1. INTRODUCTION

Medicinal chemistry or Pharmaceutical chemistry is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. It involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It is also includes the study of existing drugs, their biological properties, and their quantitative structure activity relationships (QSAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products\(^1\).

During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic compounds as drugs. Medicinal chemistry is almost always geared toward drug discovery and development \(^2\). The approach to the practice of medicinal chemistry has developed from an empirical one involving organic synthesis of new compounds, based largely on modification of structures of known activity, by a more logical approach. Now computers have been pressed into the service of medicinal chemists. Computers augment the scientific process in drug discovery by assisting the chemist with collecting, storing, manipulating, analyzing and viewing the data. Further, computers provide a link to theoretical chemistry and graphic modeling, providing calculated estimates of molecular properties, models of molecules, models of biological sites and sometimes even models of drug-receptor interactions \(^3\).
1. 1. Chemistry of Benzimidazoles:

The benzimidazole nucleus is an important pharmacophore in medicinal chemistry. The synthesis of novel benzimidazole derivatives remains a main focus of modern drug discovery. The versatility of new generation benzimidazole would represent a fruitful pharmacophore for further development of better medicinal agents. Since now, researchers have been attracted toward designing more potent benzimidazole derivatives having wide range of biological activity.

Several benzimidazoles are commercially available as pharmaceuticals. Benzimidazoles are most widely studied drugs as antihelmintics. Studies have established that benzimidazole carbamates such as albendazole (1), mebendazole (2), flubendazole (3), and fenbendazole (4) inhibit the in vitro growth of \textit{Trichomonas vaginalis} and \textit{G. lamblia} and have a broad antiparasitic spectrum of activity, low toxicity and have been used successfully to treat gastrointestinal helmintic infections.

\[
\begin{align*}
\text{Albendazole} & \quad \text{Mebendazole} \\
\text{(1)} & \quad \text{(2)}
\end{align*}
\]
Another area of important use of benzimidazole has recently been as proton pump inhibitor. Omeprazole (5) is appeared for the treatment and reduction of risk of recurrence of duodenal ulcer, gastric ulcer and pathological hypersecretory conditions. Lansoprazole (6) is used for the treatment of duodenal ulcer, and Zollinger-Ellison syndrome.

The other therapeutic agents such as H₁ antihistaminic agent clemizole (7), a potent opioid analgesic etonitazene (8), non-nucleoside antiviral compound enviroxime (9), for promotion of excretion of uric acid irtemazole (10), non
sedating antihistaminic agent astemizole (11), antinematodal agent nocodazole (12) are based on benzimidazole heterocyclic nucleus.
1.1.1. Synthetic routes of benzimidazole nucleosides:

A variety of methods have been developed for the preparation of substituted benzimidazoles. The traditional synthesis (13) of benzimidazoles involves the reaction between a phenylenediamine and a carboxylic acid or its derivatives under harsh dehydrating reaction conditions.7-10.

\[
\text{PhNH}_2 + \text{RCOOH} \xrightarrow{4N \text{HCl}} \text{Imidazole} + \text{R}
\]

(13)

Subsequently, several improved protocols have been developed for the synthesis of benzimidazoles via the condensation of o-phenylenediamines with aldehydes in the presence of acid catalysts under various reaction conditions.

Byeong Hyo Kim et al11 described indium-mediated reductive inter-molecular coupling reaction of 2-nitroaniline with aromatic aldehydes to benzimidazoles (14).

\[
\text{PhNH}_2 + \text{ArCHO} \xrightarrow{\text{BNP, In, MeOH, H}_2\text{O, RT}} \text{Imidazole} + \text{Ar}
\]

(14)

Takashi Itoh et al12 synthesized 2-arylbenzothiazoles and imidazoles using scandium triflate as a catalyst for both a ring closing and an oxidation steps (15).
Donglai Yang et al \(^{13}\) reported a highly efficient and versatile method for the synthesis of benzimidazoles in one step via the Na\(_2\)S\(_2\)O\(_4\) reduction of o-nitroanilines by heating a solution of o-nitro aniline and an aldehyde in EtOH or another appropriate solvent, in the presence of aqueous or solid Na\(_2\)S\(_2\)O\(_4\), provided facile access to a series of 2-substituted benzimidazoles containing a wide range of functional groups not always compatible with the existing synthetic methods \(^{16}\).

Khodabakhsh Niknam et al\(^{14}\) developed a highly selective synthesis of 2-aryl-1-aryl methyl-1H-1,3-benzimidazoles from the reaction of o-phenylenediamines and aromatic aldehydes in the presence of metal hydrogen sulfates [M(HSO\(_4\)]\(_n\)] in water and also under solvent-free conditions in good to excellent yields \(^{17}\).

\[ \text{R}^N\text{H} + \text{ArCHO} \xrightarrow{\text{DMSO, 100}^\circ\text{C, 10 h}} \text{R}^N\text{H} + \text{ArCHO} \xrightarrow{\text{1 eq. R}^N\text{H}_2, 3 \text{eq. Na}_2\text{S}_2\text{O}_4} \text{R}^N\text{R} \]
1.1.2. Reactions of benzimidazoles

Benzimidazoles undergoes following types of reactions:

1.1.2.1. Reactions with electrophilic reagents:

 Preferential position of attack by electrophil is 5\textsuperscript{th} position of unsubstituted benzimidazole, and 2\textsuperscript{nd} preferential position is 6\textsuperscript{th} in absence of influence by the attached substituent but if the 5-substituent is powerfully electron releasing the second substituent enters at 4\textsuperscript{th} position\textsuperscript{15}. While an electron withdrawing substituent at 5\textsuperscript{th} position directs the entering electrophils to 6\textsuperscript{th} position and to a lesser extent the 7\textsuperscript{th} position. Examples of electrophilic aromatic substitution reaction are

Nitration:

\[
\begin{align*}
\text{F} & \quad \text{HNO}_3/\text{H}_2\text{SO}_4 \\
\text{N} & \quad \text{CF}_3 \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{CF}_3 \\
\text{F} \quad & \text{NO}_2 \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{R} \\
\text{R} \\
\text{NO}_2 \\
\text{R} = \text{H, Ar}
\end{align*}
\]

(18)
1.1.2.2. Substitution in the Imidazole ring:

Electrophilic substitution does not occur in the imidazole ring of benzimidazole. Benzimidazole is quantitatively iodinated on treatment with iodine in aqueous sodium hydroxide solution to give product that was believed to be 2-iodobenzimidazole\(^{16}\).

Benzimidazole and 1-methyl benzimidazole react with bromine in chloroform at room temperature to give dicoordinate complex and $n$-donor complexes that are formulated\(^{17}\)

![Chemical Structure](image)

1.1.2.3. Electrophilic attack at the 1-(or 3-) position: Alkylation and Related Reactions:

There are four possible mechanisms for the alkylation depending on the alkylation of substrate i.e. whether alkylated by base, an anion or conjugate acid. Alkylation
of neutral imidazoles and benzimidazoles by alkyl halides usually occurs by $S_{E2}$ mechanism in which electrophilic attack is directed at the pyridine like nitrogen. Under neutral conditions, the benzimidazolium intermediate reacts with unchanged benzimidazoles$^{18}$.

1.1.2.4. Electrophilic Attack at Side-Chain Substituents:

Reactions in this category include substitution and addition processes. Some of the reactions in this category are shown$^{19}$

\[
\text{Ph}_2\text{CHCl} \rightarrow \text{R} \quad \text{(22)}
\]

R= alkyl, aryl

\[
\text{RCHO} \rightarrow \text{N=CHR} \quad \text{(23)}
\]

R= alkyl, aryl

1.1.2.5. Reactions with Nucleophilic Reagents:

Substitution in the imidazole Ring:

In this type of reaction, the benzimidazole is heated in xylene with sodium amide. For the compounds of this type, formation of anion of heterocyclic prohibits the nucleophilic attack at 2- position. Various other derivatives such as 5-alkyl and thioalkyl derivatives are formed$^{20}$. 
1.2. Pyrazolones and Isoxazolinone:

1.2.1. Chemistry of Pyrazolones

The oxo derivatives of pyrazolines, known as pyrazolones, are best classified as follows: 5-pyrazolone, also called 2-pyrazolin-5-one (25); 4-pyrazolone, also called 2-pyrazolin-4-one (26); and 3-pyrazolone, also called 3-pyrazolin-5-one (27). Within each class of pyrazolones many tautomeric forms are possible; for simplicity only one form is shown.

Substitution at N1 decreases the possible number of tautomers: for 3-pyrazolones, two tautomeric forms are possible, (28) and (29), which in nonpolar solvents are both present in about the same ratio. 5-Pyrazolones exhibit similar behavior.

\[ \text{R=alkyl, aryl} \]
In 4-pyrazolones, the enol form predominates, although the keto form has also been observed. The tautomeric character of the pyrazolones is also illustrated by the mixture of products isolated after certain reactions. Thus alkylation normally takes place at C4, but on occasion it is accompanied by alkylation on O and N. Similar problems can arise during acylation and carbamoylation reactions, which also favor C4. Pyrazolones react with aldehydes and ketones at C4 to form a carbon–carbon double bond, eg (30). Coupling takes place when pyrazolones react with diazonium salts to produce azo compounds, eg (31).

Compounds of type (31) are widely used in the dye industry. The Mannich reaction also takes place at C4, as does halogenation and nitration. The important analgesic aminoantipyrine (32) on photolysis in methanol undergoes ring fission to yield (33)\(^2\).
1.2.2. Synthesis of pyrazolone derivatives

The pyrazolone-3-carboxylic acid (35) has been isolated by reaction of oxazolone (34) with hydrazonyl chloride\textsuperscript{22}.

\[
\text{Ar}_2\text{O}^+\text{Ar}_1\text{H} + \text{Ar}_3\text{NH}-\text{N}=\text{COOR} \xrightarrow{(\text{C}_4\text{H}_9)_4\text{N}^+\text{Br}^-} \text{Ar}_1\text{NCH}_3\text{COOR} \xrightarrow{\text{Na}_2\text{CO}_3} \text{Ar}_1\text{NH}_2\text{COOR} \xrightarrow{\text{O}} \text{Ar}_2\text{C}=\text{Ar}_2
\]
The preferred synthetic method for the title compounds utilizes the reaction of hydrazines with bifunctional compounds, such as β-diketones and esters, and β-keto acetylenic compounds. In an alternative procedure, diazo compounds replace hydrazines and ring formation takes place via 1,3-dipolar cycloaddition. Pyrazoles and pyrazolones are widely used in the pharmaceutical industry to alleviate inflammation, fever, pain, and infections. To a lesser extent, they are also used as insecticides and herbicides. Pyrazolones linked to azo compounds are extensively used in the dye industry; some pyrazolines display insecticidal activity\textsuperscript{23}.

Pyrazolones with a free NH group are easily nitrosated and give rise to nitrosamines, which cause tumors in the liver of test animals. The analgesics antipyrine (37) and aminopyrine (38), if admixed with nitrites, are mutagenic when tested \textit{in vitro}; however, when tested in the absence of nitrites, negative results are obtained\textsuperscript{24}.

![Chemical structures](image1.png)

Pyrazolone-type drugs, such as phenylbutazone and sulfinpyrazone, are metabolized in the liver by micro-somal enzymes, forming glucuronide metabolites that are easily excreted because of enhanced water solubility.
The pyrazolone derivatives, which include dipyrone (39), antipyrine (37), aminopyrine (38) and propyphenazone, are widely used analgesics. Dipyrone, the most widely used pyrazolone, has been the most studied. Dipyrone is an inhibitor of cyclo-oxygenase but, unlike aspirin, its effect is rapidly reversible. The inhibition of prostaglandin biosynthesis contributes to the analgesic activity of the pyrazolone derivatives. Unlike the Non-steroidal anti-inflammatory agents (NSAIDs) generally, the pyrazolone derivatives antipyrine, aminopyrine and propyphenazone are minimally bound to plasma proteins. The pyrazolones undergo extensive biotransformation, aminopyrine and dipyrone being converted to active metabolites. The most frequently reported side effects of the pyrazolone derivatives are skin rashes. Gastrointestinal side effects are rare.

1.2.3. Important Pyrazolone and isoxazoline derivative in pharmaceuticals:

Some of the pharmaceuticals that incorporate the pyrazole nucleus are given below. Their main uses are as antipyretic, anti-inflammatory, and analgesic agents. To a lesser extent, they have shown efficacy as antibacterial/antimicrobial, antipsychotic, anti-emetic, and diuretic agents. The analgesic aminopyrine, the antipyretic dipyrone, and the anti-inflammatory phenylbutazone (40), though once
widely prescribed, are rarely used in the 1990s on account of their tendency to cause agranulocytosis. Pyrazolone and pyrazolidinedione derivatives as like benzimidazole derivatives have been found to possess some interesting pharmacological activities. eg. Antipyrin, Ampyrone, edaravone, etc.

(40)

(41) butaglyon, an antidiabetic;

(42) feclobuzo, an antiinflammatory;

(43) kebuzone, an antirheumatic;

(44) sulfinpyrazone, an anti gout
Pyrazolones react with diazonium salts, an important process in the dye industry. The majority of dyes are having pyrazolone nucleus with an azo linkage attached at C4, eg, (49) and (50).
The survey of the pertinent literature reveals that isoxazolidine have been found to possess a wide range of biological activity such as anti bacterial, anti HIV, anti-inflammatory, anticancer, etc. Some isoxazole derivatives have been reported as anti-tubercular, anti bacterial and antifungal agents.
Azopyrazoles (52) and azoisoxazoles (53) are possessing good antifungal activity\textsuperscript{30}. Similarly, 2-alkyl isoaxazolidine derivatives have been as antifungal agents\textsuperscript{31}.

1.3. \textit{IN-SILICO DRUG DESIGN}

Drug discovery and development is an essential, intense, lengthy and an interdisciplinary endeavor. Drug discovery is mostly portrayed as a linear, consecutive process that starts with target and lead discovery, followed by lead
optimization and pre-clinical *in vitro* and *in vivo* studies to determine if such compounds satisfy a number of pre-set criteria for initiating clinical development.

Traditionally drugs were discovered by synthesizing compounds in a time consuming multi-step processes against battery *in-vivo* biological screens and further investigating the promising candidates for the pharmacokinetic properties, metabolism and potential toxicity. Such a development processes has resulted in high attrition rates with failures attributed to poor pharmacokinetics (39%), lack of efficacy (30%), animal toxicity (11%), adverse effects in humans (10%) and various commercial and miscellaneous factors. Today, the processing of drug discovery has been revolutionized with the advent of genomics, proteomics, bioinformatics and efficient technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening, *de novo* design *in vitro*, *in silico* ADMET screening and structure- based drug design.

Computer aided drug design is an interdisciplinary of bioinformatics, medicine and biophysics. Bioinformatics and computational methods recently were used to design new drug candidates that could potentially bind with target proteins, thus producing drug molecules for many disease. They also promise to speedup drug research by predicting potential effectiveness of designed compounds prior to experimental studies and preclinical trials.

*In-silico* methods can help in identifying the drug targets via bioinformatics tools. They can also be used to analyze the target structure for possible binding/ active sites, generate candidate molecules, check for their drug likeness, dock these
molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics. The use of computers and computational methods permeates all aspects of drug discovery today which is essential core of structure-based drug design. The use of in-silico drug design techniques increases the chance of success in many stages of the drug discovery process, from the identification of novel targets and elucidation of their function to the discovery and development of lead compounds with desired properties. Computational tools provide the advantage of delivering the new drug candidates more quickly and at lower cost\textsuperscript{32}.

1.3.1. RATIONAL DRUG DESIGN

In-silico techniques save great amounts of time and money in R&D projects. A good modeling support is often what makes the difference between a successful drug design project and one that fails. With a strong background in the fields of molecular modeling, molecular biology and computational chemistry, we are able to offer full in-silico support for projects of drug design, protein engineering and intermolecular recognition. The possibility of developing software to tailor the in-silico approach to different problems is what makes us unique.

1.3.2. TECHNIQUES

- **Molecular Docking and Virtual Screening**: Docking studies are computational techniques for the exploration of the possible binding modes of a substrate to a given receptor, enzyme or other binding site. Docking is the process by which two molecules fit together in 3D space. Docking studies may help to
increase ligand specificity; and also better therapeutic index can be achieved if the
drug produces undesirable side effects due to its binding with another site, the
affinity for that competing site can be diminished. Different types of docking
include- flexible protein-ligand docking, flexible protein-protein docking and
hydrophobic docking. Docking may play an important role in the QSAR studies
and homology modeling very useful in structure based drug design. Various
docking programs are available DOCK, FLOG, ADAM, and UGIN.

- **Molecular Dynamics**: The prediction of the evolution of molecular
  systems over time, the study of protein conformation, protein-protein interactions,
  the simulation of biological membranes.

- **Quantum Mechanics**: The study of chemical reactions, the effects of
  substitutions on electronic properties and reactivity of molecules.

- **QSAR**: Quantitative structure-activity relationship. The ability of
  predicting biological properties of molecules without even the need of knowing
  their target.

- **Homology Modelling**: Predicting the structures of proteins that has not
  been yet crystallized.

**1.3.3. DOCKING STUDIES:**

The ability to propose reasonable binding modes of a designed structure to a
known receptor site called docking studies, which is crucial to the success of
structure based design. One approach is to dock or position ligand or receptor
molecules together in many different possible ways and then scores each
orientation according to an evaluation function of some kind. These studies can
predict binding confirmations and affinities of millions of molecules without the need of a single synthetic step. These rational drug design methods accelerate the process by speeding up the discovery of new chemical substances that may become a new drug.

1.3.4. DRUG-LIKENESS AND LEAD-LIKENESS

Christopher A. Lipinski$^{33}$ defined the Drug likeness as the compounds those have sufficiently acceptable absorption, distribution, metabolism and elimination properties to get successful entry in to human Phase 1 clinical trials. For the drug development, drug properties are important prominent component. A chemically synthesized compound library can contain many non-drug-like compounds. Therefore, recent technologies helped to develop recognized drug-like compounds from a diverse compound library$^{34-39}$. These drug-like measuring and filtering technologies have partly solved the screening problems. However, they have not been good enough to completely solve these problems. It has been observed that many drug-like compounds, which should be potential candidates; do not come up as hits when they are screened against biological targets. Drug-likeness is the descriptors of all important pharmacological properties such as potency, selectivity toward receptor, absorption, distribution, metabolism and toxicity. In the past, these parameters were optimized sequentially. Now, it is mandatory that these parameters should be optimized simultaneously. Properties that have been associated with oral drug-likeness include:

- Oral bioavailability
• Appropriate toxicity to pass phase I clinical trials.
• Aqueous solubility
• Synthetics accessibility
• Pharmacokinetic viability
• Blood-brain barrier permeability.

Lipophilicity is a key property for pharmacological activity in drug discovery and used to estimate the permeability of a drug molecule in the cell membrane. It is measured as logP value that distribution coefficient of compounds between n-octanol and water.

When logP value is very low or very high, the permeability of drug components get dropped due to the inability of weakly lipophilic compounds to penetrate the lipid portion of the membrane and the excessive partitioning of strongly lipophilic compounds into the lipid portion of the membrane and their subsequent inability to pass through the aqueous portion of the membrane.

Lipinski’s rule helps to predict the poor absorption and permeability of potential drug candidates. It will occur if,
• A molecular weight less than 500.
• An octanol-water partition coefficient log P of less than 5.
• Molar refractivity not more than 150
• Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
• Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms).
1.4. NON-Steroidal ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics, primarily for the treatment of inflammation, especially arthritis. In addition to their anti-inflammatory effects, agents belonging to the NSAID class possess both analgesic and antipyretic activities. Hence, NSAIDs are sometimes referred to as non-narcotic analgesics or as aspirin-like drugs. They provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteo- and rheumatoid arthritis, and in more acute inflammatory conditions such as sports injuries, fractures, sprains and other soft tissue injuries. They also provide relief from postoperative, dental and menstrual pain, and from the pain of headaches and migraine.

1.4.1. Pharmacological Actions:

All the NSAIDs have actions very similar to those of aspirin. The three main therapeutic effects are an anti-inflammatory effect: modification of the inflammatory reaction, an analgesic effect: reduction of certain types of (especially inflammatory) pain and an antipyretic effect: lowering of body temperature when this is raised in disease (i.e. fever).

In addition, all the NSAIDs share, to a greater or lesser degree, the same types of mechanism-based side effects. These include:

- gastric irritation, which may range from simple discomfort to ulcer formation
- an effect on renal blood flow in the compromised kidney
• a tendency to prolong bleeding through inhibition of platelet function.

Controversially, it is argued that they may also all-but especially COX-2 selective drugs-increase the likelihood of thrombotic events such as myocardial infarction by inhibiting prostaglandin (PG I₂) synthesis.

A number of aryl and heteroaryl substituted compounds such as Diclofenac⁴² (1), Lumiracoxib⁴³ (2), Lonazolac (3), Etodolac⁴² (4) have been commercialized as non-steroidal anti-inflammatory drugs (NSAIDS).

**Important Non-Steroidal Anti-inflammatory Drugs:**
Diclofenac (56)  Indomethacin (57)  Sulindac (58)

PROFEN DERIVATIVES:

Ibuprofen (59)  Flubiprofen (60)
Ketoprofen (61)

Naproxen (62)

**OXICAMES:**

Piroxicam (63)

Tenoxicam (64)

**Others:**

Tolmetin (65)

Ketorolac (66)

**Selective COX-2 Inhibitors:**

Celecoxib (67)

Rofecoxib (68)
While there are differences between individual drugs, all these effects are generally thought to be related to the primary action of the drugs—inhibition of the fatty acid COX enzyme, and thus inhibition of the production of prostaglandins and thromboxanes. There are three known isoforms—COX-1, COX-2 and COX-3—as well as some non-catalytic species. As it is not yet certain that COX-3 actually occurs in humans in a functional form, we will confine the discussion mainly to a consideration of COX-1 and COX-2. While they are closely related (> 60% sequence identity) and catalyse the same reaction, it is clear that there are important differences between the expression and role of these two isoforms. COX-1 is a constitutive enzyme expressed in most tissues, including blood platelets. It has a 'housekeeping' role in the body, being involved in tissue homeostasis, and is responsible for the production of prostaglandins involved in, for example, gastric cytoprotection, platelet aggregation, renal blood flow autoregulation and the initiation of parturition).
In contrast, COX-2 is induced in inflammatory cells when they are activated, and the primary inflammatory cytokines-interleukin (IL)-1 and tumour necrosis factor (TNF)-α are important in this regard. Thus the COX-2 isoform is responsible for the production of the prostanoid mediators of inflammation, although there are some significant exceptions. For example, there is a considerable pool of 'constitutive' COX-2 present in the central nervous system (CNS) and some other tissues, although its function is not yet completely clear.

Although, non-steroidal anti-inflammatory drugs (NSAIDS) have been used in the treatment of various inflammatory diseases, their usage is limited by the side effects produced by them, thereby necessitating the need for searching new molecular entities.

1.5. Anti bacterial activity:
The emergence of resistance to the major classes of antibacterial agent is recognized as a significant medical crisis and serious health concern. Particularly, the emergence of multi drug-resistance strains of Gram-positive bacterial pathogens is a problem of ever increasing significance. As the limited number of antimicrobial classes and the common occurrence of resistance within and between classes, the search for antibacterial agents with novel mechanism of actions is always remains an important and challenging task.

The control of microorganism is critical for the prevention and treatment of disease. Microorganisms also grow on and within other organism, and microbial colonization can lead to disease, disability, and death. Thus the control or
destruction of microorganisms residing within the bodies of humans and other animals is great importance.

Modern medicine is dependant on chemotherapeutic agents, chemical agents that are used to treat disease. Chemotherapeutic agents destroy pathogenic microorganisms or inhibit their growth at concentrations low enough to avoid undesirable damage to the host. Most of these agents are antibiotics, microbial products or their derivatives that can kill susceptible microorganisms or inhibit their growth. Drugs such as the sulfonamides are sometimes called antibiotics although they are synthetic chemotherapeutic agents, not microbially synthesized.

Antibiotics are chemical substances excreted by some microorganism which inhibit the growth and development of other microbes. Some of these drugs that were obtained naturally were put to chemical modifications in attempts to enhance beneficial effects while minimizing the toxic effects. The resultant modified product is termed as semi synthetic antibiotics. Most antibiotic currently used are semi synthetic. The chemist has synthesized many drugs that have got the antibacterial property and less toxicity. These drugs are called synthetic antibiotic drugs. Naturally occurring antibiotic, their semi synthetic derivatives and synthetic antibiotics have got the same target. i.e., antimicrobial action. Hence all these drugs were put together to be called antimicrobial agents.

1.5.1. Drug resistance:

The emergence of drug resistance bacteria is posing a major problem in antimicrobial therapy. The frequency varies with the organism and the antibiotic
used. At first, there is an emergence of a small number of drug resistant bacteria which sooner multiplies selectively in the presence of the drug at the cost of sensitive bacteria.

### 1.5.2. Types of drug resistance:

Drug resistance is of two types, primary and acquired.

1. Primary resistance: some bacteria possess an innate property of resistance to certain drug, e.g. resistance of *E.coli* to penicillin.

2. Acquired resistance: it results either from mutation or gene transfer.

### 1.5.3. Recent targets for finding antibacterial agents

Beta-Ketoacyl-acyl carrier protein (KAS) synthase III encoded by the fabH gene is thought to catalyze the first elongation reaction of type II fatty acid synthesis in bacteria and plant plastids. Beta-ketoacyl-acyl carrier protein synthase (KAS) I is important enzyme system for the construction of the unsaturated fatty acid carbon skeletons characterizing *E. coli* membrane lipids. Recent research reported that Type II fatty acid synthesis (FAS II) pathway is an attractive target for their efficacy against infections caused by multi-resistant Gram-positive bacteria and Gram-negative bacteria. Among the related FAS II enzymes, beta ketoacyl-acyl carrier protein synthase (KAS) is an essential target for novel antibacterial drug design. The enzyme bacterial peptide deformylase (PDF) is another novel target for novel antibacterial agents. The metalloproteases enzyme, Bacterial peptide deformylase (PDF) deformylates the N-formyl methionine of newly synthesized
polypeptides through Fe\textsuperscript{2+}-mediated catalytic reaction. PDF is essential in prokaryotes and this enzyme is absent in mammalian cells and provides a unique target for antimicrobial chemotherapy\textsuperscript{47-50}. Thus, it may be another target for new chemotherapeutic agents.

Lipopolysaccharides constitute the outer leaflet of the outer membrane of Gram-negative bacteria and are therefore essential for cell growth and viability. The glycosyltransferase (GT) enzyme, heptosyltransferase WaaC involved in the synthesis of the inner core region of lipopolysaccharides. It catalyzes the addition of the first l-glycero-d-manno-heptose molecule to one molecule of 3-deoxy-d-manno-oct-2-ulosonic acid (Kdo) residue of the Kdo2-lipid A molecule. These heptose is an essential component of the Lipopolysaccharides core domain; its absence results in a truncated lipopolysaccharide associated with the deep-rough phenotype causing a greater susceptibility to antibiotic. Thus, WaaC represents a promising target in antibacterial drug design\textsuperscript{51}.

1.6. Anti fungal activity:

The object of antifungal drug discovery has become a subject of greater challenge due to increasing incidences of fungal drug resistance. This appears due largely to the extensive use of antifungal agents to treat fungal infections. In the past decade, number of patients diagnosed with fungal infections have increased drastically, whereas, relatively very few clinically useful drugs were discovered. The azole derivatives such as such as clotrimazole, fluconazole, itraconazole, ketoconazole, etc. have been widely used to treat a verity of fungal infections.
These azole derivatives inhibit the fungal enzyme 14-alpha demethylase which is essential for the ergosterol synthesis pathway leads to the depletion of this steroidal compound in the cell membrane and accumulation of toxic intermediate sterols, leads increased membrane permeability and inhibition of fungal growth\textsuperscript{52-54}. But broad usage of these drugs led to development of acquired resistance especially among \textit{Candida albicans}. Thus, searching not only improved version of existing drug but also for new drug targets has become an urgent need\textsuperscript{55}.

Recent reports showed that 2-glutamine, D-fructose-6-phosphate aminotransferase known as a new target for antifungals, it catalyzes a complex reaction involving ammonia transfer from L-glutamine to fructose-6-phosphate, followed by isomerisation of the formed fructosamine-6-phosphate to glucosamine-6-phosphate\textsuperscript{56}.

\textbf{1.7. Antioxidant activity:}

The knowledge of free radicals and reactive oxygen species is producing a revolution in the field of medicine that promises a new age of health and disease management. The formation and activity of a number of compounds, known as reactive oxygen species, which have a tendency to donate oxygen to other substances are producing various potential harmful effects. Evidences show that free radical damage contributes to the etiology of many chronic health problems such as cardiovascular and inflammatory disease, cataract and cancer. Antioxidants can prevent free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition\textsuperscript{57-59}. 
Reference:


