An Introduction to Drugs and Their Action

Introduction:

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 an outline knowledge of these fields.

What are drugs and why do we need new ones?

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 β-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 resistance to that drug by both the patients, microorganisms 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. For example, the effectiveness of barbiturates often decreases with repeated use because repeated dosing causes the body to increase its production in the liver of mixed function oxidases that metabolize the drug, thereby reducing the drug's effectiveness. An increase in the rate of production of an enzyme that metabolizes the drug is a relatively common reason for drug resistance. Another general reason for drug resistance is the down-regulation of receptors. Down-regulation 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. For example, 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 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.

Drug discovery and design, a historical outline:

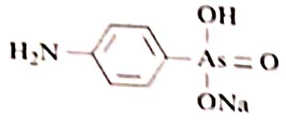
Since ancient times, the peoples of the world have used a wide range of natural products for medicinal purposes. These products, obtained from animal, vegetable and mineral sources, were sometimes very effective. However, many of the products were very toxic. Information about these ancient remedies was not readily available to users until the invention of the printing press in the 15th century. This invention led to the widespread publication and circulation of herbals and pharmacopoeias. This resulted in a rapid increase in the use, and misuse, of herbal and other remedies. However, improved communications between practitioners in the 18th and 19th centuries resulted in the progressive removal of preparations that were either ineffective or too toxic from herbals and pharmacopoeias. It also led to a more logical development of new drugs. Initially this development was centred 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 centred 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 10000 compounds synthesized one is suitable for medical use.

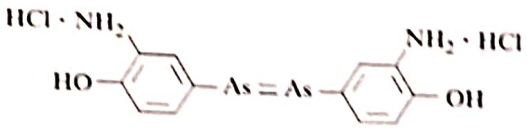
The first rational development of synthetic drugs was carried out by Paul Ehrlich and Sacachiro Hata, who produced the antiprotozoal arsphemamine in 1910 by combining synthesis with reliable biological screening and evaluation procedures. Ehrlich, at the begining of the 20th century, had recognized that both the beneficial and toxic properties of a drug were important to its evaluation. He realized that the more effective drugs showed a greater selectivity for the target microorganism than its 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, which he defined as

$$\text{chemotherapeutic index} = \frac{\text{minimum curative dose}}{\text{maximum tolerated dose}}$$

Determination and cataloging of the chemotherapeutic index of the 600 compounds Ehrlich and Hatasynthesized enabled them in 1909 to discover arsphemamine (Salvarsan). This drug was very toxic but safer than the then currently used Atoxyl. It was used up to the mid-1940s, when it was replaced by penicillin.



Atoxyl



Arsphenamine (Salvarsan)

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 (see section 4.4). 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 and ranitidine. Both SARs and QSARs are important parts of the foundations of medicinal chemistry.

An alternative approach to drug design was initiated by the work of John Langley. In 1905 he proposed that so called receptive substances in the body could accept either a stimulating compound, which would cause a biological response, or a non-stimulating compound, which would prevent a biological response. It is now universally accepted that the binding of a chemical agent, referred to as a ligand (see also section 7.4), to a so called receptor sets in motion a series of biochemical events that result in a biological or pharmacological effect. Furthermore, a drug is most effective when its structure or a significant part of its structure, both as regards molecular shape and electron distribution (stereoelectronic structure), is complementary with the stereoelectronic structure of the receptor responsible for the desired biological action. The section of the structure of a ligand that binds to a receptor is known as its **pharmacophore**. Furthermore, it is now believed that side effects can arise when the drug binds to either the receptor responsible for the desired biological response or to different receptors.

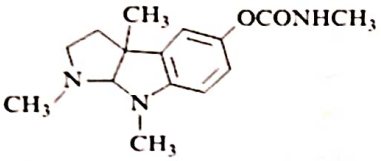
The mid- to late 20th century has seen an explosion of our understanding of the chemistry of disease states, biological structures and processes. This increase in knowledge has given medicinal chemists a clearer picture of how drugs are distributed through the body and transported across membranes and their mode of operation and metabolism. It has enabled medicinal chemists to place groups that influence absorption, stability in a bio-system, distribution, metabolism and excretion in the molecular structure of a drug. For example, the introduction of a sulphonic acid group

into the structure of a drug will increase its water solubility. This may improve its absorption and/or its rate of excretion from the body. However, because of the complex nature of biological systems, there is always a degree of uncertainty in predicting the effect of structural changes on the activity of a drug. As a result, it is always necessary to carry out extensive testing to determine the consequences of modifying a structure. Furthermore, changing a group or introducing a group may change the nature of the activity of the compound. For example, the change of the ester group in procaine to an amide (procainamide) changes the activity from a local anaesthetic to anti-rhythmic.

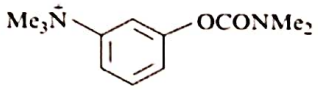
Procaine

Procainamide

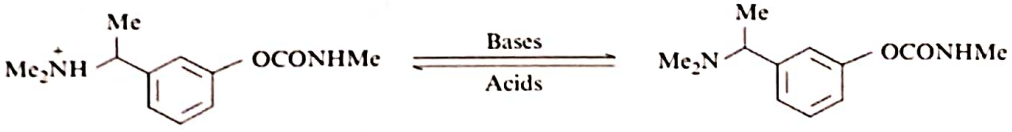
The introduction or removal of charged groups or groups that can form ions into or out of a structure may also have a marked affect on drug action. This is because drugs normally have to cross nonpolar lipid membrane barriers in order to reach their site of action. Consequently, as the polar nature of the drug increases, it usually becomes more difficult for that drug to cross these barriers. For example, quaternary ammonium salts, which are permanently charged, can be used as an alternative to an amine in a structure in order to restrict the passage of a drug across a membrane. The structure of the anticholinesterase neostigmine, developed from physostigmine, contains a quaternary ammonium group, which stops the molecule from crossing the blood–brain barrier (Appendix 11). This prevents unwanted CNS activity. However, its analogue miotine can form the free base. As a result, it is able to cross lipid membranes, which may cause unwanted CNS side effects.



Physostigmine



Neostigmine



Miotine

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 modelling and combinatorial chemistry introduced in the 1970s and 1990s respectively are likely to reduce the number of intuitive discoveries.

Computer modelling 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.

Sources of drugs and lead compounds:

The discovery of a new drug is part luck and part structured investigation. It originally started with drugs and lead compounds derived from natural sources, such as animals, plants, trees and microorganisms. Marine sources were not utilized to any extent until the mid-20th century. Today, natural sources are still important, but the majority of lead compounds are synthesized in the laboratory. The nature of these synthetic compounds is initially decided from a consideration of the biochemistry of the pathogenic condition. Today, many discoveries start with biological testing (bioassays or screening programme) by pharmacologists of the potential sources in order to determine the nature of their pharmacological activity as well as their potencies. These screening programmes may be random or focused. In random screening programs all the substances and compounds available are tested regardless of their structures. The random screening of soil samples, for example, led to the discovery of the streptomycin and tetracycline antibiotics as well as many other lead compounds. Random screening is still employed, but the use of more focused screening procedures where specific structural types are tested is now more common. Once a screening programme has identified substances of pharmacological activity of interest, the compound responsible for this activity is isolated and used as a lead compound for the production of related analogues. These compounds are subjected to further screening tests. Analogues are made of the most promising of these compounds and they in turn are subjected to the screening procedure. This sequence of selective screening and synthesis of analogues may be repeated many times before a potentially useful drug is found. Often the sequence has to be abandoned as being either unproductive or too expensive.

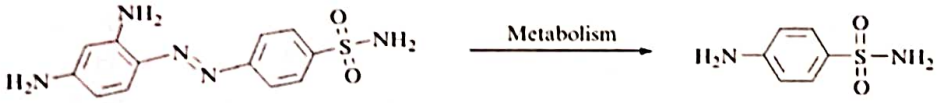
Drug synthesis:

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 labour 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.

Classification of drugs:

Drugs are classified in a number of different ways depending on where and how the drugs are being used. The methods of most interest to medicinal chemists are chemical structure and pharmacological action, which includes the site of action and target system. Unfortunately, classifying drugs according to their chemical structural type has the disadvantage that members of the same structural group often exhibit very different types of pharmacological activity. Steroids, for example, may act as hormones (testosterone), diuretics (spironolactone) actibacterial agents (fusidic acid) amongst other forms of activity. The term **prodrug** is often used for drugs whose active form is produced by enzyme or chemical action at or near to its site of action. However, it is emphasized that other classifications, such as the nature of the illness and the body system on which the drug acts (physiological classification), are also used in medicinal chemistry as well as other fields depending on the purpose of the information.

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 oftoxic 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 bacteriacide prontosil, discovered in 1935, is not active but is metabolized in situ to the antibacterial sulphanilamide.



Prontosil Sulphanilamide

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.

Drugs are usually administered topically or systemically. The routes are classified as being either parenteral or enteral (Figure 2.3). 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 underdosing. 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 the entire 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 favourable 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 limit between which the drug is an effective therapeutic agent is known as its therapeutic window. 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 low a dose will result in the plateau below the therapeutic window and ineffective treatment.

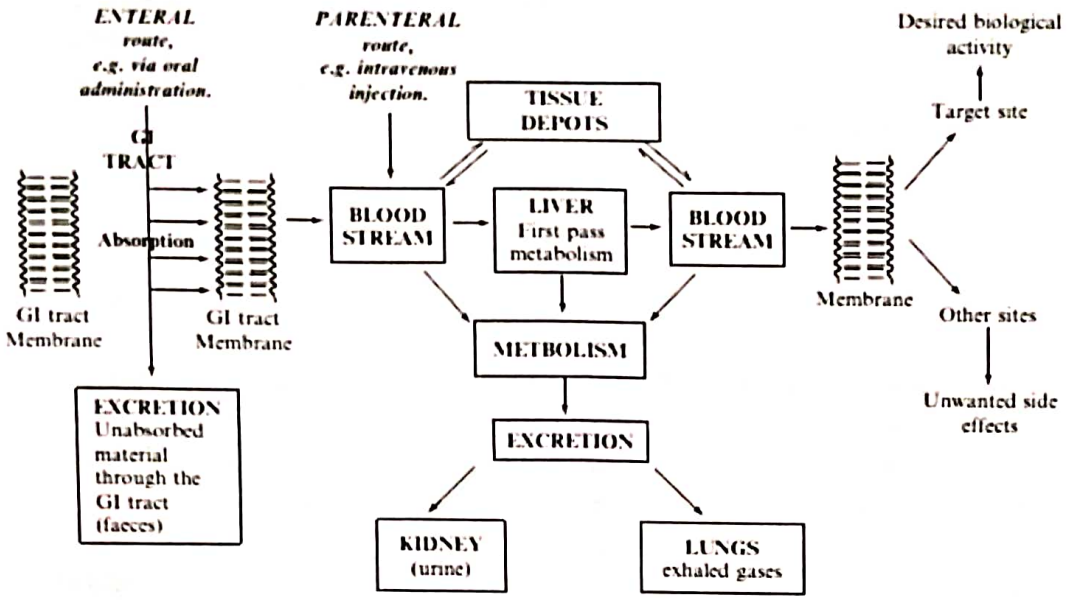


Figure 2.3 The main routes of drug administration and distribution in the body. The distribution of a drug is also modified by metabolism, which can occur at any point in the system

Introduction to 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 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.

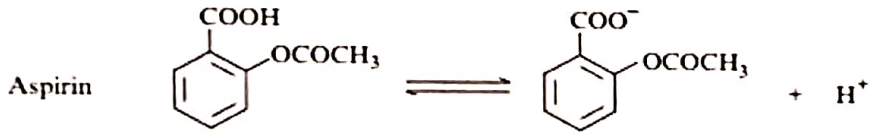
The pharmacokinetic phase:

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.

A. 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.



B. Distribution:

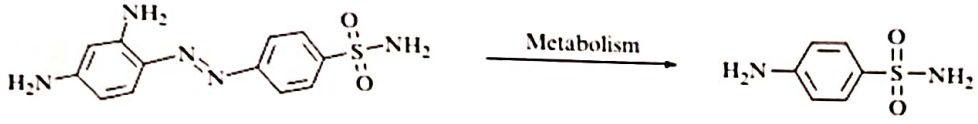
Distribution is the transport of the drug from its initial point of administration or absorption to its site of action. The main route is the circulatory system; however, some distribution does occur via the lymphatic system. In the former case, once the drug is absorbed, it is rapidly distributed throughout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

$$\text{Drug} \rightleftharpoons \text{Drug} - \text{Protein complex}$$

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 catalyse 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 bacteriacide prontosil, discovered in 1935, is not active but is metabolized in situ to the antibacterial sulphanilamide.



Prontosil

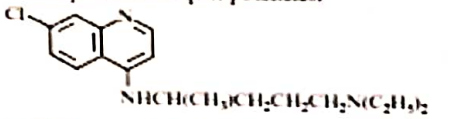
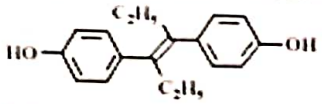
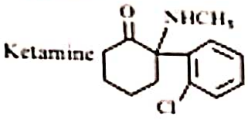
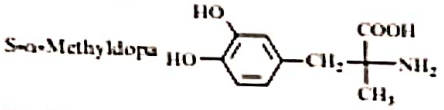
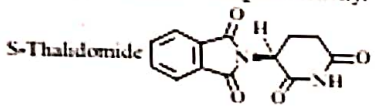
Sulphanilamide

C. Metabolism

Drug metabolism is the biotransformation of the drug into other compounds referred to as metabolites. These bio-transformations 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 pro-drugs, 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 metabolities of a drug must be considered in the development of a potential drug. Metabolities are frequently more water soluble than their parent drug and because of this are usually excreted in the urine.

D. 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 maintaining the therapeutic effect can be reduced, which in turn reduces the chances of unwanted side effects.

First stereoisomer	Second stereoisomer	Example
Active	Activity of same type and potency	The R and S isomers of the antimalarial chloroquine have equal potencies. 
Active	Activity the same type but weaker	The E isomer of diethylstilbesterol, an estrogen is only 7% as active as the Z isomer 
Active	Activity of a different type	S-Ketamine is an anaesthetic R-Ketamine has little anaesthetic action but is a psychotic 
Active	No activity	S-α-Methyldopa is a hypertensive drug but the R isomer is inactive. 
Active	Active but different side effects	Thalidomide: the S isomer is a sedative and has teratogenic side effects. The R isomer is also a sedative but has no teratogenic activity. 

(1) Explain the meaning of the terms (a) lead compound, (b) excipient, (c) parenteral administration, (d) pharmacophore and (e) prodrug.

(2) State the general factors that need to be considered when designing a drug.

(3) Distinguish between parenteral and enteral routes of administration.

(4) Define the terms pharmacokinetic phase and pharmacodynamic phase in the context of drug action. List the main general factors that affect these phases.

(5) The drug amphetamine ($PhCH_2CH(NH_2)CH_3$ binds to the protein albumin in the blood stream. Predict how a reduction in pH would be expected to influence this binding. Albumin is negatively charged at pH 7.4 and electrically neutral at pH 5.0.

(6) Discuss the general effects that stereoisomers could have on the activity of a drug.

An Introduction to Drug Discovery

Drug discovery is part luck and part structured investigation. At the begining of the 19th century it was largely carried out by individuals but it now requires teamwork, the members of the team being specialists in various fields, such as medicine, biochemistry, chemistry, computerized molecular modelling, pharmaceutics, pharmacology, microbiology, toxicology, physiology and pathology. This section outlines a general approach to drug discovery by design. It also introduces the stereochemical and water solubility factors that should be taken into account when selecting a structure for a lead compound. The approach to drug design depends on the objectives of the design team. These objectives will normally require a detailed assessment of the pathology of the disease and in some cases basic biochemical research will be necessary before initiating a drug design investigation. Once the point of intervention has been selected, the team has to propose a structure for a lead compound that could possibly bring about the required change. Molecular modelling techniques are sometimes used to help the team reach a decision.

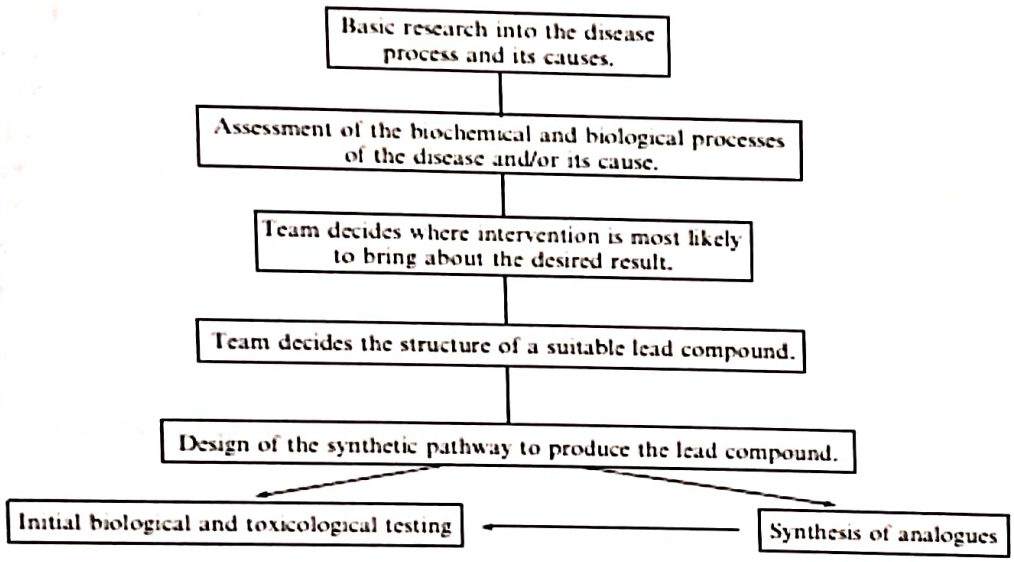


Figure 3.1 The general steps in the design of a new drug

A more random approach for discovering a lead is the combinatorial chemistry approach. This uses a simultaneous multiple synthesis technique to produce large numbers of potential leads. These potential leads are subjected to rapid high throughput biological screening to identify the most active lead compounds. Once identified, these lead compounds are subject to further development.

Once the structure of the proposed lead has been agreed, it becomes the responsibility of the medicinal chemist to devise a synthetic route and prepare a sample of this compound for testing. Once synthesized, the compound undergoes initial pharmacological and toxicological testing. The results of these tests enable the team to

decide whether it is profitable to continue development by preparing analogues (Figure 3.1), since it is unlikely that the lead compound itself will be suitable for use as a drug. The usual scenario is to prepare a series of analogues, measure their activity and correlate the results to determine the structure with optimum activity. This analysis may make use of SARs, QSARs, computational chemistry and combinatorial chemistry to help discover the nature of this structure.

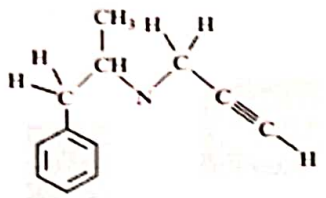
The selection of a lead compound and the development of a synthetic pathway for its preparation is not the only consideration at the start of an investigation. Researchers must also devise suitable in vivo and in vitro tests to assess the activity and toxicity of the compounds produced. There is no point in carrying out an expensive synthetic procedure if at the end of the day it is impossible to test the product.

Stereochemistry and drug design:

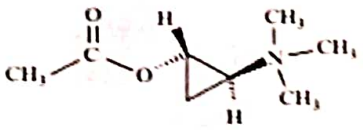
It is now well established that the shape of a molecule is normally one of the most important factors affecting drug activity. Consequently, the overall shape of the structure of a molecule is an important consideration when designing an analogue. Some structural features impose a considerable degree of rigidity on a structure, whilst others make the structure more flexible. Other structures give rise to stereoisomers, which can exhibit different potencies, types of activity and unwanted side effects. This means that it is necessary to pharmacologically evaluate individual stereoisomers and racemates. Consequently, one must take into account all these stereochemical features when proposing structures for potential leads and analogues. However, the extent to which one can exploit these structural features will depend on our knowledge of the structure and biochemistry of the target biological system.

A. Structurally rigid groups:

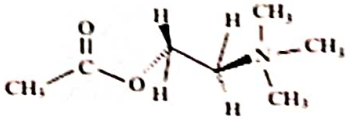
Groups that are structurally rigid are unsaturated groups of all types and saturated ring systems (Figure below). The former includes esters and amides as well as aliphatic conjugated systems, aromatic and heteroaromatic ring systems. The binding of these rigid structures to a target site can give information about the shape of that site as well as the nature of the interaction between the site and the ligand. Furthermore, the fact that the structure is rigid means it may be replaced by alternative rigid structures of a similar size and shape to form analogues, which may have different binding characteristics and possibly as a result a different activity or potency.



Selegiline (MAO inhibitor)



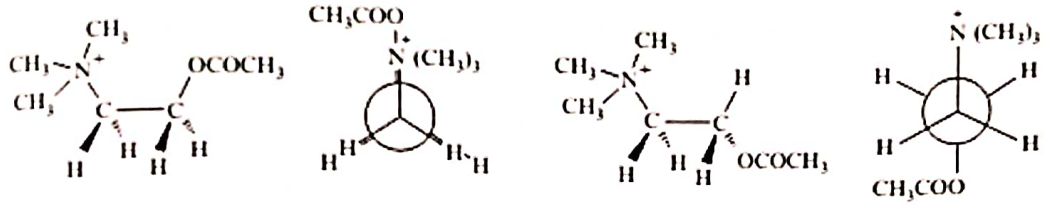
1-Ethoxycarbonyl-2-trimethylaminocyclopropane (Acetylcholine mimic)



Acetylcholine

B. Conformation

Early work in the 1950s and early 1960s by Schueler and Archer suggested that the flexibility of the structures of both ligands and receptors accounted for the same ligand being able to bind to different sub-types of a receptor. Archer also concluded that a ligand appeared to assume different conformations when it bound to the different sub-types of a receptor. For example, acetylcholine exhibits both muscarinic and nicotinic activity. Archer et al. suggested that the muscarinic activity was due to the anti or staggered conformation, whilst the nicotinic activity was due to the syn or eclipsed form as shown below.



Syn-acetylcholine

Anti-acetylcholine

The main methods of introducing conformational restrictions are by using either bulky substituents, unsaturated structures or ring systems. Ring systems are usually the most popular choice (Figure 3.4).

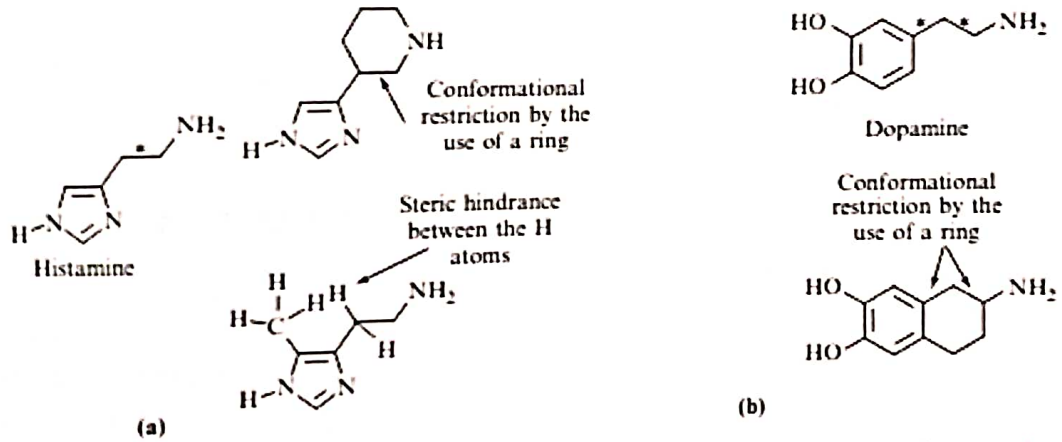


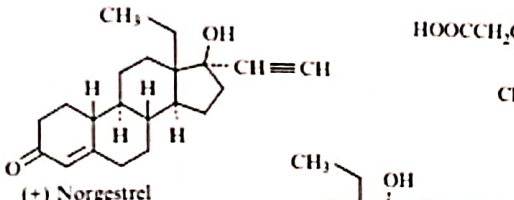
Figure 3.4 Examples of the use of conformational restrictions to produce analogues of (a) histamine and (b) dopamine. Bonds marked * can exhibit free rotation and form numerous conformers

In all cases, the structures used must be chosen with care, because there will always be the possibility that steric hindrance will prevent the binding of the analogue to the target. However, if sufficient information is available, molecular modelling can be of considerable assistance in the choice of structures.

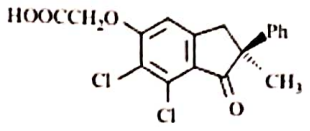
C. Configuration

Configurational centres impose a rigid shape on sections of the molecule in which they occur. However, their presence gives rise to geometric and optical isomerism. Since these stereoisomers have different shapes, biologically active stereoisomers will often exhibit differences in their potencies and/or activities (Table given before). These pharmacological variations are particularly likely when a chiral centre is located in a critical position in the structure of the molecule. The consequence of these differences is that it is now necessary to make and test separately all the individual stereoisomers of a drug.

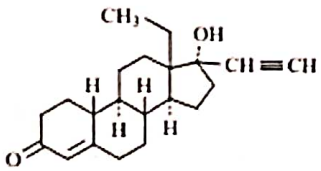
As well as an effect on the activity, different stereoisomers will also exhibit differences in other physiochemical properties, such as absorption, metabolism and elimination. For example, (-)norgestrel is absorbed at twice the rate of (+)norgestrel through buccal and vaginal membranes. The plasma half-life of S-indacrinone is 2–5 hours whilst the value for the R isomer is 10–12 hours.



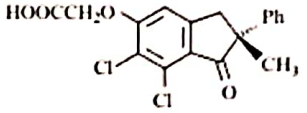
(+) Norgestrel



S-Indacrinone



(–) Norgestrel



R-Indacrinone

Solubility and drug design:

The relative solubilities of drugs in the aqueous media and lipid tissues of the body play a major part in their absorption and transport to their sites of action. To pass through a membrane a drug must usually exhibit a reasonable degree of both water and lipid solubility. An appropriate degree of water solubility will often improve drug distribution within the circulatory system as well as drug action.

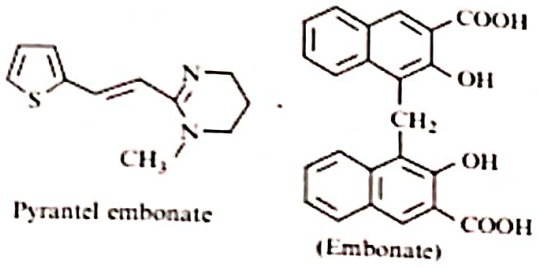
The importance of water solubility:

A drug's solubility and behaviour in water is particularly important since the cells in our bodies normally contain about 65 % water. In living matter, water acts as an inert solvent, a dispersing medium for colloidal solutions and as a nucleophilic reagent in numerous biological reactions. Furthermore, hydrogen bonding and hydrophobic interactions in water influence the conformations of biological macromolecules, which in turn affect their biological behaviour. It also makes drug toxicity testing and bioavailability evaluation as well as clinical application easier. This means that there is

usually a need to design a reasonable degree of water solubility into the structure of a new drug early in the development of that drug.

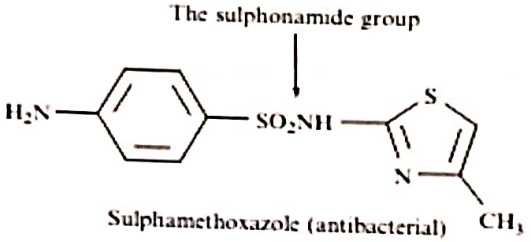
Drugs administered orally as a solid or in suspension have to dissolve in the aqueous gastric fluid (dissolution) before they can be absorbed and transported via the systemic circulation to their site of action. The rate and extent of dissolution of a drug is a major factor in controlling the absorption of that drug. This is because the concentration of the drug in the fluid in the gut lumen is one of the main factors governing the transfer of the drug through the membranes of the gastrointestinal tract (GI tract). The rate of dissolution depends on the surface area of the solid, which is dependent on both the physical nature of the dosage form of the drug and the chemical structure of the drug. However, the extent of dissolution depends only on the drug's solubility, which depends on the chemical structure of the drug. The dosage form is a formulation problem that is normally beyond the remit of the medicinal chemist, but the design of the structure of lead compounds with regard to solubility is within the realm of the medicinal chemist.

Once the drug has entered the circulatory system, either by absorption or by direct administration, its water solubility will influence its ease of transport to the body compartments available to that drug. Drugs that are sparingly soluble in water may be deposited en route to their site of action, which can clog up blood vessels and damage organs. For example, many sulphonamides, such as sulphamethoxazole, tend to crystallize in the kidney, which may result in serious liver and kidney damage. Water solubility also affects the ease of drug transport through membranes.



Pyrantel embonate

(Embonate)



Sulphamethoxazole (antibacterial)

Although a reasonable degree of water solubility is normally regarded as a essential requirement for a potential drug, it is possible to utilize poor water solubility in drug action and therapy. For example, pyrantel embonate, which is used to treat pinworm and hookworm infestations of the GI tract, is insoluble in water. This poor water solubility coupled with the polar nature of the salt means that the drug is poorly absorbed from the gut and so the greater part of the dose is retained in the GI tract, the drug's site of action. The low water solubility of a drug can also be used to produce drug depots, chewable dosage forms and mask bitter tasting drugs, because taste depends on the substance forming an aqueous solution.

The importance of water solubility in drug action means that one of the medicinal chemist's development targets for a new drug is to develop analogues that have the required degree of water solubility.

Solubility and drug structure:

The solubility of a compound depends on its degree of solvation in the solvent. Structural features in a solute molecule that improve the degree of solvation will result in a more soluble solute. Consequently, the water solubility of an organic compound depends on the number and nature of the polar groups in its structure as well as the size of its carbon–hydrogen skeleton. In general, the higher the ratio of polar groups to the total number of carbon atoms in the structure the more water soluble the compound. Furthermore, aromatic compounds tend to be less soluble than the corresponding nonaromatic compounds.

The water solubility of a lead compound can be improved by three general methods: salt formation, by incorporating water solubilising groups into its structure, especially those that can hydrogen bond with water, and the use of special dosage forms. In salt formation, the activity of the drug is normally unchanged although its potency may be different. However, when new structural groups are incorporated into the structure of a drug the activity of the drug could be changed. Consequently, it will be necessary to carry out a full trial programme on the new analogue.

The structural factors controlling a compound's lipid solubility are the opposite of those responsible for a compound's water solubility. Consequently, lipid solubility may be improved by replacing polar groups by nonpolar structures or groups that are significantly less polar in nature.

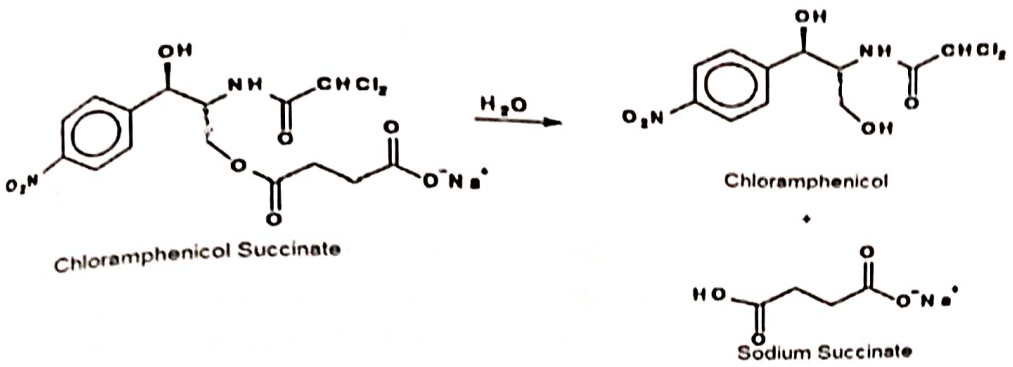
The prodrug approach can be used to **increase** or **decrease** the solubility of a drug, depending on its ultimate use. For example, chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility, respectively.

On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration. Administration of a drug parenterally may cause pain at the site of injection, especially if the drug begins to precipitate out of solution and damage the surrounding tissue.

This situation can be remedied by preparing a drug with increased solubility in the administered solvent. Since chloramphenicol has low water solubility, the succinate ester was prepared to increase the water solubility of the agent and facilitate parenteral administration.

The succinate ester itself is inactive as an antibacterial agent, so it must be converted to chloramphenicol for this agent to be effective. This occurs in the plasma to

give the active drug and succinate. The ester hydrolysis reaction can be catalysed by esterases present in large amounts in the plasma.



Salt formation:

Salt formation usually improves the water solubility of acidic and basic drugs because the salts of these drugs dissociate in water to produce hydrated ions:

Salt = Cation + Anion

Hydrogen and hydroxide ions can disturb this equilibrium if they combine with the appropriate cation or anion to form less soluble acids or bases. Consequently, the pH of the biological fluid may affect the solubility of a drug and, as a result, its activity. In general, increasing the hydrophilic nature of the salt should increase its water solubility. However, there are numerous exceptions to this generalization, and each salt should be treated on its merits.

Acidic drugs are usually converted to their metallic or amino salts, whilst the salts of organic acids are normally used for basic drugs.

The degree of water solubility of a salt will depends on the structure of the acid or base used to form the salt. For example, acids and bases whose structures contain water solubilizing groups will form salts with higher water solubility than compounds that do not contain these groups. However, if a drug is too water soluble, it will not dissolve in lipids and so will not usually be readily transported through lipid membranes. This normally results in either its activity being reduced, or the time for its onset of action being increased. It should also be noted that the presence of a high concentration of chloride ions in the stomach will reduce the solubility of sparingly soluble chloride salts because of the common ion effect.

The incorporation of water solubilizing groups in a structure:

The discussion of the introduction of water solubilizing groups into the structure of a lead compound can be conveniently broken down into four general areas:

1. the type of group introduced;

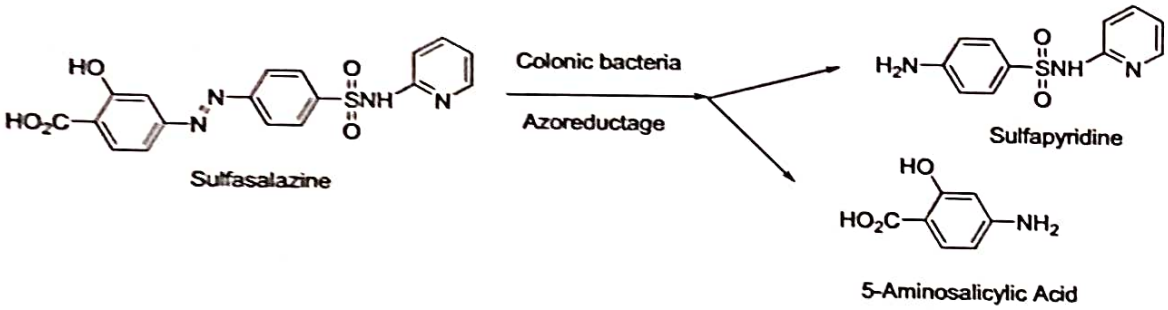
2. whether the introduction is reversible or irreversible;

3. the position of incorporation and

4. the chemical route of introduction.

Prodrug:

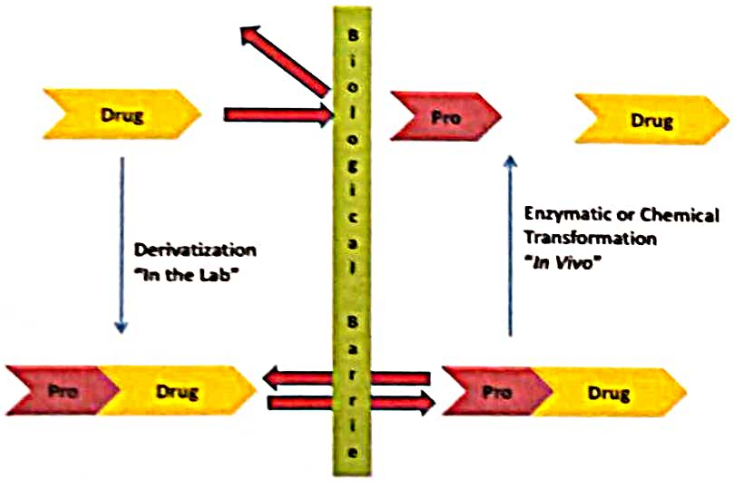
Prodrugs are pharmacologically inactive chemical compounds that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/or to decrease associated toxicity. Prodrugs are metabolized to an active metabolite, which is responsible for the drug's action. Thus a prodrug is a masked latent drug. This masking of the drug can modify its solubility and alter its distribution allowing it to reach its site of action more effectively. It may enable the compound to cross barriers such as blood:brain barrier and may prevent the deactivation and excretion of a drug. It can also produce slow-release form of the drug. One of the simplest examples of produrg is sulfasalazine (Used to treat ulcerative colitis), which is cleaved by amidases in the colon to release sulfapyridine and 5-aminosalicylic acid. It enabled a useful concentration of sulfapyridine to be established at the site of action.



Sulfasalazine

Sulfapyridine

5-Aminosalicylic Acid



Schematic Representation of Prodrug Concept

The Applications of Prodrugs:

The various applications of prodrug approach are:

1. Improved physicochemical properties (e.g., better solubility in the intended formulation).
2. Enhanced delivery characteristics and/or therapeutic value of the drug.
3. To improve drug penetration through biological membranes.
4. To increase site specificity of the drug.
5. To improve the drug's stability and solubility.
6. To increase duration of pharmacological activity.
7. To decrease the drug's toxicity and adverse effects.
8. To improve patient acceptance.

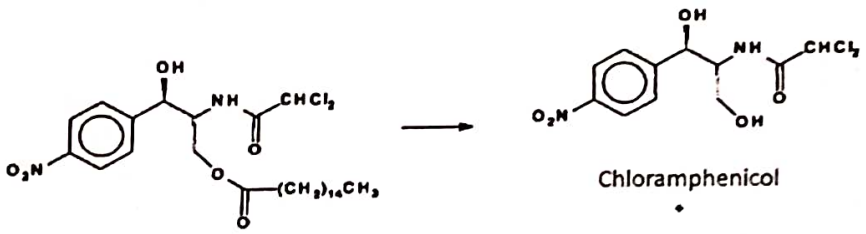
Ideal Requirements of Prodrugs

An ideal prodrug must meet the following requirements:

1. The prodrug is inactive or less active than the parent compound.
2. The linkage between the drug and the carrier must be cleaved *in vivo.*
3. The carrier molecule released *in vivo* must be non-toxic.
4. The metabolic fragments of carrier molecule, apart from the drug should be non toxic.

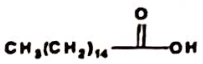
Chloramphenicol produces a bitter taste when given as the parent drug. The hydrophobic palmitate ester does not dissolve to any appreciable extent in the mouth so there is little chance for interaction with taste receptors.

The ester moiety is subsequently hydrolyzed in the GI tract, and the agent is absorbed as chloramphenicol.



Chloramphenicol Palmitate

Chloramphenicol



Palmitic Acid

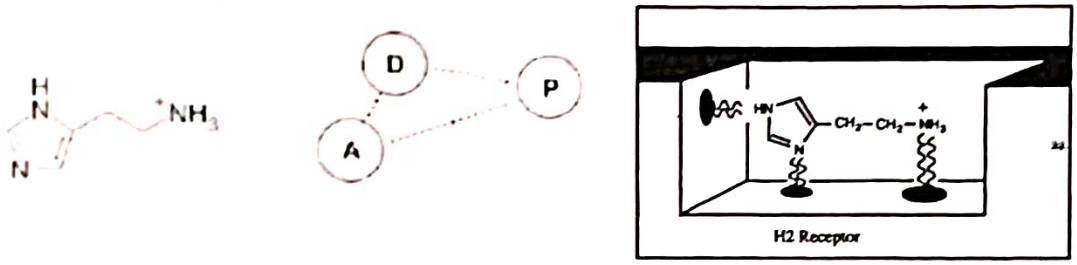
Pharmacophore:

A Pharmacophore may be defined as the essential geometric arrangement of atoms or functional groups necessary to produce a given biological response. Another definition properties that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure, to modulate or inhibit a biological response. A Pharmacophore does not represent a concrete molecule, but an abstract

concept which describes the common molecular properties of interaction with the receptor. Therefore, a pharmacophore model explains how structurally diverse ligands can bind to a common receptor site.

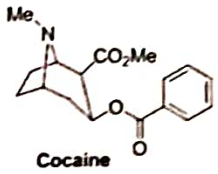
Pharmacophore mapping is one of the major elements of drug design in the absence of structural data of the target receptor. The tool initially applied to discovery of lead molecules now extends to lead optimization. Pharmacophores can be used as queries for retrieving potential leads from structural databases (lead discovery), for designing molecules with specific desired attributes (lead optimization), and for assessing similarity and diversity of molecules using pharmacophore fingerprints.

An example of a histamine-pharmacophore: proton donor (D) and acceptor (A), charge (P)



Lead compound:

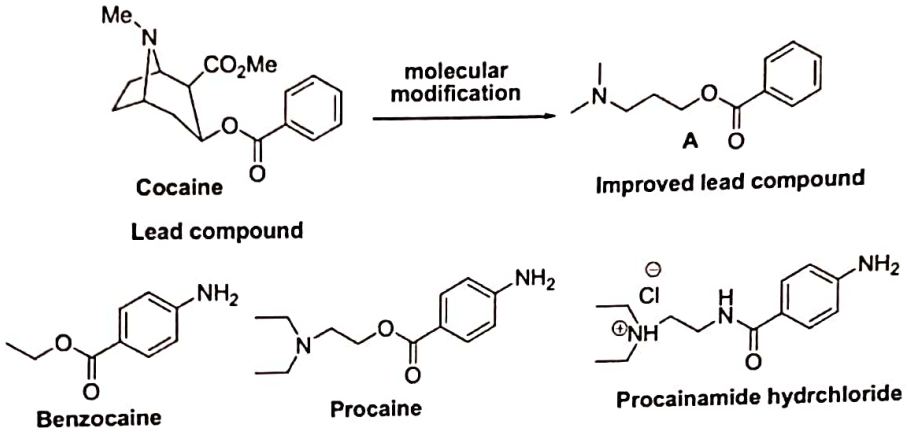
In order to design a drug with a particular biological activity, the medicinal chemist requires a lead compound-a compound which shows a useful pharmaceutical activity. The level of activity may not be very great and there may be undesirable side-effects, but the lead compound provides a start. By altering the structure using the strategies, a useful drug may be developed with improved activity and reduced side-effects. Lead compounds are often found from natural sources or herbs used in traditional medicine, but these are not the only sources. Pharmaceutical companies routinely screen a large variety of novel compounds synthesized in industrial and academic laboratories. These compounds may be intermediates in a purely synthetic research study, but there is always the chance that they may have useful biological activity.



Cocaine

Molecular Modification

Changing the structure of the lead compound to get desired enhanced biological activity and reduced side effect is known as a **molecular modification**. For example, cocaine is an effective local anesthetic, but it produces a disturbing effect of the nervous system that leads to severe depression. However, the modification of the portion of cocaine structure led to another molecule **A** which exhibit local anesthetic activity without damaging the central nervous system. Based on this several esters have subsequently been synthesized, and benzocaine and procaine have been found to be anesthetic agents. However, procaine was rapidly hydrolyzed by enzymes. Thus, analog amide derivatives have been further synthesized when procainamide hydrochloride has been found to be an effective antiarrhythmic agent.



Cocaine

Lead compound

Improved lead compound

Benzocaine

Procaine

Procainamide hydrchloride