1. General introduction

1.1 Introduction to Organic Chemistry

Organic Chemistry is the area of chemistry that involves the study of carbon and its compounds. Carbon is now known to form a seemingly unlimited number of compounds. The uses of organic compounds impact our lives daily in medicine, agriculture, and general life. Organic Chemistry erupted as an important branch in chemical science around 1900, until which the subject, chemistry remained undivided. The unprecedented number of factual research enforced a progressive segmentation of the subject into sub disciplines. Organic Chemistry is one of a special branch in chemistry and is concerned with the synthesis of organic compounds via use of several reactions and reagents. Organic synthesis has emerged as a subject of interest and centre of attraction for many scientists because of its ability to produce several beneficial products artificially, for the smooth functioning of human life.

Scientists believed that organic chemical found in nature contained a special "vital force" that directed their natural synthesis, and therefore, it would be impossible to accomplish a laboratory synthesis of the chemicals. Fortunately, Frederich Wohler (1828) that urea, a natural component in urine, could be synthesized in the laboratory by heating ammonium cyanate. His discovery meant that the natural "vital force" was not required to synthesis of organic compounds, and paved the way for many chemists to synthesize organic compounds. Organic Chemistry has helped to construct many different useful drugs and also in synthesizing other compounds, what a basic human needs. A keen investigation in the Organic Chemistry has helped to serve the mankind with lifesaving molecules – drugs and medicines and other basic necessities. Along with the development of Organic Chemistry, the advances in the interdisciplinary knowledge of relationship between biological activity and chemical structures has made a remarkable appearance in the support of synthesizing novel and useful organic molecules, thus ensuring a limitless scope for the development of structurally novel organic compounds with wide range of biological applicability.

Advances in Organic Chemistry have made possible the synthesis of complex molecule. Today the chief source of agents for cure, the mitigation or prevention of
diseases are organic, natural or synthetic, together with so called organometallics. Along with the development of Organic Chemistry; a great improvement in structural and functional development occurred, which helped the researchers to undertake their research and reach the conclusions more effectively. The instruments developed for characterizing organic molecules were much advanced technologically and were able to produce high quality results in less time span.
1.2 Introduction and importance of Medicinal Chemistry

Drug discovery is a complex process where Chemistry and preclinical and clinical pharmacology have prevalent role but it is also supported by the knowledge of several other life science discipline such as genetics, physiology, pathology, microbiology and molecular biology. Chemistry is involved in fundamental step of drug discovery process such as synthesis or extraction, drug analysis, formulation and pharmaceutical technology, but its main contribution is in drug design, discovery and development, that is, Medicinal Chemistry. In fact, Medicinal Chemistry relates to the design, study, development and production of drug that can be used as medicine for disease treatment.

In 1974 IUPAC gave following definition of Medicinal Chemistry: "Medicinal Chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drug, but interest of the medicinal chemists is not restricted to drugs but include bioactive compounds in general. Medicinal Chemistry is also concerned with the study, identification and synthesis of metabolic products of these drugs and related compounds."

The treatment of pain and disease is one of humanity’s most vital tasks to serve mankind, to accomplish their fundamental rights towards health. It is inevitable for the scientific fraternity and medicinal chemists to create equitable access to essential medicines for the priority diseases. This demanding activity for the betterment of humans requires creativity, a vast range of scientific knowledge and great persistence. Medicinal chemistry comprises of both art and science, henceforth requires a comprehensive mind to collect and synthesize mountains of data - chemical and biological, instinct to select the right direction to pursue, intellect to plan and execute the strategy that leads to the formation of desired compounds.

Medicinal Chemistry is an important at outset that drug discovery is not an unambiguous term in the pharmaceutical R & D world. For example, it can be defined using either programmatic or organizational approaches (or both), with several option on each category. Hence, it is important first to understand this variability and to adopt a specific definition for the purpose of this discussion. However it concerns with the
science that strive to identify, create and modify molecules for their therapeutic applications. Medicinal Chemistry basically deals with the understanding of mechanisms of actions of drugs. Although associated with several challenges in upbringing a drug candidate from bench top to clinic, the art of Medicinal Chemistry has enriched greatly from the developments in the areas of Organic Chemistry, biology, biophysical and chemical methodology and computational tools resulting in significant acceleration of drug discovery process.

Chemistry related with pharmaceutically important compounds mainly divided in two parts. The first, chemotherapy, concerns the treatment of infection, parasite or malignant disease by chemical agent, usually substance that shows selective toxicity towards the pathogen. The other division relates to disease of bodily disfunction and the agents employed are mainly compounds that effect the functioning of enzyme, the transmission of nerve impulse or the action of hormones on receptors. Medicinal Chemistry recognized as a scientific discipline for the benefit of humanity, operates by collaborating with chemists, biologist, pharmacists and computational experts for the search of molecules, which will become future’s new medicines. Today, major pharmaceutical companies are focused on discovery of low molecular weight drug-like molecules, which not only interact with the target but also have specific pharmacokinetic and toxicological properties that make them a drug.

The aim of the present study is to capture and harness the already accumulated experience of the world of the pharmaceutical research scientist and rolling for word in the research to construct a successful drug design. The study of these drugs and their structures deconvolute a large amount of information and also give us an initiative and inspirational push towards our research for successful drug design. Major duties of medicinal chemists involve design and synthesis of biologically active compounds and also to improvise the existing methods of synthesis for bioactive molecules put forward by several pharmaceuticals. Before a medicinal chemist synthesizes new molecules, he tries to study and establish structure activity and structure property relationships amongst series of compounds. This has always been a challenge for a medicinal chemist to optimize biological activity in parallel with other drug-like properties, such as
molecular weight, solubility, toxicity, metabolic stability and bioavailability. Also, emphasis is given on adsorption, distribution, metabolism and excretion (ADME) like features along with drug-drug interaction so that the drug does not fail in the last stage of development, which is observed more commonly in large set of molecules.

Medicinal Chemistry mainly focuses on the broad based variations embracing influences on number of possible permutations and combinations with regard to the chemical structure on the biological activity. With respect to the above statements of facts supported by several volumes of scientific evidences, it is very important for a chemist to logically understand overall physiochemical properties of the molecule along with ‘mechanism of drug action’. The physiochemical properties associated with molecule includes acid/base character, partition co-efficient, water solubility, lipid solubility, stereochemistry, chirality etc. It is, however, pertinent to mention here that most of the aforesaid properties exert significant influence upon various biological activities; such studies are more familiarly referred as Structural Activity Relationship (SAR). A creative medicinal chemist should ponder over presence of each functional group in the molecule with an aim to arrive towards non-toxic and potent medicinal agents.

There are many such natural products which have come in human observation since very ancient time for the treatment & curing of human illnesses. Later in the modern times, such substance and products have been isolated by modern scientific & medicinal research. Having been purified, modified and improved, these substances have come out brilliantly as medicinal drugs i.e. the Chinese drug "Mauhang" which has been known to be used as medicine since last 5000 years. But its active principle ephidrin was isolated only as late as 1887.

A large number of important drugs have been introduced during the period of 1940-1960. This period is known as the "Golden period" of new drug discovery. A medicinal chemistry project initiates with the designing of a lead compound with specific pharmaceutical property. Nowadays, the aim of medicinal chemistry is shifted from activity to selectivity. The more selective a compound is for a particular target, the more effective it is likely to be a lead molecule. Medicinal chemists are much interested...
in development of molecules with fewer side effects. Much interest is taken in identifying the effect of biologically active compound at molecular level. Medicinal Chemistry has introduced several new techniques over the last few years in order to speed up the drug discovery process, such as combinatorial chemistry, microwave-assisted organic synthesis and green synthesis methodologies.
1.3 About drugs

The word drug is derived from the French word “drogue” which means ‘a dry herb’. It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment / cure of a disease. This disease oriented definition of drug does not include contraceptives or use of drugs for improvement of health. According to “WHO” a drug may be defined as “Any substance or product which is used or intended to be used for modifying or exploring physiological system as pathological status for the benefit of the recipient”.

Pharmacology

Pharmacology is the science of drugs. In a broad sense, it deals with interaction of exogenously administered chemical molecules (drugs) with living system. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purposes. For thousands of years most drugs were crude natural products of unknown composition and limited efficiency. Only the over effects of these substances on the body were rather imprecisely known, but how the same were produced was entirely unknown. Over the past 100 years or so, drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs has been developed. The two main divisions of Pharmacology is pharmacodynamics and pharmacokinetics.

Pharmacodynamics: It is derived from the Greek word “dynamic” means power. What the drug does to the body? This includes physiological and biochemical effects of drugs and their mechanism of action at macromolecular / sub cellular organ systems.

Pharmacokinetics: It is derived from the Greek word ‘Kinesis’ means movement. What the body does to the drug? This refers to movements of the drug in and alternation of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug. Some other important aspects of pharmacology are given as under:
Pharmacotherapeutics: It is the application of pharmacodynamics information together with knowledge of the disease for its prevention, mitigation or cure.

Clinical Pharmacology: It is the scientific study of drug in man. It includes pharmacodynamics and pharmacokinetic investigation in healthy volunteers and in patients; evaluation of efficiency and safety of drugs and comparative trials with other forms of treatments; surveillance of patterns of drug uses, adverse effects, etc.

Chemotherapy: It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/malignant cell with less effect on the host cells.

Drugs in general, can thus be divided into

Pharmacodynamics agents: These are chemical substances designed to have pharmacodynamics effect in the recipient.

Chemotherapeutic agents: These are chemical substances designed for the treatment of infectious diseases or by the proliferation of malignant cells.

Essential Drug Concept: The ‘WHO’ has defined Essential Drugs as “those that satisfy the healthcare needs of majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage form”.

It has been realized that only a handful of drugs out of the multitude available can meet the health needs of majority of the people in any country, and that may be well tested and cheaper drugs are equally (or more) efficient and safe as their newer more expensive congeners. For optimum utilization of resources, governments (especially in developing countries) should concentrate on these drugs by identifying them as Essential Drugs. The “WHO” has laid down criteria guide selection of an essential drug:

1. Adequate data on its efficiency and safety should be available from clinical studies.
(II) It should be available in a form in which quality, including bioavailability, and stability on storage can be assured.

(III) Its choice should depend upon pattern of prevalent diseases; availability of facilities and trained personnel; financial resources; genetic, demographic and environmental factors.

(IV) In case of two or more similar drugs, choice should be made on the basis of their relative efficiency, safety, quality, price, availability and cost benefit ratio should be a major consideration.

(V) Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.

(VI) Most essential drug should be single compound. Fixed ratio combination products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage.

(VII) Selection of essential drug should be a continuous process which should take into account the changing priorities for public health action, epidemiological condition as well as availability of better drugs/ formulations and progress in pharmacological knowledge.

**Drug Development**

Many natural products by trial and error, came into practice for combating human ailments existent during early human observation. With the advent of modern scientific approach, various plant medicines came under chemical scrutiny, ultimately leading to the isolation of active principles since early.

Such compounds either in extract form or in pure form became a part of pharmacopoeias. For instance, though the Chinese drug, Mauhang was in use for over 5000 years for the treatment of various types of fever and respiratory ailments, its active principle, Ephidrine was isolated in 1887. In 1925 chemical investigations followed by pharmacological evaluation led this compound into the modern medicine. Similarly during this period, urea stibamine was introduced as the first drug in 1920 for the treatment of Kala-azar. In 1930, De Rauwolfia preparations were first employed for sedative and hypotensive properties. A drug is a substance having abnormal effect on certain body functions eg. Strychnine stimulates the action of heart and aspirin retards
its action. Since both of them effects abnormally, the two substances are known as drugs. Chemical sciences contributed extensively new discoveries leading to useful drugs since after 1930. The modern concept of drug discovery started in 1933 by Gerhand Domagk with his finding of “Prontosil Red”, a compound responsible for the antibacterial activity. The advent of sulphonamides drew the attention for the different activities of various chemicals for bacterial and human cells, this important factor prompted Florey and Chain in 1939 to investigate penicillin which was discovered ten years earlier by Alexander Fleming. The spectacular chemotherapeutical properties of penicillin and its dramatic war-time development for the treatment of wounds made penicillin, a most commonly used inexpensive drug. A large number of important drugs have been introduced during the period of 1940 to 1980. This period is known as “Golden period” of new drug discovery. Thus starting from 1933 - the first antibacterial drug prontosil leading to various sulpho drugs; 1940 – penicillin; 1945 – chloroquine – antimalarial; 1950 – Methyldopa – anti-hypertensive; 1967 – chlorothiazine -diuretic; 1958 – adrenergic beta blockers coronary vasodilatory; 1960 - semi synthetic penicillin - antibacterial; 1965 - trimethoprim-antimicrobial; 1967- disodiumchromoglycoate - antiallergic; 1972 - cimetidine H2 – antagonist; 1975 -verapamil- calcium antagonist and 1981 - captopril- antihypertensive. There are some specific examples representing new therapeutic agent eg. Metormineglipizide anti diabetic.

**Latest Drug Developments**

The current interest in the creation of large, searchable libraries of organic compounds has captured the imagination of organic chemists and the drug discovery community. In numerous laboratories the Efforts are focused on the introduction of chemical diversity, which have been recently reviewed and pharmacologically interesting compounds have been identified from libraries of widely different compositions.

Today, the chief source of agents for the cure, the mitigation or the prevention of diseases are the organic compounds, natural or synthetic, together with so-called organometallics. Such agents have their origin in a number of ways (a) from naturally
occurring materials - of both plant and animal origin, and (b) from the isolation of organic compounds synthesized in laboratory whose structures are closely related to those of naturally occurring compounds for eg. atropine, steroids, morphine, cocaine etc. that have been known to possess useful medicinal properties.

For a molecule to be drug-like, it must possess some basic properties such as, it should be much small molecule so that it can be easily transported throughout the body, hydrophilic and lipophilic enough to dissolve in the blood stream and cross the fat barriers within the body respectively. Also there must be enough number of polar functional group present in the molecule so that to enable it to bind to the receptor. Lipinski’s rule of five helps to conduct tests for identifying such properties in a molecule which can help it promote towards becoming a drug-like molecule. It has been estimated that the number of possible molecules with much less molecular weight and possessing basic drug-like properties are very few. The proportion of these drug-like molecules synthesized till date is much less, roughly the ratio of mass of one proton to mass of the sun!

It has been proved beyond any reasonable doubt that the success rate of discovery of novel molecules are exclusively dependent on the ability to identify and characterize novel targeted drug molecules more familiar as New Chemical Entities (NCE’s). The newly identified entities must possess inherent property of controlling a specific disease, besides being non-toxic. The Research and development process for most of the drugs available today has required 12-24 years from initiating a project to the their launch.

There are several methods available to initiate with a drug discovery project of finding biologically active molecules. Hits can be obtained via virtual screening approach or by studying the scientific or patent literature. More often, a drug designing and discovery process start with a screening campaign of commercially available compound libraries against the target of interest. We performed a literature survey of commercially available combinatorial libraries presenting the biological properties of several heterocyclic compounds followed by screening the compounds via Lipinski’s
rule of five – first stage of QSAR for identifying the drug-likeness properties of the designed molecules.
Chapter 1
General introduction

1.4 **Introduction to Heterocyclic Chemistry and its service to mankind**

Organic chemists synthesize hundreds of new heterocyclic compounds every week. In most cases the chemist has specific reason for synthesizing a particular compound, usually based on theoretical consideration, medicinal chemistry, biological mechanisms or a combination of all three. We must always continue to search for drugs which exhibit clear advantages over the already existing respective drugs. Such advantages may be: (1) A qualitative or quantitative improvement in activity, (2) a partial or total absence of undesirable side effects, (3) a lower toxicity, (4) more nutritive value, (5) improved stability and (6) a decrease in production cost.

The search for biologically active compounds is the driving force in pharmaceutical synthesis. The drugs used in human medicine cover the whole range of chemical entities including organic and inorganic compounds, but majorities are heterocyclic scaffolds or have a heterocyclic structural components viz. N, O, S etc. These cyclic systems containing at least one other element than carbon atom are called heterocyclic compounds. The modification of these ring systems plays an important role during drug development. Heterocycles are considered “versatile” due to their properties of possessing specific chemical reactivity and therefore have always attracted the attention of scientists working in both the area of natural products and synthetic organic chemistry. Heterocyclic compounds have great applicability in pharmaceuticals as anticancer agents, anti-tubercular agents, analgesics, hypnotics, anti-malarial, antimicrobials and as pesticides and insecticides. Heterocyclic compounds are enormous, their chemistry is complex yet interesting and various synthetic procedures have been developed resulting in diverse ring formations. The heterocyclic compounds are of immense importance biologically, hence have stimulated considerable research work in recent years leading to medicinal utility.

Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity. The major of synthetic heterocyclic compounds have found widespread use, for example as anticancer agents, antitubercular, analeptics, analgesic, hypnotics and as pesticides, insecticides and weed killers. Various synthetic procedures have been developed and considerable diversity in the ring is achieved.
Heterocyclic compounds are enormous, their chemistry is complex and synthesizing them requires great skill. Advances in organic chemistry have made possible synthesis of complexes molecule. Enantiometry is an important process in medicinal chemistry since life is inherently chiral and the drug target within the body are chiral. As such, they can distinguish between the enantiomers of a chiral drug, so the use of recemic drug is inherently wasteful, since only one enantiomer is ideally to interact with its target. Moreover, the existences of the "wrong" enantiomer could create problems if it interacted with a different receptor, resulting inside effects.

Several heterocyclic compounds occurring in nature involved biologically, includes nucleic acids (in DNA are found to possess nitrogen containing purine and pyrimidine bases), Vitamins (Thiamine $B_1$, Riboflavin $B_2$, Nicotinamide $B_3$), essential amino acids (proline, histidine and tryptophan)\(^\text{13}\) and heme (haemoglobin).\(^\text{14}\)

The heterocyclic compounds also occupy key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution because they have specific chemical reactivity. Majority of the large number of drugs being introduced in pharmacopeias in recent year are heterocyclic compounds. A wide variety of modern drugs such as chlordiazepoxide (tranquillizer)\(^\text{15-16}\), imipromine (antidepressant)\(^\text{17}\), guanethidine (antihypertensive)\(^\text{18}\), indapamide (diuretic and antihypertensive)\(^\text{19-20}\), etc. Many non-steroidal drugs such as ketoprofen\(^\text{21}\), fenoprofen and flubiprofen\(^\text{22}\) are well known anti-inflammatory agents; these derivatives were found to more potent with fewer side effect. Many antibiotics including penicillin\(^\text{23}\), cephalosporin\(^\text{24}\), norfloxacin\(^\text{25}\), streptomycin\(^\text{26-27}\) etc. also contain heterocyclic ring. Many veterinary products like pyrantel and morantel are the drug of choice as broad spectrum anthelmintics\(^\text{28}\). The herbicides atrazine and Simazine are well known example of heterocyclic agrochemicals\(^\text{29-30}\). Plant pigment such as indigo\(^\text{31}\), hemoglobin\(^\text{12}\) and anthiocyanins\(^\text{31}\), chlorophyll\(^\text{14}\) has contributed much to colour chemistry and all these contain heterocyclic ring. Further, many other heterocyclic colouring matters are in use since prehistoric times. Further, the heterocyclic tetra selena fulvalene was the first ionic molecular crystal to superconductivity.\(^\text{15}\)
Compounds not necessarily have to be heterocyclic in nature to exhibit pharmaceutical properties, but nature itself has selected heterocyclic compounds as the bases of most of the biological systems and the introduction of heteroatom into a cyclic compound impart new properties and responds much better to the many demands of biological systems.

Heterocyclic compounds have been in service to mankind since the day hetero atoms were identified. Even the first antibacterial drug prontosil developed in 1933, was found to possess hetero atoms. Several other important drugs discovered viz. penicillin (antibiotic, 1940), chloroquine (anti-malarial, 1945), trimethoprim (antimicrobial, 1965) were possessing heterocyclic skeletal as their basic structure. Majority of the drugs available in the market have either hetero atoms present as a substituent (functional group) or the core structure of the drug is found to be a heterocyclic skeletal.

1.4.1 Antifungal drugs

An antifungal drug is a medication used to treat fungal infection such as athlete's foot, ringworm, candidiasis, serious systematic infection such as cryptococcal meningitis and others. Theazole antifungals include two broad classes, imidazole and triazole which inhibit the cytochrome P450- dependent enzyme 14-sterol demethylase. This enzyme converts lanosterol to ergosterol and is required in fungal cell membrane.
synthesis. These drugs also block steroid synthesis in humans and thus inhibiting growth of fungi. Several heterocyclic analogues of triazole used as antifungal are fluconazole, isavuconazole, voriconazole, ravuconazole.

1.4.2 Anti- HIV drugs

Antiviral drugs used specifically for treating viral infections have heterocyclic scaffold as their basic structure. The antiviral drugs designed nowadays are used for treating HIV, herpes viruses, hepatitis B responsible for causing liver cancer. Abacavir – a nucleoside analog, reverse transcriptase inhibitor used to treat HIV and AIDS, Darunavir – a protease inhibitor used to treat HIV infection, Entecavir – an oral drug is a nucleoside analog used for treating hepatitis B infection and Lopinavir – an antiretroviral drug of the protease inhibitor class used for treating HIV infection and AIDS.
1.4.3 Antihelmintics drugs

Infections with parasitic helminthes and protozoa are important causes of morbidity and mortality worldwide. Anthelminthics can act by causing narcosis or paralysis of worm, or by damaging its cuticle, leading to partial digestion or to ejection by immune mechanism. Mebendazole, albendazole, thiabendazole, and fenbendazole are broad spectrum agent and constitute one of main group of antihelmintics used.
The thiazole derivatives niridazole, and levamisole are used as antihelmintics drugs.

1.4.4 Anti-Diabetic drugs

Anti-diabetic drugs treats diabetes mellitus by lowering glucose levels in the blood. Except insulin, all are administered orally and are thus called oral hypoglycemic or antihyperglycemic agents. There are several anti-diabetic drugs and their selection depends on the nature of diabetes, age and situation of the person, as well as other
factors. For diabetes mellitus I: caused due to lack of insulin, hence insulin must be injected to the patient suffering from diabetes I. Diabetes mellitus II is caused by resistivity of insulin by cells. The treatment for diabetes II includes i) agents that increase the amount of insulin secreted by pancreas, ii) agents that increase the sensitivity of target organs to insulin and iii) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract. Glimepiride is a medium-to-long acting sulfonylurea antidiabetic drug used to treat diabetes mellitus type II, The drugs helps to increase the production of insulin by pancreas. 

Miglitol is an oral antidiabetic drug that acts by inhibiting the ability of the patient to break down complex carbohydrate into glucose. Primarily it is used in diabetes mellitus II for establishing greater glycemic control by preventing the digestion of carbohydrates into monosaccharide which can be absorbed by the body. As miglitol prevents digestion of carbohydrates, it lowers the degree of postprandial hyperglycemia. It must be taken at the start of meals to have maximal effect. Pioglitazone is a drug of the class thiazolidinedione (TZD) with hypoglycemic activity to treat diabetes. It is used to improve glucose control in adults over the age of eighteen with diabetes II.
1.4.5 Anticonvulsants drugs

The anticonvulsants are diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of dipolar disorder, since many seem to act as a mood stabilizers. The heterocyclic compounds mostly used as anticonvulsants are barbexaclone, phenobarbital, nimetazepam, lorazepam, oxacarbazepine, rufinamide are carboxamide type anticonvulsants widely used for the control generalized myoclonic seizures.
1.4.6 Anti-bacterial drugs

Antibacterial drugs comprises of such agents that inhibits the growth of bacteria or kills them. Antibacterial agents are generally divided into two classes: bactericidal agents responsible for killing bacteria, and bacteriostatic agents that slowdown bacterial growth. Metronidazole is a nitroimidazole antibiotic used particularly against anaerobic bacteria and protozoa.\textsuperscript{64} It is a drug used for treating mild-to-moderate \textit{Clostridium difficile} infection.\textsuperscript{65,66} Ciprofloxacin – a second generation fluoroquinoline antibacterial is found to be active against most strains of bacterial pathogens responsible of respiratory, urinary tract, gastrointestinal and abdominal infections.\textsuperscript{67,68} Ciprofloxacin is found to exhibit excellent antibacterial property against a broad spectrum of gram-positive and gram-negative bacteria.\textsuperscript{67}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{antibacterial_drugs.png}
\caption{Antibacterial drugs}
\end{figure}

1.4.7 Anti-Inflammatory drugs

Non-steroidal anti-inflammatory drugs are the drugs with analgesic, antipyretic, and in higher doses, with anti-inflammatory effects. The term "non-steroidal" is use to distinguish these drugs from steroids which have a similar eicosanoid-depressing anti-inflammatory action. The NSAIDs covered in this section include pyrazolone derivatives,\textsuperscript{69-70} phenazone, metamizole, aminophenazone, phenylbutazone and apazone. Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins act as messenger molecule in the process of inflammation.\textsuperscript{71}
1.4.8 Anti-Histamine drugs

Anti-histamine can be used to describe ant histamine antagonist that act upon the $H_1$ histamine receptor. It has been discovered that these $H_1$-antihistamine are actually inverse agonists at the histamine $H_1$ receptor and are used to treat urticaria, anaphylaxis, asthma and allergic rhinitis. The heterocyclic compounds most used as histamine antagonist are phenothiazine derivatives, promethazine, methdilazine and mequitazine. Piperazine analogues such as levocetrizine, hydroxyzine and niaprazine act as sedating antihistamine. Heterocyclic analogues include diphenylpyraline,
Clemastine and meclizine are potent antihistamines with antiemetic activity useful in the treatment of motion sickness.\(^7\)

\[\begin{align*}
\text{Promethazine} & \quad \text{Methdilazine} \\
\text{Levocetirizine} & \quad \text{Hydroxyzine} \\
\text{Niaprazine} & \\
\end{align*}\]

### 1.4.9 Antiulcer agents

A peptic ulcer, also known as peptic ulcer disease (PUD), is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. It is defined as mucosal erosions equal to or greater than 0.5 cm. As many as 70 to 90% of such ulcers are associated with *Helicobacter pylori*, a helical-shaped bacterium that lives in acidic environment of stomach. Nizatidine and ranitidine are histamine H\(_2\)-
receptor antagonist that inhibits stomach acid production, and commonly used in the
treatment of peptic ulcer disease and gastroesophageal reflux disease (GERD).\textsuperscript{78,79}
Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer
disease and gastroesophageal reflux disease. Omeprazole is one of the most widely
prescribed drugs all over the world.\textsuperscript{80,81}
1.5 Introduction to QSAR study and description of QSAR models applied in our study

Nearly 40 years ago, quantitative structure-activity relationship (QSAR) paradigm was first introduced in all facets of chemistry.\textsuperscript{82} The stability of the technique for so long time may be attributed to the postulate of the theory that activity of a molecule was due to the presence of substituent (functional group - skeletal arrangement in three dimensions) and several properties associated with it like electronic attributes, hydrophobicity and steric properties.\textsuperscript{81} The QSAR methodology helps in finding the mechanism of action of drugs at molecular level and many other physiochemical phenomena like hydrophobicity.\textsuperscript{84,85} Hansch was the first to use QSAR to explain the biological activity of series of structurally related molecules.\textsuperscript{86} Hansch first used the descriptors and proposed a correlation between the molecule’s electronic environment and its hydrophobicity.\textsuperscript{84,85} The study by Hansch regarding the relation of biological properties and molecular structures helped him to lead to great conclusions.

QSAR – \textit{in-silico} studies is the name usually applied to methods where molecular structure is correlated to some kind of \textit{in vitro} or \textit{in vivo} biological properties. QSAR has been applied extensively to predict models for activity of bioactive molecules. QSAR study includes predicting drug-likeness of molecules, toxicity prediction, drug metabolism, pharmacokinetic properties. Several stages are involved in the QSAR study viz. first stage of QSAR study includes study of Lipinski’s rule of five for designed molecules, second stage and third stage involves carcinogenicity and mutagenicity respectively.

1.5.1 Descriptors applied in our study: First stage of QSAR – Lipinski’s rule of five

The first stage of QSAR includes the study of Lipinski’s rule of five which was formulated by Christopher A. Lipinski. Lipinski’s rule of five is a rule to evaluate drug-likeness\textsuperscript{87} or to determine presence of certain pharmacological properties in a molecule that would make it a likely active drug in humans. According to Lipinski’s rule of five, an orally active drug has no more than one violations of the following criteria;\textsuperscript{88}
1. Molecular weight under 500gm/mol.
2. Not more than 5 hydrogen bond donors.
3. Not more than 10 hydrogen bond acceptors.
4. Value of partition coefficient (log P) must be less than 5.
1.6 Studies on Benzoxazole derivatives

1.6.1 Introduction to Benzoxazole derivatives

Benzoxazole is a fused organic heterocyclic compound – bicyclic fused ring of benzene and oxazole. It contains one nitrogen atom and one oxygen atom in its core structure in the oxazole nucleus. Substituted benzoxazole derivatives and their analogues such as benzimidazoles and benzothiazoles have been the aim of many researchers for many years, because they constitute an important class of heterocyclic compounds. The structural variation of these compounds are that different substituents can be incorporated on the benzene ring and diverse heterocycles and other active groups can be introduced at the 2-position in order to create good biological activity. The substitution at second position in benzoxazole skeleton is influential for the biological activity of the molecule. Benzoxazole is used primarily in industry and research, and has no household use. Being heterocyclic compound, benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Benzoxazole can be considered as structural isosteres of the naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems.

Benzoxazole is an aromatic organic compound having benzene fused oxazole ring structure with a molecular formula C₇H₅NNO, molar mass 119.12 g/mol, and an odor similar to pyridine with IUPAC name 1-Oxa-3-aza-1H-indene, Insoluble in water and boiling point 182°C.

1.6.2 Synthesis of benzoxazole derivatives

Benzoxazoles have been synthesized by number of methods using variety of precursors, reagents and via different reactions. Balaswamy et al have synthesized benzoxazole derivatives from 3-amino 4-hydroxy benzoic acid methyl ester and aliphatic acid under reflux for 4 hr.
Chandramouli et al have reported novel regioselective one-pot synthesis of 2-aryl benzoxazole in excellent yields promoted by imidazolium based ionic liquid \([\text{bmin}]\text{BF}_4\)^{90} under ambient condition at higher temperature.

Priyanka et al have synthesized novel benzoxazole derivatives, taking equimolar quantities of 2-amino phenol and anthranilic acid were refluxed in PPA\(^{91}\) at 190\(^\circ\)-195\(^\circ\)C for 4 hrs.

Ynag D et al have optimization of Condition for Magnetic Copper (II) Ferrite\(^{92}\) Catalyzed Cyclization of N-(2-Bromophenyl) benzamide to 2- Phenyl-1,3-benzoazole.
Praveen et al has reported a convenient method for the synthesis of 2-substituted benzoxazoles with excellent yields via microwave assisted reaction:\(^{91}\)

\[
\begin{align*}
\text{Praveen et al} \\
\text{OH} & \quad \text{+} \quad \text{ArCHO} \\
\text{NH}_2 & \quad \text{PIFA(1.05 equiv),EtOH} \\
\text{R} & \quad \text{uw,80°C, 15 min.}
\end{align*}
\]

Parlapalli et al have reported synthesis of methyl-2-aminobenzoxazole-5-carboxylate using methyl alcohol and cyanogen bromide in good yield.\(^{94}\)

\[
\begin{align*}
\text{Parlapalli et al} \\
\text{OH} & \quad \text{MeOH} \\
\text{NH}_2 & \quad \text{CNBr} \\
\text{H}_3\text{COOC} & \quad \text{H}_3\text{CO}
\end{align*}
\]

Wang et al have reported the synthesis of benzoxazole derivatives were evaluated for binding affinities at the 5-HT\(_{1A}\) and 5-HT\(_{2A}\) receptors, Antidepressant activities of the compounds were screened using the Forced Swimming Test(FST) and tail suspension test(TST).\(^{95}\)

\[
\begin{align*}
\text{Wang et al} \\
\text{NH}_2 & \quad \text{PPA} \\
\text{OH} & \quad \text{+} \quad \text{HNOC} \\
\text{NH} & \quad \text{PAA}
\end{align*}
\]

Santhoshi et al have reported a series of thio-substituted benzoxazole analogues were synthesized from Balis-Hillman bromides in a clean and efficient way. Benzoxazole compounds were subjected to \textit{in vitro} COX-1 and COX-2 inhibitory activity.\(^{96}\)
Lokwami et al carried out a copper catalyzed\textsuperscript{97} one-pot synthesis of benzoxazoles using bromoanilines and acyl halides in the presence of a base and a solvent.

A simple and efficient procedure for the synthesis of substituted benzoxazole compounds were synthesized by treating 4-thiocynoaniline with o-aminophenol and carbon-di-sulphide, easy and quick isolation of the products, and excellent yields was reported by Stella et al.\textsuperscript{98}

Bao et al have synthesized benzoxazole by treating 2-aminophenols with β-diketones catalyzed by a combination of Bronsted acid and Cu\textsuperscript{99}. Various 2-substituted benzoxazoles were obtained through these reaction.
Sekar et al have reported benzoxazole derivatives were prepared and screened for antimicrobial activity.\textsuperscript{100} The reaction of DIPOD with different o-amino phenol in ethanol gave benzoxazole derivatives.

Patel et al have synthesized benzoxazole derivatives by treating with o-haloanilides, CuO nanoparticals in water at 100°C, however a complete change in selectivity was observed in the presence of an organic base/ligand (TMEDA)\textsuperscript{101}, giving 2-arylbenzoxazole as the exclusive product.
Sarode et al\textsuperscript{102} have reported the synthesis of 2-substituted benzoxazole by using 2-nitrophenol and benzyl amine as starting materials in the presence of copper ferrite nanoparticles (copper ferrite NPs).

\begin{center}
\includegraphics[width=\textwidth]{reaction_diagram}
\end{center}

1.6.3 Therapeutic importance of Benzoxazole derivatives

Various Heterocyclic compounds have received considerable attention during last few decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. The earlier sources of drugs i.e. plant, animal and mineral sources, resulted somehow lesser therapeutic efficacy and even more toxicities comparatively. So the process of new drug discovery has been accelerated by the necessity of synthesizing compounds possessing better therapeutic and least possible toxicological parameters.

During recent years there have been some interesting developments in the pharmacology of benzoxazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities.

It has been investigated in past decade that benzoxazoles possess a wide range of promising biological activities\textsuperscript{101}. The substituted benzoxazoles have been shown to exhibit antitumor\textsuperscript{104}, antioxidant, antihelmintic\textsuperscript{105}, cyclooxygenase inhibitory\textsuperscript{106}, antifungal\textsuperscript{107}, Antitubercular\textsuperscript{108}, 5HT\textsubscript{3} receptor antagonists\textsuperscript{109}, anti-inflammatory, analgesic & cyclin dependent kinase inhibitory, 5-lipoxygenase inhibitory\textsuperscript{110}, melatonin receptor agonist\textsuperscript{111}, anticancer\textsuperscript{112}, antibacterial\textsuperscript{113} and anti-HIV\textsuperscript{114} activities.

Recent observations suggested that substituted benzoxazoles and related heterocycles possessed potential activities with lower toxicities chemo-therapeutically\textsuperscript{115} e.g. benzoxazole derivative, Calcimycin, is a carboxylic polyether antibiotic isolated from the culture of \textit{Streptomyces chartreusis} (NRRL 3882). It was found to be very active against Gram-positive bacteria including some \textit{Bacillus} and \textit{Micrococcus} microbes. Two
calcimycin analogues, Routiennocin\textsuperscript{116} and Cezomycin\textsuperscript{117} were found to be highly active against \textit{Bacillus cereus, Bacillus negaterium, Micrococcus luteus} and \textit{Streptomyces rimosus}. Additionally Frankamide\textsuperscript{118} that is 11-demethyl cezomycin showed some activity against \textit{Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis} and against several plant pathogenic fungal strains\textsuperscript{119}.

Vinsova \textit{et al}\textsuperscript{120} have synthesized antibacterial derivatives possessing benzoxazole derivatives. These benzoxazole derivatives have shown activity against \textit{Mycobacterium tuberculosis} and some nontuberculous strain where isoniazid has been inactive.

Revial \textit{et al}\textsuperscript{121} have synthesized antifungal derivatives by reacting 4-substituted -2-(chloroacetylamino) thiazoles with benzoxazole-2-thioles in acetone and in the presence of K$_2$CO$_3$.

Yildiz-Oren \textit{et al}\textsuperscript{122} have synthesized multisubstituted benzoxazoles as non-nucleoside fused isosteric heterocyclic compounds were synthesized and tested for their antibacterial activities against various Gram-positive and Gram-negative bacteria.
Kumar et al\textsuperscript{123} have reported a series of analogues of the bis (benzoxazole) natural product UK-1 in which the carbomethoxy-substituted benzoxazole ring of the natural product was modified were prepared and evaluated for their anticancer and bacterial properties.

Alper-Hayta et al\textsuperscript{124} have synthesized a new series of 2-substituted benzoxazole derivatives. The \textit{in vitro} antimicrobial activity of the compounds was determined against some Gram-positive and Gram-negative and fungi and their resistant isolates in comparison with standard drug.
Jauhari et al have developed a series of 2-substituted benzoxazoles derivatives and found that the derivatives were assayed for antifungal activity against *Aspergillus flavus* and *Aspergillus niger*.\(^\text{125}\)

Murty et al\(^\text{126}\) have reported some 2-substituted benzoxazole coupled with 1,3,4-oxadiazole-2-thiol which have been evaluated for their cytotoxicity towards human cancer.

Jyothi et al have reported some newly substituted benzoxazole derivatives. All the derivatives showed good antifungal activity against *A. niger* and *A. flavus* Mild activity was seen against *F. oxysporum* and *C. lunata*.\(^\text{127}\)
Gautam et al\textsuperscript{128} have reported a novel benzoxazole substituted thiazolidinone derivatives were synthesized through cyclization of unsymmetrical imine with mercapto acid in the presence of stanus chloride dehydrate.

Ampati et al have reported series of anti-inflammatory derivatives possessing benzoxazole nucleus. All the compounds were found to possess significant anti-inflammatory activity.\textsuperscript{129}

Russo et al\textsuperscript{130} have synthesized benzoxazole derivatives which were evaluated for their potential analgesic activity in phenylquinone-induced writhing test in mice.
1.7 Studies on 1,3,4-oxadiazole derivatives

1.7.1 Introduction to 1,3,4-oxadiazole derivatives

Oxadiazole, a heterocyclic nucleus has attracted a wide attention for the chemist in search for the new therapeutic molecules. Oxadiazoles and their derivatives are considered as simple five membered heterocycles. The first synthesis of 1,2,4-oxadiazoles, initially named furo [ab-1]diazoles, was achieved by Tiemann and Kruger in 1884.

1,3,4-oxadiazole is a five member heterocyclic compound containing an oxygen atom and two nitrogen atoms. It resembles a little with the structure of furan. The two methylene =CH of furan if replaced by –N=, it forms 1,3,4-oxadiazole. The other known isomers of 1,3,4-oxadizoles include 1,2,3-oxadiazole, 1,2,4-oxadiazole and 1,2,5-oxadiazole. However 1,3,4-oxadiazole is widely used and more better studies by researchers because of its many important chemical and biological properties.

1,3,4-oxadiazole bearing compounds have a broad biological activity spectrum, which includes antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant and anti-diabetic properties. A variety of therapeutically active compounds viz. raltagravir – HIV integrase inhibitor, furamizole – an antibacterial, nesapidil – anti-hypertensive agent and anticancer activity are found to possess 1,3,4-oxadiazole as a core nucleus.
1.7.2 Synthesis of 1,3,4-oxadiazole derivatives

There are number of different methods reported for the synthesis of 1,3,4-oxadiazoles. Zarghi et al have reported the synthesis of 5-aryl-2-amino-1,3,4-oxadiazole compounds in good yield. The reaction was carried out in presence of CNBr and methanol was used as a solvent for carrying out this reaction.¹⁴²

\[ \text{CONHNH}_2 \xrightarrow{\text{CNBr, NaHCO}_3,} \text{MeOH, rt, 3hr} \]

Rashidi et al¹⁴³ have also synthesized a novel series of 1,3,4-oxadiazole bearing compounds by reacting acid hydrazide with p-chlorophenyl isocynodichloride with suitable solvent chloroform and NH₄OH.

\[ \text{R} \text{N} \xrightarrow{\text{CHCl}_3, \text{NH}_4\text{OH}} \]

Katritzky et al have synthesized 5-aryl-2-amino-1,3,4-oxadiazole derivatives in high yields by reacting arylhydrazides and di(benzotriazol-1-yl)methanimine as under.¹⁴⁴
Dewangan et al\textsuperscript{145} have synthesized N-ethyl-5-(pyridine-4-yl)-1,3,4-oxadiazole-2-amine with KI and iodine.

Keshavayya et al\textsuperscript{146} have synthesized a series of 2,2'-(5-nitrobenzene -1, 3-diyl) bis (5-alkyl-1,3,4-oxadiazole) by reacting 5-nitrobenzene-1,3-dicarbohydrazide and the appropriate long chain fatty acids in POCl\textsubscript{3}.

Dolman and co-workers have reported a new method of synthesis for the formation of 5-aryl(alkyl)-2-amino-1,3,4-oxadiazoles from acylsemicarbazides, using tosyl chloride.\textsuperscript{147}
Kumar et al\textsuperscript{148} synthesized a new series of 1,3,4-oxadiazole from Biphenyl 4-carboxylic acid on treatment with various chemicals and prepared 2-((biphenyl-4yl)-5-phenyl-1,3,4-oxadiazole derivatives.

Abd El-Samii et al\textsuperscript{149} have synthesized a novel 1,3,4-oxadiazole derivatives from 3-hydroxy-5,6-biphenyl-1,2,4-triazine. Synthesized derivatives have shown promising anti-inflammatory activity in comparison to phenylbutazone.

Pouliot and co-workers reported a procedure for the preparation of 1,3,4-oxadiazoles using diethylaminodifluorosulfinium tetrafluoroborate (XtalFlour-E) as a novel cyclodehydration agent.\textsuperscript{150}
Yang et al\textsuperscript{151} have reported a novel agrochemicals with high activity and low toxicity, of diheterocyclic compounds containing 1,2,4-triazole[1,5-α] pyrimidine and 1,3,4-oxadiazole.

Pardeshi et al\textsuperscript{152} , using a mixture of N-chlorosuccinimide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) oxidatively cyclized structurally diverse acylhydrazones, thereby providing an efficient and convenient method for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles.

Polshettiwar and Varma reported a novel one-pot solvent free synthesis of 1,3,4-oxadiazoles by condensation of benzohydrazide and triethylorthoalkanates under microwave irradiation. The reaction was efficiently catalyzed by using Nafion ®NR50 and phosphorous pentasulfide in alumina (P$_4$S$_{10}$ / Al$_2$O$_3$).\textsuperscript{151}
1.7.3 Therapeutic importance of 1,3,4-oxadiazole derivatives

The need for new, safer and more efficient antimicrobial agents has been fulfilled upto a great extent with the development of 1,3,4-oxadiazole possessing antimicrobial drugs. Researchers around the globe have reported several 1,3,4-oxadiazole derivatives possessing different biological properties, which includes antibacterial, antifungal, antimalarial, antiviral, anticancer, anti-inflammatory and antitubercular activity. A variety of drugs possessing 1,3,4-oxadiazole ring have been reported viz. raltegravir – an antiretroviral drug used to treat HIV infection, furamizol is used as a nitrofuran anti-bacterial, nesapidil as an antihypertensive, antimicrobial and anticancer agent.

Maslat et al have reported antibacterial and antifungal activities of 1,3,4-oxadiazolines against the strain S.aureus and B. Subtilis.

Patel et al verified the antimicrobial activity of a series of derivatives containing the 1,3,4-oxadiazole nucleus against Gram-positive and Gram-negative bacteria using ampicillin as the drug standard.
2,5-disubstituted 1,3,4-oxadiazole compounds synthesized by Fuloria and co-workers; when evaluated against a broad spectrum of bacterial and fungal strains were found to exhibit excellent antimicrobial properties.\textsuperscript{165}

Chen \textit{et al} have synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives tested for their antifungal activity.\textsuperscript{166}

Bakal and Gattani investigated anti-tubercular activity for a series of 2,5-disubstituted 1,3,4-oxadiazoles against M. tuberculosis H\textsubscript{37}Rv.\textsuperscript{167}
Burbuliene and co-workers have investigated for the anti-inflammatory activity of synthesized derivatives having 1,3,4-oxadiazole core. The results obtained for the designed compounds were found to be more potent than ibuprofen.\(^\text{168}\)

![Image of Burbuliene et al compound](image)

Johns and co-workers reported antiviral activity for new derivatives containing the 1,3,4-oxadiazole unit in combination with a ring system of 8-hydroxy-1,6-naphthyridine.\(^\text{169}\)

![Image of Johns et al compound](image)

Karthikeyan et al have synthesized 2,4-dichloro-5-flourophenyl containing 1,3,4-oxadiazoles and then final compounds were tested for their antimicrobial activity with standard drug Greseofluvin.\(^\text{170}\)

![Image of Karthikeyan et al compound](image)
Ouyang and co-workers\textsuperscript{171} as well as Tuma and co-workers\textsuperscript{172} have synthesized and evaluated various 1,3,4-oxadiazole derivatives as to their ability to inhibit tubulin polymerization and block the mitotic division of tumor cells\textsuperscript{171}.

\begin{center}
\includegraphics[width=\textwidth]{oxadiazole_structures.png}
\end{center}

Rajak and co-workers have synthesized and evaluated semicarbazones containing the 1,3,4-oxadiazole units for anticonvulsant potential in a three model test, (MES), (scPTZ) and (scSTY).\textsuperscript{174}

\begin{center}
\includegraphics[width=\textwidth]{semicarbazone结构.png}
\end{center}

Bankar \textit{et al}\textsuperscript{175} have synthesized a compound exhibiting vasorelaxant effect in rat aortic rings by blocking L-type calcium channels. The compound 4-(3-acetyl-5-(pyridine-3-yl)-2,3-dihydro-1,3,4-oxadiazole -2-yl)phenylacetate synthesized by Banker and his co-workers exhibited excellent anti-hypertensive activity.
1.8 Studies on Schiff’s base derivatives

1.8.1 Introduction to Schiff’s base

The condensation of primary amines with carbonyl compounds was first reported by Schiff, and the condensation products are often referred to as Schiff’s base. The general structure of these bases is

\[
\begin{array}{c}
R_2 \\
N \\
R_1 \\
\end{array}
\]

Where \( R, R_1, R_2 \) are \( H, \text{alkyl, cyclohexyl, aryl or heterocyclic radicals} \), which may be variously substituted. These condensation reactions, along with the chemical and physical properties of Schiff base have been reviewed. Schiff bases are also known as anils, imines, or azo methines.

Various studies have been shown that the \( \text{N}=\text{C} \) group has considerable biological importance, this can be substantiated by the fact that the possibility of having a lone pair of electrons in either a \( \pi \) or an \( sp^2 \) hybridized orbital on trigonally hybridized nitrogen in the \( \text{N}=\text{C} \) group; which is of fundamental chemical and biological importance, and together with the variability of angles of hybridization it makes possible formation of nitrogen containing molecules with all the delicate differences in physicochemical properties necessary to produce the various phenomena of life.

In recent years, interest has also focused on aza-analogs such as Schiff’s bases derivatives which show a very similar pharmacological profile to classical. Over the past few years, several lead compounds have been developed. Schiff’s bases are well known intermediates for the preparation of the azetidinones, thiazolidinone, formazan, arylacetamide and many other entities of pharmaceutical potential. These are the compounds containing characteristic \(-\text{HC}=\text{N}-\) group.

Schiff’s bases are obtained mainly by warming the aldehyde and aromatic amine together. However, it is more convenient to work in a solvent such as alcohol, dilute acetic acid or glacial acetic acid. Some time the reaction is aided by trace of acid in other cases the hydrochloride of the amines can be used in the synthesis. In the general Schiff’s bases do not react further with either of the reagent used in their preparation as do most
of the other types of simple intermediates. Synthetic Schiff’s base derivatives contribute in huge libraries owing to their wide applicability in different fields.

1.8.2 Synthesis of Schiff’s bases

A variety of methods are available for the synthesis of Schiff’s bases, and most convenient is the one that involves the simple condensation reaction utilizing substituted anilines with varied aldehydes in presence of glacial acetic acid and alcohol solution. Several methods adopted by researchers are reported as under.

Shi et al\textsuperscript{176} have been synthesized a series of Schiff’s bases by reacting 5-chlorosalicylaldehyde and primary amines, these compounds were assayed for antibacterial and antifungal activities.

\[
\text{ClCHO} + \text{H}_2\text{N-R-NH}_2 \rightarrow \text{ClN=N-C=N-R-NH}_2
\]

Vora et al\textsuperscript{177} have reported a procedure for the synthesis of Schiff’s base by condensing aldehyde obtained from pyrazole with 4-methylpyridin-2-amine.

\[
\begin{align*}
\text{R}_3\text{R}_2\text{R}_1\text{N} & \text{N}\text{H}_2 \rightarrow \text{R}_3\text{R}_2\text{R}_1\text{N} = \text{HC} \\
\text{R}_3\text{R}_2\text{R}_1\text{N} = \text{HC} & \rightarrow \text{R}_3\text{R}_2\text{R}_1\text{N} = \text{HC} + \text{H}_2\text{N-R-NH}_2
\end{align*}
\]
Parikh et al\textsuperscript{178} have synthesized a series of substituted schiff's bases have been prepared by the treatment of 2-chloro-6-methoxyquinoline-3-carbaldehyde with different aryl amines.

Prakash et al\textsuperscript{179} have reported a novel method for the synthesis of schiff base by ethylenediamine with nitro benzaldehyde in reflux condition.

Vijayakumar et al\textsuperscript{180} have an approach towards the synthesis of novel schiff's bases from Aloin, were developed. The prepared derivatives, glycones showed strong antibacterial activities.
Raval et al\textsuperscript{181} have reported a series of 5-substituted indolin-2-one derivatives were synthesized, characterized and were screened for antibacterial, antifungal and antitubercular activity.

Prabhu et al reported a series of several benzthiazole clubbed Schiff bases. All the compounds have shown significant antibacterial activity with the reference standard Ampicilline and Ketoconazole\textsuperscript{182}.

Singh et al\textsuperscript{183} have synthesized different Schiff bases with chloroacetyl chloride and thioglycolic acid, respectively. Antimicrobial activities of compounds were investigated using the standard method against different bacterial and fungal strains in comparison with standard dugs.
Kamaria et al\textsuperscript{184} have reported a series of Schiff bases of indole-3–aldehyde were synthesized by microwave assisted synthesis by taking DMF as solvent and evaluated for their antimicrobial activity.

\begin{center}
\textbf{Kamaria et al}
\end{center}

\begin{center}
\textbf{Abd El et al}\textsuperscript{185} have reported a series of pyridine-bridged 2,6-bis-carboxamide Schiff's bases has been prepared. The newly synthesized compounds were screened for their bactericidal and fungicidal activities.
\end{center}

\begin{center}
\textbf{Abd El et al}
\end{center}

Wadher et al\textsuperscript{186} have reported a series of Schiff base. 4,4'-diamino diphenylsulphones was condensed with various aromatic or heterocyclic aldehyde in ethanol in the presence of Con. sulphuric acid as a catalyst to yield the Schiff base.
Vibhute et al\textsuperscript{187} have synthesized new technique for Schiff base synthesis, 3,5-dichloro-2,4-dihydroxy benzaldehyde with substituted anilines in ethanol containing traces of glacial acetic acid occurs to afford Schiff base in quantitative yield using Grindstone technique.
1.8.3 Therapeutic importance of Schiff bases

Azomethine group (-C=N-) containing compounds typically known as Schiff bases have been synthesized by the condensation of primary amines with active carbonyls. Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications.

Kumar et al\textsuperscript{188} have been synthesized Schiff bases by treating triazole with coumarin derivatives and evaluated for antimicrobial activity by cup-plate method using norfloxacin and griseofulvin as standard.

\begin{center}
\includegraphics[width=0.5\textwidth]{schiff_base_kumar.png}
\end{center}

Kumar et al\textsuperscript{189} reported a series of quinoline based Schiff bases. The compounds on investigation of antimicrobial activity were found to be active against fungal strain.

\begin{center}
\includegraphics[width=0.5\textwidth]{schiff_base_creaven.png}
\end{center}

Abdallah et al\textsuperscript{190} reported a moderate antibacterial activity was shown by some new tetradentate Schiff base while their Cu(III) and Fe(III) complexes showed both antibacterial and antifungal activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{schiff_base_abdallah.png}
\end{center}
Xia et al have synthesized some Schiff bases by the study of structural activity relationship study of some novel Schiff base derivatives indicates that furan ring is essential for antibacterial activity\textsuperscript{191}.

Panneerselvam et al\textsuperscript{192} have synthesized a novel series of Schiff bases of morpholine derivatives were screened for antibacterial and antifungal activities.
Pandeeya et al\textsuperscript{191} have reported a novel series of isatin based schiff base. All these synthesized compounds were evaluated for antimicrobial and anti-HIV activities.

Patil et al have synthesized a series of schiff bases derived from thiosemicarbazone were complexed with Cu(II), Ni(II) and Co(II) and evaluated for their antibacterial and antifungal activities\textsuperscript{194}.
Tarafder et al\textsuperscript{195} have synthesized novel Schiff bases. The lead (II) complexes of Schiff bases showed high cytotoxicity against leukemic cells.

Bawa et al\textsuperscript{196} have synthesized a novel series of quinoline based Schiff bases, derivatives have been evaluated for their anti-inflammatory and antimicrobial activities.
Khan et al have synthesized a novel series of pyrazol based schiff base and screened for their antibacterial activities\textsuperscript{197}.

\[ \text{Khan et al} \]
1.9 Spectral studies

1.9.1 Infrared spectroscopy

Infrared spectroscopy is one of the most common techniques for the determination of functional groups in organic and inorganic compounds. IR study helps to determine different functional groups present in the chemical compounds. Different functional groups absorb characteristic frequencies of IR radiation at different wavelength and are found to respond accordingly in the spectra obtained. IR spectrometers can be used to determine samples of any types such as solid, liquid and gas. IR spectrometry is thus an important technique for structure elucidation and identification of compounds.

IR spectrometry more precisely gives information about the transitions between vibration and rotational energy levels in a molecule. Absorption of radiation in IR region results in the excitation (bond deformations) resulting in either stretching or bending. These stretching and bending vibrations occurs at certain quantized frequencies. When infrared light of that frequency is incident on the molecule, energy is absorbed by the functional group and the amplitude of that vibration increases confirming its presence. Thus an infrared spectrum is obtained when the frequency of molecular vibration matches to the frequency of the infrared radiation absorbed.

The normal range of IR spectrum (also called middle infrared region), used by organic chemists for structural determination of organic compounds extends from 4000 cm\(^{-1}\) to 667 cm\(^{-1}\). The position of absorption spectra is usually expressed in the terms of wave number (cm\(^{-1}\)) of the absorbed light. The compounds entitled here were scanned in ATR module of Bruker-alpha-t IR spectrophotometer.

1.9.2 \(^1\)H NMR spectroscopy

The phenomena of nuclear magnetic resonance was first reported independently in 1946 by two group of physicists namely, 1) Block, Hansen and Packard at Stanford university detected a signal from the protons of water, and 2) Prucell, Torrey and Pound at Harvard university observed a signal from the protons of paraffin wax.

Nuclear Magnetic Resonance spectroscopy is one of the latest methods of investigating the organic compounds. The shift observed as nuclear magnetic resonance
The signal for a particular proton is on the basis of the electronic environment around it. The $^1$H NMR spectral data were conducted on Bruker Avance II 400 spectrometer (400 MHz) with TMS as an internal reference. DMSO-$d_6$ was used as a suitable solvent.

### 1.9.3 Mass spectroscopy

Francis Aston, a physicist was the first to put the concept of mass spectroscopy into practice in 1919. In 1922 he was awarded Nobel Prize. The technique was used to determine mass of elements (isotopes) and now this technique has turned into one of the most powerful tools in analytical chemistry.

Mass spectroscopy is used to determine the mass of known and unknown compounds. The technique uses the interaction of electric and / or magnetic fields with matter to determine mass of the matter under study. A very minute quantity of compound is needed for mass spectrometric determination. Mass spectroscopy is based upon the motion of charged particle, called an ion, in an electric and magnetic field. The mass to charge ratio (m/z) of the ion affects this motion.
1.10 Introduction to microbes and antimicrobial agents

1.10.1 Microbes

Despite of useful functional activities of microorganisms for humans in manufacture of dairy and food products, processing of certain medicines and therapeutics and in other numerous ways, these microscopic organisms are more familiar as causal agents of human beings. All the people around the globe have experienced diseases caused by microbes.

It is much necessary to control the population of microbes in order to prevent the transmission and generation of diseases, infections and contamination caused by them. This is possible only by developing potent antimicrobial agents which can either cease the growth of microbes or kill them.

In 1928, a German scientist C.E. Chrenberg first used the term “bacterium” to denote small microscopic organisms. These microorganisms are capable of producing diseases in the host and are known as pathogens. There are mainly two types of bacteria: gram-positive bacteria and gram-negative bacteria. For the evaluation of antibacterial properties of the compounds synthesized in present study, gram-positive bacterial strains used were *S. aureus* and *E. faecalis* while gram-negative bacterial strains were *E. coli* and *P. aeruginosa*.

Fungi are non-photosynthetic eukaryotes growing either as colonies of single cell or as multicellular aggregates. A small number of fungi are responsible for producing diseases in humans as well as animals. The fungal strains used for determining the antifungal properties of synthesized derivatives include *C. albicans* and *A. niger*.

1.10.2 Antimicrobial agents

A significant increase in microbial disease is observed in past few decades. Microbial diseases are caused by bacteria, fungi, viruses etc. Henceforth a huge amount of contribution is seen in this class of drugs in this century. Scientists are focusing greatly on developing more potent, effective and medicinally important antibacterial and antifungal agents. Antimicrobial agents kill bacteria or inhibit their growth, therefore are called bactericidal or bacteriostatic. Similarly fungicidal agents are also found to exist. In several instances it is necessary to combine different antimicrobial agents for
broadening the bioactivity spectrum and to minimize the development of microbial resistance. Combination therapy has proved its value as latest therapy for antimicrobials as sometimes bacteriostatic agents on novel combinations gives bactericidal activity. Both sulfamethoxazole and trimethoprine are bacteriostatic, but combination of these drugs is now widely used as bactericidal. This is termed as synergism.

1.10.3 Evaluation technique implemented for antimicrobial screening of compounds

The conditions to be taken into consideration for the screening of antimicrobial activity are

- There should be intimate contact between the test organisms and synthesized compounds to be evaluated.
- The minimum conditions required for the growth of microorganisms should be established and maintained.
- Sterile environment should be maintained.

The different method adopted by researchers to evaluate the antimicrobial activity includes turbidometric method, agar streak dilution method, serial dilution method, agar diffusion method, broth dilution method etc. The method used for the evaluation of antimicrobial activities in present study was broth dilution method. This method yielded a quantitative result for the amount of antimicrobial agents that is required to inhibit the growth of specific microorganisms. DMSO was used as a diluent to get the desired concentration of drugs for evaluating their antibacterial and antifungal potency. The values of antimicrobial properties of the synthesized derivatives were recorded in form of Minimum Inhibitory Concentration (MIC). The standard drug used for antibacterial and antifungal tests included ciprofloxacin and fluconazole. The highest dilution showing at least 99% inhibition is considered as MIC.
1.11 Objectives of the study

Since the existence of mankind it has become an important and integral part to find a suitable remedy for the diseases prevailing in the society. Henceforth the general objective is to synthesize new effective bio-molecules which can be established as lead compounds in future. The present approach undertaken by most of the chemists includes combination of biologically active moieties into one molecule as a major technique to discover a new drug. Literature survey revealed that molecules with benzoxazole and 1,3,4-oxadiazole nucleus are key building blocks used to develop compounds with medicinal interests. The vast applications of Schiff-base compelled us to synthesize several Schiff-base derivatives. Thus the objectives of present study include:

1. To design newer heterocyclic derivatives by evaluating the molecules using Lipinski’s rule of five – first stage of QSAR.

2. To synthesize novel derivatives possessing different heterocyclic rings (benzoxazole and 1,3,4-oxadiazole) by undertaking various types of chemical reactions.

3. To characterize the synthesized derivatives by various spectral-analytical techniques like $^1$H NMR, IR, Mass and elemental analysis.

4. To screen the synthesized derivatives for their antimicrobial properties against a broad spectrum of bacterial and fungal strains.

5. To undertake SAR study, in order to prove the presence of a particular functional group as a responsible factor for the exhibition of higher biological activity as antibacterial or antifungal agents.
1.12 Significance of the study

The study will produce novel heterocyclic derivatives exhibiting excellent to good antibacterial and antifungal properties. The compounds with excellent antimicrobial activity can be further optimized to gain some better leads. The SAR study will help to conclude the correlation between the nature of substitution (i.e. electron-withdrawing or electron-donating functional groups) and the biological activity results related to it. Overall the entitled study will help in generating promising antimicrobial heterocyclic motifs.
1.13 Work plan

1.13.1 Chapter-2 Studies on 1,3,4-oxadiazole derivatives

General nomenclature for compounds III\textsubscript{a-h}

$4'-(5$-Aryl-[1,3,4]oxadiazol-2-ylsulfanylmethyl)-biphenyl-2-carbonitrile

General structure for compounds III\textsubscript{a-h}

![Chemical structure](image)

R: 3-NO\textsubscript{2}; 4-NO\textsubscript{2}; 4-Cl; 2-Cl; 3-Cl; 3-CH\textsubscript{3}; 4-CH\textsubscript{3}; H

Derivatives possessing 1,3,4-oxadiazole scaffold and bearing a -CN group were synthesized in this chapter. To prove the importance of -CN functional group in medicinal chemistry, it was kept in mind that during the synthesis of each entity of this chapter, -CN group must be included along with the oxadiazole nucleus. The formation of each derivative was confirmed by spectral data. IR proved to be the backbone for spectral characterization specifically for this series of derivatives, in this chapter, Cyano group bearing amphoteric nature played a vital role in proving its importance as an enhancement tool for the biological activity of the compounds.
1.13.2 Chapter-3  Studies on benzoxazole derivatives

General nomenclature for compounds III\textsubscript{1-14}

2-(5-chlorobenzof[d]oxazol-2-ylthio)-N-arylacetamide

General structure for compounds III\textsubscript{1-14}

The biological importance of benzoxazole depicted from other sections gave us an idea to synthesize a novel series of 14 derivatives possessing benzoxazole scaffold bearing –Cl group. The formation of these derivatives was confirmed by spectral data and their biological study undertaken. Lipinski's rule was included for this chapter too, which proved the potency of electron-donating functional group in enhancing the biological potency of synthesized derivatives.
1.13.3 Chapter-4  Studies on acetamide clubbed with 1,3,4 oxadiazoles

General nomenclature for compounds III_{1-13}

N-Aryl-2-(5-phenyl-[1,3,4]oxadiazol-2-yl sulfanyl)- N-arylacetamide

General structure for compounds III_{1-13}

In this chapter have been synthesized indicating formation of different acetamide derivatives bearing different derivatives substituted 1,3,4-oxadiazole derivatives. 13 derivatives have been synthesized, characterized and tested for their antimicrobial properties. Biological activity conducted here confirmed the presence of electron-withdrawing substitution as responsible agents for the excellent exhibition of antimicrobial properties of the derivatives synthesized in this chapter.
1.13.4 Chapter-5  Studies on benzoxazole clubbed-Schiff bases

General nomenclature for compounds III_{1-11}

(N-Benzylidene-N’-(5-chloro-benzo[d]oxazol-2-yl)-hydrazine

General structure for compounds III_{1-11}

This chapter deals with the synthesis of Schiff base possessing benzoxazole derivatives. Total eleven derivatives have been synthesized in this series and have been characterized by using different spectral data. The formed entities have been tested against gram-positive bacteria, gram-negative bacteria and fungi. Most of the compounds were found to possess excellent activity against both bacterial and fungal strain. The Lipinski’s rule was conducted which concluded that the derivatives bearing electron-donating functional group exhibited much better activity than the one with electron with-drawing groups.
1.13.5 Chapter-6  Studies on 1,3,4-oxadiazole clubbed-Schiff base

General nomenclature for compounds III_{1-11}

2-(2-arylbenezylidenehydrazinyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole

General structure for compounds III_{1-11}

\[
\text{R}= \text{p-OH; p-Cl; p-NO}_2; \text{3,4,5-triOCH}_3; \text{2,5-diOCH}_3; \text{2,4,5-triOCH}_3; \text{o-NO}_2
\]

2-OH-1- Napthaldehyde; N,N- diCH$_3$; 4-OH-3-OCH$_3$; m-OH

This chapter deals with the synthesis of schiff base possessing 1,3,4-oxadiazole derivatives. Total eleven derivatives have been synthesized in this series and have been characterized by using different spectral data. The formed entities have been tested against gram-positive bacteria, gram-negative bacteria and fungi. Most of the compounds were found to possess excellent activity against both bacterial and fungal strain.
1.14 References


35. Iwasawa, N., Saito, G., Imaeda, K., Mori, T. and Inokuchi, H., (1987). Synthesis and physical properties of Tetrakis (methylthio)-tetraselenafulvalene (TTC\textsubscript{1}-TSeF) and Tetrakis (methylseleno)-tetraselenafulvalene (TSeC\textsubscript{1}-TSeF) *Chem. Lett.*, 2399-2402.


oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives. *Bioorganic and Medicinal Chemistry*, 16(4), 1822-1831.


