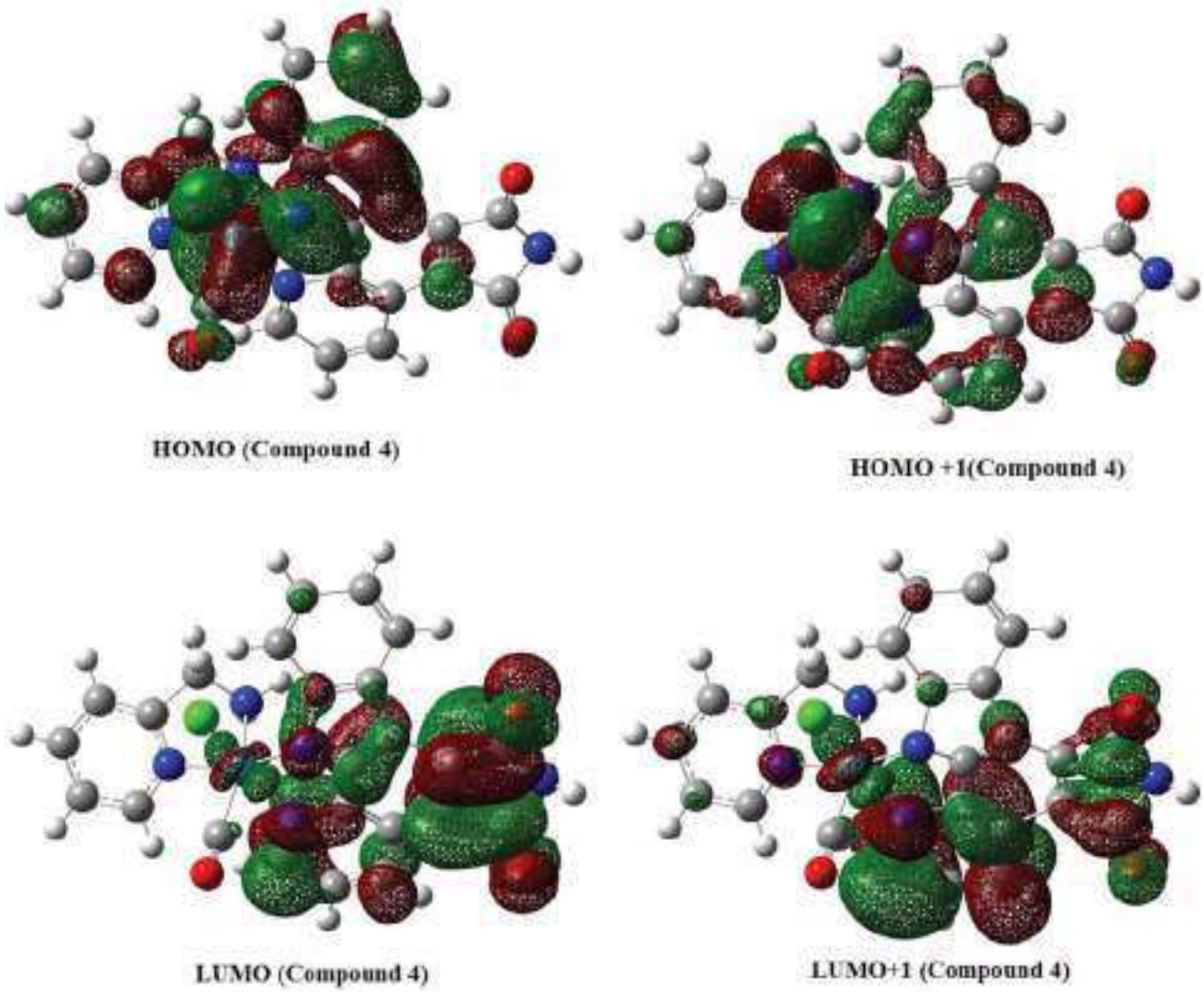


Figure 7. HOMO and LUMO molecular orbitals of the staurosporine complex (**4**) using the LANL2DZ method.

Table 4. Electronic impact on antitumor activity of (OCNHCO) pharmacophore site by coordination of drug (**1**) to electron rich organometallic moiety (**2**–**4**).

Compd	IC_{50} (nM)	Charge of Ru-(NN) Organometallic Moiety			Charge of OCNHCO Pharmacophore Site		
		Ru	N-1	N-2	O	N-3-H	O
1	$150 \cdot 10^3$	---	–0.3827	–0.6016	–0.5289	0.4422	–0.5383
2	70	–0.4886	–0.3827	–0.4391	–0.6292	0.4422	–0.6349
3	0.45	–1.0243	–0.4561	–0.5440	–0.6292	0.4169	–0.6349
4	8	–0.3461	–0.3979	–0.4591	–0.5808	0.2277	–0.5605

sites N1 and N2 are most favorable for electrophilic attack, in addition to oxygen in the case of **1**. It is interesting to note that the negative transferred charge of Ru(II) have important effect on the efficiency of inhibition of enzyme, like the effect of the terminal substituents on the organometallic moiety. This is in perfect agreement with the experiments (**3**: –1.0243; **2**: –0.4886; **4**: –0.3461 u.a).

4. Conclusions

The present work provided additional structure–activity and structure–cytotoxicity information for the staurosporine-ruthenium(II) complexes family. Indeed, this study proved that a simple control of nature of simple coordination to non-toxic transition metals leads to com-

pounds with high activities and reduced cytotoxicities of staurosporine as parent and clinical standard drug.

Tumor inhibition of kinase through staurosporine ligand and its complexes was elucidated by means of density functional theory (DFT)-derived reactivity indexes. The DFT calculated parameters and experimental cancer inhibition efficiency (IC_{50}) indicate that their inhibition effect is closely related to the frontier orbital energies, polarizability, electronic chemical potential and global nucleophilicity. The quantum chemistry calculations were performed at the B3LYP/6-31G(d) level. The theoretical results predicted by using DFT-based reactivity indexes, are in good agreement with experimental outcomes.

In comparing the percentages of inhibition efficiency (IC_{50}) of the studied compounds with the theoretical results, we note that their inhibitory effects are closely related to HOMO–1, HOMO–1-LUMO+1 gap, and the partial negative charge of Oxygen atoms of pharmacophore site. These parameters were calculated by the DFT method. The bioactivity decreases when HOMO–1 increases, and when the HOMO-1-LUMO+1 gap decreases. Therefore, complexes **2–4** are better kinase inhibitors (presence of donor organometallic moiety on the ligand-Ru) than free ligand **1** (presence of withdrawing nitrogen bidente groups on the staurosporine derivative ring's). The DFT calculations indicate that it is not convenient to consider only a single parameter (partial charges). However, several parameters were considered to characterize the inhibitory activity of the molecules, in particularly bioavailability (cLog*P*). The partial atomic charges of the series of complexes were discussed in a simple but precise manner.

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Povzetek

Razvili smo računski model Petra/Osiris/Molinspiration/DFT(POM/DFT) za določitev fizikalno-kemijskih parametrov, ki določajo biološko aktivnost rutenij-stavrosporin kompleksov **2**–**4** s farmakofornim mestom antitumor-kinaze (TK). Analiziranim štirim spojinam **1**–**4** so bile že predhodno testirane njihove antitumorne aktivnosti; spojini **2** in **4** sta nevtralni, medtem ko je analog **3** monokation z rutenijevim(II) centrom. Največja antitumorna aktivnost je bila dosežena pri spojinah **3** in **4**, ki imata nizko IC_{50} vrednost (0.45 in 8 nM), kar prekaša derivat stavrosporina (piridokarbazol **1,** 150 · 10^3 nM). IC_{50} vrednost za **3** (0.45 nM) predstavlja 20.000-kratno povečanje aktivnosti glede na derivat stavrosporina **1**. Povečanje bioaktivnosti je možno pripisati nastanku pi-prenosa naboja s kompleksa kovina-stavrosporin na $CO^{\delta-}$–$NH^{\delta+}$ antitumorno farmakoforno mesto.