

# *Chapter-1*

## *General Introduction*

## 1. General introduction

Medicinal chemistry is a scientific discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal chemistry is a highly interdisciplinary science combining organic chemistry with biochemistry, computational chemistry, pharmacology, pharmacognosy, molecular biology, statistics, and physical chemistry. Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It 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. The primary objective of medicinal chemistry is the design and discovery of new compounds that are suitable for use as drugs. The discovery of a new drug requires not only its design and synthesis but also the development of testing methods and procedures, which are needed to establish how a substance operates in the body and its suitability for use as a drug. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. This and other aspects of drug design and discovery require input from specialists in other fields, such as biology, biochemistry, pharmacology, mathematics, computing and medicine amongst others, and the medicinal chemist to have outline knowledge of these fields. Drugs are strictly defined as chemical substances that are used to prevent or cure diseases in humans, animals and plants. The activity of a drug is its pharmacological effect on the subject, for example, its analgesic or b-blocker action. Drugs act by interfering with biological processes, so no drug is completely safe. All drugs can act as poisons if taken in excess. For example, overdoses of Paracetamol can cause coma and death. Furthermore, in addition to their beneficial effects, most drugs have non-beneficial biological effects. Aspirin, which is commonly used to alleviate headaches, may also cause gastric irritation and bleeding. The non-beneficial effects of some drugs, such as cocaine and heroin, are so undesirable that the use of these drugs has to be strictly controlled by legislation. These unwanted effects are commonly referred to as side effects. The over-usage of the same drugs, such as antibiotics, can result in the development of

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resistance to that drug by both the patients, micro organisms and virus the drug is intended to control. Resistance occurs when a drug is no longer effective in controlling a medical condition. Drug resistance or tolerance, often referred to as tachyphylaxis, arises in people for a variety of reasons. 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 the improvement in 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.

Over the past few decades organic chemistry has seen tremendous progress and this has enabled the synthetic chemist to assemble virtually any molecular structure imaginable given reasonable time and sufficient resources. A steady increase in architectural complexity and the incorporation of more diverse molecular functionality has been a notable feature of pharmaceutical research and development. This general trend has emerged as a consequence of the better understanding of the genome and has resulted in many highly specific therapeutic targets being elucidated.

However, even today it might be argued that because of the perceived simpler structures of drug molecules when compared to complex natural products, only a limited repertoire of synthetic transformations are utilized for their construction. Furthermore, many of the modern pioneering developments in organic synthesis including new highly selective and mild bond forming reactions such as metathesis and C–H activation, asymmetric transformations as well as polymer- and technology assisted syntheses are underused. In order to evaluate the validity of this hypothesis we decided to investigate the syntheses of the best-selling pharmaceutical substances focusing not only on the type of transformations involved but more importantly on the way the heterocyclic components were assembled. Aromatic and non-aromatic heterocyclic rings are a predominant architectural constant of pharmaceuticals and allow for variable interactions with the biological target which are not possible using simpler carbocyclic motifs. Based on our observations, we will moreover be able to evaluate the degree these privileged structures utilize innovative and challenging synthetic strategies. In addition, it will be possible to establish which reactions are most frequently employed and which ones are

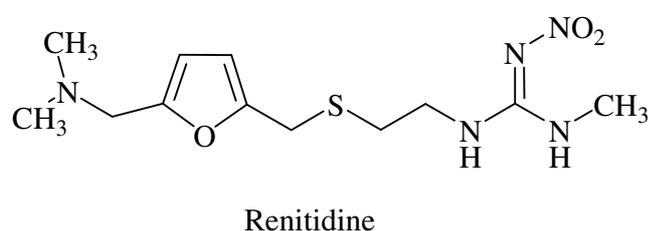
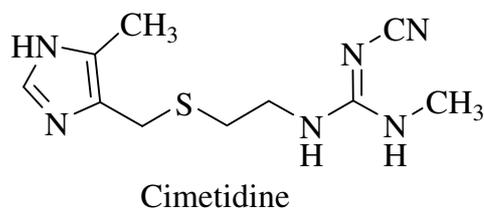
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surprisingly rare or notably absent. Furthermore, from this study it will be possible to judge whether novel methods and transformations developed within the academic community are commonly applied in the later stages of drug research. In order to illustrate the diversity of synthetic methods used by the pharmaceutical industry to generate heterocycle containing molecules they decided in the first part of this review to focus mainly on five-membered aromatic heterocycles represented within the top 200 best selling drugs [1,2]. Many literature sources including patents to provide a selection of the most commonly used routes in drug synthesis.

### **Drug discovery and design**

Since ancient times the people of the world have used a wide range of natural products for medicinal purposes. These products, obtained from animal, vegetable and mineral sources, were sometimes very effective. However, many of the products were very toxic. Initially this development was centered around the natural products isolated from plant and animal material, but as knowledge increased a wider range of pharmaceutically active compounds were used as the starting point for the development of drugs. The compounds on which a development is based are now known as lead compounds, while the synthetic compounds developed from a lead are referred to as its analogues. The work of the medicinal chemist is centered around the discovery of new lead compounds with specific medical properties. It includes the development of more effective and safer analogues from both these new and existing lead compounds. This usually involves synthesizing and testing many hundreds of compounds before a suitable compound is produced. It is currently estimated that for every 10 000 compounds synthesized one is suitable for medical use. The first rational development of synthetic drugs was carried out by Paul Ehrlich and Sacachiro Hata, who produced the Antiprotozoal “Arsphemamine” in 1910 by combining synthesis with reliable biological screening and evaluation procedures. Ehrlich, at the beginning of the 20th century, had recognized that both the beneficial and toxic properties of a drug were important to its evaluation. The term structure–activity relationship (SAR) is now used to describe Ehrlich’s approach to drug discovery, which consisted of synthesizing and testing a series of structurally related compounds. Attempts to quantitatively relate chemical structure to biological action were first initiated in the 19th century, but it was not until the 1960s that

Hansch and Fujita devised a method that successfully incorporated quantitative measurements into SAR determinations. The technique is referred to as QSAR (quantitative structure–activity relationships). One of its most successful uses has been in the development in the 1970s of the antiulcer agents Cimetidine (1) and Ranitidine (2). Both SARs and QSARs are important parts of the foundations of medicinal chemistry.



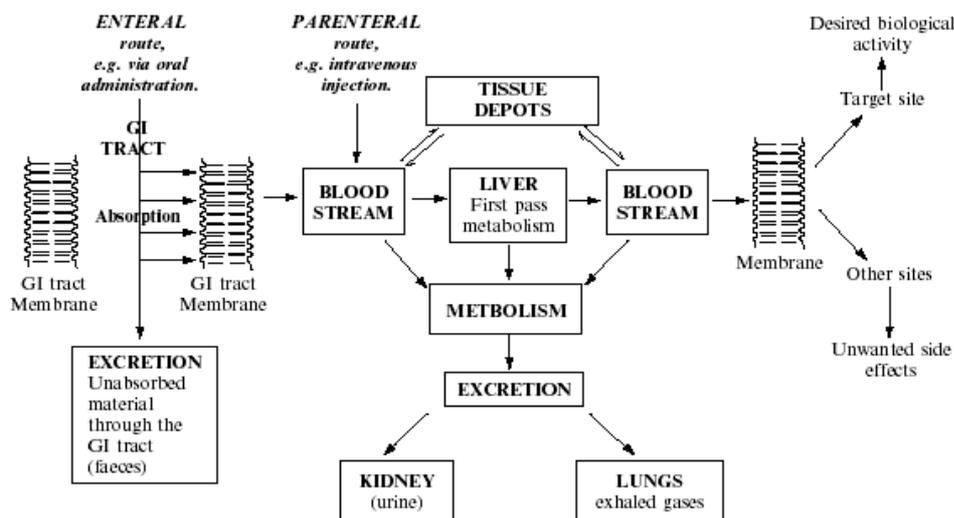
Both SAR and QSAR studies rely on the development team picking the correct starting point. Serendipity inevitably plays a significant part in selecting that point. However, modern techniques such as computer modeling and combinatorial chemistry introduced in the 1970s and 1990s respectively are likely to reduce the number of intuitive discoveries. Computer modeling has reduced the need to synthesize every analogue of a lead compound. It is also often used retrospectively to confirm the information derived from other sources. Combinatorial chemistry, which originated in the field of peptide chemistry, has now been expanded to cover other areas. The term covers a group of related techniques for the simultaneous production of large numbers of compounds for biological testing. Consequently, it is used for structure action studies and to discover new lead compounds. The procedures may be automated.

### Drugs and Their Action

**Sources of drugs and lead compounds:** The most popular approach to drug design by synthesis is to start with the pathology of the diseased state and determine the point where intervention is most likely to be effective. This enables the medicinal chemist to suggest possible lead compounds. These compounds are synthesized so that their

pharmacological action may be evaluated. Once a suitably active lead is found, structural analogues of that lead are produced and screened in the hope that this procedure will eventually produce a compound that is suitable for clinical use. Obviously this approach is labor intensive and a successful outcome depends a great deal on luck. Various modifications to this approach have been introduced to reduce this element of luck.

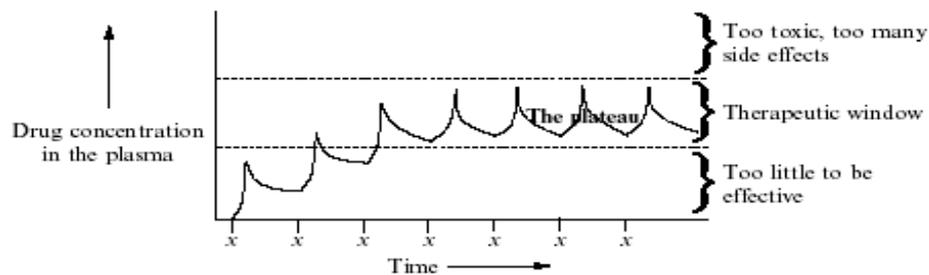
**Routes of administration, the pharmaceutical phase:** The physical form in which a medicine is administered is known as its dosage form. Dosage forms normally consist of the active constituent and other ingredients known as excipients. Excipients can have a number of functions, such as fillers (bulk providing agent), lubricants, binders, preservatives and antioxidants. A change in the nature of the excipients can significantly affect the stability of the active ingredient as well as its release from the dosage form. Similarly, changes in the preparation of the active principle, such as the use of a different solvent for purification, can affect its bioavailability and consequently its effectiveness as a drug. This indicates the importance of quality control procedure for all drugs especially when they reach the manufacturing stage. The design of dosage forms lies in the field of the pharmaceutical technologist but it should also be considered by the medicinal chemist when developing a drug from a lead compound. It is no use having a wonder drug if it cannot be packaged in a form that makes it biologically available as well as acceptable to the patient.



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**Figure-1:** The main routes of drug administration and distribution in the body. The distribution of a drug is also modified by metabolism, which can occur at any point in the system

Drugs are usually administered topically or systemically. The routes are classified as being either parenteral or enteral (Figure 1). Parenteral routes are those that avoid the gastrointestinal tract (GI. tract), the most usual method being intramuscular injection (IM). The enteral route is where drugs are absorbed from the alimentary canal (PO per oral), rectal and sub-lingual routes. The route selected for the administration of a drug will depend on the chemical stability of the drug, both when it is transported across a membrane (absorption) and in transit to the site of action (distribution). It will also be influenced by the age, and physical and mental abilities, of the patients using that drug. For example, age related metabolic changes often result in elderly patients requiring lower dosages of the drug to achieve the desired clinical result. Schizophrenics and patients with conditions that require constant medication are particularly at risk of either overdosing or under dosing. In these cases, a slow release intramuscular injection, which need only be given once in every two to four weeks, rather than a daily dose, may be the most effective use of the medicine. Consequently, at an appropriately early stage in its development, the design of a drug should also take into account the nature of its target groups. Once the drug enters the bloodstream it is distributed around the body and, so, a proportion of the drug is either lost by excretion metabolism to other products or is bound to biological sites other than its target site. As a result, the dose administered is inevitably higher than that which would be needed if all the drug reached the appropriate site of biological action. The dose of a drug administered to a patient is the amount that is required to reach and maintain the concentration necessary to produce a favorable response at the site of biological action. Too high a dose usually causes unacceptable side effects whilst too low a dose results in a failure of the therapy. The limits between which the drug is an effective therapeutic agent is known as its therapeutic window (Figure 2).



**Figure-2:** A simulation of the therapeutic window for a drug given in fixed doses at fixed time intervals  $X$

The amount of a drug the plasma can contain coupled with processes that irreversibly eliminate the drug from its site of action results in the drug concentration reaching a so called plateau value. Too high a dose will give a plateau above the therapeutic window and toxic side effects. Too low a dose will result in the plateau below the therapeutic window and ineffective treatment. The dose of a drug and how it is administered is called the dosage regimen. Dosage regimens may vary from a single dose taken to relieve a headache through regular daily doses taken to counteract the effects of epilepsy and diabetes to continuous intravenous infusions for seriously ill patients. Regimens are designed to maintain the concentration of the drug within the therapeutic window at the site of action for the period of time that is required for therapeutic success. The design of the regimen depends on the nature of the medical condition and the medicant. The latter requires not just knowledge of a drug's biological effects but also its pharmacokinetic properties, that is, the rate of its absorption, distribution, metabolism and elimination from the body.

**Drug action:** The action of a drug is believed to be due to the interaction of that drug with endogenous and exogenous substrate molecules found in the body. When one or more active drug molecules bind to the target endogenous and exogenous molecules, they cause a change or inhibit the biological activity of these molecules. The effectiveness of a drug in bringing about these changes normally depends on the stability of the drug-substrate complex, whereas the medical success of the drug intervention usually depends on whether enough drug molecules bind to sufficient substrate molecules to have a marked effect on the course of the disease state. The degree of drug activity is directly

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related to the concentration of the drug in the aqueous medium in contact with the substrate molecules. The factors affecting this concentration in a biological system can be classified into the pharmacokinetic phase and the pharmacodynamic phase of drug action. The pharmacokinetic phase concerns the study of the parameters that control the journey of the drug from its point of administration to its point of action. The pharmacodynamic phase concerns the chemical nature of the relationship between the drug and its target: in other words, the effect of the drug on the body.

**The pharmacokinetic phase:** The pharmacokinetic phase of drug action includes the Absorption, Distribution, Metabolism and Elimination (ADME) of the drug. Many of the factors that influence drug action apply to all aspects of the pharmacokinetic phase. Solubility, for example, is an important factor in the absorption, distribution and elimination of a drug. Furthermore, the rate of drug dissolution, that is, the rate at which a solid drug dissolves in the aqueous medium, controls its activity when a solid drug is administered by enteral routes as a solid or suspension.

**Absorption:** Absorption is the passage of the drug from its site of administration into the plasma after enteral administration. It involves the passage of the drug through the appropriate membranes. Good absorption normally requires that a drug molecule has the correct balance between its polar (hydrophilic) and nonpolar (hydrophobic) groups. Drugs that are too polar will tend to remain in the bloodstream, whilst those that are too nonpolar will tend to be absorbed into and remain within the lipid interior of the membranes. In both cases, depending on the target, the drug is likely to be ineffective. The degree of absorption can be related to such parameters as partition coefficient, solubility, pKa, excipients and particle size. For example, the ionization of the analgesic aspirin is suppressed in the stomach by the acids produced from the parietal cells in the stomach lining. As a result, it is absorbed into the bloodstream in significant quantities in its unionized and hence uncharged form through the stomach membrane.

**Distribution:** Distribution is the transport of the drug from its initial point of administration or absorption to its site of action. The main route is the circulatory system; however, some distribution does occur via the lymphatic system. In the former case, once the drug is absorbed, it is rapidly distributed throughout all the areas of the body reached

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by the blood. Drugs are transported dissolved in the aqueous medium of the blood either in a 'free form' or reversibly bound to the plasma proteins. Drug- Protein complex Drug molecules bound to plasma proteins have no pharmacological effect until they are released from those proteins. However, it is possible for one drug to displace another from a protein if it forms a more stable complex with that protein. This may result in unwanted side effects, which could cause complications when designing drug regimens involving more than one drug. Moreover, low plasma protein concentrations can affect the distribution of a drug in some diseases, such as rheumatoid arthritis. Major factors that influence distribution are the solubility and stability of drugs in the biological environment of the blood. Sparingly water soluble compounds may be deposited in the blood vessels, leading to restriction in blood flow. Drug stability is of particular importance in that serum proteins can act as enzymes that catalyze the breakdown of the drug. Decompositions such as these can result in a higher dose of the drug being needed in order to achieve the desired pharmacological effect, which increases the risk of toxic side effects in the patient. However, the active form of some drugs is produced by the decomposition of the administered drug. Drugs that function in this manner are known as prodrugs. For example, the bactericide prontosil, discovered in 1935, is not active but is metabolized in situ to the antibacterial sulphanilamide.

**Metabolism:** Drug metabolism is the biotransformation of the drug into other compounds referred to as metabolites. These biotransformations occur mainly in the liver but they can also occur in blood and other organs such as the brain, lungs and kidneys. Metabolism of a drug usually reduces the concentration of that drug in the systemic circulation, which normally leads to either a lowering or a complete suppression of the pharmacological action and toxic effects of that drug. Exceptions are prodrugs, such as prontosil, where metabolism produces the active form of the drug. Metabolism usually involves more than one route and results in the formation of a succession of metabolites. Each of these metabolites may have a different or similar activity to the parent drug. Consequently, the activities of all the metabolites of a drug must be considered in the development of a potential drug. Metabolites are frequently more water soluble than their parent drug and because of this are usually excreted in the urine.

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**Elimination:** Elimination is the collective term used for metabolic and excretion processes that irreversibly remove a drug from the body during its journey to its site of action. It reduces the medical effect of the drug by reducing its concentration at its site of action. A slow elimination process can result in a build-up of the drug concentration in the body. This may benefit the patient in that the dose required to maintain the therapeutic effect can be reduced, which in turn reduces the chances of unwanted side effects. Conversely, the rapid elimination of a drug means that the patient has to receive either increased doses, with a greater risk of toxic side effects, or more frequent doses, which carries more risk of under- or over-dosing. The main excretion route for drugs and their metabolites is through the kidney in solution in the urine. However, a significant number of drugs and their metabolic products are also excreted via the bowel in the faeces. Drugs are eliminated in the kidneys by either glomerular filtration or tubular secretion. However, some of the species lost by these processes are reabsorbed by a recycling process known as tubular reabsorption. Tubular reabsorption is a process normally employed in returning compounds such as water, amino acids, salts and glucose that are important to the well-being of the body from the urine to the circulatory system, but it will also return drug molecules. The reabsorption of acidic and basic drugs is reduced if the pH favours salt formation as charged molecules are not readily transported across membranes. Elimination occurs in the liver by biliary clearance, very large molecules being metabolized to smaller compounds before being excreted. However, a fraction of some of the excreted drugs is reabsorbed through the enterohepatic cycle. This reabsorption can be reduced by the use of suitable substances in the dosage form, for example, the ion exchange resin cholestyramine is used to reduce cholesterol levels by preventing its reabsorption.

**Bioavailability of a drug:** The bioavailability of a drug is defined as the fraction of the dose of a drug that is found in general circulation. It is influenced by such factors as ADME. Bioavailability is not constant but varies with the body's physiological condition.

**The pharmacodynamic phase:** Pharmacodynamics is concerned with the result of the interaction of drug and body at its site of action, that is, what the drug does to the body. It is now known that a drug is most effective when its shape and electron distribution, that

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is, its stereoelectronic structure, is complementary to the stereoelectronic structure of the active site or receptor. The role of the medicinal chemist is to design and synthesize a drug structure that has the maximum beneficial effects with a minimum of toxic side effects. This design has to take into account the stereoelectronic characteristics of the target active or receptor site and also such factors as the drug's stability in situ, its polarity and its relative solubilities in aqueous media and lipids. The stereochemistry of the drug is particularly important, as stereoisomers often have different biological effects, which range from inactive to highly toxic.

**Drug Discovery and Drug Development:** Discovering and bringing one new drug to the public typically costs a pharmaceutical or biotechnology company nearly \$900 million and takes an average of 10 to 12 years. In special circumstances, such as the search for effective drugs to treat AIDS, the Food and Drug Administration (FDA) has encouraged an abbreviated process for drug testing and approval called fast-tracking. The drug discovery and drug development process is designed to ensure that only those pharmaceutical products that are both safe and effective are brought to market. New drugs begin in the laboratory with chemists, scientists and pharmacologists who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects. Out of every 5,000 new compounds identified during the discovery process, only five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds is ultimately approved as a marketed drug for treatment. The following sequence of research activities begins the process that results in development of new medicines.

**Target identification and validation:** Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Scientists use a variety of techniques to identify and isolate a target and learn more about its functions and how these influence disease. Compounds are then identified that have various interactions with drug targets helpful in treatment of a specific disease. To select targets most likely to be useful in the development of new treatments for disease, researchers analyze and compare each drug target to others based on their association

with a specific disease and their ability to regulate biological and chemical compounds in the body. Tests are conducted to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells. Research scientists can then identify compounds that have an effect on the target selected.

**Lead identification:** A lead compound or substance is one that is believed to have potential to treat disease. Laboratory scientists can compare known substances with new compounds to determine their likelihood of success. Leads are sometimes developed as collections, or libraries, of individual molecules that possess properties needed in a new drug. Testing is then done on each of these molecules to confirm its effect on the drug target.

**Lead optimization:** Lead optimization compares the properties of various lead compounds and provides information to help pharmaceutical and biotechnology companies select the compound or compounds with the greatest potential to be developed into safe and effective medicines. Often during this same stage of development, lead prioritization studies are conducted in living organisms (*in vivo*) and in cells in the test tube (*in vitro*) to compare various lead compounds and how they are metabolized and affect the body.

**Preclinical studies:** In the preclinical stage of drug development, an investigational drug must be tested extensively in the laboratory to ensure it will be safe to administer to humans. Testing at this stage can take from one to five years and must provide information about the pharmaceutical composition of the drug, its safety, how the drug will be formulated and manufactured, and how it will be administered to the first human subjects. During the preclinical development of a drug, laboratory tests document the effect of the investigational drug in living organisms (*in vivo*) and in cells in the test tube (*in vitro*). The results of preclinical testing are used by experts in pharmaceutical methods to determine how to best formulate the drug for its intended clinical use. For example, a drug that is intended to act on the sinuses may be formulated as a time-release capsule or as a nasal spray. Regulatory agencies require testing that documents the characteristics chemical composition, purity, quality and potency of the drug's active ingredient and of

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the formulated drug. Pharmacological testing determines effects of the candidate drug on the body. Toxicology studies are conducted to identify potential risks to humans.

**Clinical studies:** Testing of an investigational new drug begins with submission of information about the drug and application for permission to begin administration to healthy volunteers or patients. INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed.

**Phase I clinical studies:** Phase I studies are designed to verify safety and tolerability of the candidate drug in humans and typically take six to nine months. These are the first studies conducted in humans. A small number of subjects, usually from 20 to 100 healthy volunteers, take the investigational drug for short periods of time. Testing includes observation and careful documentation of how the drug acts in the body -- how it is absorbed, distributed, metabolized and excreted.

**Phase II clinical studies:** Phase II studies are designed to determine effectiveness and further study the safety of the candidate drug in humans. Depending upon the type of investigational drug and the condition it treats, this phase of development generally takes from six months up to three years. Testing is conducted with up to several hundred patients suffering from the condition the investigational drug is designed to treat. This testing determines safety and effectiveness of the drug in treating the condition and establishes the minimum and maximum effective dose. Most Phase II clinical trials are randomized, or randomly divided into groups, one of which receives the investigational drug, one of which gets a placebo containing no medication and sometimes a third that receives a current standard treatment to which the new investigational drug will be compared. In addition, most Phase II studies are double-blinded, meaning that neither patients nor researchers evaluating the compound know who is receiving the investigational drug or placebo.

**Phase III clinical studies:** Phase III studies provide expanded testing of effectiveness and safety of an investigational drug, usually in randomized and blinded clinical trials. Depending upon the type of drug candidate and the condition it treats, this phase usually

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requires one to four years of testing. In Phase III, safety and efficacy testing is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats

**New Drug Application (NDA)/Marketing Authorization Application (MAA):** NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such applications document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities in other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed, recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes between six months and two years

**Development costs:** Usually, biotech and meditech companies underestimate the costs in connection with non-clinical and clinical development. In 2001, the total cost of developing a new drug was estimated at 820M US\$. 58% of all costs are in clinical development, having completed the preclinical studies.

### **Synthesis of drugs**

The systematic research in pharmaceutical laboratories has led to the introduction of more and more drugs in modern times. The synthetic work is carried out along the following lines:

- (a) Compounds are synthesized whose structures are more or less similar to naturally occurring substances. This sometimes produces drugs whose price is much less than the naturally occurring one.
- (b) Attempts are made to prepare compounds with simplified structures without losing efficiency.
- (c) Attempts are made to synthesize new drugs, which have the properties of certain natural products, but have no relation to them in structure.
- (d) Attempts are made to synthesize new drugs which are unrelated in structure and properties to natural products.

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## Mechanisms of drug action

1. Physical Action: physical property of the drug is responsible for its action, e.g.

Mass of the drug	- bull laxative
Adsorptive property	- charcoal
Osmotic activity	- menthol
Radioactivity	- radioisotopes
Radio opacity	- contrast media

2. **Chemical Action:** The drug reacts extracellularly according to simple chemical equations, e.g.

(a) Antacids neutralize gastric HCL

(b) Oxidizing agents ( $\text{KMnO}_4$ ,  $\text{I}_2$ ) are germicidal and inactivate ingested alkaloids.

3. **Through Enzymes:**

(c) Stimulation e.g. Adrenalin stimulates adenylyl cyclase

(d) Inhibition e.g. Physostigmine and neostigmine compete with acetylcholine for cholinesterase.

4. **Through Receptors:** Macromolecule or the component of a cell or organism that interacts with drug and initiates the chain of biochemical events leading to the drug's observed effects are called receptors. *Agonist* activates a receptor to produce an effect e.g. adrenalin, histamine, morphine. *Partial agonist* activates a receptor to produce submaxial effector but antagonises the action of a full agonist e.g. Nalorphine. *Inverse agonist* activates a receptor to produce an effect in the opposite direction to that of the well-recognized agonist e.g. DMCM. *Antagonist binds* to the receptor, does not activate it and it does not have any effect of its own. Main effects prevent agonist from binding and activating the receptor.

### Chemotherapy:

The term chemotherapy was introduced by Paul Ehrlich to indicate the treatment of microbial disease by the administration of a drug which had a lethal or inhibitory effect on the microbe responsible, and was described as a "magic bullet" which when introduced into the body, would destroy only the bacteria at which it was aimed. He also pronounced many of the current concepts of chemotherapy.

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During the 20<sup>th</sup> century, a number of compounds have been isolated, synthesized and subjected to detailed investigation for their structure and pharmacological action. Some of the compounds have been found to possess definite physiological activity and later on it was observed that physiological activity was associated with a particular structural unit and hence structural similarity to other compounds. The part of the drug, which is responsible for the actual physiological activity, is known as pharmacophore group. This has been somewhat modified by the common and simple unit processes to give more active compounds with low toxicity.

The chances of devising clinically useful medicinal chemicals are indeed very slim now, since several restrictive conditions have been imposed. Even on the best laboratory findings, high potency should be maintained in humans. There should be minimum side effect and acute toxicity, and there should be no chronic toxicity.

### **Ideal characteristics of chemotherapeutics agents**

For chemical compounds to be ideal chemotherapeutic agents used for treating microbial infections, it should have the following qualities:

1. **Selective toxicity:** The drug should demonstrate selective toxicity. This means that, at the optimum concentration, the drug should be toxic for microorganism, but not for the host.
2. **Antimicrobial Spectrum:** The drug should be able to destroy or inhibit many kinds of pathogenic microorganisms. The greater the number of different microbial pathogenic species affected the better. For instance, the most widely used antibiotics are broad-spectrum antibiotics. A narrow-spectrum drug is active against one or only a few species, either Gram-positive or Gram-negative groups. (E.g. Penicillin).
3. **No side effects:** The drug should not produce undesirable side effect, such as allergic reactions, nerve damage, irritation of the kidney or damage to blood cells etc.
4. **No killing effect on normal flora:** The drug should not eliminate the normal microbial flora that inhabits the intestinal tract or other areas of the body. The normal flora also plays an important role in preventing pathogens from growing.

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5. No inactivation: If the drug is given orally, stomach acids should not inactivate it and it should be absorbed into the body from the intestinal tract. If it is administered by injection, it should not be inactivated by binding to blood proteins.
  6. Solubility in body fluids: The drug must have solubility in body fluids because it must be in a solution to be active and can rapidly penetrate body tissues.
  7. Sufficient concentration of the drug in target tissues: The drug must be able to reach sufficiently high concentration in the tissues or blood of the patient to kill or inhibit the pathogen.
  8. Low break-down rate of drug: The rates at which the drug is broken down and excreted from the body must be low enough so that the drug remains in the infected body tissues long enough to exert its effects.
  9. No development of drug-resistance: The drug should inhibit microorganisms in such a way as to prevent the development of drug-resistant forms of pathogens.
  10. Stable viability: The drug should have long viable activity even if stored at room temperature.
  11. Easily availability at affordable cost/price: Clinicians must make comparison amongst the available chemotherapeutic agents to select the one best suited for the treatment of a specific infection. However, developers of a drug attempt to obtain the best possible combination of properties for effective human use.

### **Mechanism of action of chemotherapeutic agents**

It is important to know the exact mechanism of action of specific chemotherapeutic agents because such knowledge helps to explain the nature and degree of selective toxicity of individual drugs and sometimes aids in the design of new chemotherapeutic agents.

The cell is structural and functional unit for unicellular microorganisms. Various types of metabolic activities proceed in a young active multiplying cell. The antibiotics as a main chemotherapeutic agent can attack the structural organization of the microbial cell or prevent the biosynthesis of cell macromolecules. Thus antibiotics and other chemotherapeutic agents attack on cell wall synthesis or cell membrane structure and cause cell lysis. Certain broad-spectrum antibiotics prevent the synthesis of protein and

nucleic acids in the target microbial cell, which leads to death. Some synthetic chemotherapeutic agents act by interfering with enzyme activity of microbial cell that prevents biochemical reactions that leads to death of cell or cessation of growth.

Modes of action of various chemotherapeutic agents can be grouped as follows:

1. Inhibition of cell-wall synthesis.
2. Damage to the cytoplasmic membrane.
3. Inhibition of protein synthesis.
4. Inhibition of nucleic acid synthesis.
5. Inhibition of enzymatic activity.

A small number of drugs are introduced into clinical practice every year. Virtually every kind of drug needs improvement and should be replaced by more specific agents with fewer side effects. One cannot abandon the hope of perfecting the action of existing compounds by structural modifications.

In the present thesis, efforts have been made to devise some new organic compounds containing moieties, which have shown encouraging biological activities.

The different types of compounds have been prepared or synthesized and tested for biological activity using *in vitro* method. The spectroscopic analysis, elemental analysis and physical properties of the compounds have been studied.