CHAPTER 1

General Introduction
1. General introduction

1.1 Introduction to Organic chemistry

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.

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 life saving 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.

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

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 has its roots in several branches of chemistry and biology. 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.

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.

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.

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.
IUPAC specified commission defines medicinal chemistry as “it concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at molecular level.” The discoveries of the medicinal properties of compounds have always led to the development of newer method for the synthesis of substances similar to that of available lead molecules.
1.3 About drugs

The word ‘drug’ is derived from the French word ‘drogue’ which means a dry herb. In general, a drug may be defined as “all chemicals other than food that affect living process.” If the affect helps the body, the drug is a medicine. However, if a drug causes harmful effects on the body, the drug is a poison. 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 or pathological status for the benefit of recipient.”

Below indicated are the ways in which a drug can be classified:

1. **According to their pharmacological effect** – for example, analgesic drugs (pain killing effect); antipyretic drugs (lowering the body temperature); antimicrobial drugs (bacteriostatic, bactericidal and fungicidal).

2. **Effective towards a particular biochemical process** – for example, antihistamines act by inhibiting the action of inflammatory agent histamine in the body.

3. **According to their chemical structure** – drugs of this kind share a common structural skeletal – for example, penicillin and cephalosporins contains β-lactum ring and kills bacteria by the same mechanism.

4. **In accordance to their molecular target** – for example, anticholinesterases are compounds that inhibit an enzyme called acetyl cholinesterase.

A drug molecule is designed in a way that the functional groups enacted with the primary skeletal or nucleus are positioned in a defined geometrical array such that, it enables the molecule to get bind specifically to a targeted biological macromolecule, known as a receptor. A particular position of a functional group in three-dimensional framework of the drug molecule helps it to exhibit a desired biological response, thereby minimizing the probability of toxicity. A drug like molecule to be successful in encountering a disease must have several other additional properties along with
biological and chemical properties viz. it must be able to remain stable during journey; from its point of administration until it finally reaches the receptor site.

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.
1.4 Introduction to heterocyclic chemistry and its service to mankind

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. 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.

The greatest advantage of heterocyclic compounds in drug industries lies in the ability to manifest substituent around a core scaffold in defined three dimensional representations. Among other hetero atoms, heterocyclic compounds possessing nitrogen and oxygen have maintained the interest of researchers through historical development of novel synthetic procedures for the synthesis of N and O containing heterocyclic entities. 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 B₁, Riboflavin B₂, Nicotinamide B₃), essential amino acids (proline, histidine and tryptophan) and heme (haemoglobin). Heterocyclic scaffolds have widespread therapeutic uses such as antibacterial, antifungal, antimycobacterial, anti-HIV, anti-tubercular, analgesics, anti-malarial, anticancer, antidepressant, anthelmintic and antitumor. Other than being medicinally important, heterocyclic compounds are found to be potent fungicides, herbicides, agrochemicals, anticorrosive agents, dyestuff, flavouring agent and photo stabilizers. Compounds not necessarily have to be heterocyclic in nature to exhibit medicinal properties.
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 Antiviral 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. \(^{33}\)

### 1.4.2 Antimicrobial drugs – antifungal drugs

Antimicrobial drugs comprises of both the antibacterial as well as antifungal drugs. Antifungal drugs are used for treating skin infections, ringworm and candidiasis. Several different class of heterocyclic compounds are used as antifungal drugs viz. bifonazole – an imidazole antifungal drug helps in blocking the transformation of 24-methylenedihydrolanosterol to desmethylsterol in fungi together with the inhibition of HMG-CoA. \(^{34,35}\) Another well-known drug fluconazole belongs to triazole class of

antifungal drugs, is used in the treatment of superficial and systematic fungal infections.\textsuperscript{36}

1.4.3 Antimicrobial drugs – antibacterial 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{37} It is a drug used for treating mild-to-moderate \textit{Clostridium difficile} infection.\textsuperscript{38,39} 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{40,41} Ciprofloxacin is found to exhibit excellent antibacterial property against a broad spectrum of gram-positive and gram-negative bacteria.\textsuperscript{40}
1.4.4 Antihypertensive drugs

Antihypertensive therapy helps to prevent the complications of high blood pressure such as stroke and myocardial infraction. Several heterocyclic drugs responsible for lowering human blood pressure by different means are available today. The different antihypertensive drugs used for treating hypertension includes thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers and the angiotensin II receptor antagonists. Chlorothiazide, flumethiazide, hydorchlorothiazide and trichloromethiazide drugs belong to thiazide diuretics class of antihypertensive drugs and are found to reduce the risk of death due to stroke, heart attack and heart failure due to hypertension.

1.4.5 Antipyretic drugs

Antipyretics are drugs used to treat fever. Antipyretics cause the hypothalamus to override an interleukin-induced increase in temperature. Once treated with antipyretic drug, the body then works to lower temperature, resulting in a reduction in fever. The most common antipyretics used are ibuprofen and aspirin.
1.4.6 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs, usually abbreviated as NSAIDs are a class of drugs that provide antipyretic and analgesic effect in higher doses along with anti-inflammatory effects. The term “nonsteroidal” distinguishes these drugs from steroids, which among a broad range of other effects, have a similar anti-inflammatory action. NSAIDs are usually used in treatment of acute conditions where pain and inflation are present. Celecoxib is a sulfonamide nonsteroidal anti-inflammatory drug and a selective COX-2 inhibitor used in the treatment of acute pain, painful menstruation and menstrual symptoms. Droxican is a NSAID of the oxicam class.

1.4.7 Analgesic drugs

An analgesic or pain killer is any member of the group of drugs used to achieve analgesia – relief from pain. Analgesic drugs act in various ways on the peripheral and the central nervous system. They differ from anesthetics, which reversibly eliminate sensation. Analgesics also include nonsteroidal anti-inflammatory drugs (NSAIDs) and...
can also be used as antipyretic agents. Phenazone is an analgesic as well as antipyretic drug with elimination half life of 12 hrs.\textsuperscript{62,63} The other pyrazolone derivatives\textsuperscript{64,65} include aminophenazone\textsuperscript{66} and apazone as analgesic drugs. These drugs are also much potent antipyretic as well as anti-inflammatory drugs.

![Chemical structures of Phenazone, Aminophenazone, and Apazone](image)

### 1.4.8 Anticonvulsant drugs

Anticonvulsant drugs, more accurately called antiepileptic drugs are a diverse group of pharmaceuticals used in the treatment of epileptic seizures – abnormal activities in the brain. Many of the anticonvulsant entities seem to act as mood stabilizers,\textsuperscript{67} are used in the treatment of bipolar disorder and neuropathic pain. The goal of anticonvulsants is to suppress the rapid and excessive firing of the neurons that start a seizure. Barbiturates are drugs that act as central nervous system (CNS) depressants, and by virtue of this they produce a wide spectrum of effects, from mild sedation to anesthesia. phenobarbital,\textsuperscript{68,69} barbexaclone\textsuperscript{70,71} and mephobarbital (methylbarbitol)\textsuperscript{72} are barbiturate derivatives used as anticonvulsant drugs. Benzodiazepines are a class of drugs with hypnotic, anxiolytic, anticonvulsive and muscle relaxant properties.\textsuperscript{71} They include nimetazepam and lorazepam drugs.\textsuperscript{74} Paramethadione and trimethadione are anticonvulsant drugs in the oxazolidinedione
class, used in the treatment of fetal trimethadione syndrome and epileptic conditions respectively.

![Phenobarbital](image1.png) ![Barbexacone (Malasia)](image2.png) ![Methylphenobarbital](image3.png) ![Nimetazepam](image4.png) ![Lorazepam](image5.png) ![Paramethadione](image6.png) ![Anticonvulsant drugs](image7.png) ![Trimethadione](image8.png)

### 1.4.9 Anti-diabetic drugs

Anti-diabetic drugs treat 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.

1.4.10 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 H₂-blockers.
receptor antagonist that inhibits stomach acid production, and commonly used in the
treatment of peptic ulcer disease and gastroesophageal reflux disease (GERD). 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.
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. 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. The QSAR methodology helps in finding the mechanism of action of drugs at molecular level and many other physiochemical phenomena like hydrophobicity. Hansch was the first to use QSAR to explain the biological activity of series of structurally related molecules. Hansch first used the descriptors and proposed a correlation between the molecule’s electronic environment and its hydrophobicity. The study by Hansch regarding the relation of biological properties and molecular structures helped him to lead to great conclusions.

QSAR – *in-silico* studies is the name usually applied to methods where molecular structure is correlated to some kind of *in vitro* or *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’s rule of five is a rule to evaluate drug-likeness 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;

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 benzimidazole derivatives

1.6.1 Introduction to benzimidazole derivatives

Benzimidazole is a fused organic heterocyclic compound – bicyclic fused ring of benzene and imidazole. It contains two nitrogen atoms in its core structure in the imidazole nucleus. More emphasis is given on synthesis of newer medicinally important entities after the discovery of presence of benzimidazole nucleus as 5,6-dimethylbenzimidazole in the structure of vitamin-B$_{12}$. Benzimidazoles are weakly basic, somewhat less basic than imidazoles. Also they are found to be sufficient acidic which makes them soluble in alkali, resulting in the formation of N-metallic compounds. Moreover benzimidazole is an isoster of naturally occurring nucleotide and therefore it is capable of interacting easily with the biopolymers of the living system.

The first benzimidazole was prepared by Hoebrecker, who obtained 2,6-dimethylbenzimidazole by reduction of 2-nitro-4-methylacetanilide. Several years later the same compound was obtained by Ladenburg by refluxing 3,4-diaminotoluene with acetic acid.

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1.6.2 Synthesis of benzimidazole derivatives

Benzimidazoles have been synthesized by number of methods using variety of precursors, reagents and via different reactions. Beaulies et al have synthesized benzimidazoles from 1,2-phenylenediamines and aldehydes under solvent phase synthesis using Oxone® as a medium. The composition of oxidizing agent Oxone® is $2\text{KHSO}_5\cdot\text{KHSO}_4\cdot\text{K}_2\text{SO}_4$.\(^{94}\)

![Beaulies et al](image)

Fokas D et al have reported the procedure for the synthesis of benzimidazole derivatives from o-nitroanilines and aldehydes by one step reductive cyclization using $\text{Na}_2\text{S}_2\text{O}_4$.\(^{95}\)

![Fokas D et al](image)

One pot synthesis procedure for the conversion of aromatic and heteroaromatic 2-nitroamines into bicyclic benzimidazoles has been reported by Hanan et al.\(^{96}\) Formic acid, Fe and ammonium chloride were employed to reduce the nitro group and affect the imidazole cyclization.

![Hanan et al](image)

The versatility of a new approach of reacting o-substituted anilines with functionalized orthoesters yields benzimidazole derivatives in an efficient quantity was
reported by bastug et al. The success of these derivatives led to the development of new libraries of heterocycles containing multifunctional sites.97

Bahrami et al has reported a convenient method for the synthesis of 2-substituted benzimidazoles with excellent yields in short reaction time.98

Kim et al have reported a one pot, three component syntheses of 2-haloanilines, aldehydes and NaN₃ using CuCl and TMEDA as catalyst in good yield.99

Diao et al have reported the synthesis of benzimidazoles under acidic conditions with in situ additive cyclization. The synthesis of benzimidazole derivatives were attained by utilizing Cul and l-proline as a catalyst for carrying out a coupling reaction between aq. Ammonia and 2-iodoacetanilides.100
Saha et al.\textsuperscript{101} have reported a very simple, efficient and ligand free synthesis of substituted benzimidazoles via intramolecular cyclization of o-bromoaryl derivatives using Cu(II) oxide nanoparticles in DMSO as catalyst. The group was also able to recover the heterogeneous catalyst and reuse the same.

\begin{center}
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An efficient method for the transformation of $N$-benzyl bisarylhydrazones to functionalized 2-aryl-$N$-benzylbenzimidazoles involving a copper (II)-mediated cascade C-H functionalization C-N bond formation under neutral conditions was reported by Guru et al.\textsuperscript{102}

\begin{center}
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\end{center}

Chlorotrimethylsilane in DMF was used as a promoter and water acceptor agent for the synthesis of benzimidazole from aromatic ortho-diamines and aldehydes, followed by air oxidation by Ryabukhin et al.\textsuperscript{103}

\begin{center}
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\end{center}

A simple and efficient procedure for the synthesis of substituted benzimidazoles through a one-pot condensation of o-phenylenediamines with aryl substituted aldehydes
in the presence of H$_2$O$_2$ and HCl in acetonitrile at room temperature featuring short reaction time, easy and quick isolation of the products, and excellent yields was reported by Bahrami et al.\textsuperscript{104}

![Diagram](image1)

Du and Wang have reported various 2-arylbenzimidazoles were synthesized from phenylenediamines and aldehydes via one-step process using hypervalent iodine as oxidant. This method features mild conditions, short reaction times, high yields, and a simple procedure for the synthesis of derivatives.\textsuperscript{105}

![Diagram](image2)

Cui et al\textsuperscript{106} have reported a mild and efficient one pot process for the synthesis of 2-substituted benzimidazole from 1,2-phenylenediamines and triacyloxyborane intermediates generated \textit{in situ} from carboxylic acids and borane-THF.

![Diagram](image3)

Another procedure for the synthesis of 1,2-disubstituted benzimidazole was reported by Yu et al utilizing Cu as catalyst. The benzimidazoles were derived from imidoyl chlorides.\textsuperscript{107}
She et al have reported an efficient and general cascade reaction of o-aminoanilines with terminal alkynes and p-tolylsulfonyl azide – a one pot synthesis resulting in the formation of benzimidazoles in good yields.  

A NaH-mediated reaction of carbonitriles and N-methyl-1,2-phenylenediamine was undertaken for the formation of N-methylbenzimidazole by Sluiter et al.  

A straightforward, efficient, and sustainable method for intramolecular N-arylation provides a library of benzimidazoles in high yields using Cu$_2$O as the catalyst, DMEDA as the ligand, and K$_2$CO$_3$ as the base was reported by Peng et al.
Wary and Stambuli have reported the synthesis of benzimidazoles derivatives from common arylamino oximes in good to excellent yields depending upon the base used in the reaction. Trimethylamine promoted the reaction as a base. 111
1.6.3 Therapeutic importance of benzimidazole derivatives

The immense pharmacological properties of benzimidazole make it most prominent among all the nitrogen bearing heterocycles. Benzimidazole has evolved as an important heterocyclic system due to its presence in several bioactive compounds like antiparasitic, analgesics, anticancer, anthelmintic, antifungals, antihypertensives, antiulcer, antiviral, antifungal, anticoagulants and anti-inflammatory agents.\textsuperscript{112-118} Many drugs and lead compounds have resulted from the optimization of different substituents around the benzimidazole nucleus viz. albendazole, mebendazole, thiabendazole, omeprazole, lansoprazole, pantoprazole, enviradine etc. Benzimidazole nucleus is of much importance as it is found as an important core in many of the bioactive compounds.

Yadav \textit{et al}\textsuperscript{119} have synthesized antihypertensive derivatives possessing benzimidazole derivatives. These benzimidazole derivatives were found to act as potent AT1 receptor antagonist.

\begin{center}
\textbf{Yadav \textit{et al}}
\end{center}

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Sabat \textit{et al} have synthesized anti-inflammatory derivatives by substituting the benzimidazole nucleus at position-1 resulting in the formation of 1-(substituted)pyrimidin-2-yl)benzimidazoles.\textsuperscript{120}
Taniguchi et al have synthesized still simpler anti-inflammatory molecules possessing benzimidazole nucleus as 2-aminobenzimidazole derivatives. The 2-aminobenzimidazole derivative with C₆H₄-4-OCH₃ substituent at R₁ and c-hexyl at R₂ was found to be more potent than the standard drug used.¹²¹

Iwahi et al¹²² have reported 2-(substituted pyridyl methylsulfinyl)benzimidazole as an antibacterial agent. The derivative was found to be active against *Campylobacter pylori*.

Furthermore, the above produced antibacterial lead was further modified by Masaki et al resulting in the formation of a similar compound having antibacterial activity similar to that of omeprazole.¹²³
Hu et al have developed a series of benzimidazole derivatives and found that the derivative with ethereal linkage in benzimidazole was exhibiting antimicrobial activity even better than penicillin.\textsuperscript{124-126}

Garuti et al have reported some 2-substituted benzimidazole-N-carbamates as potent antiviral compounds, amongst which derivative with isopropylcarboxamide group at position-2 was found to exhibit excellent antiviral activity.\textsuperscript{127}
Fonseca *et al* have reported dihydroabietic acid derivatives of benzimidazole and were found to inhibit both cella-zoster virus (VZV) and cytomegalovirus (CMV) replication.\textsuperscript{128}

Animisova *et al* have reported a series of 2-(heteroaryl)imidazo[1,2-a]benzimidazoles possessing 1-methylbenzimidazol-2-yl and 5-bromo-2-thienyl at R\textsubscript{2} with varied dialkylaminoalkyl substituents at R\textsubscript{1}. These two derivatives were found to possess antioxidant activity.\textsuperscript{129}

Neff *et al* have reported another series of anticancer derivatives possessing benzimidazole nucleus. All the compounds were found to possess significant anticancer activity.\textsuperscript{130}
Ishikawa et al have synthesized a potent and metabolically stable GK activator by making modifications in the 2-(pyridine-2-yl)-1H-benzimidazole, the synthesized compound demonstrated glucose lowering efficacy in a dose-dependent manner.\textsuperscript{131}
1.7 Studies on 1,3,4-oxadiazole derivatives

1.7.1 Introduction to 1,3,4-oxadiazole derivatives

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. Patel and Patel 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.\(^\text{143}\)

Kerimov et al\(^\text{144}\) have also synthesized a novel series of 1,3,4-oxadiazole bearing compounds by reacting cyanogen bromide with 2-(2-(4-substituted-phenyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide. The reaction medium used here was ethanol.

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.\(^\text{145}\)
Electro-cyclization of semicarbazones to their corresponding 5-aryl-2-amino-1,3,4-oxadiazoles have been reported by Lotfi et al and Sharma et al.\textsuperscript{146,147} Rivera et al have reported the synthesis of 1,3,4-oxadiazole in excellent yield by using an effective oxidizing agent 1,3-dibromo-5,5-dimethylhydantion. The cyclization reaction of acylthiosemicarbazide lead to the formation of 1,3,4-oxadiazole derivatives.\textsuperscript{148}

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{149}
Amir and Kumar have reported a multi-step synthesis procedure for the production of 2,5-disubstituted-1,3,4-oxadiazole derivatives. The starting material used for the synthesis of oxadiazole derivatives was anti-inflammatory drug ibuprofen.\textsuperscript{150}

Sharma \textit{et al} developed a simple method for the synthesis of 1,3,4-oxadiazoles from diacylhydrazines using ZrCl\textsubscript{4} as a catalyst. The yield obtained here is higher with less reaction time and the catalyst used here is inexpensive.\textsuperscript{151}
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{152}

![Pouliot et al](image1)

Li and Dickson have developed a convenient one-pot reaction for the synthesis of 1,3,4-oxadiazole from carboxylic acids and hydrazides using HATU as coupling agents and Burgess reagent as dehydrating agent.\textsuperscript{153}

![Li and Dickson](image2)

Guin et al have reported a procedure for the synthesis of both symmetrical and unsymmetrical 2,5-disubstituted -1,3,4-oxadiazoles using Cu(OTf)\textsubscript{2} as catalyst.\textsuperscript{154}

![Guin et al](image3)

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 \textregistered\textsubscript{NR50} and phosphorous pentasulfide in alumina (P\textsubscript{10}S\textsubscript{10} / Al\textsubscript{2}O\textsubscript{3}).\textsuperscript{155}
Chapter 1
General introduction

1.7.3 Therapeutic importance of 1,3,4-oxadiazole derivatives

The need for new, safer and more efficient antimicrobial agents has been fulfilled up to 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, nesapil as an antihypertensive, antimicrobial and anticancer agent.

Oliveira et al have reported antistaphylococcal activity of 1,3,4-oxadiazolines against the strain S.aureus. All the derivatives were showing better activity than the standard chloramphenicol by 2-8 folds.

Sahin et al have synthesized a new series of derivatives of 5-(1-/2-naphthoxyxymethyl)-1,3,4-oxadiazol-2-(3H)-thione and 5-(1-/2-naphthoxyxymethyl)-1,3,4-oxadiazol-2-amino. These derivatives, when evaluated for antimicrobial properties were found to possess excellent microbial activity against S. aureus, P. aeruginosa, C. albicans etc.
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{167}

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

Kashaw \textit{et al} have synthesized a new series of oxadiazole derivatives possessing quinazoline nucleus exhibiting excellent anticonvulsant property.\textsuperscript{168}

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

A few more derivatives possessing 1,3,4-oxadiazole nucleus and exhibiting anticonvulsant activity were synthesized by Rajak and co-workers. Most of the derivatives showed positive results in a three model test MES, scPTZ and scSTY.\textsuperscript{169}
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.\textsuperscript{170}

Gilani and co-workers have synthesized compound possessing 1,3,4-oxadiazole ring bearing 2,4-dichlorophenyl group at position-2 on the oxadiazole ring. The maximal analgesic activity showed by the synthesized compounds was almost equivalent to that of ibuprofen.\textsuperscript{171}
Savariz et al. have synthesized and evaluated the *in vitro* antitumor activity of novel 1,3,4-oxadiazole based manich bases.\textsuperscript{172}

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

Ouyang and co-workers\textsuperscript{173} as well as Tuma and co-workers\textsuperscript{174} 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{173}.

\begin{center}
\textbf{Ouyang et al} \quad \textbf{Tuma et al}
\end{center}

Wang and co-workers have synthesized a series of raltegravir derivatives by modifying the 5-hydroxyl group of the pyrimidine ring and were evaluated for their
anti-HIV activity. This modification in raltegravir derivatives significantly increased their anti-HIV activity to a great extent.\(^{175}\)

Bankar \textit{et al}\(^{176}\) 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 chalcone derivatives

1.8.1 Introduction to chalcones

Chalcones are the compounds with a conjugated π system represented as -C=C-C=O, where aromatic or aliphatic substituent are introduced at terminal position of this system. Chalcones are characterized by their position on a R-CO-CH=CH-R’ system, in which two aromatic rings/aliphatic chains (R and R’) are linked by an aliphatic three carbon chain system. The alternative names given to chalcone include phenyl styryl ketone, benzalacetophenone, β-phenylacrylophenone, α-phenyl-β-benzoylethylene. Chalcones or 1,3-diaryl-2-propen-1-ones, belong to flavanoid family and chemically they consist of open-chain flavanoids in which two aromatic rings are joined by a three α, β-unsaturated carbonyl system. Chalcones are in general, colored compounds because of the presence of the auxochrome.

The chemistry of chalcones has generated great interest among the researchers around the world. Along with the chemistry of chalcones, the biological and industrial applications of chalcones have generated intensive scientific studies throughout the world. Chalcones can be synthesized in laboratory by Claisen-Schmidt condensation of various substituted acetophenones with aldehydes.

The first condensation was reported by Kostanecki, who gave the linkage, the name “Chalcones”. The important feature of chalcones is that they serve as starting materials for the formation of various heterocyclic compounds viz. pyrimidines,
pyrazolines, flavones, flavanols, flavones etc. Chalcones are also found to exhibit excellent biological activities. The above facts and the potent biological properties possessed by chalcones make them desired synthetic targets for medicinal purpose.
1.8.2 Synthesis of Chalcones

A variety of methods are available for the synthesis of chalcones,\textsuperscript{181,182} and most convenient is the one that involves the Claisen-Schmidt condensation reaction utilizing substituted acetophenones with varied aldehydes in presence of an aqueous alkaline solution. Cannizaro reaction also takes place and formation of chalcones occurs with appropriate amount of yield.\textsuperscript{183} Several methods adopted by researchers are reported as under.

Russell and Todd reported a simple procedure for the synthesis of chalcones from ketones by condensation with aldehydes in presence of dry hydrochloric acid gas. The dry HCl gas has been used as a condensing agent in a suitable solvent like dry ethyl acetate at 0°C.\textsuperscript{184}

![Chemical structure of Russell and Todd's synthesis of chalcones](image)

Kruoda and Matsukama have reported a procedure for the synthesis of chalcones by condensing acetophenones obtained from anisole and other polymethoxy benzene with various mehoxy aldehydes in presence of anhydrous AlCl\textsubscript{3}.\textsuperscript{185}

![Chemical structure of Kruoda and Matsukama's synthesis of chalcones](image)

Bhat et al\textsuperscript{186} have synthesized a series of chalcones and their corresponding pyrazole derivatives using KOH/EtOH and hydrazine hydrate respectively. The resulting chalcones were found to possess E-geometry.
Climent *et al.*\(^{187}\) have reported a novel method for the synthesis of chalcones using Zeolites as a catalyst. Zeolite based catalyst were used for the Claisen-Schmidt condensation of acetophenones and benzaldehydes.

Pore and co-workers have invented a novel efficient synthesis process for the preparation of chalcones at room temperature, utilizing potassium phosphate (K\(_3\)PO\(_4\)) as a catalyst.\(^ {188}\)

Narender and Reddy have reported a simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate. The products were obtained in excellent yields and purity.\(^ {189}\)

Smith and Paulson have developed and reported a method for the synthesis of chalcones by reacting hydroxy and methoxy aldehydes with ketones.\(^ {190}\)
Paradis and Lyle\textsuperscript{191} have adopted an acid catalyzed condensation for the synthesis of chalcones. The acid catalyzed condensation was carried out by using methanolic hydrogen chloride solution. The products were obtained in excellent yields.

An improved synthesis method was carried out by Mazza and Guarna in 1980. Phosphorous oxychloride was used for the synthesis of 1,3-diphenyl-2-buten-1-ones (β-methylchalcones).\textsuperscript{192} Another novel method for the synthesis of chalcones was adopted by Trivedi and co-workers.\textsuperscript{191}
Calloway and green have reported a process where $\beta$-unsaturated ketone formation occurred as a side reaction in friedel-crafts acylation. The reaction was carried out in presence of metallic halides (catalyst).

![Calloway and Green](image)

Iranpoor and Kazemi have reported a procedure describing the aldol condensations of aldehydes and ketones. The duo has conducted the reaction under solvent free conditions in presence of anhydrous RuCl$_3$ (aldol condensation catalyst). It was also kept in mind while performing the reaction that the self condensation of reactants should not occur. The yield for most of the derivatives was obtained in high amount.

![Iranpoor and Kazemi](image)
Jadhav and Kulkarni have reported a procedure for the synthesis of chalcones by condensing substituted aldehydes and various acetophenones in presence of aqueous solution of borax.\textsuperscript{196}
1.8.3 Therapeutic importance of chalcones

The chalcones are found to be of great pharmaceutical interest due to their wide applicability as antimicrobial, antitumor, anti-malarial, antibacterial, antifungal, antitubercular and antiviral agents. Chikhalia and co-workers have synthesized novel quinolyl chalcones possessing antibacterial properties.

A series of chalcone derivatives were synthesized by Baviskar et al. and were studied for their antimicrobial properties.

Dawane and his co-workers have synthesized new 1,3-diaryl-2-propene-1-ones (chalcones) and were evaluated for their antibacterial and antifungal activities. The activity obtained in the study exhibited excellent results. PEG-400 was used as a recyclable solvent in this procedure.
Vyas et al have synthesized chalcones namely (2E)-3-(3,5,,-dibromo-4-methoxyphenyl)1-arylethynyl-2-en-1-one and were found to exhibit excellent anti-tubercular property. These derivatives were also found to possess antimicrobial properties.\textsuperscript{210}

Another series of chalcones synthesized using methanolic KOH solution by Yar et al were also found to report excellent antimycobacterial activity.\textsuperscript{211}

Jadhav and Ramaa have prepared a series of fluorinated chalcones using Claisen-Schmidt condensation reaction process. The compounds synthesized were screened for their anti-inflammatory activity.\textsuperscript{212}
Cheng et al have introduced Claisen-Schmidt condensation method for the synthesis of novel chalcones, 2,5-dialkoxychalcones. The resultant chalcone derivatives were screened for their cytotoxicity, anti-inflammatory and anti-oxidant activity.\textsuperscript{213}

Modzelewska et al\textsuperscript{214} have synthesized novel chalcones and bis-chalcones containing boronic acid moieties and were evaluated for their antitumor activity against the human breast cancer MDA-MB-231 and MCF-7 cell lines. The chalcones as well as bis-chalcones were found to exhibit potent inhibition results against most of the cell lines.

Xia and co-workers\textsuperscript{215} have synthesized a novel series of 2-amino chalcones. The synthesized derivatives were exhibiting potent antitumor activity.

Zhao \textit{et al} have synthesized trihydroxychalcones and were evaluated for their antiplatelet activity.\textsuperscript{216}
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 \(^1\text{H}\) 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 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 the Nobel Prize. The technique was used to determine the 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 benzimidazole and 1,3,4-oxadiazole nucleus are key building blocks used to develop compounds with medicinal interests. Along with the designing and development of molecules with above mentioned heterocyclic rings, inclusion of electronegative fluorine atom and its various substituent (-CF₃ and -OCHF₂) on the benzimidazole and 1,3,4-oxadiazole rings has also been studied. The vast applications of chalcones compelled us to synthesize several chalcone 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 (benzimidazole and 1,3,4-oxadiazole) by undertaking various types of chemical reactions.

3. To characterize the synthesized derivatives by various spectral-analytical techniques like ¹H 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 fluorine based 1,3,4-oxadiazoles

(Under review with Journal of Chemical Sciences – Springer JCSC-D-13-00442)

**General nomenclature for compounds 5_{a-j}**

2-(5-aryl-1,3,4-oxadiazol-2-ylthio)-N-(3-(trifluoromethyl)phenyl)acetamide

**General nomenclature for compounds 5_{k-t}**

N-(4-chloro-3-fluorophenyl)-2-(5-aryl-1,3,4-oxadiazol-2-ylthio)acetamide

**General structure for compounds 5_{a-t}**

![Chemical structure](image)

This chapter will deal with the synthesis of derivatives possessing fluorine based 1,3,4-oxadiazole. To prove the importance of fluorine atom here, it is kept in mind that during the synthesis of each entity of this chapter, fluorine atom must be included along with the oxadiazole nucleus. Two different series are synthesized comprising of 10 derivatives each possessing 1,3,4-oxadiazole ring along with –CF$_3$ and –F substituted phenyl nucleus. The formation of derivatives will be confirmed by spectral data. Spectral analysis via IR and $^{19}$F NMR will be undertaken in order to confirm the formation of derivatives. Also these data will be helpful in proving the presence of fluorine in each compound. SAR study in this chapter will play a vital role in proving the importance of fluorine in enhancing the biological activity of the compounds.
1.13.2 Chapter-3 Studies on 1,3,4-oxadiazole based chalcones
(Under minor revision with Medicinal Chemistry Research MCRE-3678)

General nomenclature for compounds $V_{1-14}$

(Z)-N-((4-(3-(4-aryl)acryloyl)phenyl)-2-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-ythio)acetamide

General structure for compounds $V_{1-14}$

![Chemical structure](image)

The biological importance of chalcones and heterocyclic compounds depicted from literature studies and other series of work carried out influenced to synthesize a novel series of 14 derivatives possessing 1,3,4-oxadiazole scaffold bearing -NO$_2$ group. The formation of the derivatives will be confirmed by spectral data and their biological study will be undertaken. SAR study will be carried out in order to prove the importance of electron-donating functional group in enhancing the biological potency of synthesized derivatives.
1.13.3 Chapter 4  Studies on benzimidazole derivatives

Section 1 (IIIa): under review with Arabian Journal of Chemistry ARABJC-13-00802

Section 2 (III11): accepted for publication with Medicinal Chemistry Research - doi: 10.1007/s00044-013-0732-z)

General nomenclature for compounds III1-13

2-(5-methoxy-1H-benzo[d]imidazol-2-ylthio)-N-arylacetamide

General nomenclature for compounds IIIa-j

2-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)-N-arylacetamide

General structure for compounds III1-13 and IIIa-j

In this chapter, two series will be synthesized indicating the formation of different acetamide derivatives bearing methoxy and fluoromethoxy substituted benzimidazole derivatives. Thirteen derivatives possessing methoxy substituted benzimidazole and ten derivatives with fluoromethoxy substitution will be synthesized, characterized and tested for their antimicrobial properties. SAR study if carried out here will help to confirm the importance of electron-withdrawing substitutions present in the derivatives as responsible agents for the excellent exhibition of antimicrobial properties. 19F NMR will be included exclusively for the confirmation of formation of benzimidazole derivatives with fluoromethoxy substituent.
1.13.4 Chapter-5  Studies on benzimidazole clubbed-chalcones

(Published with Medicinal Chemistry Research (2013) Vol. 22; Issue 8; 3688-3697)

**General nomenclature for compounds III<sub>1-16</sub>**

(E)-2-(1H-benzo[d]imidazol-2-ylthio)-N-(aryl)phenylacetamide

**General structure for compounds III<sub>1-16</sub>**

This chapter will deal with the synthesis of chalcones possessing benzimidazole derivatives. Total sixteen derivatives will be synthesized in this series and characterized by using different spectral data. The formed entities will be tested against gram-positive bacteria, gram-negative bacteria and fungi. The SAR study conducted here can help to conclude that among the derivatives bearing either electron-donating or electron-withdrawing functional group will be helpful in enhancing the biological activity.
1.14 References


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Chapter 1

General introduction


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