Introduction To
Medicinal Chemistry
The discovery of efficacious new human therapeutic agents is one of humanity's most vital tasks. Equitable access to essential medicines for priority diseases is one of the requirements for fulfilling the fundamental right to health. The treatment of pain and disease is one of the most important goals of mankind. It is an enormously demanding activity that requires creativity, a vast range of scientific knowledge and great persistence. Medicinal chemistry, like synthetic chemistry, comprises of both art and science. It requires a comprehensive mind to collect and synthesize mountains of data, chemical and biological. It requires the instinct to select the right direction to pursue, and the intellect to plan and execute the strategy that leads to the desired compound. Most of all, it requires a balance of creativity and perseverance in the face of overwhelming odds to reach the goal that very few achieve - a successfully marketed drug. The art of medicinal chemistry, the science that strives to identify, create or modify molecules for therapeutic application has enriched greatly from developments in the areas of organic chemistry, biology, biophysical/biochemical methods, and computational tools. While opportunities are enormous, advancing a drug candidate from bench top to clinic is associated with challenges as well, and a good understanding on both these aspects would significantly accelerate drug discovery process. Really, the unprecedented increase in human life expectancy, which has almost doubled in a hundred years, is mainly due to drugs and to those who discovered them.

Today, medicinal chemistry is recognized as scientific discipline which lies for the benefit of humanity. The medicinal chemist operates at the hub of the exciting multidisciplinary search for molecules, which will become tomorrow's new medicines. Contemporary Drug Synthesis examines how leading researchers and manufacturers have integrated chemistry, biology, pharmacokinetics and a host of other disciplines in the creation and development of leading drugs. The dominant activities of medicinal chemists are the generation, design and synthesis of biologically active compounds as well they also work on improving the process by
which other pharmaceuticals are made. Synthesizing new molecules is a key activity but before this happens, medicinal chemists establish structure activity and structure-property relationships amongst series of compounds. The challenge, irrespective of the target disease, is to optimise biological activity in parallel with drug like properties, such as solubility, metabolic stability, lack of toxicity and bioavailability.

Medicinal chemistry undoubtedly rests its main focus on the broad based variations embracing the influence of numerous possible manipulations with regard to the chemical structure on the biological activity. In the light of the above statement of facts supported by copious volumes of scientific evidences reported in literatures, it is almost important and necessary for the ‘medicinal chemist’ to decipher and logically understand not only the ‘mechanism of drug action’ in vivo by which a drug substance exerts its effect, but also the overall physicochemical properties of the molecule. In a rather most recent conceptualized theoretical basis, the specific terminology ‘physicochemical characteristics’ invariably refers to the cognizable influence of the plethora of organic functional moieties strategically positioned within a drug substance, namely: acid/ base characteristics, partition coefficient, water solubility, lipoidal solubility, crystal structure, stereochemistry, chirality to name a few. It is, however, pertinent to mention here that most of the aforesaid properties covertly and overtly exert a significant influence upon the various biological phenomenon in vivo, such as: absorption, distribution, metabolism and excretion (ADME) of the newer ‘target-drug molecule’. Therefore, a creative ‘medicinal chemist’ should ponder over the intricacies, complexities and legitimate presence of each functional moiety to the overall physical chemical properties of the ‘target drug molecule’ with a view to arrive at or design safer, better and efficacious medicinal agents. Nevertheless, such critical studies have to be carried out in a rather methodical and systematic manner vis-a-vis their effect upon biological activities. Generally, such elaborated studies are commonly referred to as ‘structure activity relationship’ (SAR); and more recently as ‘quantitative structure activity relationship’ (QSAR).¹
Medicinal chemistry was defined by IUPAC specified commission as “it concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level.” Highly productive age of medicinal discovery lies ahead, for three reasons:

1. The discovery of numerous important new targets for effective disease therapy,
2. The increasing power of high-throughput screening and bio-target structure-guided drug design in identifying lead molecules and
3. The ever-increasing sophistication of synthetic and computational chemistry.

The first rational development of synthetic drugs was carried out by Paul Ehrlich and Sacachiro Hata who produced arsphenamine in 1910 by combining synthesis with reliable biological screening and evaluation procedures. Ehrlich, at the beginning of the nineteenth century, had recognised that both the beneficial and toxic properties of a drug were important in its evaluation. He realised that the more effective drugs showed a greater selectivity for the target micro-organisms than in host. Consequently, to compare the effectiveness of different compounds, he expressed a drug’s selectivity and hence its effectiveness in terms of its chemotherapeutic index. Ehrlich method of approach is still one of the basic technique used to design and evaluate new drugs in medicinal chemistry.

**About drugs**

A very broad definition of a drug would include “all chemicals other than food that affect living processes.” If the affect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use and the person using it. Another definition would be “medicinal agents used for diagnosis, prevention, treatment of symptoms, and cure of diseases.” Contraceptives would be outside of this definition unless pregnancy was considered a disease. All drugs have the potential for producing more than one response. Some adverse drug responses which are unavoidable are appearing at therapeutic doses are termed as side effects. In contrast, adverse drug effects appearing at extreme drug doses are described as toxic effects.
Classification of drugs

There are several ways in which drugs can be classified:

1. According to their pharmacological effect – for example, analgesic drugs which have a pain-killing effect.

2. Depending on whether they act on a particular biochemical process – for example, antihistamines act by inhibiting the action of the inflammatory agent histamine in the body.

3. According to their chemical structure – drugs classified in this way share a common structural feature and often share a similar pharmacological activity – for example, penicillin contains β-lactum ring and kills bacteria by the same mechanism.

4. According to their molecular target – this is the most useful classification as far as medicinal chemist is concerned, since it allows rational comparison of the structures involved. For example, anticholinesterases are compounds that inhibit an enzyme called acetyl cholinesterase.

Many drugs are either organic acids or organic bases that are used as salts. These bring about: (a) modifications of physiochemical properties, such as solubility, stability, photosensitivity and organoleptic characteristics. (b) Improvement of bioavailability through modification of absorption, increase of potency and extension of effect and (c) reduction of toxicity.

Properties of a drug molecule

A molecule is the smallest particle of a substance that retains the chemical identity of that substance. It is composed of two or more atoms held together by chemical bonds (i.e., shared electron pairs). Although molecules are highly variable in terms of structure, they may be organized into families on the basis of certain groupings of atoms called functional groups. A functional group is an assembly or cluster of atoms that generally reacts in the same way, regardless of the molecule in which it is located, e.g., the carboxylic acid functional group
(-COOH) generally imparts the property of acidity to any molecule in which it is inserted. It is the presence of functional groups that determines the chemical and physical properties of a given family of molecules. A functional group is a centre of reactivity in a molecule.

A drug molecule possesses one or more functional groups positioned in three-dimensional space on a structural framework that holds the functional groups in a defined geometrical array that enables the molecule to bind specifically to a targeted biological macromolecule, the receptor. The structure of the drug molecule thus permits a desired biological response, which should be beneficial (by inhibiting pathological processes) and which ideally precludes binding to other untargeted receptors, thereby minimizing the probability of toxicity. The framework upon which the functional groups are displayed is typically a hydrocarbon structure (e.g., aromatic ring, alkyl chain) and is usually chemically inert so that it does not participate in the binding process. The structural framework should also be relatively rigid (“conformationally constrained”) to ensure that the array of functional groups is not flexible in its geometry, thus preventing the drug from interacting with untargeted receptors by altering its molecular shape. To be successful in countering a disease, a drug molecule must have additional properties beyond the capacity to bind to a defined receptor site. It must be able to withstand the journey from its point of administration (i.e., the mouth for an orally administered drug) until it finally reaches the receptor site deep within the organism (i.e., the brain for a neurologically active drug).

A drug-like molecule (DLM) possesses the chemical and physical properties that will enable it to become a drug molecule should an appropriate receptor be identified. What are the properties that enable a molecule to become a drug-like molecule? In general, a molecule should be small enough to be transported throughout the body, hydrophilic enough to dissolve in the blood stream, and lipophilic enough to cross fat barriers within the body. It should also contain enough polar groups to enable it to bind to a receptor, but not so many that it...
would be eliminated too quickly from the body via the urine to exert a therapeutic effect. Lipinski’s Rule of five does a good job of quantifying these properties.

**Figure-1: Drug-like molecules and druggable targets:** Certain properties permit a molecule to become a drug-like molecule and certain properties permit a macromolecule to become a druggable target. When a drug-like molecule interacts with a druggable target to give a biological response, it becomes a drug molecule and the druggable target becomes a receptor. When a drug molecule is successfully and beneficially distributed to people with a disease, it becomes a useful drug molecule.
**Tools in medicinal chemistry**

The tools of medicinal chemistry have changed dramatically over the past few decades, and continue to change today. Most medicinal chemists learn how to use these tools by trial and error once they enter the pharmaceutical industry, a process that can take many years. Medicinal chemists continue to redefine their role in the drug discovery process, as the industry struggles to find a successful paradigm to fulfil the high expectations for delivering new drugs. But it is clear that however this new paradigm works out, synthetic and medicinal chemistry will continue to play a crucial role. As the chapters in this volume make clear, drugs must be successfully synthesized as the first step in their discovery. Medicinal chemistry consists of designing and synthesizing new compounds, followed by evaluation of biological testing results and generation of a new hypothesis as the basis for further compound design and synthesis. This chapter will discuss the role of both synthetic and medicinal chemistry in the drug discovery process in preparation for the chapters that follow on the syntheses of marketed drugs. To overcome the many hurdles to discovering a new drug, medicinal chemists must focus on synthesizing compounds with drug-like properties. One of the first tools developed to help chemists design more drug-like molecules takes advantage of an area totally under the chemist’s control—the physical properties of the compounds being designed. These are the rules developed by Chris Lipinski, sometimes referred to as the “Rule-of-Five” (Ro5), which describe the attributes drug-like molecules generally possess that chemists should try to emulate.

The Ro5 states that drug-like molecules tend to exhibit four important properties, each related to number 5:

1. Substance should have a molecular weight of 500 or less.
2. It should have less than five hydrogen-bond donating functions.
3. It should have less than ten hydrogen-bond accepting functions.
4. The substance should have calculated ClogP between approximately 1 to 5.
In short, the compound should have a comparatively low molecular weight, be relatively non-polar and partition between an aqueous and a particular lipid phase in favour of the lipid phase, but at the same time, possess perceptible water solubility. The Ro5 can be applied all the way from library design in the earliest stages of drug discovery to the final fine-tuning process that leads to the compound selected for development. Correlating microsomal instability and/or absorption/efflux with Ro5 properties can also provide insight about the property most important for gaining improvement in these areas.

**Tailoring of drugs**

With the advent of enormous in-depth knowledge of ‘modern chemistry’, the ‘tailoring’ of drugs has become a skilful art that may result fruitful results through specific modes of attack on a drug molecule. Various configurational and stereochemical changes afford flexibility and overall dimension of a drug molecule. Such alterations may be conveniently achieved through different means and ways, namely: ring fission or fusion, formation of lower or higher homologues, introduction of optically active centers, formation of double bonds towards geometrical isomerism, and lastly introduction of bulky groups towards restricted rotation or the removal and replacement of such groups. Alterations of various physical and chemical characteristics through the insertion of newer functional moieties or by the replacement of such groups already present by others that essentially differ in degree or in type. These types of changes may be effectively brought about by: isosteric replacement, changes of orientation or position of given moieties, introduction of polar character of given functional groups or replacement of other groups with different electrical features, and finally such changes which either promote or inhibit the presence of different electronic conditions achieved through inductive effects, mesomeric effects, tautomerism, chelation, hyperconjugation, etc.

**Factors governing drug-design**

A few cardinal factors governing the efficacy towards the evaluation of drug design include: (a) The smaller the expenditure of human and material resources involved
to evolve a new drug of a particular value, the more viable is the design of the programme. (b) Experimental animal and clinical screening operations of the new drugs. (c) Relationships between chemical features and biological properties need to be established retrospectively. (d) Quantitative structure activity relationships (QSARs) vary to an appreciable extent in depth and sophistication based on the nature of evaluation of structure or activity. A purposeful relation of structural variables must include steric factors, electronic features of component functional groups and, in general, the molecule as a whole. (e) The trend to synthesize a huge number of newer medicinal compounds indiscriminately for exploratory evaluation still prevails which exclusively reflects the creative genuineness and conceptual functions of a highly individualized expression of novelty by a medicinal chemist. (f) Introduction of functional groups in a molecule that need not essentially resemble metabolites, but are capable of undergoing bonding interactions with important functional groups of biochemical components of living organisms affords an important basis for exploration. (g) Disease etiologies and various biochemical processes involved prove useful.

Sites of drug action

1. **Enzyme inhibition:** Drugs act within the cell by modifying normal biochemical reactions. Enzyme inhibition may be reversible or non-reversible; competitive or non-competitive. Antimetabolites may be used which mimic natural metabolites.

2. **Drug-receptor interaction:** Drugs act on the cell membrane by physical and/or chemical interactions. This is usually through specific drug receptor sites known to be located on the membrane. A receptor is specific chemical constituent of the cell with which a drug interacts to produce its pharmacological effect. Some receptor sites have been identified with specific parts of proteins and nucleic acids. In most cases, the chemical nature of the receptor site remains obscure.

3. **Non-specific interactions:** Drugs act exclusively by physical means outside cells. These sites include external surfaces of skin and gastrointestinal tract. Drugs also act outside cell membranes by chemical interactions. Neutralization of stomach acid by antacids is a good example.
Introduction to antimicrobial agents

The past few decades have witnessed a significant increase in microbial diseases. Infection caused by bacteria, fungi, viruses etc. has affected human and animals.

Mode of drug action

It is important to distinguish between action of drugs and their effects. Actions of drugs are the biochemicals, physiological mechanisms by which the chemical produces a response in living organisms. The effect is the observable consequence of a drug action. For example, the action of penicillin is to interfere with cell wall synthesis in bacteria and the effect is the death of bacteria. One major problem of pharmacology is that no drug produces a single effect. The primary effect is the desired therapeutic effect. Secondary effects are all other effects beside the desired effect which may be either beneficial or harmful. Drugs are chosen to exploit differences between normal metabolic processes and any abnormalities, which may be present. Since the differences may not be very great, drugs may be nonspecific in action and alter normal functions as well as the undesirable ones, this leads to side effects. The biological effects observed after a drug has been administered are the result of interaction between that chemical and some part of the organism. Mechanisms of drug action can be viewed from different perspectives, namely, the site of action and the general nature of the drug-cell interaction.

1. Killing foreign organisms: Chemotherapeutic agents act by killing or weakening foreign organisms such as bacteria, worms and viruses. The main principle of action is selective toxicity, i.e. the drug must be more toxic to the parasite than to the host.

2. Stimulation and depression: Drugs act by stimulating or depressing normal physiological functions. Stimulation increases the rate of activity while depression reduces it.

3. Irritation: It is a non-specific action of a drug that can occur in all the body tissues. Certain drugs act by causing irritation. Ex: Drugs like senna and castor oil show their laxative effects by their irritant action on gastrointestinal tract.

4. Replacement: Drugs serve as replacement of essential body chemicals that are either absent or present in less than required quantity due to disease. Ex: Insulin is used in diabetes. Levodopa therapy in parkinson’s disease.
Hence, this class of drugs is the greatest contribution of the 20\textsuperscript{th} century to medicinal chemistry. Substantial attention has been focused on developing a more potent and effective antimicrobial agent. Most of this attention has been devoted to the study of medicinally important antibacterial and antifungal agents during the past development in antimicrobial agents. Bacterial cells grow and divide, replicating repeatedly to reach the large numbers present during an infection or on the surfaces.

**Figure-2: Site of action of different antimicrobial agents**

of the body. To grow and divide, organisms must synthesize or take up many types of biomolecules. Antimicrobial agents may be either bactericidal, killing the target bacterium or fungus, or bacteriostatic, inhibiting its growth. Different antibiotics destroy bacteria in different ways. Following picture shows interference of antibacterial agent in living cell.

**Figure-3: Interference of antibacterial agent in living cell.**
Bactericidal agents are more effective, but bacteriostatic agents can be extremely beneficial since they permit the normal defence of the host to destroy the microorganisms. On occasions, it is useful to combine different antimicrobial agents for broadening the activity spectrum and to minimize the possibility of the development of bacterial resistance. Some antibiotic combinations are more effective together than the combined effectiveness of a single agent. This is termed as synergism. Combination therapy has proved its value as latest therapy for antimicrobials. Some bacteriostatic agent on novel combination gives bactericidal activity. Sulfamethoxazole is bacteriostatic and Trimethoprim is also bacteriostatic but combination of both the drugs is now widely used as bactericidal combination. Two such bactericidal drugs are also used in combination therapy. Rifampin + Dapson is used in leprosy and Rifampin + Isoniazide in tuberculosis. WHO has also approved these types of combinations.

**Why do we need new drugs?**

Drug resistance or tolerance (tachyphylaxis) occurs when a drug is no longer effective in controlling a medical condition. It arises in people for a variety of reasons. For example, the effectiveness of barbiturates often decreases with repeated use because the body develops mixed function oxidases in the liver that metabolise the drug and reduces its effectiveness. The development of an enzyme that metabolises the drug is a relatively common reason for drug resistance. Another general reason for drug resistance is the downregulation of receptors. Downregulation occurs when repeated stimulation of a receptor results in the receptor being broken down. This results in the drug being less effective because there are fewer receptors available for it to act on. Drug resistance may also be due to the appearance of a significantly high proportion of drug-resistant strains of microorganisms. These strains arise naturally and can rapidly multiply and become the currently predominant strain of that microorganism. Antimalarial drugs are proving less effective because of an increase in the proportion of drug-resistant strains of the malaria parasite.
New drugs are constantly required to combat drug resistance even though it can be minimized by the correct use of medicines by patients. They are also required for improving the treatment of existing diseases, the treatment of newly identified diseases and the production of safer drugs by the reduction or removal of adverse side effects.

**Discovery of drugs**

It has been proved beyond any reasonable doubt that the ‘rate of success’ in drug discovery of novel molecules is exclusively dependent on the ability to identify and characterize novel, patentable newer ‘target-drug molecules’ usually termed as **New Chemical Entities (NCEs)**, which essentially possess the inherent capability and potential in the management and control of a specific disease/ailment; besides, being efficacious and safer in character. Inventing and developing a new medicine is a long, complex, costly and highly risky process that has few peers in the commercial world.

![Figure-4: The process of new drug discovery](image-url)

Research and Development (R&D) for most of the medicines available today has required 12–24 years for a single new medicine, from starting a project to the
launch of a drug product (Fig. 4). In addition, many expensive, long-term research projects completely fail to produce a marketable medicine. The cost for this overall process has escalated sharply to an estimated US $1.4 billion for a single new drug. In research (‘R’; discovery) phase, only a fraction of the scientific hypotheses that form the basis for a project actually yield a drug candidate for development. Discovery often begins with target identification - choosing a biochemical mechanism involved in a disease condition. Drug candidates, discovered in academic and pharmaceutical/biotech research labs are tested for their interaction with the drug target. Upto 5,000 to 10,000 molecules for each potential drug candidate are subjected to a rigorous screening process which can include functional genomics and/or proteomics as well as other screening methods. Once scientists confirm interaction with the drug target, they typically validate that target by checking for activity versus the disease condition for which the drug is being developed. After careful review, one or more lead compounds are chosen.

Development of drugs

Once the compound(s), have been chosen, they must be transformed into a drug. This process involves several series of trials on animals and humans, all intended to ensure that the drug may be administered to humans with a minimum possible risk and that it is superior to, or otherwise complements, existing drugs with the same therapeutic function. In the drug development (‘D’) phase, experience has shown that only approximately 1 out of 15-25 drug candidates survive the detailed safety and efficacy testing (in animals and humans) required for it to become a marketed product. And for the few drug candidates that successfully become marketed products, some will not recover their cost of development in the competitive marketplace, and only approximately one in three will become a major commercial product. Clearly, this is a high-stake, long-term and risky activity, but the potential benefits to the millions of patients with serious diseases provide a constant motivating force.
Clinical trials: overview
Clinical trials are a peculiar hybrid between a formalized and strictly regulated process on one hand and a sophisticated stratagem on the other, particularly when it comes to patient selection, statistical methodology, disease markers, and endpoints employing cutting-edge research. They are also expensive, accounting for 50 to 70 percent of the drug discovery and development cost. They can be long-lasting for many years depending on therapeutic area. Clinical studies are grouped according to their objective into three types or phases:

Phase I: Clinical development (Human pharmacology): Thirty days after a biopharmaceutical company has filed its IND, it may begin a small-scale Phase I clinical trial unless the FDA places a hold on the study. Phase I studies are used to evaluate pharmacokinetic parameters and tolerance, generally in healthy volunteers. These studies include initial single-dose studies, dose escalation and short-term repeated-dose studies.

Phase II: Clinical development (Therapeutic exploratory): Phase II clinical studies are small-scale trials to evaluate a drug’s preliminary efficacy and side-effect profile in 100 to 250 patients. Additional safety and clinical pharmacology studies are also included in this category.

Phase III: Clinical development (Therapeutic confirmatory): Phase III studies are large-scale clinical trials for safety and efficacy in large patient populations. While phase III studies are in progress, preparations are made for submitting the Biologics License Application (BLA) or the New Drug Application (NDA). BLAs are currently reviewed by the FDA’s Center for Biologics Evaluation and Research (CBER). NDA’s are reviewed by the Centre for Drug Evaluation and Research (CDER).

Phase IV: In addition to these three phases, Phase IV, also known as Post Marketing Surveillance is also carried out once the drug is approved and marketed. The aim of Phase IV is to find out safety profile in large patient pool across the world and to establish the safety profile of the drug. It is estimated that
success rate of drugs making to market from lab is very less. One drug, from among the thousands tested, makes it to the market.

**Pharmacogenomics** is based on the recognition that drugs developed for mass markets will not work for many people who have the disease targeted. Beta blockers do not work for between 15% and 35% of patients, tricyclic antidepressants have no effect on 20% to 50% of patients, while interferons are of no use to 30% to 70%. Part of the reason for this variation in response among patients is due to differing genetic make ups. As the genome is better understood, the genetic variation in response will be correlated with other factors such as drug metabolism and toxicokinetics to help predict how an individual patient will respond to a given drug in terms of efficacy and safety. Pharmacogenomics is expected to have a number of positive effects on drug discovery, development and marketing. It will enable doctors to prescribe the medicines best suited to a patient’s genetic profile as well as the optimal dose. It will also enable drug companies to improve the selection of participants in clinical trials as it will weed out those that will not respond to the drug. It will also rescue drugs that might have failed in clinical trials because of adverse reactions from very small groups in the population. While these effects are largely positive, the possibility of multiple variants of drugs for multiple sub groups of the population could increase the cost of drug development and manufacture for pharmaceutical companies if individualized therapies are demanded by patients or managed care intermediaries.

**Current trends in drug industries**

The pharmaceutical industry is unquestionably vibrant today, with drug synthesis making a vital contribution. Whether in the early developmental stages of identifying and optimizing a lead, or the latter stages of process development and cost-effective scale-up, the ability to design elegant and economical synthetic routes is often a major factor in the eventual viability and commercial success of a drug. Almost 300 antibacterial products are available in the world market, but successful treatment of bacterial disease is becoming increasingly problematic as
the number of elderly and immunocompromised patients increase, the pathogens undergo changes, and resistance to current agents become more widespread. These factors are driving the pharmaceutical industry to develop new and more powerful agents from existing classes of antibacterial drugs and to reevaluate their approaches to antibacterial drug discovery. Bacterial genomics, supported by fundamental research on bacterial physiology, environmental adaptation, and host-pathogen interactions are expected to supply the drug targets of the future. Although products of this research are some way off, new and improved agents continue to emerge from established screening and chemical modification programs. The criteria of novelty and competitive advantage for new agents therefore become increasingly difficult to attain. The relentless spread of antibacterial resistance to agents that were initially thought to have overcome all resistance problems is now offering necessary scope for novelty and innovation. The message coming from many opinion leaders in the medical profession is also one of strong encouragement for the pharmaceutical industry to pursue the quest for new and better antibacterials. Drug resistance is seen as a serious potential threat to the continuing effectiveness of current antibacterial agents, and a new compound that can address an important resistance problem is likely to find a place in the crowded market. Other potential areas for innovation relate to the changing pattern of infectious disease brought about by the AIDS epidemic and the increasing frequency of organ transplantation, implanted prosthetic devices, and other developments in invasive medical procedures, together with a demographic shift to a more elderly and institutionalized population in the developed world. Antibiotics are now increasingly required to be effective in patients who are immunocompromised or debilitated through age-underlying disease.