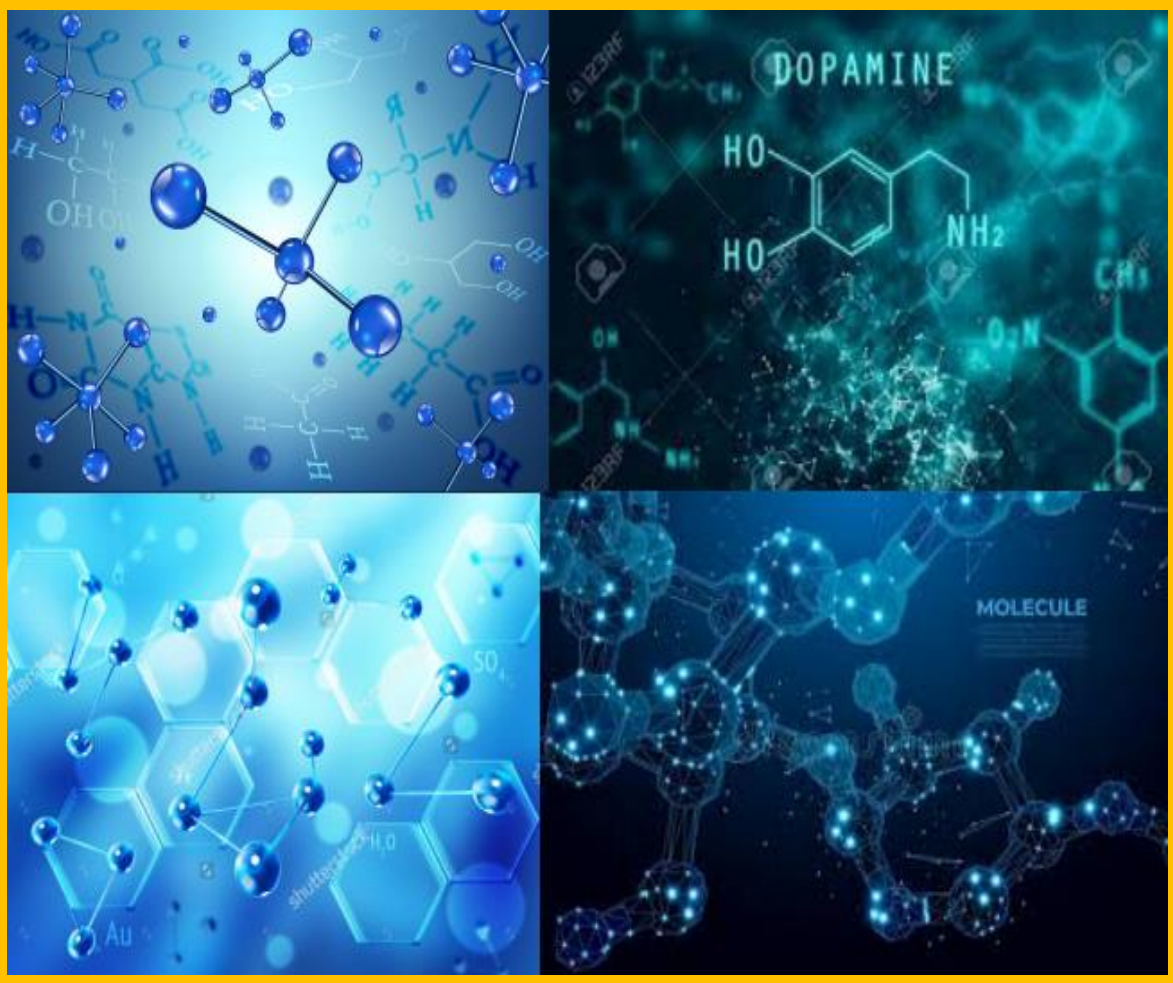
MSCCH-608

# M.Sc. IV Semester

# MEDICINAL CHEMISTRY




SCHOOL OF SCIENCES
DEPARTMENT OF CHEMISTRY
UTTARAKHAND OPEN UNIVERSITY
HALDWANI (NAINITAL)

MSCCH-608

# MEDICINAL CHEMISTRY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# UNIT- I: DRUG DESIGN

## CONTENTS:



## *1.1 INTRODUCTION*

The English term "drug" is derived from the French word "drogue," which literally translates to "dry plant." The field of medicine makes extensive use of pharmaceuticals, which may both prevent and cure a wide variety of illnesses. A drug is "any substance or product that is used or intended to be utilised to examine physiological systems for the benefit of the recipient," according to the WHO (1966) definition of the term.

Essential drugs are defined as those that are able to satisfy the bulk of the healthcare needs of the general population and are intended to always be easily available via functioning

healthcare systems. Essential drugs are having a profound impact on a variety of aspects of public health, including public health objectives, epidemiological conditions, the availability of new treatments, formulations, and pharmacological breakthroughs, and more. The utilisation of clinical studies is recommended in order to collect sufficient data about its efficacy and safety. There is the possibility of providing assurances on the drug's quality, bioavailability, storage stability, cost, and safety.

Various countries use different brand names for their medicines. The tropical method exemplifies how the medicine has a regional impact (skin and mucous membranes, deep tissue route and by arterial router). There are many different kinds of systemic actions; the drug is given through systemic channels, then absorbed by the blood, and then spread throughout the regions that are being targeted.

Drugs that are taken orally are less dangerous, more convenient, less expensive, and do not cause any discomfort. When a drug is administered sublingually, it is kept under the tongue and is disseminated throughout the body via the buccal mucosa. If the patient has recently vomited, the rectal route is used to deliver the medication; otherwise, the drug is applied topically, in the form of an ointment, to a specific area of the patient's skin. Additional administration routes include the nasal route, the paternal route, and inhalation of the drug (subcutaneous injection, intramuscular, intravenous and intradermal injection).

An unfavourable effect of a medication is any unintended consequence that may arise as a result of taking that medication. This term encompasses all types of unfavourable outcomes, regardless of how serious or fatal they may be. Every medication carries with it the possibility of producing undesirable side effects. Asking about drug diseases, exercising caution, and using the appropriate dosage, frequency, and route of drug administration in accordance with the clinical conditions of the patient are all important things to do. One way to reduce the likelihood of adverse effects is to slowly inject aminophylline into an intravenous line. It is also important to avoid the possibility of drug interactions when multiple medications are prescribed to a patient.

For the sake of this discussion, the process of imagining and producing specific new molecules that have the potential to more rapidly result in productive drug discovery is referred to as drug design. Not only was it possible to determine the structure of naturally occurring medicines because of the rapid growth of organic chemistry and medicinal chemistry, but it also was able to determine the structure of naturally occurring medicines.

Both the exploration and the exploitation of leads are examples of several sorts of exploratory behaviours that may be used to broadly define the creation of novel drugs. In the first step, a new potential lead is searched for; in the second step, the potential lead is examined, enhanced, and extended; and rational methods have been used in the creation of effective medications. The amount of time and money that must be invested in order to develop a new drug of a certain quality is directly proportional to the degree to which the programme is well designed. In addition to the compounds that needed to be made before the most satisfactory was identified, medicinal chemists may be able to boost the efficiency of developing or capitalising on a lead by preparing compounds with the lowest number of unwanted characteristics. There is an element of luck involved in the process of finding a useful new treatment or lead. However, the likelihood of a pleasantly manifesting chance can be increased by taking into account the possibility of interaction with life systems by participating steric and electronic properties of designed molecules as well as probable biochemical target moieties. This will increase the likelihood of a pleasantly surprising chance occurring.

## *1.2 OBJECTIVES*

The examination of the process and creation of innovative medicines, which may include lead compounds and modifications, is the major objective of this unit.

- In addition, we learn about prodrugs and soft drugs.
- The development of unique medications is also covered. It is essential to have a solid understanding of the structure-activity relationship (SAR) as well as the factors that contribute to it.
- The stereochemistry of medicines includes bio-isosterism as well as isosterism that takes spatial concerns into account.
- The theory of pharmacological activities, which takes into account drug receptors as well as physicochemical features, occupancy, rate theory, and the induced fit theory. Unrestricted investigation of Wilson and Hansch, as well as their relationship.
- To disscuss the $LD_{50}$ and $ED_{50}$ doses, which stand for "lethal" and "essential," respectively, for the medicine.

## *1.3 DEVELOPMENT OF NEW DRUGS*

Hippocrates, the father of modern medicine, claimed that "A disease is a pathological process, involving a cause and nature, and its treatment with medicine is not a miracle." This statement was based on scientific observations, analyses, and conclusions. Prior to the completion of this study, it was often believed that the bulk of the success in treating an illness was due to a combination of prior experience and informed conjecture.

In the eleventh century, two Persian scientists named Rhazes and Avrienna created a remedy for the pain associated with gout by using an extract made from the seed of wild autumn crocus, also known as colchicum. Both of these pharmaceuticals are still used frequently in today's medical practise.

The era of synthetic pharmaceuticals could not begin until the techniques and methods used in organic synthesis had been sufficiently advanced, and until the physiology of the many human body systems had been properly researched. Both ether and chloroform, which were synthetic or organic chemicals at the time, were first used as anaesthetic throughout the first half of the nineteenth century. In the year 1899, aspirin was developed as a result of efforts made to reduce the nausea caused by salicylates. Study into the hydrolysis and conjugation of aniline led to the discovery of phenacetin during this time period. The synthesis of phenacetin was the result of this research. Antipyrine was discovered as a result of research into the chemistry of quinine, which led to its discovery. Poul Ehrlich, who is credited as being the "Father of Chemotherapy," lived from 1854 until his death in 1915. He put out some innovative ideas concerning the workings of the pharmacological mechanism. He was given the position of director of the Institute for Experimental Therapy in Frankfurt, Germany, in the year 1899, when he was already 45 years old.

In 1891, Ehrlich was the one who discovered the antimalarial effects of methylene blue. Additionally, he was the one who discovered the antibacterial compound known as acriflavine. Ehrlich also claimed that the link between the chemoreceptor and the alkaloid was not strong, that it could be broken, and that it was not irreversible. He continued his research into dyes and eventually found that trypan red and trypaflavin were both effective in killing trypanosomes.

In the year 1891, Ehrlich was the first person to discover the antimalarial characteristics of atabrine (932), as well as plsmoquine (1926). The development of the

theory of therapeutic action, as well as the discovery of sulfonamides and antibiotics, were all shaped by advancements in our knowledge of the chemistry of natural products, most notably enzymes. Enzymology had extraordinary growth in the years after Ehrlich's groundbreaking work in the field. In the year 1897, Buchner made the first observation on the capacity of cell-free yeast broth to ferment. By the summer of 1926, the unrease enzyme had been successfully crystallised.

### 1.3.1 Factors affecting development of new drugs

(a) The chemist's capability of comprehending the biology of the medical disease that is the focus of the investigation into possible remedies. the ability to plan and organise a research project such that it will get the best possible results.

(b) In the next paragraph, the ability of the drug screening facility to evaluate a large number of drugs is discussed.

(c) The procedure for searching for medications that may have potential therapeutic usefulness.

(d) Research and development centre: In order to successfully develop a brand-new pharmaceutical, a sterile setting that has all necessary physico-chemical equipment, such as an electron microscope, is needed. to conduct research on the ways in which bioactive chemicals exert their effects.

(e) The cost of developing new medications: If a molecule is developed by an expensive process, the cost of manufacturing it may grow dramatically as well, which will drive up the cost of bringing the therapy to market. In 1958, there were 14600 unique chemicals that were synthesized, but only 94 of them were commercially available (I in 332 compounds). In a situation somewhat similar to this one, 1.5 million compounds were developed as new drugs in 1964, but only 17 of them were commercially viable.

## *1.4 PROCEDURE FOLLOWED IN DRUG DESIGN*

The development of brand-new medicines that is not only secure but also highly effective and expensive to manufacture. A medicine does not have any adverse effects and does not leave behind any genetic material that might be harmful to the health of the kids. The drug scientist is tasked with developing a degree of efficiency in the synthesis, testing, and clinical trial processes. This will allow them to both retain the resources they have

available while also increasing the possibility that they will find new medications. The information provided by this process offers a connection between structure and activity (SAR). The search for a SAR for a particular research may be broken down into two stages:

a. The building of a functional SAR from chemical and biological studies is an intellectual exercise; a connection between a systemic structural change in a series of molecules and the observed changes in the biologic activity throughout the series may be accomplished if the series is studied well enough.

b. The hunt for a SAR is a component of drug manufacturing and research that does not involve experimentation. This is connected to the conceptual phase in the creation of new medications.

## *1.5 CONCEPTOF LEADCOMPOUND*

The pharmaceuticals that are used in the practise of medicine are generated from lead compounds, which are also referred to as tailor-made compounds. When developing a novel medication, the "lead chemical" is the substance that serves as the foundation for the subsequent development of a molecule that has the potential to have therapeutic applications. Compounds containing lead are very unlikely to be dangerous or to exhibit the kinds of undesirable side effects that would render them unfit for use in medical settings. Compounds containing lead may come from a wide variety of naturally occurring sources, including plants, animals, and the products of either (such as artemisinin, venom, and poisons). These are the sorts of compounds that include things like lovastantin and asperlicin, which are created by microbes; curacin-A, which is formed by marine chemistry; epinephrine and histamine, which are produced by biochemistry.

There was a discovery of a lead compound. It is necessary to carry out the appropriate tests in order to locate the lead chemical. These tests are essential for determining not only how the chemical interacts with the physiology and cells of the body, but also whether or not it can mix with another substance to produce a pharmacologically active compound.

## *1.6 CONCEPTS OF PRODRUGS AND SOFT DRUGS*

These medications must first be transformed by the body into one or more active metabolites before the body may utilise them. A prodrug is a substance that exhibits these characteristics.

In comparison to the medications themselves, the prodrugs are more stable, bioavailable, poisonous, and exhibit undesirable side effects less often.

## 1.6.1 Phasesin Prodrug Action

a. Pharmaceutical

b. Pharmacokinetics

c. Pharmacodynamics

### 1.6.1.1 Pharmaceutical Phase

(a) **Aesthetic Concerns:** Concerns Regarding the Appearance of the Medicine Because of the chemical make-up of the cure, there is a problem with the way that it smells. Ethylmercaptane is a helpful treatment since it can treat both lepra and tuberculosis at the same time, making it a dual-action therapy.

(b) **Physicochemical Issues:** Certain drugs have physicochemical problems, such as the fact that the sodium salt of ampicillin creates a polymer of ampicillin that has been degraded when it is placed in a solution that is highly concentrated. This is only one example of a physicochemical problem that might arise with a certain medication; there are many more.

### 1.6.1.2 Pharmacokinetics Phase

During this stage of prodrug synthesis, the following problems manifest themselves:

**Absorption:** The medicine is difficult to absorb via the gastrointestinal tract and other membranes.

**Elimination**: When a medication departs the body, its physiological effects are no longer possible for a longer period of time. Medicine metabolism: The active ingredient in the drug is swiftly converted into inactive metabolites. The site where the medicine is administered may become toxic.

### 1.6.1.3 Pharmacodynamics Phase

Formation of Prodrugscontaining variouschemical groups:

(a) ***Mercaptans:*** Mercaptans may be synthesised as ester prodrugs, much as alcohols. Because the sulphur atom in mercaptans is more chemically active than the oxygen in alcohols, they are more reactive than alcohols.

(b) In order to release the insect propellant known as undecylenic acid, the following two kinds of chemicals were created as insect repellants. $CH_2$ = CH-$(CH_2)_8$-COOH.

I. To serve as a "anchoring group," the quaternary ammonium group was added. An anchoring group helps the molecule adhere to cutaneous tissue.

II. The alkyl group, which is present in the aforementioned compounds, will aid in the binding of esters to dermal tissues as well as their hydrolysis.

## 1.6.2 Configurational Properties

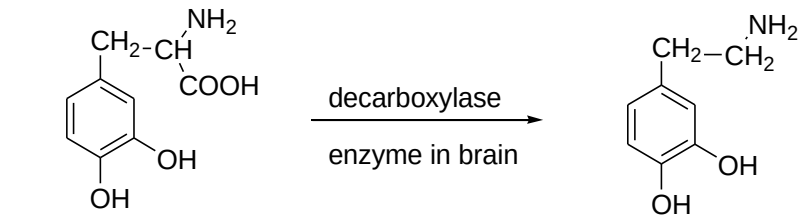
When an acid combines with a racemic alcohol, an ester is created that has a combination of 50% (+) and 50% (-) isomers.

a. If an ester is created with the (+) alcohol during the hydrolysis of this Easter by the enzyme esterases, the acid is released quickly.

b. If an ester is created with the (-) alcohol, there will be a slow release of the acid.

## 1.6.3 Formation of Amines from Amino Acids

Levodopa is an amino acid that, in the brain, is turned into dopamine by the decarboxylase enzyme. Dopamine is the active form of L-dopa, which is a prodrug.




**L-dopa (prodrug)** **Dopamine**

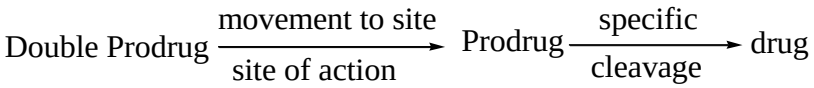
## 1.6.4 Double prolog

The prodrug has two possible drawbacks:

(a) The link between the drug and the carrier component may be too unstable both in vivo and during storage.

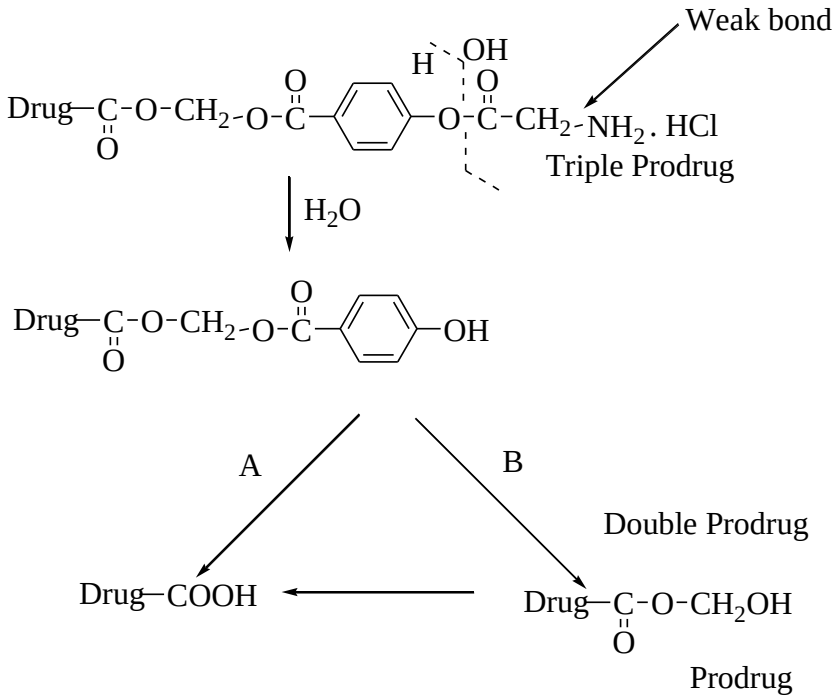
(b) The prodrug's carrier component may not be sufficient to release the prodrug at the site of action.

Distribution of a two fold prodrug to a particular site:




### 1.6.5 Triple Pro drugs

Because the drug is released from both the double prodrug and prodrug, cephalosporin was needed, and the molecule, in particular, needed to be water soluble to enhance the drug's half-life (its duration of action).




## *1.7 SOFT DRUGS*

The concept of hard and soft acids and bases gave rise to the term "soft drug." A substance that can be metabolised with relative ease, as opposed to a "hard drug," which is a substance that may either be metabolised with great difficulty or cannot be metabolised at all.

(a) The component of the soft medication has an effect on the body's physiological processes.

(b) The fundamental objective in the development of soft drugs is not an increase in the potency but rather an increase in the therapeutic indices.

(c) Soft medicines are designed to avoid the presence of the pharmacologically active metabolites.

(d) Eliminating the pharmaceutical interactions that were brought on by the indications of enzyme metabolites; and

$$T.I.= \frac{TD_{50}}{ED_{50}}$$

where,T.I.=Therapeuticindex

$TD_{50}$ = Median toxic dose

$ED_{50}$=Medianeffectivedose

### 1.7.1 Soft Analogs

The bioactive chemicals are represented by their soft equivalents. They are constructed in such a way that a piece of the molecule experiences a metabolite process that is carried out in one stage and is attentively monitored throughout. The hydrolysis process will be beneficial to the metabolic process. Formaldehyde and a tertiary amine are the products of the breakdown of released alcohol.

This ester quickly became less stable. At a concentration of $10^{-8}$ M, the activity was observed to continue for an entire minute in human plasma. It is quickly absorbed into the body and then undergoes hydrolysis. This ester has a structure that is analogous to that of the pharmaceutical compound glycopyrolate.

### 1.7.2 Activated Soft Compounds

The activated soft molecules that are typically thought of as the chemical counterparts of bioactivity are incorrect. They begin with a proven inactive non-toxic metabolite as their starting point. An activated group that is connected to a non-toxic inactive molecule has the potential to be liberated from the molecule and exert a pharmacological action in vivo.

In contrast to many common N-chloramines, which are exceedingly unstable, these compounds produce $Cl^+$ both internally and externally to the bacterial cell in which they are found.

## *1.8 RELATIONSHIP OF STRUCTURE AND ACTIVITY (SAR)*

The nineteenth century saw the discovery of a variety of naturally occurring compounds, many of which were then subjected to analysis to determine their chemical make-up and pharmacological potential. It has been demonstrated that there is a connection between the physiological activity of a molecule and a certain structural group or unit. If this is the case, then there is also biological activity. The term "pharmacophore group" refers to the

component of the chemical that is actually in charge of producing the desired physiological effect.

## 1.8.1 Factors

### 1.8.1.1 Effectof Alkyl Groups

A chemical reaction occurs when a group of alkyl molecules is used in place of an active hydrogen atom.

When an alkyl group is substituted for an active hydrogen atom in a chemical eg.

$$HCN \rightarrow RCN$$

$$ArOH \rightarrow ArOR$$

$$RNH_2 \rightarrow RNHR$$

R=alkyl group

(a) Antipyrine is a potent antipyretic, but its inactivity is shown by the reduction of a methyl group.

### 1.8.1.2 Effectof Hydroxyl Group

The addition of a hydroxyl group to an aliphatic molecule reduces its biological and physiological activity in a manner that is roughly proportional to the number of hydroxyl groups.

(i) Hexanol has higher physiological activity than sorbitol.

(ii) Butyraldehyde is more active than its -hydroxy counterpart.

(iii) Propanol is much more active than glycerol.

(iv) Hexaldehyde is a poisonous chemical, but glucose, its hydroxyl counterpart, is physiologically inert.

(v) Caffeine's physiological activity is eliminated in hydroxy-caffeine.

(vi) Tertiary alcohol is substantially more physiologically active than primary alcohol among alcohols with the same number of carbon atoms. Their activity is organised as follows: tertiary > secondary > primary.

(vii) When compared to the inert parent chemical, benzoic acid, salicylic acid has antibacterial and antirheumatic effects.

(viii) Phenol is an antiseptic chemical with a higher toxicity than benzene.

(ix) In nature, polyphenols are more poisonous than phenol.

### 1.8.1.3 Effect of Aldehydes and Ketones

Ketones are less reactive than aldehydes. Their physiological impact is likewise far stronger. Formaldehyde, for example, is an antibacterial and has a hardening effect on tissues. Ketones have a narcotic effect. They have pharmacological characteristics comparable to secondary alcohols. Aliphatic ketones with alkyl groups have hypnotic action, while mixed ketones do not.

### 1.8.1.4. Effect of Acidic Groups

The presence of an acidic group in a chemical reduces or eliminates the biological activity of the parent molecule. For instance,

(a) Nitrobenzene is a toxic chemical, although its acid counterpart nitrobenzoic acid is not.

(b) Phenol is toxic, whereas benzene sulphonic acid is not.

(c) Morphine has a high level of physiological activity, while morphine sulphuric acid is absolutely inert.

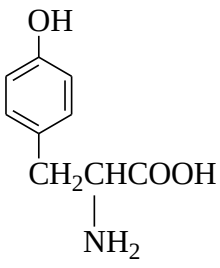
(d) Aniline is poisonous, but meta-amino benzoic acid is not.

(e) Amines are harmful substances, while amino acids are food.

The following is a list of several acyl derivatives in decreasing order of solubility:

Lactyl > Acetyl > Benzoyl > Slicyl

Acetyl derivatives are less expensive and easier to hydrolyze, making them more convenient in general. The hydrolysis of benzoyl derivaties is relatively sluggish. Benzoyl is present. group is of great importance to the physiological activity of ester compounds. The poisoningeffectoftyrosine canberestored byesterification.




Tyrosine

The basicity of the molecule is reduced via acylation. After hydrolysis in the organism, the activity of the acylated derivative becomes very important and exerts its physiological function.

**1.8.1.5 Effects of Halogens**

(a) Positive Halogens: The presence of a 'positive halogen' atom in the chemical reduces toxicity while also providing other helpful features.

(b) Negative Halogens: In general, the presence of a 'negative halogen' atom improves both the helpful and harmful qualities. Negative halogen is present in the compound's non-conjugated position. It is vital to note that the halogenation process has a minor effect on toxicity. Aliphatic fluorocarbons are shown to be substantially less biologically active than other halogens, and even less than the analogous nonfluorinated compounds.

**1.8.1.6 Effect of Nitroand Nitrite Groups**

(a) Nitro Groups: The addition of a nitro group to an aromatic molecule increases its toxicity.

(b) Nitrite Groups: Increased physiological activity.

**1.8.1.7 Effect of Amino Group**

In nature, the amino group is poisonous. Their toxicity is reduced by alkylation. Acylation also reduces the parent compound's physiological activity. Aniline, for example, is physiologically poisonous, yet acetanilide, an acylated derivative, is a significant fabrifuge. Aromatic amines and hydrazines, on the other hand, have analgesic and antipyretic effects.

**1.8.1.8 Effect of Nitrile Group**

For example, KCNS (potassium thiocyanate) is a mild poison, but $Na_2Fe(CN)_5$-NO (sodium nitro prusside) is a lethal poison.

**1.8.1.9 Effect of Unsaturation**

With increasing unsaturation, the compound's toxicity rises. Alkyl alcohol ($CH_2$=CH - $CH_2OH$) is very toxic, while propanol is a saturated molecule ($CH_3CH_2CH_2OH$).

**1.8.1.10 Effect of Isomerism**

Isomerism also plays a significant part in the physiological effect of medications. Ordinary cocaine, for example, is a well-known anaesthetic chemical, but its structural isomer α-

cocaine lacks this effect. Sulphanilamide, for example, is a highly potent sulpha medication, although its other two isomers are inert in nature.

(a) Natural l-adrenaline is twelve times more potent than the dextro isomer.

(b) l-nicotine is twice as toxic as d-nicotine.

(c) Atropine (dl-hyoscyamine) is more active than l-hyocyamine.

## 1.8.2 Isosterism

Langmuir developed the notion of isosterism in 1919. He noted that the atoms, groups, radicals and molecules which have comparable physicochemical qualities and similar electronic structure, are known as 'Isosters' and this phenomena is termed "isosterism". Such similarities arose in atoms that are in the same vertical column of the periodic table and had identical or nearly identical outer shells of electrons. Recognized for continuous atoms in a horizontal row of the periodic table. Chlorine and bromine share more chemical characteristics than carbon and chlorine or chlorine and iodine. Chlorine has an atomic weight of 35.46 and a radius of 1.80 $A^o$, while iodine has an atomic weight of 126.91 and a radius of 2.15 $A^o$.

| | **PhysicalProperties** | **$N_2O$** | **$CO_2$** |
|---|---|---|---|
| 1. | Viscosity(at 20°C) | 148 x $10^{-6}$ | 148 x $10^{-6}$ |
| 2. | Density(at 10°C) | 0.856 | 0.858 |
| 3. | Refractiveindex ofliquid,Dline16° | 1.193 | 1.190 |
| 4. | Dielectricconstantat 0° | 1.593 | 1.582 |
| 5. | Solubilityin alcoholat15° | 3.250 | 3.130 |

Grimn published a set of hydride displacement rules in 1925. He proposed that vertical columns of isosteric groups were generated by moving the members of a horizontal row one position to the right and adding a hydrogen atom, i.e., a hydride ion, and repeating this process. The next example shows each vertical column representing a set of isosteres, and the procedure is repeated with the next horizontal row of components.

## 1.8.3 Bioisosterism

Bioisosteres are isosteric substances that have similar biological action. Friedman created the word biosterism in 1951, and its definition has progressively expanded since then.

**(a) ClassicalBioisosteres**

I. Single-valent atoms and groups

II. Divalent atoms and groups

III. Trivalent atoms and groups

IV. Tetra substituted atoms

V. Ring analogies

**(b) Non-classicalbioisosteres**

I. Exchangeable groups

II. Rings versus noncyclic structures

III. The halogens and the group-XHn, where n is C, N, O, or S, make up the monovalent bioisoteres. The R-O-R', R-NH-R', R-$CH_2$-R', and R-Si-R' atoms and groups were divalent. The trivalent bioisoteres are made up of C and N in groups of three, like R-N=R' and R-CH=R'.

IV. The tetrasubstituted atoms can only contain the elements C, N, and P.

**1. True bioisosteres**

Like its analogues, these branches of biology elicit a similar range of biological effects.

**2. Partial bioisotere**

Although all partial bio isoteres exhibit the same general pattern of bioactivity, their responses vary in intensity. If the modified ethylenediamine still has the required bioactivity while having less unwanted side effects, it is called a "partial bio isostere."

### 1.8.3.1 Applicationof RecentBioisosterism

Exchangeable groups are shown by the sulfonamido isosteres of the catecholamines. Some catecholamines have had their phenolic hydroxyl group replaced with an alkyl sulfonamido group. Only a small fraction of the resultant chemicals are agonists; the rest are antagonists. It

is possible that there are parallels to be drawn between catecholamines and alkyl sulfonamidophen ethanol amines.

Phenylephrine with ethanotamine in alkyl sulfonamidophene. The alkyl sulfonamido molecule and phenylephrine, both of which elevate blood pressure by 20% when delivered intravenously, have the same bioactivity. Physiochemical properties of molecules may be affected by a variety of atomic characteristics, including acidity or basicity, electronegativity, polarizability, van der Waals radius, bond angles, charge, and number of substituents. Drug molecules exert their therapeutic effects by binding to and stimulating certain receptor sites throughout the body. It's also important to remember that this causes a biological response by changing the molecule's physical properties.

## *1.9 THEORIES OF DRUGA CTIVITY*

In the case of structurally non-specific medications, the pharmacological action is either caused by their physiochemical qualities or by their chemical structure in the case of structurally specific pharmaceuticals. The structurally specialized medications only need extremely little amounts to have an effect, and they do so by complexing with receptors that are located in the molecules of the body. Aliphatic alcohols, which are structurally non-specific medicines, exert their effects when taken in high amounts by covering certain cell types with a monomolecular layer.

### 1.9.1 OccupancyTheory

Clark and Gaddum proposed the template hypothesis, also known as the occupancy principle, which holds that the magnitude of a pharmacological action is proportional to the number of receptors that are filled by the active substance. The following equation may be used to demonstrate how occupancy theory can be used to illustrate that interactions between drugs and their receptors obey the rule of mass action.

$$R + D \underset{}{\overset{K_1}{\rightleftharpoons}} RD \longrightarrow E$$

where R is the receptor and D is a drug molecule.

RD = Drug-Receptor Complex

E is the pharmacological effect, while $k_1$ and $k_2$ are the absorption and desorption rate constants, respectively.

Both the drug concentration in the receptor compartment and the overall number of receptors in the unit area or volume affect the number of occupied receptors.

### 1.9.2 Affinity and Intrinsic activity

As an example, the alkyltrimethylammonium series of acetylcholine congeners do not all elicit the same peak response, according to the occupancy hypothesis. This idea falls short of explaining how certain medications work. They claimed that there are two steps involved in drug-receptor interaction:

(a) Complexation of the drug with its receptors.

(b) The creation of an impact.

It has been established where certain drug acceptors or receptors are located. The majority of them are either allosteric or active sites for enzymes or pieces of DNA or RNA. Some medications work by intercalating between DNA base pairs, as chloroquine does, or by alkylating or cross-linking DNA strands, as mitomycin does.

### 1.9.3 Rate Theory

The rate hypothesis is predicated on the idea that a medication is only effective when it comes into contact with its receptor.

According to Paton, the total number of times a medication interacts with a receptor within a certain period of time, rather than the number of occupied receptors, determines how many times a receptor is activated. For a drug to activate a receptor, the rate theory does not need the creation of a stable Michaelis-Menten complex. The pharmacological activity, according to this hypothesis, has simply been a function of the rate of association and dissociation between drug and receptor molecules, not of the creation of a stable drug-receptor complex. For a biological relationship, each association creates a little amount of stimulation.

The rate of association and dissociation is quicker and produces more impulses per unit of time in the case of agonists. Numerous empirically proven events cannot be explained by the rate hypothesis. For instance, the agonist has properties that encourage the creation of a complex that doesn't dissociate easily.

Both the rate theory and the occupancy theory have come under heavy fire since they are unable to comprehend events that are discovered at the molecular level or explain why a medicine works as an agonist or antagonist.

An alternative to dissociation hypothesis was presented by Paton and Rang. In their research, they discovered that the dissociation rate constant is a function of how much the drug molecule alters the secondary protein structure rather than how strong the binding forces are. The relationship between stimulus and rate of dissociation, with this rate being proportional to receptor occupancy, has not been properly distinguished between the occupancy theory and the dissociation theory.

### 1.9.4 Induced Fit Theory

The induced-fit theory is predicated on the idea that new evidence of induced conformational changes in enzymes is accumulating. According to Koshland's theory, an isolated crystalline enzyme's active site does not have a morphology that is either complementary to or in some way adverse to that of the substrate. Only after interacting with the substrate, which results in a conformational shift, does it acquire such shape. The enzyme's active site is flexible, not rigid, meaning that it may alter or be distorted but also has the capacity to go back to its original state. According to the induced-fit hypothesis, a reversible disturbance or alteration in the tertiary structure of enzymes or proteins results in the activation or deactivation of enzymes or non-catalytic proteins, which causes the biological impact caused by pharmaceuticals. Proteins are not the only molecules that can alter their conformation. Drugs with flexible structures are also capable of changing conformation as they get closer to the site of action or the receptor. The biological impact is produced by the dynamic, reversible interaction of drug receptors.

The induced fit hypothesis has been refined by Koshland et al. to account for cooperative effects. One ligand molecule's binding speeds up the binding of succeeding ones

### 1.9.5 Quantum Mechanical Approaches: History&Development of QSAR

A description of matter that is founded on basic presumptions of natural occurrences is explained by quantum mechanics or wave mechanics. Atoms, molecules, protons, neutrons, and electrons make up matter. These basic particles' characteristics must be effectively described by quantum mechanics. The most crucial molecular particles for a drug scientist are the electrons since they play a role in chemical reactions. The idea of atomic orbitals is a logical extension of this theory.

The likelihood that an electron will be found at a certain location inside a molecule and the energy of that electron are what control chemical processes. Calculations on drug

compounds, electron placement probability, and energies are made possible using molecular orbital theory.

The Hansch Model's debut in 1964 served as the foundation for QSAR.

(1) In 1968 Crum-Brown and Fraster studied the effects of several straightforward quaternary ammonium salts and quarternized alkaloids on animal neuromuscular blocking.

These investigations led researchers to the conclusion that a molecular's chemical makeup determined how it behaved physiologically.

(2) Richardson found that the molecular weight of aliphatic alcohols affected their hypnotic properties.

The foundation of QSAR was these observations.

The Quantitative Structure Activity (QSAR) approach is an effort to link the activities of a molecule to its structural or physical characteristics. These physico-chemical descriptors, which also include electronic parameters, steric effects, and parameters to account for hydrophobicity topology, are calculated experimentally or, more recently, by computer approaches.

Physical characteristics characterise QSAR. biological characteristics and intrinsic traits. Since the Hansch technique was developed in 1964, chemists have been able to quantify SAR research. The following is a summary of the methods used in QSAR analysis: -

(a) Linear free energy connection using the Hansch method

(b) Free Wilson model

## *1.10 DRUG RECEPTORS*

### 1.10.1 Nature of Drug Receptors

Biological activity may be seen even at very low quantities. These medications are known as structurally specific medications. A semi-rigid macromolecule that serves a biological purpose must come before a chemical. This macromolecule might be an enzyme or include a "receptor," for example.

A receptor is a marcomolecule with locations, according to

a) It has chemorecognitive abilities for a particular natural endogenous chemical or for certain medications.

b) The function of a certain endogenous molecule and the specificity of the sites on the receptor macromolecule are genetically defined.

c) A particular disturbance or state change of the receptor macromolecule results from the binding of agonists, whether they be drugs or endogenous molecules.

d) The formation or dissolution of covalent bonds in the agonist is not necessary for the start of a response by binding to a receptor site.

e) The absorption of the toxic substances by certain side chains of the cell, which I have referred to as "receptors," is how the toxic substances cause harm to the cell.

i. **High Potency:** Many medications work at $10^{-9}$ M and $10^{-11}$ M concentrations, which is a relatively low level.

ii. **Chemical Specificity:** The variations in outcomes brought about by optical isomers. Chloramphenicol contains four isomers, although only one of them has ever been active.

iii. **Biologically selective:** Epinephrine, which has a strong impact on heart muscle but a very mild influence on striated muscle, is biologically selective. That receptors have a special capacity to interact with natural substrates at their active sites and are located in macromolecules, the majority of which have protein-like features. The active site of enzymes has probably always resembled nature, and they are around the same size as the drug molecule that may form a compound with them. The structural, configurational, and conformational properties of the drug and the receptor both influence how the drug is converted to a receptor.

## 1.10.2 Receptor Interaction

Finding out the kinds of atoms and functional groups that are crucial for a drug's ability to connect to its target binding site is one of the most helpful information that can be gleaned from SAR investigations. There are several ways that bonding may happen. These are often dipole-dipole interactions, van der Waals contacts, ionic bonds, hydrogen bonds, and other intermolecular bonding interactions. Some medications, nevertheless, may create covalent connections with their targets.

## 1.10.3 Direct Method

In the direct technique, a chemical that may bind to a receptor's functional groups permanently, or via covalent bonding, is added before isolating the resulting drug-receptor complex. The following chemical reagents, among others, may react with the serine hydroxyl group: phosphorylating agents, carbamylating agents, sulfonyl flourides, alkylating agents, and N-alkyl maleimides.

### 1.10.4 Indirect Method

Through the use of molecules that may reversibly compound with the macromolecule, the receptor is attached to it in the indirect way.

## *1.11 PHYSICO-CHEMICAL PARAMETERS*

The chemical proved to only be useful in humans when combined with anaesthetics, and the move away from profound anaesthesia looked to render the compound useless as a medicine. It was hypothesised as an intriguing side effect that the molecule's two lipophilic groups may cause the agent to attach to the body's lipophilic sites of loss, and that the earlier injection of lipophilic aesthetics might enhance the blocker by concealing these sites of loss.

The biological activity and ionisation of a drug series containing an ionizable functional group are somewhat correlated. Maximum pka value range for evoking the desired biological response. The electron or charge distribution may change across various structures in quaternary ammonium salts, which can significantly affect activity. It's possible that phenolic, mercapto, and enolic gps with H-bondig are more important.

Attention has been drawn to the creation of change or electron transfer complexes as a potentially significant biochemical and pharmacological bonding. Receptor-friendly compounds with aromatic and hetero aromatic ring systems are created via resonance delocalized, IT-electron cloud. Drug compounds may often cause conformational changes at receptor sites.

### 1.11.1 Molecular Orbital Indices

Calculations of molecular orbitals may provide numerical indices that represent the likely location of an electron and its energy in a molecular orbital, which is important information.

**Charge:** It is claimed that a wave function Ψ, in a molecular orbital contains an electron's three-dimensional coordinates. A linear combination Ψ of the values from the contributing atoms in a molecule is thought to make up the wave function of the molecular orbital.

Coefficient, C is responsible for designing the contributions. It provides an equation for a molecule with n atoms' molecular orbital.

$$\Psi = C_a \Psi_a + C_b \Psi_b + \ldots\ldots C_n \Psi_n$$

Because a molecular orbital can only hold two electrons, a medicine molecule needs several molecular orbitals to hold the many electrons. To get electron probability or electron density in any area of the molecule, add the individual $2C^2$ values of each molecular orbital.

$$qi = \Sigma 2C^2_i$$

Thevalueof qmay deviatedue tothe natureofatom,i,andasimplecountofthe numberofelectrons contributedbyatomi, tothemolecular orbital.

IonizationenergyE,isrelatedtothewavefunction$\Psi$,ofthemolecularorbital.

AccordingtoSchrodingerequation:

$$H\Psi = E\Psi$$

whereH=Hamiltonianoperator

Kier and Hall created a SAR technique. This approach, known as molecular connection, is significantly simpler than quantum mechanics and is helpful in describing structures.

## 1.11.2 Electronic Ionization constants

The hydrophilicity of a molecule rises with ionisation; hence it is possible to calculate the molecule's real partition coefficient by assuming that the ion is only present in the aqueous phase.

$$P = C_{octanol}/C_{water}\ (1-\alpha)$$

P = partition coefficient, 1-octanol is the compound's 1-octanol concentration, and $C_{water}$ is the compound's concentration in water, $\alpha$ = the compound's degree of ionization.

## 1.11.3 Steric factors

Meyer 1895 proposed that the atomic weight of an o-substituent affected how easily aromatic acids may be esterified. Taft gave a numerical definition of the steric constant $E_s$ as an equation:

$$Es = \log (k_x/k_H)\ A$$

k = rate constant for acid hydrolysis of esters of type X-$CH_2$COOR

Following equation may be used to determine redox potential of a system:

$$E = E' - \frac{0.06}{n}[\text{conc. of}\frac{\text{reductant}}{\text{oxidant}}]$$

E = redox potential studied

E' = standard potential at given pH

n = number of electrons transferred

When substances are surface-active, they do so when they are manomers in diluted solution. They begin to form polymers as the concentration rises, and since the polymers are micelles, the concentration at which they begin to form is known as the Critical Micelle Concentration (CMC). Utilizing surface active agents has the benefit of allowing polymers to solubilize chemicals that are insoluble in water, such as lipophilic phenols. Therefore, three antibacterial zones are noticed while measuring the antimicrobial activity of 4-benzylphenol in the presence of sodium lauryl sulphate. Antibacterial activity increases the antibacterial activity of 4-benzylphenol.

## 1.12 EMPIRICAL FRAGMENT EVALUATION: FREE AND WILSON ANALYSIS

An approach to the structure-activity connection was created by Free and Wilson. With this method, numerical values on a logarithmic scale may be obtained from changes in biologic activity within a group of connected molecules.

The effects of a number of phenethylamines on the isolated heart were investigated by Ban and Fujita.

If $A_0$ = activity of the parent skeleton

And A = activity of any particular molecule in a series,

The model may be written as follows:

$$log\left(\frac{A}{Ao}\right)\Sigma GiXi$$

Where X = 1 or 0, according to the feature of substituent,

Depending on the feature or substituent, Gi is either missing or present when X is either 1 or 0. Compounds may be optically active or racemic, and substitutes can be found in rings or chains.

$$\text{Log a} = \Sigma Gi\ Xi + k$$

Thus for ± Noradrenaline, the equation is in the form

The equation for noradrenaline has the following form: The computer solves the "best-fit" value for all G2 and k. The G value indicates how much a certain characteristic or replacement contributes to activity. G value comparisons enable the identification of significant characteristics. It is possible to create a more powerful molecule by utilising substituents with high positive G values.

## *1.13 HANSCH ANALYSIS*

This approach looks for connections between common physical characteristics, such as molecule size, degree of ionization, or lipid solubility, and biological activity. This strategy uses a physical model to describe biological activity. Biologic activity and a linear combination of indicators may be correlated (parameters).

A medicinal molecule's activity may be correlated with probability p. In relation to the likelihood that a medication will go through each of the three processes listed above, a, b, and c:

$p = p_a p_b p_c$

if k = proportionality constant and

c = molar concentration then,

Activity = k. c. p.

$$= k.\ c\ .\ p_a\ .\ p_b\ .\ p_c$$

$$\log 1/c = \log \quad pa + pb + pc + k$$

DOSE,C |k| → → → Response random walk receptor

$$\log 1/c\ k_1 \log pa + k_2 \log k + k_3$$

Here, we have expressed.

Intrinsicactivityandlinearfreeenergyrelationship:If adrugislogpa=0.Asamodelthe equationis

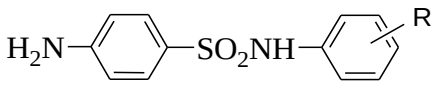
$$\log 1/c = k_1 \log k + k_2$$

## *1.14 SULFONANILIDES*

Sulfonanilides are a class of synthetic organic compounds that contain a sulfonamido group, which is a functional group composed of a sulfonamide ($SO_2NH_2$) linked to an aromatic ring. They are used in a variety of applications, such as dyes, pharmaceuticals, agrochemicals, and surfactants. Sulfonanilides are usually synthesized via condensation reactions between an aromatic ring-containing amine and a sulfonyl chloride. These compounds are amphiphilic and have a wide range of solubilities in both aqueous and organic solvents. They also exhibit a variety of biological activities, such as fungicidal, insecticidal, and herbicidal activity.

### 1.14.1 AntibacterialEffect

Insulfonamidedrugs, theeffect of thesubstituent Rwas parameterized by σ. Between σ and potency, a good relationship wasfound.




$$\text{Log } 1/c = 1.05\,\sigma - 1.28$$

$$r = 0.97,\ N = 17$$

Expandingaboveequationtoincludehydrophobicbonding,ageneralmodelequationinvitrocan be written as:

$$\log 1/c = k_1\,\pi + k_2\sigma + k_3$$

## *1.15 RELATIONSHIP BETWEEN FREE-WILSON AND HANSCH ANALYSIS (MIXEDAPPROACH)*

The Hansch and Free-Wilson model combination has been offered by Kubinyi as a mixed method. The formula for the mixed approach is log 1/c = Σaij + Σkjϕ + k parameters. The Free-Wilson component for the substituents and the contributions of the current skeleton are represented in this equation by the letters ϕj = π, α and Es. To uncover potential interactions between Free-Wilson parameters and the physicochemical characteristics of the employed substituents, the mixed approach was devised. The fact that the symmetry equations do not need to be developed is another benefit of this equation. By lowering the increments of the substituents of one selected reference chemical to zero, the matrix is reduced.

The Free-Wilson approach's fundamental presumptions are:

(a) That it can be used to congeneric series with a shared skeleton.

(b) Different derivatives had to have been created by adding various substituents to the parent skeleton at the same precise locations.

(c) It is important to ensure that every substituent appears at least twice in the same location when choosing derivatives for the synthesis.

(d) It is stated that there must be at least ten derivaties, or the same number of increments, in the regression analysis answers. to minimise the amount of substances that must be produced. The symmetry criteria put out by Free and Wilson assumed that the sum of increments at a substitution position was equal to zero.

## *1.16 $LD_{50}$ AND $ED_{50}$*

$LD_{50}$ is the abbreviation for Lethal Dose 50 and $ED_{50}$ is the abbreviation for Effective Dose 50. $LD_{50}$ is the amount of a substance that is required to cause the death of 50% of the test population. It is usually expressed as the milligram of substance per kilogram of body weight. $ED_{50}$ is the dose of a drug or other treatment which produces a specified therapeutic response in 50% of the test population. It is usually expressed as the milligram of substance per kilogram of body weight.Both $LD_{50}$ and $ED_{50}$ are measurements of a substance's potency and are used to evaluate how toxic or effective a substance is in a given population.

The median lethal dose ($LD_{50}$) is a measure of the lethal dose of a toxin, radiation, or pathogen. It is expressed as the dose required to kill half the members of a tested population after a specified test duration. $LD_{50}$ is used to measure the short-term poisoning potential of a substance, and is expressed as the mass of substance administered per unit of body mass. The median effective dose ($ED_{50}$) is a measure of the effective dose of a drug, toxin, or pathogen. It is expressed as the dose required to produce a specified response (e.g., 50% reduction in symptoms) in half the members of a tested population after a specified test duration. $ED_{50}$ is used to measure the therapeutic efficacy of a substance, and is expressed as the mass of substance administered per unit of body mass.

Therapeutic Index = Median Lethal dose / Median Effective dose

$= LD_{50} / ED_{50}$

## *1.17 SUMMARY*

You would have learned about and accomplished the objectives listed earlier in the unit after completing it. Let's review the topics we've covered thus far.

- Drugs are prevalent in medicine and are used as treatments to prevent and treat various ailments. Drugs that are considered essential provide for the public's top healthcare needs.
- Various countries have different medicine brand names.
- The oral route of administration of medication is less painful, convenient, and safe than the nasal and parental routes of inhalation.
- New drug discoveries can be broadly categorised as investigations and exploitation. There is a chance aspect involved in the discovery of a valuable new medication or lead. There is a correlation between biological activity and ionisation in a drug class with an ionizable functional group.
- The discovery of sulfonamides and antibiotics, as well as the theory behind how they work, were all marked by an increase in the chemistry of natural products, particularly enzymes.
- It has become expensive and costly to produce new, safe, and efficient medications.
- During the procedure, information known as Structure Activity Relationship (SAR) was discovered.
- Drug development and design are done on computers. Prodrugs and bioactive compounds that have been modified in vivo into drugs from inactive bioactive molecules. The idea of Hard and Soft acids and bases is where the phrase "soft medications" originates. So, although a soft drug is easily metabolised, a hard substance is difficult to metabolise and is nonmetabolisable.
- Connections between biological activity and common physical qualities, such as degree of ionisation, molecular size, or lipid solubility, through the application of the Free and Wilson analysis and the Hansch analysis.
- An effort to link the structural or property descriptors of a chemical with its activities is known as quantitative structure activity (QSAR).

- The sorts of atoms and functional groups that bind a medicine to its target binding sites are the most helpful information that can be gleaned from SAR investigations regarding the receptor idea.
- According to occupation theory, various agonists acting on the same receptor system do not provide the same maximum effects. As opposed to just affinity as suggested by Clark's theory, this approach led to the development of words like intrinsic activity and affinity as two distinct dimensions from drug action.

  Biological effect = intrinsic activity x drug receptor complex
- According to the induced fit theory, the enzyme's active site is flexible—better yet, plastic or elastic-rather than stiff.
- A drug's lipophilicity can be easily determined by comparing how the chemical behaves in aqueous and non-aqueous, water-impermeable solvents. L-octanol is the nonaqueous solvent employed.
- The Hancsh π value describes how a substituent affects a compound's hydrophobicity and hydrophilicity for various bioactive substances.

  $\pi = \log (P_x / P_u)$
- Meyer proposed that the atomic weight of the O-substituent determined how easily O-substituted aromatic acids may be esterified (Taft steric parameters: Es).

  $Es = \log (K_x/K_H)$ A

## *1.18 MCQs TYPE QUESTIONS*

### A. Multiple choice questions

1. Which of the following is the most important step in drug design?

   a. Developing a structure-activity relationship

   b. Screening of libraries of compounds

   c. Synthesizing the drug

   d. Testing the drug

2. Which of the following techniques is used to identify novel drug targets?

a. Molecular modelling b. Pharmacogenomics

c. Pharmacophore modelling d. Structure-activity relationship

3. Which of the following is the most common method of drug delivery?

a. Inhalation b. Oral

c. Topical d. Intravenous

4. Which of the following is not a type of computer-aided drug design?

a. Molecular modelling

b. Quantitative structure-activity relationship

c. Ligand-based approaches

d. Virtual screening

5. Which of the following is not a type of drug?

a. Chemical b. Biologic

c. Biological d. Nanoparticle

**Answer key**

A. 1 b 2 c 3 b 4 c 5 c

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## *1.20 TERMINAL QUESTIONS*

1. What is the main goal of drug design?
2. What are some of the common techniques used in drug design?
3. What is structure-based drug design?
4. What is molecular modeling?
5. What is the difference between structure-based drug design and ligand-based drug design?
6. What is the concept of lead optimization in drug design?
7. What are the advantages of using computer-aided drug design?
8. What is combinatorial chemistry?
9. What is the difference between rational drug design and virtual screening?
10. What is the difference between in silico and in vitro drug design?
11. What is high-throughput screening?
12. How is structure-activity relationship used in drug design?
13. How can machine learning be used to speed up the process of drug design?
14. What is the role of medicinal chemistry in drug design?
15. How can bioinformatics be used to support drug design?
16. What is an in silico drug discovery platform?
17. What are the benefits of using artificial intelligence in drug design?
18. What is the role of pharmacokinetics in drug design?
19. What is the difference between pharmacodynamics and pharmacokinetics?
20. What is molecular docking?
21. How is fragment-based drug design used in drug discovery?
22. What is a pharmacophore?
23. How can computational chemistry be used to design novel drugs?

24. What are the challenges of drug design?

25. What is the future of drug design?

# UNIT-2: PHARMACOKINETICS & PHARMACODYNAMICS

## Contents:



## *2.1 INTRODUCTION*

Pharmacokinetics, or PK for short, is the study of the connection between the dose of a medication administered and its concentration at a later period. The systemic input and the disposition kinetic mechanisms in this investigation set it apart. Popular names for the kinetic processes involved include drug absorption, distribution, metabolism, and elimination (ADME concept). When a drug's efficacy reaches a certain level while still being below the toxicity cutoff, it is said to have reached therapeutic benefit. As a result, understanding drug pharmacokinetics is necessary to optimise pharmacological therapy and prescribe the proper dose in populations of interest. The phrase "what the body does to the medication" is also used to describe this. Understanding pharmacokinetic principles and having specific knowledge about a drug and a patient allows for the most individualised and efficient use of medicine (e.g. choice of drug, route of administration, dose and dosing interval).

In this part, we go over some general guidelines for using medications in conjunction with living systems. In this part, we go through the processes that contribute to drug excretion, such as drug translocation, absorption, distribution, and chemical modification. Drug treatment aims to prevent, treat, or manage a range of disorders and the symptoms that go along with them. To obtain therapeutic yet nontoxic drug levels in the tissues that are the focus of the treatment, the right medication dosages must be administered. There are four main channels via which drugs move and are modified within the body, and these routes determine the speed at which the action of the drug starts, the strength of the effect, and the length of the activity of the drug. At first, the therapeutic element can reach plasma (either directly or indirectly) due to medication absorption at the distribution point (input). The medication might also diffuse into interstitial and intracellular fluids, reversibly leaving the circulatory system (distribution). Third, the liver, kidneys, or another type of tissue may metabolise the medication. The medicine and its metabolites are ultimately eliminated from the body by the bile, the urinary tract, or bowel motions (output). Pharmacokinetics, sometimes referred to as "drug metabolism," is a branch of science that studies how the body breaks down different drugs. Pharmacokinetics is the quantitative study of a substance's metabolism and elimination from the body. Absorption, distribution, binding/localization/storage, biotransformation (metabolism), and excretion of the medication are all ways that the drug moves throughout the body and alters the organism.

Pharmacokinetics is the quantitative study of how medications travel through, out of, and into the body. Therefore, the routes of drug administration, dosage, peak effect time, duration of action, and frequency of drug administration are all determined by pharmacokinetic factors. The membranes serve as the conduit via which drugs are transported. The biological membrane is made up of phospholipids, cholesterol, and polar groups like glyceryl phosphate that are coupled to ethanol amine/choline or the hydroxyl group of cholesterol. It is a bilayer with a thickness of 100 angstroms. Polymeric sugars, amino sugars, and sialic acids are attached to the surface to create glycoproteins and glycolipids. While certain proteins are stable and present over the whole thickness of the biological membrane, protein molecules can freely float through the membrane. Fine aqueous holes that are also found in the membrane surround these proteins.

A number of procedures are employed to modify the drug's plasma concentration once it has been delivered into the systemic circulation, whether by intravascular injection or absorption from any extravascular source. These procedures may be separated into three

groups: intravascular injection, extravascular injection, and absorption from any extravascular source. In the industry, these processes are referred to as "disposition processes." The medicine enters the circulation after being delivered, where it is finally absorbed by the body. The distribution route has an influence on both the pace and the efficacy of absorption. When medicine is administered intravenously, absorption is complete, ensuring that the whole amount is delivered throughout the circulatory system. Other means of medication administration could only result in partial absorption, which would lower the medicine's bioavailability.

## *2.2 OBJECTIVES*

- This unit's goal is to look at how pharmaceuticals are transported both within and outside the body.
- In addition, learners learn about pharmacokinetics, which is a quantitative analysis of how medications move through, through, and out of the body.
- To define the drug distribution and disposition, excretion and elimination of drugs, and the pharmacokinetics of elimination in addition to drug absorption through various routes.
- In addition, we examined a number of pharmacokinetics related to drug development.
- Learners able to learn about membrane-active drugs, sulphonamides, enzyme stimulation and inhibition, drug metabolism, xenobiotics, and the role of drug metabolism in medicinal chemistry.

## *2.3 CHEMICALS ARE TRANSFERRED ACROSS THE MEMBRANE*

Moving the medicine across biological membranes is a necessary stage in the pharmacokinetic process. The nonpolar hydrocarbon chains are embedded in the matrix to form a continuous sheet, and the polar groups of the phospholipid and cholesterol molecules (glyceryl phosphate attached to ethanolamine/choline or the hydroxyl group of cholesterol) are oriented at the two surfaces of the biological membrane. The biological membrane has a thickness of around 100 microns. Extrinsic and intrinsic protein molecules can be detected adsorbed on the lipid bilayer. On the cell surface, glycoproteins or glycolipids can develop as a result of attachment to polymeric sugars, aminosugars, or sialic acids. Depending on the

type of cell or organelle they are located in; various membranes can have quite different lipid and protein compositions. While the proteins are floating freely through the membrane, they can join and organise themselves. Some of the intrinsic pores, which are those that run the length of the membrane, surround the small aqueous holes. There are also gaps or channels in some epithelial and endothelial cells that might be referred to as paracellular. Other adsorbed proteins contain enzymatic, carrier, receptor, or signal transduction properties.

The following routes enable the passage of drugs through membranes:

### 2.3.1 Passive diffusion

This is the mechanism that bears the most significance. Because villi and microvilli give such a large absorptive surface area, non-polar lipid-soluble drugs are able to be efficiently absorbed from the gastrointestinal tract, and more specifically from the small intestine. Taking vigorous action Because of this, a particular carrier is required. Mechanisms of active or facilitated transport are responsible for the absorption of polar compounds that exist naturally in the body. These include carbohydrates, amino acids, and vitamins. There is competition for transport through the carrier between drugs that are mimics of the molecules in question. Lithium, methotrexate, L-dopa, and 5-fluorouracil are some examples of such substances. The presence of food and the timing of drug administration in relation to meal times can be important factors that affect absorption. Other factors that affect absorption include:

1. Surgical interference with gastric function (a gastrectomy reduces absorption of several drugs);
2. Disease of the gastro-intestinal tract (the effects of such disease are unpredictable); and
3. Surgical interference with gastric function (gastrectomy reduces absorption of several drugs). Food and drink can bind to and dilute medications, alter the rate at which the stomach empties, and increase blood flow in the mesenteric and portal circulations;
4. The capacity of gut flora to metabolise medications can have an effect on how well pharmaceuticals are absorbed.
5. Drug metabolism by enzymes in the gastro-intestinal epithelium, such as cytochrome P450 family 3A (CYP3A).

6. Drug efflux back into the gut lumen by drug transport proteins, such as P-glycoprotein (P-gp) and ABCB1. Alterations in gut flora, such as those caused by concurrent use of antibiotics, have the potential to disrupt enterohepatic recycling, which can lead to a reduction in the effectiveness of oral contraceptives.

The following is a description of the absorption process for drugs that are taken orally:

**a.** Medications that are nonionized and lipid-soluble are absorbed rapidly by the stomach and intestines.

**b.** Acidic chemicals: salicylates, barbiturates, etc. are acidic compounds that mix in stomach fluids. These pharmaceuticals are readily absorbed by the stomach in a short amount of time.

**c.** Morphine, quinine, and a few additional medications fall into the category of highly ionised basic pharmaceuticals. These nutrients can only be absorbed via the duodenum.

**d.** The rates of abortion and dissolution control the administration of medicines that are taken in the form of solid doses.

**e.** The ingestion of food has a negative impact on the amount of medicine that is absorbed into the body. One illustration of this would be the interaction between the antibiotic "tetracycline" and the calcium that is present in milk. Other drugs can also create complex molecules when combined with elements of food. The majority of these medicines are absorbed more quickly and effectively when they are taken on an empty stomach.

**f.** Ionized drugs: Oral administration of ionised pharmaceuticals, such as streptomycin and neostigmine, does not result in optimal absorption of the drug.

**g.** Insulin is an example of a medication that may be taken orally and subsequently metabolised by the peptidase enzyme that is found in the digestive system. In a manner analogous to that of penicillin G, which is rendered useless when taken orally because it is damaged by acid, this antibiotic is given through intramuscular injection.

When many medications are consumed at the same time, a phenomenon known as the luminal effect of drugs can occur. This causes the drugs to combine into an insoluble complex. To lessen the severity of this effect, you will need to take two pills at intervals of

around two to three hours apart. Some examples of drugs that fall within this category are iron preparations, tetracycline with an antacid, and phenytoin with sucralfate.

### 2.3.2 Filtration

When we talk about filtration, what we mean is the transfer of a drug between the aqueous and paracellular pores of the membrane. Utilizing the solvents' hydrodynamic flow will speed up this process. The average pore size is 4A°. The size and molecular weight of the medication are crucial factors in filtering. If the drug molecules are too tiny to fit through the pores, they simply pass through the membrane. However, intestinal mucosal cells and RBCS have extremely tiny apertures compared to intestinal capillaries, which have large paracellular gaps (approximately 40 A°).

### 2.3.3 Transportation having a specific purpose

As it diffuses over the cellular membrane, the medication travels along the gradient of concentration. Because they disintegrated in the lipoidal matrix there, drugs that are soluble in lipids were allowed to get through the biological barrier. A drug with high lipid solubility can quickly enter the membrane and build up to higher quantities there.

The pH of the pharmaceuticals impacts how quickly they ionise since, in general, the great majority of drugs are weak electrolytes. They accomplish this in the following way:

1. Acidic drugs with a pH that is in line with stomach fluids, such as aspirin, whose $pk_a$ value is 3.5. The organ that absorbs these drugs is the stomach.
2. The body is significantly ionised by common medications like atropine, which has a $pk_a$ value of 10. They are not absorbed into the body until the digestive system.
3. Unionized acidic medications can flow through the stomach mucosal cell's surface membrane. In the cell, where the pH is 7.0, these dredges likewise change back to their ionised state before gradually dispersing into the extracellular fluid. The term "ion trapping of medicine" refers to this phenomenon.
4. When given intracellularly, common medications reach higher concentrations.
5. In urine with an alkaline pH, acidic medications ionise very fast. They do not diffuse back into the renal tubules, therefore they are quickly removed.
6. Basic drugs will be removed more quickly if the urine is acidified.

The medications go via either the paracellular gaps or the membrane's aqueous pores during the filtering process. The process proceeds more swiftly when an accessible osmotic pressure gradient is present. The bulk of cells, including intestinal mucosa and RBC, have relatively tiny holes (4 A°), which prevents drugs with molecular weights more than 100 or 200 from entering them. The rate of blood flow determines whether or not substances with a larger molecular weight, such as albumin, can pass through capillaries.

## 2.3.4 Transport requiring special considerations:

This comes in two different forms:

1. Transport by carriers
2. Pinacytosis

**1. Transport via carrier:**

When a drug interacts with a carrier that is already present in the biological membrane, a complex is created. The carrier transport system operates in this manner. Energy is needed for this sort of transport, which travels against the gradient of concentration. Moving actively, the metabolism is slowed down by toxins. This necessitates a certain form of transportation. Among the naturally occurring polar molecules that can be absorbed by active or assisted transport channels are sugars, amino acids, and vitamins. These compounds' analogues-similar drugs-compete with one another for the carrier's attention. Other examples include lithium, L-dopa, methotrexate, and 5-fluorouracil (which compete with sodium ions for absorption).

**2. Pinocytosis**

Pinocytosis is a type of endocytosis, which is a process by which cells absorb molecules from the environment in a non-specific manner. In pinocytosis, the cell takes in small droplets of extracellular fluid, along with its dissolved molecules. This process allows cells to take in substances that are necessary for their growth and development. In medicinal chemistry, pinocytosis plays an important role in drug delivery. Drugs can be encapsulated in the pinocytic vesicles, which can then be taken up by the cells, allowing for more efficient and targeted delivery of the drug to the desired location. Pinocytosis can also be used to study the uptake of drugs by cells, which can be used to optimize drug delivery and improve drug efficacy and safety.

## *2.4 ABSORPTION OF DRUGS*

Two of the most crucial parameters that impact how effectively a drug may be absorbed and, as a result, how different administration techniques may be used for the particular medication, are the speed and depth at which a drug can permeate cellular phospholipid membranes. Drugs that are more lipid-soluble can flow through them but are blocked by them if they are more water-soluble. The majority of the time, taking a medication orally is the most practical way to take it, and the digestive tract's role in absorption is among the best-known.

Pharmaceuticals must cross phospholipid membranes in the absence of intravenous delivery in order to reach the systemic circulation. This depends on the medication's solubility in lipids and the amount of membrane space available for absorption. Due to the villi and the microvilli, the ileum has a very large area of membrane that is open to absorption. On rare occasions, polar medications can be absorbed via specialised transport channels (carriers). Even if total absorption occurs, not all of the dosage could reach the systemic circulation. This may occur if the medication is broken down by the gut's epithelium, carried back into the lumen of the intestine, or broken down in the liver, which can remove the drug from the portal blood before it enters the systemic circulation through the hepatic vein. Even if absorption is complete, any of these things might still occur. Presystemic metabolism, often known as "first-pass" metabolism, is the term used to describe this kind of metabolism.

Before a medicine given intravenously may be said to have been absorbed, it must first cross the biological membrane. When a medication enters the body's circulation from the site of administration, this is known as absorption. The precepts mentioned previously in this line control how drugs are absorbed. The following are the variables that impact absorption:

a. **Aqueous solubility:** In order to be absorbed, a medication must first be dissolved in an aqueous biophase if it is in a solid state. The medication will be absorbed into the body more quickly if taken as a liquid as opposed to a solid or an oily solution.

b. **Concentration:** A drug is absorbed more quickly when administered in the form of a concentrated solution as opposed to one that is diluted.

c. **Surface area:** A greater drug absorption surface area is linked to a faster uptake of the medication.

**d. The absorbent surface's vascularity**

The blood flow removes the drug from the site of absorption and maintains a gradient of concentration across the biological membrane due to the vascularity of the absorbing surface.

**(A) Drug Absorption:** The method of distribution can have an impact on a drug's ability to be absorbed.

**(i) Oral route:**

The oral delivery of a medicine is one method that may be utilised to create local effects within the gastro-intestinal tract. Antacids are one example, and sulphasalazine is another. Sulphasalazine is a medication that distributes 5-amino salicylic acid (5-ASA) to the colon, which helps people with ulcerative colitis remain in remission for longer. Oral medication administration is preferable to intravenous drug administration since it is not only safer but also more convenient for the patient. There are two primary pathways that the digestive tract uses to absorb drugs (fig. 1).

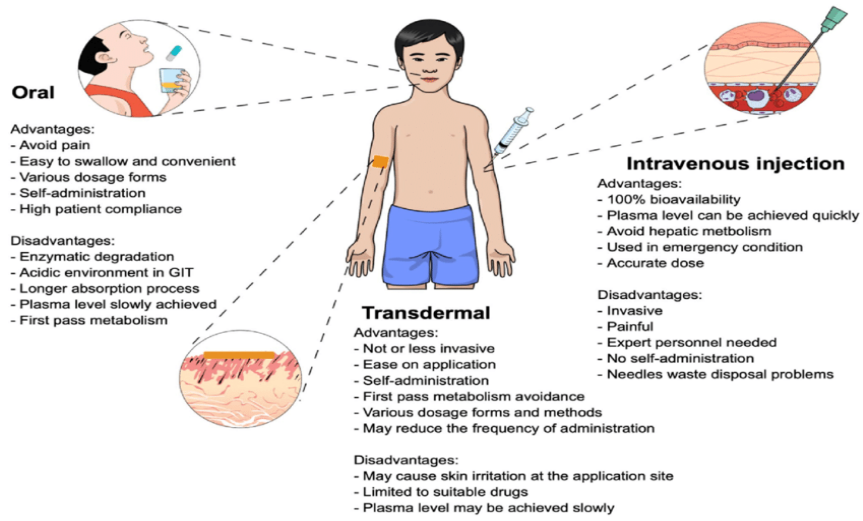



**Figure 2.1.** Showing the two most common ways for administering medicine are enteral and parenteral.

The rate of drug absorption at the intramuscular site is significantly higher than that at the subcutaneous site; nevertheless, absorption via either route is often more quicker and more dependable than absorption via the oral route. By increasing blood flow, the application

of heat as well as working out your muscles can speed up the process of medication absorption.

The capillaries get the medication as a direct deposit as a result of these approaches. Because of the great porosity of the capillaries, even large, lipid-insoluble molecules and ions are able to move through them without being obstructed. Absorption of extremely big molecules often occurs in the lymphatic system.

**(ii) Intravenous:**

The following are some advantages that come with this:

1. A rapid onset of action (such as morphine for analgesia or furosemide for pulmonary edoema);
2. The prevention of presystemic metabolism, such as with the infusion of glyceryl trinitrate in patients with unstable angina;
3. Medications that cannot be absorbed by the body through the digestive tract, such as aminoglycosides (gentamicin), and heparins, are given intravenously. Additionally, for this aim, drugs that are either very poisonous or extremely painful to inject intramuscularly are employed.
4. Because intravenous infusion may be readily managed, it makes it possible to precisely titrate drugs that have short half-lives. The leakage of cytotoxic medications from the vein must be prevented at all costs since it will result in considerable local damage and discomfort (e.g., vincristine, doxorubicin). In the case of medicines such as epoprostenol and sodium nitroprusside, this is of the utmost importance.

The following are some of the most significant problems associated with intranasal administration:

1. Once drugs have been administered, there is no way to get them back.
2. When the medication is given at too rapid of a rate, the right side of the heart receives the largest concentration.
3. Embolism caused by a foreign object or by airborne particles, sepsis, or thrombosis.
4. Toxic medication leakage or unintentional extravascular infusion leads in severe local tissue necrosis.

**5.** Accidental injection into the vascular system can lead to complications such as arterial spasm and peripheral gangrene.

**B. The application of topically applied sites:**

This technique of administering medicine includes the skin, cornea, and mucous membranes, and it is predicated on the drug's capacity to dissolve in lipids. On the other hand, only a selected few pharmaceuticals, such as estradiol, hyoscine, clonidine, and nitroglycerin, are able to significantly permeate healthy skin. It is possible for physostigmine to pass through the cornea if it has been unionized and become lipid-soluble; however, highly ionized neostigmine cannot. Injured skin has a higher rate of drug absorption than healthy skin does. When tannic acid is applied to burnt skin, the consequence is a condition known as hepatic necrosis. Corticosteroids that are given topically can have systemic effects and inhibit the pituitary and adrenal glands in a manner that is comparable to this. When they come into touch with the skin, insecticides that include organophosphates can have a harmful impact that spreads throughout the body.

## *2.5 DISPOSITION OF DRUGS AND THEIR DISTRIBUTION*

When a medicine is delivered, some of it goes into the systemic circulation and some of it goes directly to the tissues. The direction of the concentration gradient is from plasma to tissues, and as soon as a medication enters the blood stream, it begins to be disseminated to tissues in the body that were not previously exposed to any drugs. When medications are carried back and forth between the various fluid compartments of the body, this process is known as distribution. After being absorbed by the body, a medication will first enter the systemic circulation before being distributed throughout the body's fluids. The distribution of medicine is determined by its-

**a. Lipid dissolvability**

Ionization takes place at pH levels that are physiological. The extent of its interaction with proteins in tissue and plasma, the existence of transporters that is unique to each tissue.

**b. Variations in blood flow among regions**

The amount that seems to be distributed is the fictional volume of blood fluid in which a medication is equally distributed at a concentration that is equivalent to that in plasma. This definition assumes that the body has a single compartment and operates under the assumption that the body is a closed system.

**c. Redistribution**

When given intravenously (IV), a very lipid-soluble medication such as thiopentone rapidly goes to parts of the body with high blood flow, such as the brain, and causes general anaesthesia. Within a few minutes, it promptly recrosses the blood-brain barrier and is disseminated into the circulation before it reaches the tissues that receive less blood flow, such as muscle and adipose tissue. This happens before the tissue may be damaged.

**d. Drug binding to plasma proteins**

The vast majority of pharmaceuticals that may be discovered in the vascular compartment are connected in a way that is reversible to one or more plasma macromolecules. Some drugs are designed to dissolve easily in plasma water, however the vast majority of pharmaceuticals are linked to plasma components such as albumin. Substances including, but not limited to, globulins, transferrin, ceruloplasmin, glycoproteins, and lipoproteins. Basic medications often attach to multiple plasma proteins in addition to albumin, including lipoproteins and 1-acid glycoprotein, whereas the majority of acidic drugs bind to albumin as their primary target protein in the plasma (1-AGP). Because only the unbound medication is able to diffuse through the capillary wall, generate its systemic effects, be metabolised, and be excreted, the degree to which this binding occurs will have an influence on the distribution of the drug as well as the rate at which it is eliminated.

**e. The blood-brain barrier, sometimes known as the BBB**

In order for pharmaceuticals to enter the brain, they must either actively move through the endothelial cells that make up the central nervous system (CNS) or actively pass through these cells. Lipid-soluble medicines are able to reach the central nervous system with relative ease because they may dissolve in the membranes of endothelial cells. In most cases, polar or ionised medications are unable to penetrate the central nervous system because they are blocked from entering by the endothelial cells that line the blood arteries. In the central nervous system, slit junctions are not present. The blood-brain barrier is composed of tight junctions, which are formed by cells that are very closely spaced apart from one another.

**f. Barrier between the Blood and the Testes**

It appears that there is a barrier between the blood and the testes since the testicular tissue did not become stained after the intravascular injection of dyes. According to morphological studies, the barrier is thought to be positioned at the specialised Sertoli-Sertoli cell junction,

which is outside of the capillary endothelial cells. This can be found beyond the capillary endothelial cells. It would appear that the Pgp protein, which is an efflux transporter, contributes to the formation of this blood-testis barrier. This protein presumably has a role in blocking certain chemotherapeutic medicines from accessing certain testis areas, which makes it more difficult to treat the tumour. This makes it more difficult to treat the tumour.

**g. Embryonic Barrier**

The placental barrier is composed of many layers of tissue that work together to provide a physical barrier between the blood arteries of the mother and those of the baby during pregnancy. Any drugs that are able to get through this barrier and into the foetal circulation will have an adverse effect. In a manner analogous to that of the blood-brain barrier, the placental barrier does not prevent the passage of all drugs; rather, it only does so for a select few. The factors that control drug passage through any membrane, such as pKa, lipid solubility, and protein binding, are relevant in this context.

The ease with which lipid-soluble compounds are able to pass through the placenta is directly proportional to their lipid-water partition coefficient and the degree to which they are ionised. Drugs that are ionised or strongly polar have a difficult time crossing the placenta. However, the most majority of the drugs that are administered during labour and delivery are not strongly ionised and will pass through. They are generally weak bases with pKa values of about 8 and tend to be more ionised in the foetal circulation. This is because the pH of foetal blood is approximately 7.3, whereas the pH of mother blood is 7.44. Variations in the pH of the mother's and the foetus' blood can lead to differences in the amount of a medicine that is absorbed by the foetus and the mother during pregnancy.

**Among the elements affecting drug distribution are:**

I. Permeability of capillary spaces

II. A comparison of blood flow to the amount of tissue mass

III. Binding to certain organs as well as the concentration of plasma proteins,

IV. Differences in pH across different areas

The various possible modes of transportation, including unique features of permeability possessed by tissue membranes. Once the medication has been absorbed into the blood stream, it will be ready to be transported to the various tissues in the body. A drug's distribution can be affected by a number of parameters, including its solubility in lipids,

differences in regional blood flow, binding to plasma and tissue proteins, and ionization at physiological pH.

The distribution of the medication will continue until there is a balance between the bound and unbound forms of the drug. When the human body is considered to be a single, homogeneous compartment that has an apparent volume of distribution equal to volume v, the medication is promptly and equally disseminated throughout the body.

Given intravenous dose V = Intravenous dose administered / Plasma concentration

According to the definition, "V" is the volume that would be able to contain the entire drug that is in the body if its concentration were the same as it is in plasma.

Absorption of medications into the cerebrospinal fluid and the brain: Blood capillaries in the brain are characterized by having traits such as tight junctions and tiny inercellular holes. Capillaries lined with endothelial cells are shielded from damage by neural tissues in the brain. As a result, they contribute to the formation of a "blood-brain barrier." Choroidal epithelial tissues border the capillaries and produce a barrier that is analogous to the one that separates the blood from the cerebrospinal fluid.

P-glycoprotein is an efflux carrier that may be found in the endothelial cells of brain capillaries. It is responsible for the excretion of a variety of medications that enter the brain via other mechanisms. The chemical levodopa, which is a precursor to dopamine, has the ability to penetrate but is unable to enter the brain. The presence of monoamine oxidase, cholinesterase, and other enzymes in the capillary walls or cells lining the brain contributes to the formation of what is known as an "enzymatic blood-brain barrier." Due to the existence of this barrier, active versions of acetylcholine, catecholamines, and 5-hydroxytryptamine are unable to reach the brain.

Because placental membranes are lipoidal, they only let medications that are lipid-soluble to flow freely through them. On the other hand, the foetus will put on weight if the mother takes non-lipid-soluble drugs in high dosages or for a lengthy period of time while she is pregnant. As a result of this, the barrier is inadequate, and virtually every medicine that is administered to the mother has the potential to have an effect on the infant.

Acidic drugs attach themselves to plasma albumin, whereas basic drugs attach themselves to a single glycoprotein acidic in its structure. The extent to which a compound is able to bind to another molecule differs depending on the substance. For instance,

sulphamethaxine has a binding capacity of 30%, sulphadiazine has a binding capacity of 50%, sulphamethoxazole has a binding capacity of 60%, and sulfisoxazole has a binding capacity of 90%.

**The following is a list of some instances of how the binding of plasma proteins influences health:**

It is not possible to make use of drugs that have been bound. When the concentration of the free drug in plasma declines as a result of elimination and is in equilibrium with it, this fraction dissociates and disappears. If there is a particularly strong binding between the protein and the medication, the effects of the medicine will be prolonged.

A single medicine is capable of binding to several different locations on the albumin protein. On the other hand, it's possible for numerous medications to bind to the same location at the same time. Storage in tissues: Drugs can accumulate in certain organs or get attached to certain constituents of tissues. This process is known as storage. Tetracycline, for instance, attaches to the mitochondria, which is an intracellular organelle, while chloroquine, which is also an intracellular organelle, binds to the nucleus. Because of the effects of tetracycline on bone and teeth, emetine on the heart and skeletal muscle, and chloroquine on the retina, certain drugs have a high level of toxicity. This is the case with some of the following:

## 2.5.1 Elimination:

Ejection of waste and expelling of food after being taken into the body, drugs go through a process known as biotransformation, in which they undergo a series of chemical transformations while still inside the body. This leads to the production of metabolites, which may be eliminated from the body in a number of different ways, including the following:

1. **Urine**
2. **Faeces**

With the aid of exhaled air, the lungs are able to rid the body of gases and compounds that are flammable or volatile, such as alcohol, general anesthetics, and paraldehyde.When it comes to the elimination of drugs from the body, perspiration and saliva have an extremely insignificant role. Nevertheless, the excretion of thiocyanates, lithium, rifampin, heavy metals, and potassium iodide is also possible with the use of this approach.The majority of drugs enter breast milk by a process called passive diffusion. These medications include those

that are lipid-soluble and have a lower protein binding.The kidney is responsible for the excretion of any drugs that are water-soluble.

**Glomerular filtration:**

The glomerular capillaries include bigger holes that are able to filter out any medications that aren't attached to any specific protein. When a person has renal failure, their GFR will steadily decrease as they become older (after age 50).

Due to the fact that 99% of the glomerular filtrate is reabsorbed by the tubules, drugs that are lipid-soluble and that are filtered at the glomerulus are able to permeate back into the tubules. It is impossible for this to happen with drugs that are both insoluble in lipids and strongly ionized. This is a result of the approaches detailed below.

When urine has an alkaline pH, weak acids are more likely to ionise and have less of an opportunity to be reabsorbed.When urine has an acidic pH, weak bases ionise more and are reabsorbed less than when urine has a neutral pH. Implementing this principle is essential if one wishes to rid the world of harmful drugs.

Within the tube secretion process, there is an active transfer of organic acids and bases. When a baby is born, the tubular transport systems are not completely established. A large number of drugs, such as penicillin, aspirin, cephalosporins, and others, have extended durations of effect when administered to newborns. The development of these systems occurs during childhood.

## 2.5.2 Dynamics of the removal of drugs in the body

The process of drug elimination includes both the excretion of the drug and its metabolic inactivation. The study of the pharmacokinetics of drug elimination offers a framework that can be used to develop rational dosage regimens and modify those regimens to cater to the requirements of particular individuals. The following are examples of three different pharmacokinetic parameters:

**a.** Clearance

**b.** Bioavailability

**c.** The total amount that will be distributed

**(a) Clearance:** The clearance of a substance refers to the theoretical volume of plasma from which a drug is entirely removed in a certain length of time. Clearance is measured in terms of clearance. Clearance, often known as CL, can be defined as

Drug CL elimination rate = Rate of elimination of drug / Plasma concentration (c)

**(i) First order Kinetics:** As long as clearance is unchanged, the rate of drug elimination is directly proportional to drug concentration; alternatively stated, a constant amount of the drug that is present in the body is removed per unit of time. This holds true as long as clearance remains unchanged.

**(ii)** When given in increasing dosages, the kinetics of the drug alter, shifting from first order to zero order.

The length of time it takes for the concentration of medication in the plasma to drop to half of what it was at the beginning is referred to as the drug's plasma half-life.

Two slopes are discernible when the plasma concentration versus time graph for a medication with a one-compartment distribution and first order of elimination is displayed. These slopes are as follows:

(a) Initial a-phase fall owing to dispersion.

**Half-life, of the drugs. Plasma concentration:** Time plot of a drug eliminated by first order kinetics after intravenous injection elimination t½ is

Where ln2 = natural logarithm of 2 or 0.693

The "elimination rate constant" of the drug is denoted by the letter k, and it refers to the proportion of the drug's total concentration in the body that is expelled during a certain period of time.

K = Clearance (CL) / Volume of distribution (V)

$t_{1/2} = 0.693 \times V / CL$

Hence

For example, if the body weight of a drug is 2g and it is excreted at a rate of 0.1g per hour, the body weight of the drug would be 2g.

K = (0.1 - 0.05) / 2

The following are some of the ways the medications can be eliminated from the body:

1. -50% drug is eliminated from body
2. -75% (50+25) drug is eliminated
3. -87% (50+25+12.5) drug is eliminated
4. -93.75% (50+25+12.5+6.25) drug is eliminated

### 2.5.3 Administration of a medicine in a continuous fashion:

Following is an example of how the dosage rate may be computed given the therapeutic plasma concentration of the medication and the fact that its clearance has been measured.

Dose rate = target Cpss x Clearance

Dose rate = (target Cpss x Clearance) / Fraction

In the case of certain medications, the Michaelis-Menten kinetics dictate that elimination take place according to zero order kinetics over the therapeutic range. The relation between dose rate and CPSs is linear when drug elimination occurs according to first order kinetics.

In this particular scenario, the rate of medication removal is represented as:

The Drug Elimination Rate = (Vmax) (C) / Km + C

**Goal/Target-level strategy:**

Dosage for loading: In order to reach the desired concentration, it is necessary to first provide either a single dose or a few doses that are rapidly repeated, it may be expressed as

Loading dose = (Target plasma concentration x Volume) / Fraction of drug (F)

Maintenance dose rate = Target plasma concentration x clearance (CL) / Fraction of drug (F)

The bioavailability of medication is at its 100% when it is administered intravenously; however, when it is consumed orally, it is significantly reduced. This is due to the fact that

I. There is a possibility that some of the drugs will be absorbed.

II. The medicine that was absorbed may undergo first-pass metabolism in the liver, the intestinal wall, or for bile excretion, among other possible destinations.

The quantity of a medicine in an oral formulation made by the same manufacturer in different batches may be the same (chemically equivalent), but it may not yield the same blood level, which would indicate that it is physiologically in equivalent.It is necessary for a medicine

that is administered in solid form to first be broken down into active drug particles before it can be absorbed.Tablets and capsules both include a variety of chemicals, including binders, lubricants, diluents, stabilizing agents, and other compounds. Details about the manufacturing process, as well as the type of these, Particle size, solubility, crystal form, and other physical characteristics of the drug all affect how quickly it dissolves. Other physical characteristics of the drug include its crystalline form. The variance in bioavailability may have been brought on by the dissimilar speeds at which dissolution and disintegration take place.

## *2.6 PHARMACOKINETICS IN DRUGS DEVELOPMENT PROCESS*

The data from pharmacokinetic studies are utilised to make the distinction between active drugs that have good and bad pharmacokinetic characteristics. For example, substances that have poor absorption, high first-pass metabolism, and an inappropriate half-life (either too long or too short) will typically be discarded in favour of substances that have better pharmacokinetic properties. This is because of the importance of pharmacokinetics. The field of pharmacokinetics is utilised at every stage of the drug development process, from preclinical through Phase IV clinical trials. In most cases, the law requires that preclinical studies be conducted in order to define the absorption, elimination, distribution, clearance, $t_{1/2}$, and Vd of all drugs that are already on the market as well as those that will be developed in the future. It is possible, in theory, to anticipate how the chemical would behave in humans by using all of these criteria, scaled up from trials conducted on animals; however, the correlation is often just approximative. The same criteria are utilised for Phase I clinical studies. When determining whether or not additional research into a potential drug is necessary, the pharmaceutical industry takes into consideration the bioavailability and t1/2 results from phase I as one piece of evidence. Through the use of phase I clinical studies, it is also possible to forecast the optimum dosage levels for the anticipated patient population. The pharmacokinetic characteristics for the sick condition, age (both young and elderly), and gender need to be evaluated in the Phase II studies once it has been demonstrated that the medicine is both safe and effective in the Phase I trials. It is especially important to determine the impact that impaired liver and kidney function have on the elimination of the drug in patients who have these conditions in order to avoid the harmful effects that can be caused by the use of a new drug at a dose level that is too high in patients who already have these conditions. With the assistance of all of these data, new dosage forms for both already

existing pharmaceuticals and brand-new treatments may be put through rigorous testing to verify that they are both secure and effective. By preventing or delaying absorption at the place of administration:

To use a drug for longer time, it is generally advantageous to modify a drug by following manner:

**(i) By prolonging absorption from site of administration**

a. **Oral:** When the medication is taken orally, a semi permeable membrane is used to control how much of the drug is released from the capsule. Resins, polymers, and other substances are used to coat drug particles. This helps to ensure that the active components are released evenly throughout the gastrointestinal tract.

b. **Parenteral:** The subcutaneous and intramuscular injection of medicine in an insoluble form or as an oily solution pallet implantation and biodegradable implants may be used to develop drug action.

c. **Transdermal:** pharmaceutical administration is becoming more common. This method involves applying medication to the skin, either in the form of an ointment, sticky patches, or strips.

**(ii) By increasing plasma protein binding:** Medicines have been produced by increasing the plasma protein binding, which may be released gradually in the free active state. Example: sulphadoxine.


**(iii) By delaying renal excretion:** Since drug tubular secretion is an active process that may be stopped by a competing agent, such as probenecid, the duration of action of penicillin and ampicillin is lengthened. This is accomplished by delaying renal excretion.

## *2.7 INTRODUCTION OF PHARMACODYNAMICS*

The relationship between the presence of the medication at the site of action and the impact that occurs is referred to as "pharmacodynamics" (PDs). This link takes into account the length of time that an individual is exposed to the drug as well as the intensity of both

therapeutic and unfavourable effects. The effect that a drug has when it is present at the site of action is determined by the degree to which it has an affinity for the receptor there. An impact that can be seen may be the end result of either a direct reaction or a chain of processes brought about by the attachment of a drug to a receptor. Antibiotics were used in a few of the investigations that were conducted utilising the PDs concept. Over the last ten to fifteen years, owing to the emergence of resistance to an increasing number of antimicrobial medications, there has been a discernible rise in the level of interest in the role that PDs play in the development of antimicrobials.

The study of pharmacological effects, also known as pharmacodynamics, tries to shed light on the whole mechanism of action, as well as the sequence of events and the relationship between dosage and response.

In pharmacodynamics, the effects of a drug may also be altered by the simultaneous administration of another medication or by other factors.

### 2.7.1 Affects of the Drug:

**a.** The stimulation

**b.** Depression

**c.** Irritation

**d.** Replacement

**e.** Cytotoxic Action

**2.7.2 Mechanism of Drug Action:** The following are the components that together make up the mechanism of action of the drug:

**a.** Physical Action

**b.** Chemical Action

**c.** Through Enzymes

### 2.7.3 Enzyme stimulation

In reality, narcotics are just dangerous substances. It is unusual for pharmaceuticals to have an effect on enzymes. The enzymes are stimulated by endogenous mediators and modulators, such as pyridoxine, which acts as a cofactor and boosts the activity of decarboxylase, and aderenaline, which stimulates adenylyl cyclase. Other examples include acetylcholinesterase,

which is stimulated by acetylcholine, which is stimulated by acetylcholine. Stimulation raises the affinity of an enzyme for the substrate, which in turn reduces the rate constant (Km) of the enzyme process. Several other drugs, such as methicillin, are responsible for activating the microsomal enzymes. Methicillin is also responsible for activating the enzyme penicillinase, which is produced from a mould.

The creation of the protein that makes up microsomal enzymes, such as glucuronyl transferase and cytochrome P-450, may be increased by the interaction of several pesticides, compounds known to cause cancer, and drugs with DNA.

## 2.7.4 Enzymes Inhibition

**In most cases, pharmaceuticals work by blocking enzymes. There are two different types of inhibition:**

**a.** Non-specific inhibition: Enzymes may be inhibited in a non-specific manner by strong acids, salts of heavy metals, phenols, alcohol, and formaldehyde. Alkalies can also have this effect. Enzymes may have their tertiary structures changed by chemicals and drugs, which also causes the protein component of the enzymes to become denatured and inhibits their activity.

**b.** Specific inhibition: A great number of pharmaceuticals inhibit just a single enzyme while having no effect on other enzymes. The following are the two groups that fall under this kind of inhibition:

**I.** Competitive Inhibition (Equilibrium Type)

**II.** Non competitive Inhibition

This kind of medication is designed to compete with the typical substrate or coenzyme in order to bring about a new kind of equilibrium. If the concentration of the substrate is increased enough, the drug may be removed, and the maximal rate of reaction can be maintained without any changes.

**a.** Competition exists between para-aminobenzoic acid (PABA) and sulfonamides for the bacterial folate synthetase enzyme.

**b.** In the race for dopa decarboxylase, levodopa faces competition from carbidopa, methyldopa, and other medications.

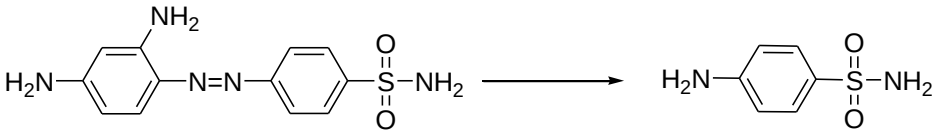
**c.** Acetylcholine is in competition for the cholinesterase enzyme with both physostigmine and neostigmine.

**d.** A drug may also compete with a coenzyme. For example, warfarin is in direct competition with vitamin K, which is a coenzyme for an enzyme that assists the liver in the production of clotting factors.

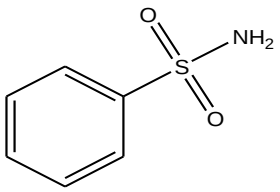
In the third kind of inhibition, known as noncompetitive inhibition, the inhibitors interact with a neighboring area rather than the catalytic site of the enzyme. Because of the inhibitor, the enzyme undergoes a change that renders it incapable of performing its normal catalytic role. In this particular kind of inhibition, Km is unchanged.

## 2.7.5 Sulphonamides

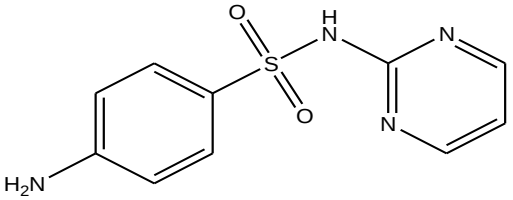
In the year 1935, the daughter of Gerhand Domagk, a physician who worked in the dye business in Germany, suffered through a terrible streptococcal sickness that was brought on by a pin prick. Domagk gave the lady an oral dose of the dye prontosil, which had been shown to inhibit streptococcal development in mice. The woman was suffering from streptococcal infection. In 1936, Ernest Fourneau demonstrated that the human body is capable of breaking down prontosil to generate sulphanilamide, which is the real active chemical and is particularly poisonous to streptococci. Prontosil to Sulponamide.



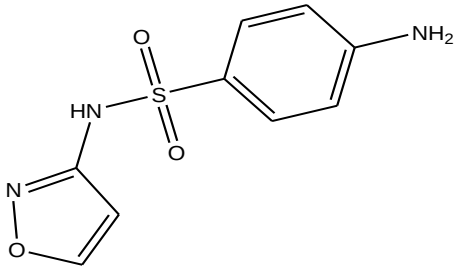

Prontosil Sulphonilamide



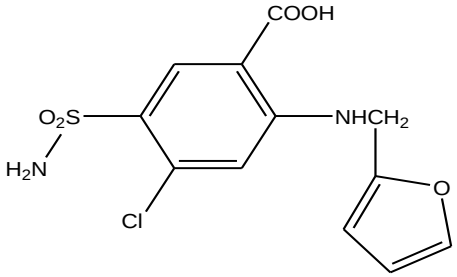

benzenesulfonamide




4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide




4-amino-*N*-(isoxazol-3-yl)benzenesulfonamide




Furosemide

### 2.7.6 Medications that have an effect on membranes

Volatile anaesthetics, which are sometimes referred to as general anaesthetics, are classified as membrane-active medications. General anaesthetics are depressive medications that cause a partial or complete lack of pain perception and, in some cases, unconsciousness as well. Anesthesia is the term used to describe this condition of unconsciousness.

The open drop method, in which a liquid anaesthetic is dropped on gauze or another absorbent material supported on the patient's nose and mouth by a wire frame, has been used to administer gas or volatile liquid anaesthetics. When a patient takes an anaesthetic, its concentration in the blood quickly increases when the anaesthetic moves towards tissues. When this concentration reaches in the arterial blood supply, the brain acquires the anaesthetic very quickly.

## *2.8 DRUGS THAT ACT ON MEMBRANES*

There have been recorded instances of many membrane-active drugs. Cyclopropane, despite the fact that it is a drug that is active on membranes, is not used any more due of its explosive properties; thus, fewer individuals are utilizing it these days.

1) **Ethers:** Low-molecular-weight hydrocarbon ethers have an increasing anaesthetic action as their chain length rises. Divinyl ether and its analogues are not particularly useful as anaesthetics. Alkane, alkene, alkyne, and alicylic ethers are powerful membrane-active

medicines. However, only those that have been replaced with vinyl and ethyl have been studied as anaesthetic medications.

2) **Halogenated anaesthetics:** The anaesthetic effectiveness of membrane active ethers may be improved while at the same time the flammability of the anaesthetic can be lessened by adding halogen atoms (CI, Br, or F). These compounds are comprised of:

3) **Fluorinated hydrocarbons:** Fluorinated hydrocarbons, such as flurorene, methoxyflurane, isoflurane, and sevoflurane, were created to be the perfect anaesthetics. Fluorinated hydrocarbons are used in medical procedures.

4) **Nitrous oxide:** Nitrous oxide is the chemical with the highest membrane-activating potential that is also the least toxic.

5) **Ketamine hydrochloride:** Ketamine hydrochloride, which is also known as 2-(o-chlorophenyl)-2-methyl- aminocyclo hexanone hydrochloride, is a drug that is active on membranes and has a rapid start of action, a high therapeutic index, and a short half-life. The inadvertent consumption of trichloroethylene and 1,1,1-trichloroethane has been connected to the development of brain injuries.

## *2.9 DRUG METABOLISM*

The term "metabolism" refers to the chemical change that takes place inside the body with regard to the medicine (biotransformation). It is important to convert nonpolar compounds that are lipid-soluble into polar substances that are lipid-insoluble in order to prevent these molecules from being reabsorbed in the renal tubules and to enable their excretion. The liver is the primary organ involved in the metabolic process of drugs, however the kidneys, intestines, lungs, and plasma are all involved. It is necessary for some pharmaceuticals to go through the process of metabolization in order for them to change from their inactive (pro-drug) forms into their active forms. It is necessary to take the drugs, then there is a pharmacological response, and eventually, the medications are eliminated from the body. The enzymes found in the liver and other organs may cause the drugs to undergo a wide variety of alterations to their chemical composition.

### 2.9.1 The investigation of xenobiotics and drug metabolism

Drug metabolism typically results in detoxication, oxidation, reduction, and other enzyme-catalyzed processes; as a result, a metabolite with hazardous or therapeutic properties may be

formed. Thus the body undergoes enzymic transformations of medications and other compounds, including some natural products, food additives, insecticides, preservatives, environmental and agrochemicals, etc., which typically result in the loss of pharmacological effectiveness.Despite the fact that the liver serves as the primary location for drug metabolism, some drug metabolising enzymes are also present in the kidney, lung, plasma, neurological system, and gastrointestinal tract.Drug metabolism should be significantly impacted by liver dysfunction. In a liver that has been injured or has a persistent illness, medication metabolism capacity is significantly impacted.The term "first-pass effect" or "presystemic hepatic elimination" refers to the liver's capacity to metabolise a chemical in a single pass.After being absorbed through the digestive tract, substances can be removed from the blood by the liver.Urine is where medicines and their metabolites are primarily excreted. if chemicals such as medications are not digested.

The animal body excretes medicines and their metabolites via a variety of routes in addition to urine. The other excretion pathways include:

**a.** Bile

**b.** Saliva

**c.** Lungs

**d.** Sweat

**e.** Milk

It is well established that bile is the primary route for the excretion of a great number of endogenous and foreign substances.

## 2.9.2 The processes that are involved in drug metabolism

**a. Phase 1 Reaction**

This biotransformation pathway is comprised of the oxidation, hydroxylation, reduction, and hydrolysis-enzymatic events that take place. In phase 1 reactions, either a new functional group is appended to the drug molecule or an existing functional group is modified. Phase 1 reactions may also entail the elimination of a functional group. As a direct consequence of this change, the drug will become more polar, which will make it potentially simpler to excrete.

**b. Phase 2 Reaction**

Conjugation Reactions Phase 2 reactions, also known as phase 2 reactions, are made up of conjugation reactions. Through the use of a different group in lieu of the functional group that was initially present, these enzymatic synthesises are able to disguise the functional group. A few amino acids, glucuronic acid, and acetyl of sulphate groups are included in these groupings. These groups increased the polarity of the medication and sped up the pace at which it was excreted.

**c. Dealkylation of Ether and Thioether**

The production of an acetal or thio-acetal is accomplished by hydroxylating the alkyl groups on sulphur and oxygen.

**2.9.2.1 Microsomal Reductions**

Several enzymes are involved in the process of reducing medications so that their azo and nitro groups may be metabolised. This process is known as microsomal reduction. These enzymes are included inside the microsomal systems. For example, the nitro group of the hypnotic benzodiazepine nitrazepam is transformed to the7-amino derivative of the compound.The most important of them has been an enzyme known as alcohol dehydrogenase, which is responsible for catalysing the transformation of ethanol into acetaldehyde.

**2.9.2.2 Hydrolysis**

A wide variety of tissues have enzymes that are able to hydrolyze esters and amides. These tissues include the brain, kidney, blood, and liver microsomes. The weighty esters go through a process called delayed hydrolysis and typically go through the body without being altered or hydrolyzed in any way.

**2.9.2.3 Phase 2 Reactions-Conjugation**

The inclusion of this group helps to limit the action of the functional group, and it also reduces the lipophilicity of the molecule, which makes it easier to excrete. The production of glucuronides is the conjugation reaction that occurs the vast majority of the time.

Acids make acid-type glucuronides, amines produce N-glucuronides, and thiols produce S-glucuronides. Alcohols and phenols are the two types of compounds that may create ether type glucuronides. These glucuronides are even less lipophilic than the original drug because they are more soluble in water and more acidic than the original medication. As a result, there is a greater likelihood that they will be ionized at neutral pH levels. The bulk of

the process of eliminating urine is carried out by the kidneys. Other conjugations that are not as important include acetylation, glycine conjugation, and those that lead to the production of mercapturic acid.

## *2.10 BIOTRANS FORMATION*

The term "biotransformation" refers to the chemical changes that occur when a drug is metabolised by the body. Transforming non-polar compounds, also known as those that are lipid-soluble, into polar substances, also known as those that are lipid-insoluble, assures that the substances will be ejected from the body and will not be reabsorbed in the renal tubules. Numerous hydrophilic pharmaceuticals, including neostigmine, decamethonium, and streptomycin, amongst others, are incapable of undergoing biotransformation and are therefore excreted in their original form.

### 2.10.1 Several Distinct Categories of Biotransformation Reactions

**[i]** Natural reactions

**[ii]** Synthetic processes and reactions

**[i] Natural processes and reactions**: Non-synthetic processes are responsible for the production of metabolites, which may either be active or inactive. Responses from Phase 1 may be divided into the following categories:

**(A) Oxidation:** Oxidation is the most important step in the metabolic process of drug elimination. During this step of the process, hydrogen is driven out while oxygen is brought in. Hydroxylation, N-or O-dealkylation, oxidative deamination, oxygenation at C, N, or S atoms, and other similar reactions are some examples of chemical reactions.

In most cases, the liver will include a collection of monooxygenases, which are enzymes that catalyse various oxidative reactions. Benzodiazepines, phenothiazines, paracetamol, phenytoin, steroids, barbiturates, and paracetamol are some of the drugs that are on the list.This oxidation happens to a number of different drugs, including theophylline. The pace at which drugs are metabolized

1. CyP 3A 4/5: This isoenzyme is responsible for about fifty percent of the drug biotransformation process. The kidney, the colon, and the liver are all potential locations for its discovery. Its action may be inhibited by a wide variety of compounds, some of which include clarithromycin, erythromycin, itraconazole, verapamil, and others.

2. CYP 2 D6: This isoenzyme is responsible for the transformation of about 20% of medications.
3. CYP 2C8/9: This enzyme plays a role in the metabolism of approximately 15 commonly used drugs, including several that have a narrow margin of safety, such as phenytoin and warfarin.
4. CYP 2 C 19: is an enzyme that is responsible for the breakdown of over a dozen regularly prescribed drugs, including omeprazole and lansoprazole, amongst others.

**(ii) Synthetic processes and reactions**

Phase 2 has been reached by these conjugation reactions. The vast majority of the metabolites that are generated as a result of these biotransformations are inert. The production of anything new requires a significant amount of energy. Conjugation refers to the process in which a drug or its phase I metabolite is joined with an internal substrate such as amino acids or carbohydrates.

**a.** The most important step in the synthesis process is the conjugation of glucuronic acid with a molecule that has a group of hydroxyl or carboxylic acid.

**b.** Acetylation: This process involves the utilization of acetyl coenzyme-A to conjugate molecules that include amino or hydrazine residues. Some examples of these types of chemicals are sulfonamides, hydralazine, p-amino sulfanilamide, isoniazid, and others.

## 2.10.2 The Significance of Drug Metabolism in Medicinal Chemistry

In the search for new and more effective therapies, there has been a considerable uptick in interest in medications that change metabolism, as well as an increase in the field's use of such drugs. In order to transform the inactive form of the azo dye, prontosil, into the active form of sulphanilamide, the body makes use of a metabolic reduction process. The metabolic acetylation of the sulphonamides led to the creation of substances with less acetylation and more soluble acetylated derivatives, both of which helped to prevent kidney damage from crystallisation in the renal tubules. This was done in an effort to protect the kidneys from damage.

The analgesic properties of phenacetin, also known as p-ethoxyacetanilide, are contingent upon its conversion via O-dealkylation into an active metabolite known as acetaminophen, also known as p-hydroxyacetanilide. This is just one of the many significant aspects of drug research that is connected to metabolism.It is believed that the antidepressant

effects of imipramine and amitriptyline may be modulated by desipramine and notriptyline, which are secondary amine metabolites of the tertiary amines imipramine and amitriptyline, respectively.It is only when cholroguanide (paludrine), also known as 1-(p-chlorophenyl)-5-isopropylbiguanide, is converted by the human body into 1-(p-chlorophenyl)-2, 4-diamino-6-dimethyl-dihydro-1,3,5-triazine that it is able to inhibit the growth of malaria-causing parasites.

Arsine-oxide is the name of the chemical that is formed when the arseno compound known as As=As is subjected to an oxidation process. In spite of its higher toxicity, arsine-oxide is a superior medicinal molecule that is formed during the process of drug metabolism. Mandelic acid was first used as a genito-urinary antiseptic treatment, which led to the finding that it is excreted intact and had potent bactericidal action in urine with an acidic pH. Mandelic acid was initially used as a therapy for genito-urinary infections.

After being broken down by the body, medications might potentially result in the following:

**a. Inactivation:** The vast majority of drugs, in addition to their active metabolites, are rendered inactive or much less active by this process. Morphine, chloramphenicol, and other similar substances are examples.

**b. Active metabolite derived from an active drug:** It has been shown that many different medications undergo a partial transformation in the body's metabolic processes, which results in the formation of one or more active metabolites. In addition to this, their bioavailability is increased, in addition to a number of other significant pharmacokinetic properties.

I. Prodrug

II. Active form

III. Sulindac

IV. Sulfide metabolite

## *2.11 SUMMARY*

If you had achieved the aforementioned objectives, then you would have finished this unit successfully. Let's revisit our past discussions:

- The study of how different medications interact with and are metabolised by the body is referred to as pharmacokinetics. Several aspects of drug absorption, distribution,

biotransformation, and excretion are discussed in this article.It is very necessary for gaseous anaesthetics to be expelled from the body through the lungs. The rate at which medicine is eliminated from the lungs is determined by a factor called the blood/air partition coefficient.

- The mechanisms that the kidney uses to transport acids and bases have numerous characteristics with the systems that transport active drugs.
- The act of distributing drugs and then removing them from circulation is sometimes referred to as the disposal of drugs.
- Clearance refers to the quantity of plasma that a drug should be able to hypothetically eliminate from the body in a certain length of time (CL).
- Determining a drug's apparent volume distribution, biological half-life, and rate constants for absorption and elimination are examples of the kind of calculations that fall under the pharmacokinetic parameters. Compartmental analysis is one method that may be used in order to investigate these parameters, which include the blood as well as the urine.
- The study of the effects of drugs, also known as pharmacodynamics, aims to shed light on the complete action-effect chain as well as the connection between dose and effect.
- The stimulation of enzymes by medications, which are in reality alien chemicals, is a very exceptional occurrence. There are several endogenous mediators and modulators that are significant to the activation of enzymes. Stimulation leads to a rise in the affinity of an enzyme for the substrate, which, in turn, causes a drop in the rate constant of the process.
- The inhibition of specific and non-specific enzymes is a common mode of action for many pharmaceutical medicines.
- The breakdown of prontosil in the human body results in the production of sulphanilamide. The sulfa medications, which are derivatives of sulphanilamide, were the very first man-made chemicals to be shown to be effective against pathogenic organisms, and they were named after their chemical structure.
- A medication is said to be membrane active if it is able to inhibit the development of a cell wall, as is the case with antibiotics.
- The term "xenobiotics" originates from the Greek words "xenos," which means "foreign," and "bios," which means "life" (life). Any compounds that are not normally found in

biological systems are referred to as xenobiotics. Carcinogens, pesticides, and drugs are all covered in this category. The liver is responsible for detoxifying these chemicals the vast majority of the time.

- The term "biotransformation" refers to the process by which a drug undergoes a chemical change inside the body. The primary sites for the metabolism of drugs are located in the plasms, liver, kidneys, colon, and lungs. The liver is home to the vast majority of enzymes involved in metabolism.

## *2.12 MCQs TYPE QUESTION*

### A. Multiple Choice Questions

1. Which of the following is NOT a pharmacokinetic parameter?

A. Bioavailability B. Therapeutic index

C. Volume of distribution D.Clearance

2. Which of the following is NOT a factor that affects the pharmacokinetic parameters?

A. Age B. Weight

C. Genetics D. Food intake

3. The duration of action of a drug is related to:

A. Volume of distribution B. Half-life

C. Bioavailability D. Clearance

4. Which of the following is NOT a type of drug metabolism?

A. Hydrolysis B. Oxidation

C. Reduction D. Photodegradation

5. Which of the following statements about pharmacodynamics is TRUE?

A. It is the study of how a drug is eliminated from the body.

B. It is the study of how a drug is absorbed and distributed in the body.

C. It is the study of how a drug affects the body.

D. It is the study of how a drug is metabolized in the body.

6. Which of the following is NOT a factor influencing drug response?

   A. Age B. Gender

   C. Genetics D. Environmental conditions

7. The therapeutic index of a drug is the ratio of:

   A. The minimum effective concentration to the maximum tolerated concentration

   B. The maximum effective concentration to the minimum tolerated concentration

   C. The minimum toxic concentration to the maximum tolerated concentration

   D. The maximum toxic concentration to the minimum tolerated concentration

8. The time between drug administration and the onset of therapeutic effect is known as:

   A. Absorption time

   B. Distribution time

   C. Onset of action

   D. Metabolism time

9. Which of the following statements about drug interactions is TRUE?

   A. They can result in an increased efficacy of the drug.

   B. They can result in an increased toxicity of the drug.

   C. They can result in an decreased toxicity of the drug.

   D. They can result in an decreased efficacy of the drug.

10. The process by which a drug is absorbed and distributed in the body is known as:

   A. Metabolism B. Excretion

   C. Pharmacodynamics D. Pharmacokinetics

11. The process by which a drug is eliminated from the body is known as:

   A. Metabolism B. Excretion

   C. Pharmacodynamics D. Pharmacokinetics

12. Which of the following is NOT a route of drug administration?

   A. Oral B. Topical

C. Sublingual D. Intravenous

13. Which of the following is NOT a factor influencing drug absorption?

A. Chemical stability of the drug

B. pH of the gastrointestinal tract

C. Blood flow to the site of administration

D. Rate of metabolism

14. The concentration of a drug at the site of action is known as:

A. Bioavailability B. Half-life

C. Pharmacodynamics D. Therapeutic index

15. The time it takes for a drug to be reduced to half its original concentration is known as:

A. Bioavailability B. Half-life

C. Pharmacodynamics D. Therapeutic index

**Answer Key**

1 B 2 C 3 B 4 D 5 C 6 D 7 A 8 C 9 B

10 D 11 B 12 C 13 D 14 A 15 B

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## *2.14 TERMINAL QUESTIONS*

### A. Short type questions

**Q. [1]** What is the difference between pharmacokinetics and pharmacodynamics?

**Q. [2]** What is the absorption phase in pharmacokinetics?

**Q. [3]** What is the primary function of metabolism in pharmacokinetics?

**Q. [4]** What is the difference between non-linear and linear pharmacokinetics?

**Q. [5]** What is the purpose of pharmacokinetic modeling?

**Q. [6]** What is the main difference between concentration-dependent and time-dependent pharmacodynamics?

**Q. [7]** What is the role of binding in pharmacodynamics?

**Q. [8]** What is the role of drug receptors in pharmacodynamics?

**Q. [9]** What is the difference between agonists and antagonists in pharmacodynamics?

### B. Long Answer type questions

**Q. [1]** What is the difference between pharmacokinetics and pharmacodynamics?

**Q. [2]** What is the absorption phase of pharmacokinetics?

**Q. [3]** Describe the distribution phase of pharmacokinetics.

**Q. [4]** What is the metabolism phase of pharmacokinetics?

**Q. [5]** Describe the excretion phase of pharmacokinetics.

**Q. [6]** What is the relationship between pharmacokinetics and pharmacodynamics?

**Q. [7]** What are the components of pharmacokinetics?

**Q. [8]** What are the main factors that influence the pharmacokinetics of a drug?

# UNIT 3: ANTINEOPLASTIC AGENTS

## Contents:



## *3.1 INTRODUCTION*

These medications, often known as antineoplastic agents, are used to treat cancer. Neoplasm (new growth), another name for a cancer cell, is an uncontrolled and aberrant cell division. More than any other illness, cancer is feared. Lung cancer, digestive tract disease, and lung disease make up at least 50% of all major diseases, and only in the 20th century. Due to the long-term impacts of air pollution, particularly from smoking, lung cancer has risen sharply in particular. Any abnormal muscle growth, which does not risk life, is commonly referred to as a tumour.

(a) **Malignant tumor:** Malignant tumours are also referred to as malignant neoplasms.

(b) **Non-lethal or malignant tumor:**This plant is regarded as a non-malignant or malignant plant that does not spread since it is not cancerous. Metastasis is a secondary plant growth factor that can spread to other parts of the body.

### 3.1.1 Classification of Cancer Cells

**(1) Sarcoma:** Sarcomas are malignancies that develop in the muscle, fat, blood vessels, lymphatic vessels, and fibrous tissue. They can also develop in the bone. E.g.,Osteosarcoma. Before a multicellular organism's first embryo develops into an organ. The cancer sarcoma is brought on by the mesodermal tissue growing abnormally.

**(2) Carcinoma:** The most prevalent form of cancer created by epithelial cells, carcinomas. Adenocarcinomas make up the majority of malignancies of the breast, colon, and prostate (cancer on glandular cells). The skin, its appendages, and nerve tissue are all made of ectodermal cells. Carcinoma is a cancer originating from ecto- or endodermal cells.

**(3) Carcinosarcoma:** A carcinosarcoma is a highly malignant tumour that resembles both a sarcoma and a carcinoma.

**(4) Leukemia:** The term "leukaemia" refers to a type of leukaemia that involves abnormal leukocyte proliferation. Leukemias are cancers that start in the bone marrow, which produces blood. E.g., Blood cancer (Leukemia; increaseno. ofWBCs).

**(5) Lymphoma:** Lymphoma is a malignancy that starts in lymphocytes (T cells or B cells). In lymphoma, aberrant cells accumulate in the body's lymph nodes, lymph arteries, and other organs. The two primary kinds of lymphoma are as follows:

**a. Hodgkin lymphoma** – Reed-Sternberg cells, which are aberrant lymphocytes, are found in people with Hodgkin lymphoma. Usually, B cells are the source of these cells.

**b. Non-Hodgkinlymphoma**–Non-Hodgkin lymphoma is a broad classification of malignancies that originate in lymphocytes. The malignancies can develop from either B or T cells and can spread swiftly or slowly.

**(6) MultipleMyeloma**: Another sort of immune cell called plasma cells are the origin of the malignancy known as multiple myeloma. Kahler disease and plasma cell myeloma are other names for multiple myeloma.

**(7)** **Melanoma**: A cancer that starts in cells that develop into melanocytes, which are specialised cells that produce melanin, is known as melanoma (the pigment that gives skin its color).

**(8)** **Germ CellTumors**: Sperm or egg-producing germ cell tumours.

**(9)** **Blastoma:** Blastoma is a prevalent condition among kids. The tumour is the one that resembles an embryonic or immature tissue. Nephroblastoma, medulloblastoma, and retinoblastoma are a few examples.

**(10)** **Neuroendocrine Tumors**: Cells that release hormones into the blood in response to a signal from the neurological system are the source of neuroendocrine tumours.

**(11)** **CarcinoidTumors**: One variety of neuroendocrine tumour is the carcinoid tumour. Typically, they are slow-growing tumours that affect the digestive system (most often in the rectum and small intestine).

**(12)** **Teratoma:** A teratoma is a tumour that originates from all three embryonic layers.

## *3.2 OBJECTIVES*

1. To study of cancer chemotherapy, role of alkylating agents, antimetabolites, antibiotics, mitotic inhibitors, hormones and natural products.
2. To study of Antineoplastic agents are used in tumor or cancer treatment.
3. Leraners able to synthesis of mechlorethabamine , cyclophosphamide, melphalan, Uracil, mustard and 6-mercaptopurine.
4. Leraners able to learn recent development of cancer chemotherapy, hormones & Natural products.

## *3.3 CHARACTERISTIC FEATURE OF CANCER*

1. Unchecked proliferation (raise telomerase, reduce apoptosis) (RNA dependent DNA polymerase expression).
2. Unchecked differentiation and function loss
3. Invasiveness–Propensity to spread to unharmed cells.
4. Metastasis-Spread to another bodily area

## *3.4 ANTINEOPLASTIC AGENTS*

Tumor or cancer treatment involves the use of antineoplastic drugs. The role of alkylating agents, antimetabolites, carcinolyte antibiotics, mitotic inhibitors, and combinations of mechlorethabamine, cyclophosphamide, melphalan, Uracil, mustard, and 6 - mercaptopurine with the most recent developments in cancer chemotherapy, hormones, and natural products are discussed in the current chapter's research on cancer chemotherapy. The following step provides an overview of cardiovascular diseases, drug inhibitors, and combinations of cardiovascular medications such amyl sitrate, sorbitrate, diltiazem, guinidine, verapamil, metyedopa, aterolo, and oxyprenolol.

(a) They can interact with other organelle cells' cell membranes and nuclei.

(b) Antitumor medications can be used to stop cellular processes at any point of the cell cycle;

(c) They affect DNA-dependent enzymes that are necessary for the transcription and replication of cellular DNA, such as DNA or RNA polymerases.

## *3.5 CHEMOTHERAPY*

The anti-cancer treatments have a harder time completely eliminating all the cells of the bigger plant in this treatment because antineoplastic agents are allowed to enter the body and work on cells that may live in other organs. After 99.9% death, larger cells weighing 100 g and containing 10-11 cells will still include 108 cells, which are typically too big to regulate a patient's immune system. The most frequent side effects of chemical therapy are nausea, hair loss, and an elevated risk of infection, among other things. Antioplastic medications also cause the immediate destruction of healthy body cells, such as hair follicles, intestinal cells, and bone marrow cells that are involved in the immune system. Drugs used to treat cancer actually make the condition worse, although there are some exceptions. Over the past 30 years, advances in cancer chemotherapy have allowed for the treatment of several scattered cancers that were once fatal because to their natural progression.

### 3.5.1 Types of Chemotherapy

**(1) Combination therapy:** To stop cell division, the treatment of cancer requires a combination of medications. The water storage mechanism enlarges the tumour as soon as the chemical treatment is finished, thus while one medicine may reduce the growth of a tumour

but not eliminate all cells, it does not completely eradicate them. Many anti-cancer medications have a second ability to kill in cells in other stages of the cell cycle in addition to killing cells during DNA synthesis or mitosis, however they should be administered for a longer period of time. For instance, the 6-mercaptopurine-resistant leukaemia cell may be resistant to methotrexate.

**(2) Adjuvant chemotherapy:** Combination therapy is another name for adjuvant chemotherapy. the old portion of the tumour is removed using a combination of chemotherapy, surgery, and radiation. A significant tumour that was left outside the scope of surgery and (b) had metastases that were clinically far away. Both cell types are still in their infancy and are highly susceptible to medication delivery following surgery. Adjuvant chemotherapy is also used for colon cancer that has progressed to the lymph nodes in the intestinal wall and breast cancer that has migrated to the axillary lymph nodes beneath the arm.

## 3.5.2 ClassificationofAntineoplasticorAnticancerAgents

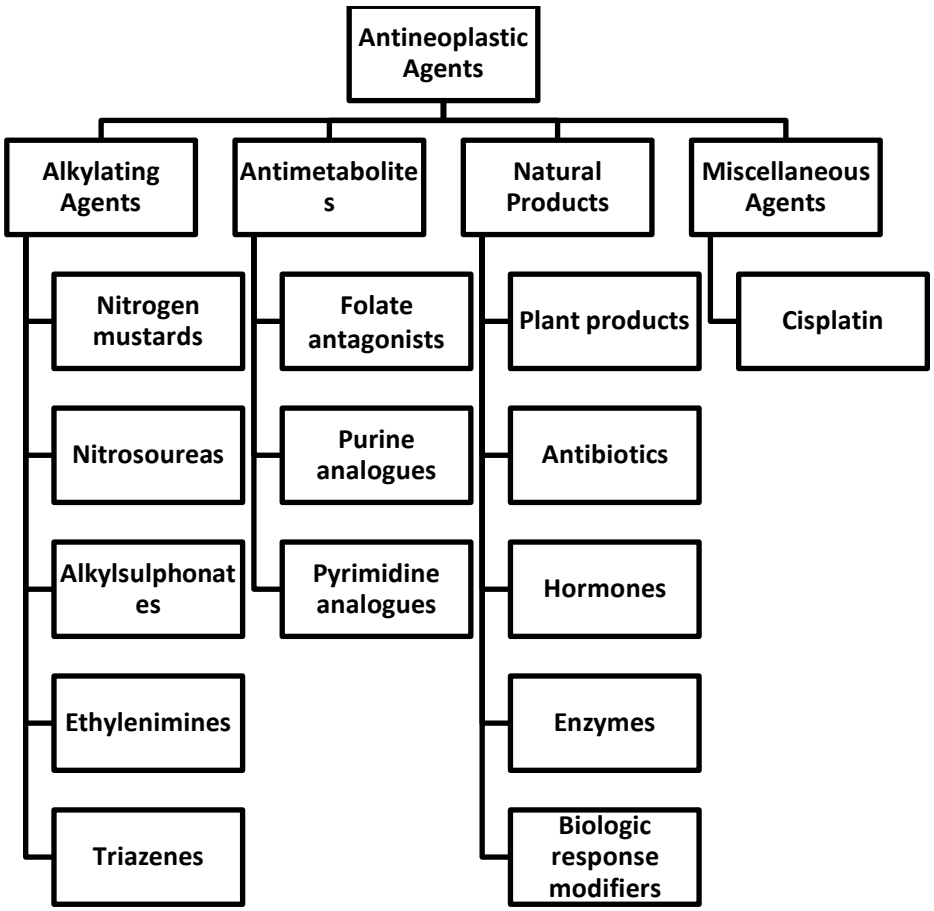



Fig 3.1Schematic diagram for classtification of Antineoplastic agents

### 3.5.2.1 Alkylating agents

A class of anticancer medications known as alkylating agents interferes with DNA to stop the growth of cancer cells. They are so named because they may modify negatively charged biological molecules like DNA and proteins by adding alkyl groups. Alkylating agents are among the first class of substances shown to be helpful in chemotherapy for cancer. Due to their well-established and strong clinical anticancer activity, they continue to be the most crucial elements of contemporary chemotherapeutic protocols (either alone or in combination with other medications).

Reactive alkyl groups are found in alkylating agents. An alkyl is a univalent reactive group with the general formula $C_nH_{2n+1}$ and solely carbon and hydrogen atoms organised in a chain, such as methyl, $CH_3$ (derived from methane), and butyl, $C_4H_9$ (derived from butane). Alkylating chemicals are capable of reacting with biological molecules like DNA and proteins, which disrupts cellular function by either killing the cell or stopping its growth. These compounds are utilised as anticancer treatments. Guanine, a nucleobase, is the biological functional moiety that is most frequently alkylated by these substances. Alkylating agents have two mechanisms for their anticancer effects: I by cross-linking two different DNA strands through a reaction with guanine nucleobases on the opposing strands of DNA, and (ii) by impeding or inhibiting the activities of vital DNA processing enzymes and thereby inducing apoptosis through a reaction with guanine nucleobases on a single DNA strand. DNA is cross-linked, making it hard for DNA to uncoil during cell division, inhibiting the expansion of the cell. Alkylating agents can be divided into two categories based on their reactivity: I monofunctional (monoalkylating, which alkylates nucleobases on a single DNA strand); and (ii) bifunctional (dialkylating – alkylate nucleobases on both DNA strands and crosslink them).

### 3.5.2.2 General mechanism of action

In aqueous solutions under physiological conditions, alkylating agents are a varied set of chemical substances that share the property of generating positively charged (electrophilic - electron deficient) alkyl groups. Alkyl groups with positive charges can react with basic, negatively charged (nucleophilic - electron-rich) groups found in DNA, proteins, and peptides. These events result in the addition of alkyl groups at oxygen, nitrogen, phosphorous, or sulphur atoms (nucleophilic centres), which changes how DNA and proteins operate biologically. In terms of their anticancer efficacy, alkylating drugs' interactions with

DNA nucleobases are the most significant. Guanine is the DNA nucleobase that is most frequently alkylated, and the alkylation predominantly takes place at the N7 position on guanine. Other nucleobases that have undergone alkylation include guanine, at the N1 and O6 positions, adenine, at the N1, N3, and N7 positions, cytosine, at the N3 position, and thymidine, at the O4 position.

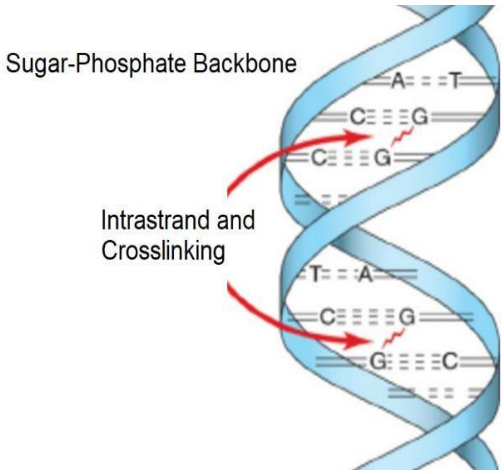
✓ AlkylatingtheDNAstands

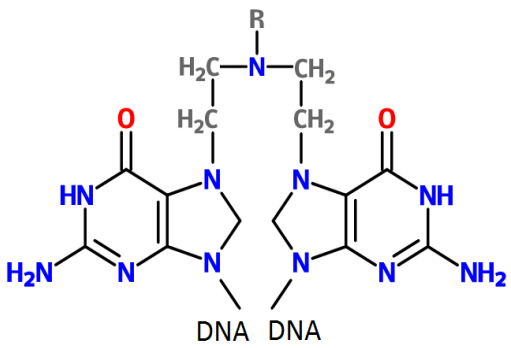
✓ Alkylating agents produce a highly reactive carbonium ion that instantly reacts with a DNA base pair that has an amine, hydroxyl, or sulfhydryl group as an electron donor.

✓ The majority of alkylating substances are bifunctional (have two alkylating groups) alkylating substances that can promote intrastrand cross linking of two nucleophilic sites in the DNA strand, such as N7 of guanine, N1 & N3 of adenine, and N3 of cytosine.

### 3.5.2.3 Role of alkylating agents in treatment of cancer

These are known as polyfunctional alkylating and are distinguished by having at least one active lakyl group and frequently two or more in the molecule performing significant biological functions. Alkylating substances affect DNA, RNA, and certain enzymes. These substances generate extremely effective carbononium ion intermediates that establish bonds with cell macromolecules to transfer alkyl groups there. Alkylating drugs were determined to be used cautiously in the treatment of lymphoid tissue tumours, such as lymphosarcoma and Hodgkin's disease, because these substances can harm the bone marrow and lymphoid tissue. The medications work well to shrink tumours, but they also kill healthy bone marrow.

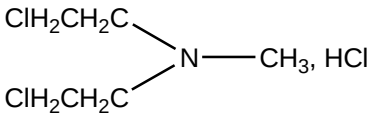



N7 interstrand crosslinked DNA

The creation of 7 guanine in each double-stranded DNA sequence, which results in the opposite link, is assumed to trigger the alkylating agents' reaction. This hinders mitosis and interferes with fiber division.

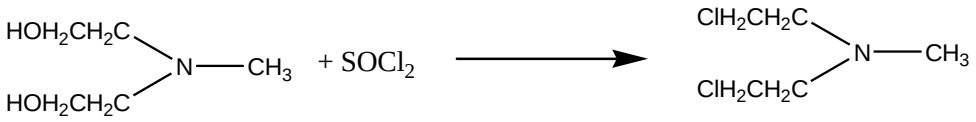
**(a) Mechlorethamine:** Mustine hydrochloride is another name for the first nitrogen mustard plant. It is commonly used as hydrochloride and has the chemical name N, N, bis (2-chloroethyl)-methyl amine.




Mustine Hydrochloride

**Consumption:** Mechlorethamine is mostly used as part of chemotherapy to treat non-lymphomas Hodgkin's and Hodgkin's disease. It can be used on animals to treat leukosis in chickens and lymphosarcoma and mast cell sarcoma in dogs.

**Synthesis:** Mechlorethamine can be synthesized with the reaction of diethanol 2.2 (methamino) and thionyl chloride.

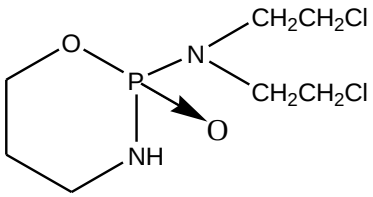



N; N'-bis (2 chloroethyl) methylamine

**Uses:**

It was utilized in the treatment of Hodgkin's disease, lung carcinoma, and other solid tumours. As a topical treatment for mycosis fugoides (T-cell lymphoma)

**(b) Cyclophosphamide:** The chemical structure of cyclophosphamide includes a phospharamide molecule and nitrogen. 2-bis (2-chlorethyl) amino acids with hydro-1,2,3-oxide phosphorinane-2-oxide is its chemical name.

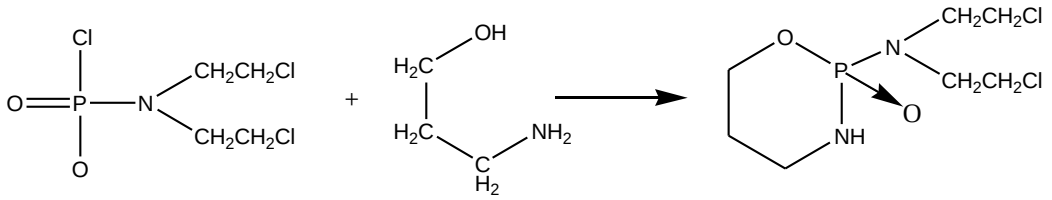



, $H_2O$

Cyclophosphamide

**Administration:** It can be administered orally, although oral absorption is only partially effective. In order to achieve optimum effectiveness, it is frequently administered intravenously.

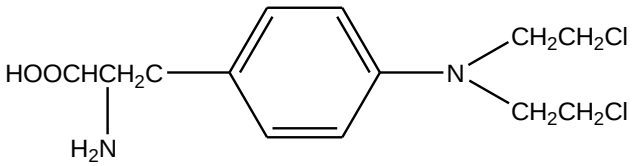
**Synthesis:** Bis-(2-chloroethyl)phosphotsmide dichloride and propanolamine can be used to mix cyclophosphamide




Bis-(2-chloroethyl) phosphoramide Propanolamine Cyclophosphamide

**Uses:** It include treating Hodgkin's disease, lung cancer, and other solid tumours, as well as acting as an immunosuppressant in conditions like multiple sclerosis, rheumatoid arthritis, and Wegener's granulomatosis.

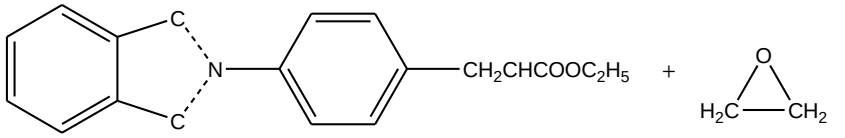
**(c) Melphalan:** A nitrogen mustard moiety is connected to the para-position of L-phenylalanine in melphalan, which is a 4-bis- (2-chloromethyl) amino L-phenyl alanine.



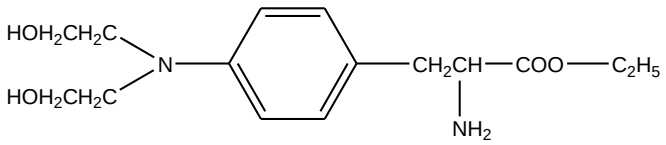

Melphalan

**Synthesis:**

It is made from L-N-phthalimido p7-aminophenylalanine ethyl ester, which creates an intermediate reaction with ethylene oxide, during the synthetic process. This substance produces 4-bis (2-choroethyl)-amino-L-phenylalanine etyl ester and phosphorus oxychloride. When hydrolyzed, melphalan is produced.

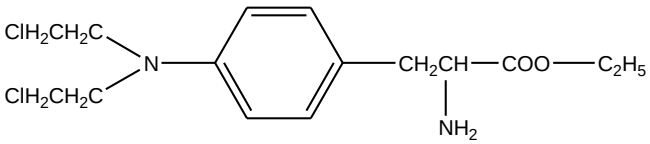



L-N-pthalimido p-amino phenylalanine ethyl ester ethylene oxide

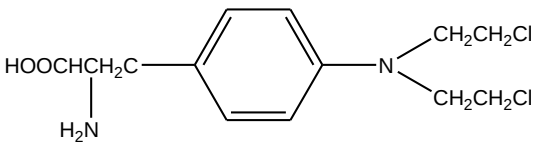



4-[Bis (2-chloroethyl)-amino] L-phenylalanine ethyl ester

$POCl_3$




HCl Hydrolysis




Melphalan

**Uses:**

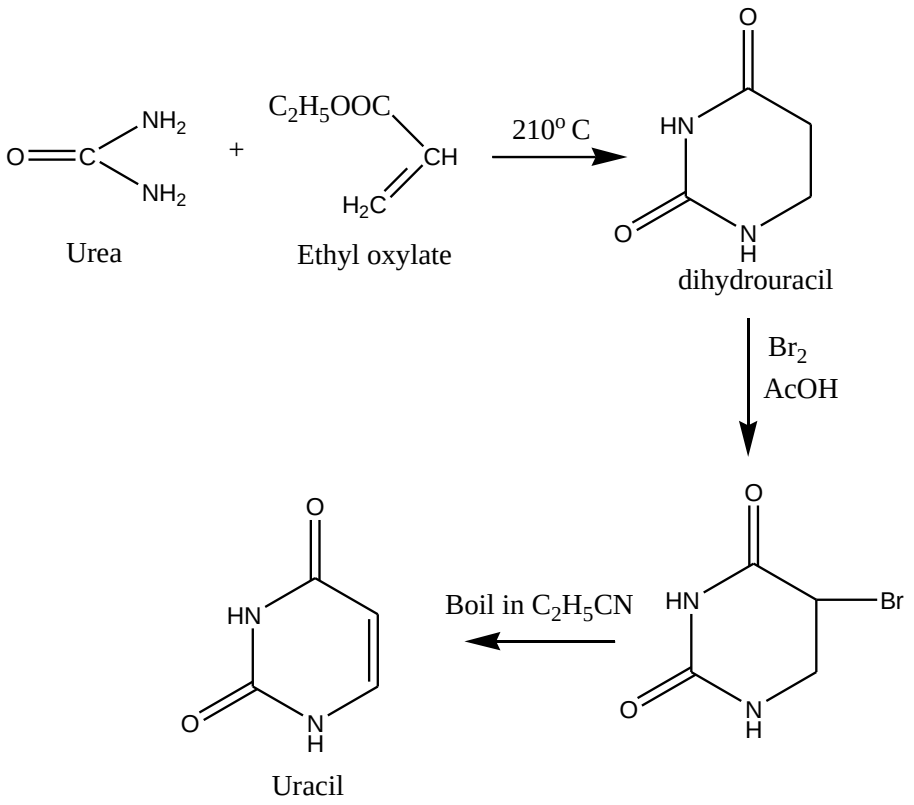
Uses include treating retinoblastoma, multiple myeloma, carcinoma of the breast and ovary, Hodgkin's disease, carcinoma of the lung, and other solid malignancies (Retinal Cancer).

**(d) Uracil**

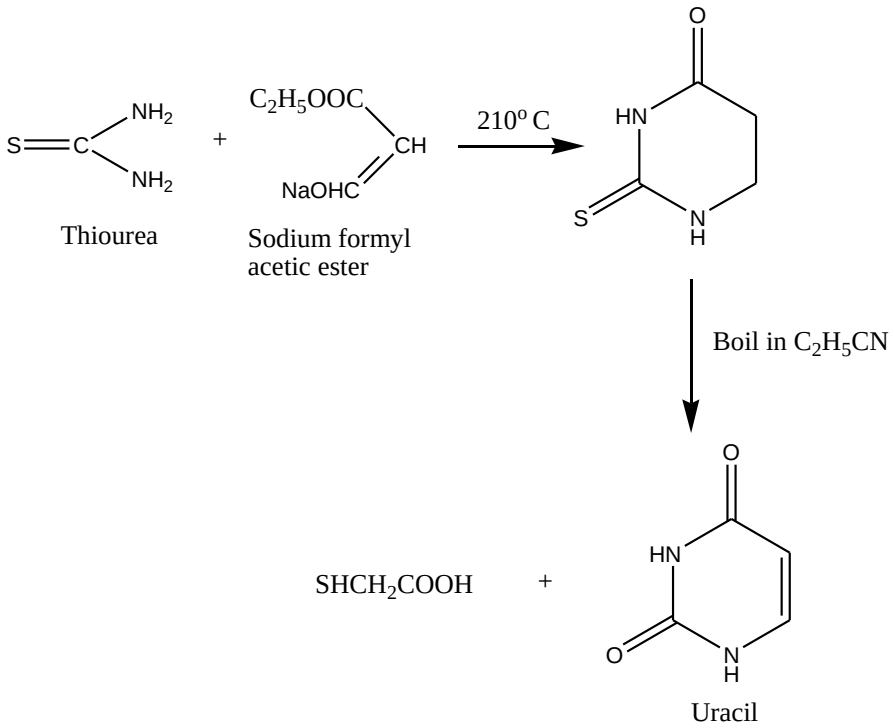
Uracil is 2, 4-di hydroxy pyrimidine. It is a hydrolysis product of nucleic acid.

**Synthesis:**

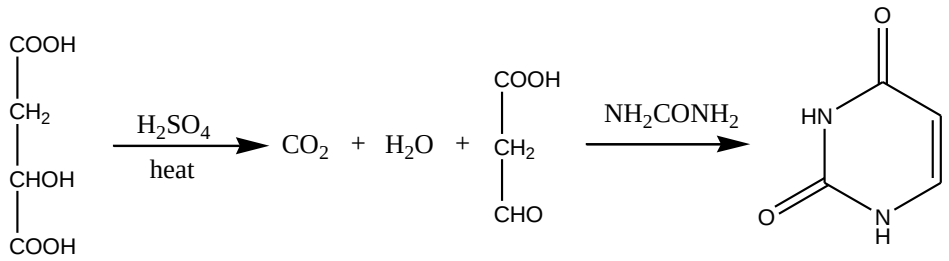
(1) First method:




(ii) Second method:



(iii) Third method:

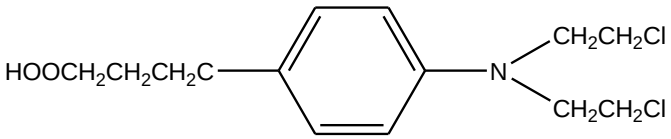



Malic acid

Uracil

**(e) Chlorambucil**

Chlorambucil is 4-[4-bis(2-chloroethyl)-aminophenyl]butyricacid.



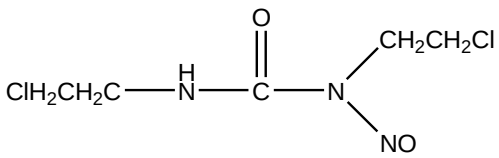

Chlorambucil

**Uses:**

Uses include treating Hodgkin's disease, lung cancer, various solid tumours, chronic lymphocytic leukaemia, non-lymphoma, Hodgkin's polycythemia, and ovarian cancer.

**(f) Carmustine**

Carmustine is 1,3-bis(2-chloroethyl)1-nitrosousea.

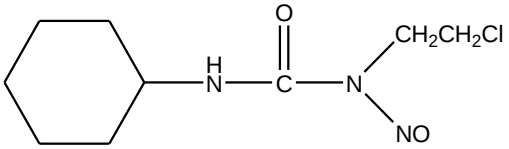



Carmustine

**Uses:** Hodgkin's disease, multiple myeloma, non-lymphomas, Hodgkin's brain tumours (due of its capacity to pass the blood-brain barrier), and multiple myeloma.

**(g) Lomustine**

Lomustine is 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.




Lomustine

**Uses:** Hodgkin's disease, lung cancer, malignant melanoma, brain tumours, and other solid tumours.

**(h) Busulfan (Busulphan)**

It selectively affects the bone marrow, inhibiting the production of platelets and granulocytes. It is 1,4-butanedioldimethanesulphonate.

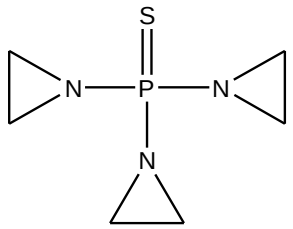
$H_3C\text{-}SO_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}SO_2\text{-}CH_3$

Busulfan

**Uses:** An immunosuppressant used to treat chronic granulocytic leukaemia.

**(i) Thiotepa**

Thiotepa is tris-(1-aziridinyl) phosphinesulphide.

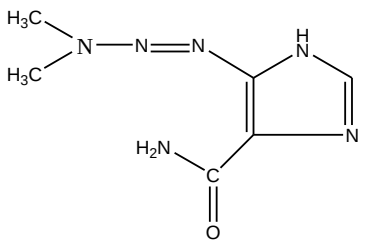



Thiotepa

**Uses:**Used to treat ovarian cancer, breast cancer, and several types of lymphomas.

**(j) Dacarbazine**

Decarbazine is 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide.




Dacarbazine

**Uses:** Used to treat sarcomas, Hodgkin's disease, and malignant melanoma.

### 3.5.1.4 Toxicology of alkylating agents

Following are the most frequent toxicities linked to using alkylating drugs to treat cancer.

**1. Hematopoietic toxicity:** In particular the suppression of granulocytes and platelets that is shown for 8–16 days after therapy, is the clinical dose-limiting toxicity for alkylating drugs in general. After 20 days, the toxicity typically goes away, and the levels of granulocytes and platelets recover to normal.

**2. Gastrointestinal toxicity (nausea and vomiting):** Damage to the gastrointestinal tract is a hazard that usually happens with high-dose regimens of alkylating drugs. It manifests as nausea and vomiting. Mucositis, stomatitis, esophagitis, and diarrhoea define these toxicities. Giving corticosteroids and antiemetics can help control this toxicity.

**3. Gonadal toxicity:** Alkylating agent treatments have been observed to result in testicular lesions that reduce ovarian follicles in female patients and deplete sperm in male patients, respectively.

**4. Pulmonary toxicity:** Alkylating agent-treated patients have also experienced pulmonary toxicities, which include interstitial pneumonitis and fibrosis, dyspnea, and nonproductive coughing that can result in cyanosis, pulmonary insufficiency, and mortality.

**5. Alopecia:** Although the link between alkylating drugs and alopecia was originally noted with the use of busulfan, this adverse effect is primarily linked to the use of cyclophosphamide and ifosfamide. Alopecia is brought on by the introduction of nicks into the hair fibres as a result of alkylating chemicals temporarily stopping the synthesis of hair in hair follicles.

**6. Teratogenicity:** In animal models, all therapeutically employed alkylating drugs result in teratogenicity, or developmental abnormalities. First-trimester mothers who were exposed to alkylating chemicals have been linked to foetal abnormalities, but not in the second or third trimesters.

**7. Carcinogenicity:** In patients receiving treatments that contain alkylating drugs, reports of leukaemia incidence and an increase in the frequency of solid tumour occurrence have been made.

**8. Immunosuppression:** It has been demonstrated that alkylating agents prevent the formation of antibodies. All alkylating drugs cause some level of immunosuppression, but chlorambucil, cyclophosphamide, and its analogues cause severe immunosuppression. As a

result, some autoimmune illnesses are now being treated using medicines like high-dose cyclophosphamide or chlorambucil without a bone marrow transplant.

## 3.5.3 Antimetabolites

Other substances created by the unique organisms in the body may contribute to the progression of cancer. For instance, the metabolism of cholesterol, cholic acid, etc. results in the production of methyl cholanthrene. Utilizing particular substances could help research the formation of these cancer-causing substances and even help treat cancer. Antimetabolites are the name for these substances.

### 3.5.3.1 General mechanism of action

Due to their near structural similarity to the metabolite, antimetabolites are medications that inhibit important cellular metabolic pathways (i.e., antimetabolites prevent the biosynthesis or utilisation of normal cellular metabolites).

### 3.5.3.2 Role of antimetabolites in the treatment of cancer

Antimetabolites prevent the synthesis of the pyrimidine nucleoside, which is required for DNA synthesis, pyrimidine, and folate, all of which are necessary for the metabolic process necessary for the survival or reproduction of cancer cells. Methotrexate is one of the principal examples of an antimetabolite. Fluorouracil, thioguanine, cytarabine, azathioprine, mercaptopurine, etc. Folic acid's antimetabolite is methotrexate. Folic acid is converted inside the cell first to dihydrofolic acid and then to tetra hydrofolic acid. The drug methotrexate has the ability to inhibit the enzyme dihydrofolate reductase, preventing the production of tetrahydrofolate, which is necessary for the fusion of purine and pyrimidine and the subsequent testing of DNA and RNA synthesis.

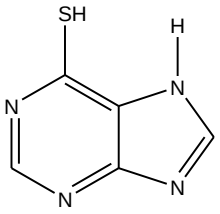
**(a) 6-Mercaptopurine**

A naturally occurring purine analogue known as adenine, which is a crucial part of DNA. It is purine 6-thiol chemically. Nucleic acid production interferes with the intercellular conversion of mercaptopurine into active nucleosides.

**Mechanism of action**

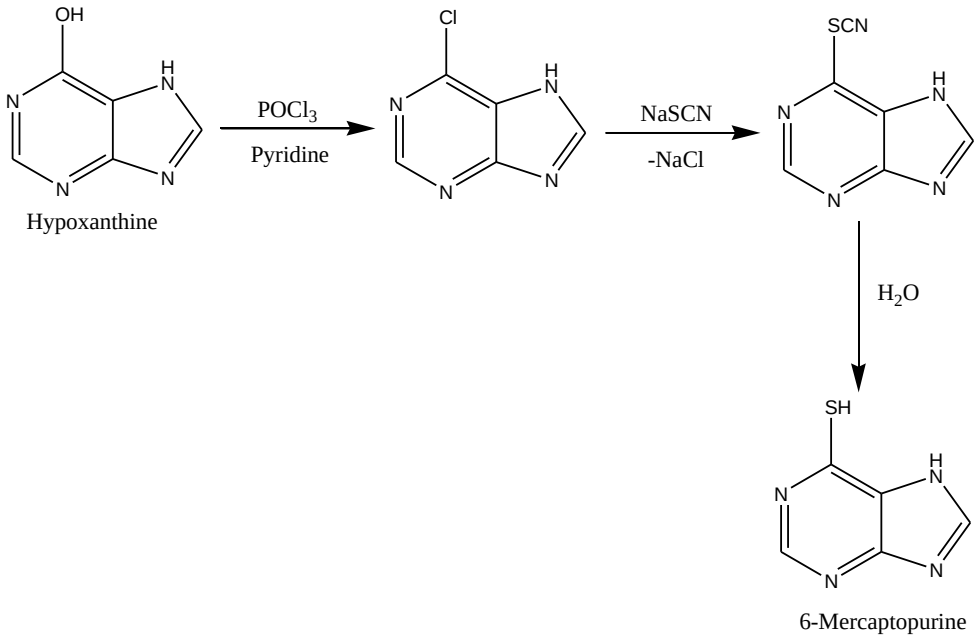
6-Mercaptopurine is metabolised to 6-methylmercaptopurine ribotide (MMPR) and thioguanylic acid in the human body, which are responsible for its cytotoxic effects. 6-Mercaptopurine is converted by hypoxanthine-guanine phosphoribosyl transferase (HGPRT)

to 6-thioinosinic acid (TIMP), which inhibits some enzymes involved in purine synthesis and consequently of DNA.




Mercaptopurine

**Synthesis**




**Physical properties:** Yellow, shiny, tasteless, odourless, and water-soluble are the physical characteristics. It is kept in tightly covered containers since it becomes dark when exposed to air.

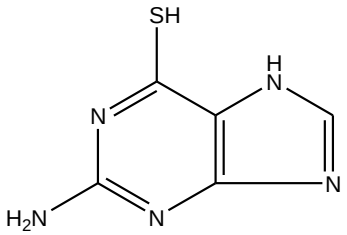
**Side effects:** Causes gut damage and bone marrow failure as side effects.

**Uses:**6-Choriocarcinoma, leukaemia, and chronic myelocytic leukaemia can all be treated with mercaptopurine.

**(b) Thioguanine**

Guanine is a purine analogue that occurs naturally and is a part of DNA. It is a 6-amino purine-6 (1H) thione chemically.

**Mechanism of action:** Purine nucleotide interconversion is inhibited, which is the mechanism of action. Strand breaks result from its absorption into DNA. It lowers the level of guanine nucleotides inside the cell, which prevents the formation of glycoproteins.




6-Thioguanine

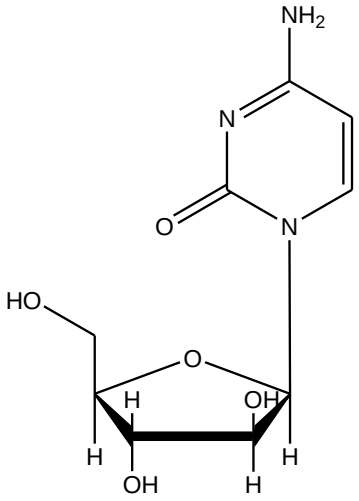
**Administration:**Thioguanine-sodium salt is administered intravenously and orally.

**Uses:**Thioguanine is a component of both cancer cells and healthy DNA.

**(c) Cytarabine**

An analogue of pyrimidine. It is 1-B-D arabinofuranosyl cytosine.

**Mechanism of action:** Cytarabine is transformed by the body into Ara-cytosine triphosphate, which inhibits DNA polymerase in a competitive manner and prevents DNA synthesis.




Cytarabine

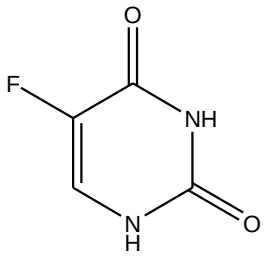
**Uses:**

Cytarabine is used as an antiviral medication in the treatment of encephalitis and acute non-lymphoblastic leukaemia. It is also used in the treatment of acute non-lymphoblastic leukaemia.

**(h) 5-Fluorouracil**

It is a pyrimidine analogue. Chemically, it is 6 = 2,4 (1H, 3H) dione of 5-fluoropyrimidine. In position 5 of the pyrimidine uracil, hydrogen takes the place of the fluorine atom.

**Mechanism of action:** This is a pyrimidine fluorinated analogue. Thymidylate synthetase, an enzyme that changes 2'-deoxyuridylic acid into thymidylic acid for DNA synthesis, is competitively inhibited by 5-fluorouracil, which is metabolised to 5-fluoro 2' deoxyuridine 5' phosphate (FdUMP). The "thymineless death" of cells is caused by the inhibition of DNA synthesis.




5-Fluorouracil

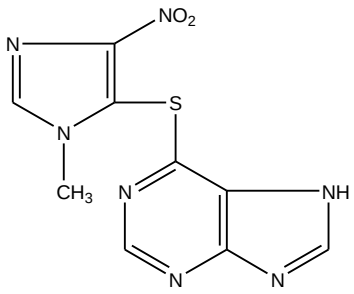
**Administration:** Because oral fluorouracil is absorbed following oral administration, intravenous fluorouracil should be used instead.

**Uses:**

It include treating skin cancer, actinic keratoses, and Bowen's disease topically as well as treating stomach, colon, rectum, breast, and ovarian cancer. It is also used as an eye drop to treat ocular surface squamous neoplasia.

**Azathioprine:**

Mercaptopurine is the source of azathioprine. It is 6- (1 methyl-4-nitroimidazol-5-yl) purine chemically.



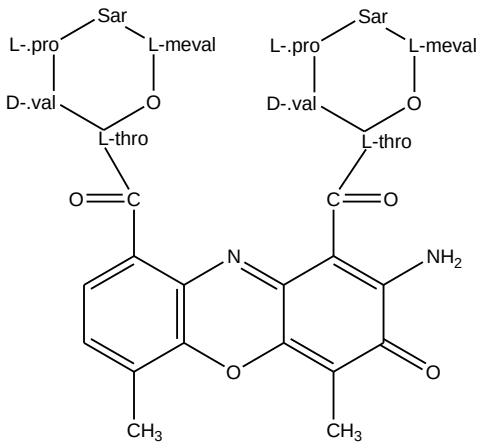

Azathioprine

**Uses:** Its primary application is as an immunosuppressant to aid in organ transplantation survival. It is also used for severe skin conditions that are regarded as typical, lupus erythematosus, reheumatoid arthritis, chronic active hepatitis, and renal problems.

## 3.5.4 Carcinolytic Antibiotics

### (a) Actinomycin D (Dactinomycin)

Actinomycins, which are most active in a series of cyclic pentapeptides, are detected in the growth of specific strains of Streptomyces parvullus. Its great potency as a bacteriostatic and eytostatic agent was originally identified in 1940. Actinomycin interferes with RNA binding to strongly bind to DNA, which in turn interferes with protein synthesis. By forming linkages between the base pairs, similar to a sandwich, and perpendicular to the main axis, actinomycin binds to DNA. like plain pears, heliz. The oxinine component of actinomycin's strong aromatic nature enables it to bind non-jointly between two succeeding bases in DNA, lengthening the DNA molecule. This procedure is referred to as a point change. Tricyclic, phenoxazin-3-one chromophore, and two identical groups of paint peptide lactone make up the chemical makeup of actinomycin. The chromophore is coupled to A and B.




Actinomycin D

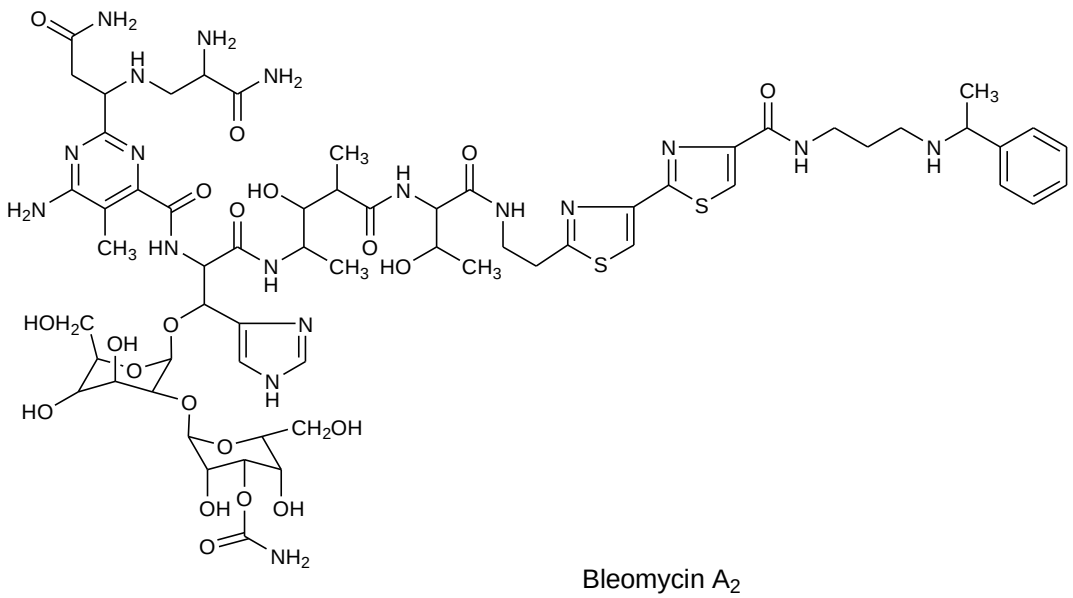
**Mechanism of action:** It intercalates in the minor groove of DNA between neighbouring guanosine-cytosine pairs, binds to double helical DNA, and blocks DNA dependent RNA polymerase, preventing transcription of the DNA molecule.

**Uses:** Used to treat cancers such as uterine, testicular, Kaposi's, osteogenic, Wilm's, and Ewing sarcomas.

**(b) Bleomycin**

A class of glycopeptides derived from Streptomyces verticillus is known as bleomycin. In its clinical preparation, bleomycin A2, A2 I, B1-4, etc. are mixed. DNA fragmentation and cord folding are the results. It functions as a cupric compound that prevents DNA gas. Bleomycin A2 is a crucial ingredient. It is an antibacterial glycopeptide. Bleomycin A2 (the primary component) and bleomycin B2 are mixed together, and it is often derived from the bacterium Streptomyces verticillus. Bleomycin hydrolase inactivates bleomycin.

DNA single and double strands are created by belomycin. Imidazole and pyrimidine are linked to the Fe2+ ion below for oxidation to $Fe^{3+}$. The phosphodiester link between the G-C or G-T sequences is attacked by superoxide and OH radicals, which liberate electrons, causing cord failure.



Bleomycin $A_2$

**Mechanism of action:** It causes DNA strand breaks, which are caused by a combination of DNA, bloemycin, and iron (II). There are additional reports of DNA biosynthesis being inhibited.

**Administration:** Using a running drug that passes the blood-brain barrier and demonstrates bone marrow toxicity, it is administered.

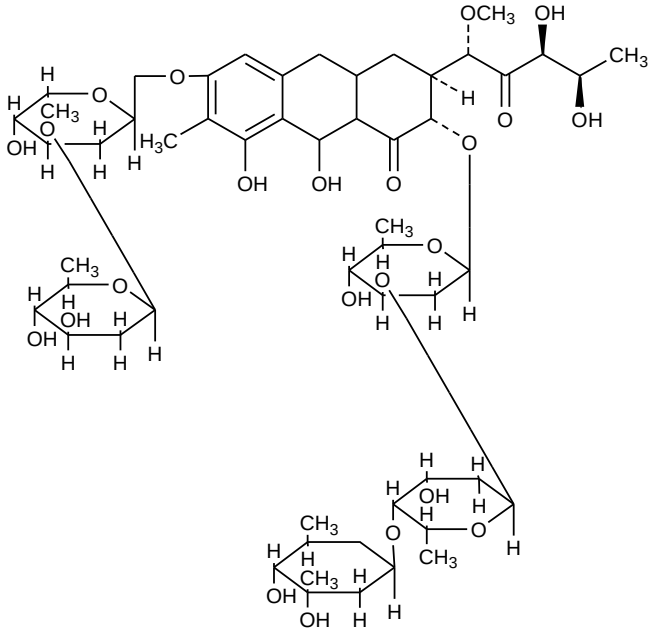
**Uses:** Bleomycin, especially when free of bone marrow toxins and antibodies, serves as the basis for novel chemicals and is effective against lymphomas and testicular cancer. Various squamous cell malignancies of the skin, head, neck, genitourinary tract, and oesophagus have

moderate activity. It is also beneficial for Hodgkin lymphoma. Additionally, it is employed in malignant neoplasms and other cancers.

**(c) Mithramycin (Chromomycin,Plicamycin)**

Itisisolated from *Streptomycesplicatus, S. argillaceus and S.tanashiensis.*

**Mechanism of action:** By attaching to DNA via the Plicamycin Mg++ complex, it prevents DNA-dependent RNA production.

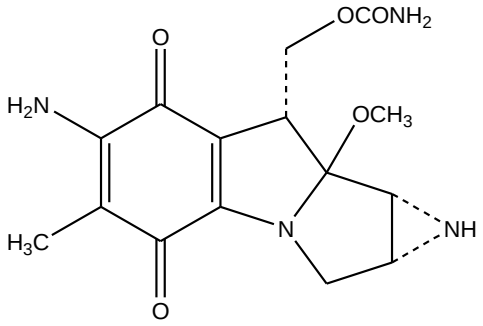


Mithramycin

**Uses:** Used in malignant hypercalcemia and chronic myelocytic leukaemia.

**(d) Mitomycin-C**

MitomycinCisobtainedfrom *Streptomycescaespitosus*.



Mitomycin C

**Mechanism of action:** It works by crosslinking double stranded DNA with guanine and cytosine to prevent DNA synthesis.

**Uses:** It is used to treat gastric adenocarcinoma, cervix, colon, rectum, breast, and lung cancer.

## 3.5.5 Natural Products

Natural antioxidants act as reducing agents, free radical scavengers, and singlet oxygen quenchers, giving natural goods the ability to fight cancer. Bioactive substances like flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignans, catechins, and isocatechins account for a larger portion of their antioxidant action. Natural products can also lessen or eliminate the toxic side effects of chemotherapy and radiation therapy by enhancing their cancer-killing action.

**(a) Etoposide:** A semi-synthetic derivative of podophyllotoxin, etoposide has shown great promise in the treatment of testicular, bronchial, and lymphoid malignancies. Through topoisomerase II cleavage, suppression of nucleoside transport, and inhibition of mitochondrial transport, etoposide causes strand breaks in DNA. It is used to treat small cell lung cancer, Wilm's tumour, hepatocellular carcinoma, Kaposi's sarcoma, and refractory testicular tumours.

**(b) Podophyllotoxin:**

Podophyllum peltatum Linnaeus (May apple) and Podophyllum emodi Wallich are two Podophyllum species from which podophyllotoxin is derived from the roots. An isomer of podophyllotoxin is epipodophyllotoxin. An active component of podophyllin, podophyllotoxin, is used to treat leukaemia, ovarian cancer, non-lymphoma, Hodgkin's and Hodgkin's disease.

**(c) Campothecins (IrinotecanandTopotecan)**

The Chinese tree Camptotheca acuminata (Nyssaceae) and a few other species from the Apocynaceae, Olacaceae, and Rubiaceae families produce this anticancer and antiviral alkaloid. Currently, the medication is sourced from seeds and bark.

**(d) Taxol (PaclitaxelandDocetaxel)**

The bark of the Pacific Yew, Taxus brevifolia Nutt, was used to isolate taxol (Taxaceae). Taxus baccata, an Indian Ayurvedic herb, is another species that has been used as a cancer

treatment. Docetaxel was created as a result of the discovery that Paclitaxel was poisonous and very marginally water soluble. Paclitaxel's semi-synthetic derivative, docetaxel (Taxotere®), was proven to be more efficient. These medications have been reported to be effective against lymphoid malignancies, lung cancer, and prostate cancer. These substances are known as anti-mitotic medicines because their mode of action involves binding to polymerized microtubules, which block the normal progression of mitosis.

**(e) Asparaginase**

It is a pure natural product that was derived from sources other than Escherichia coli. An enzyme is this. Asparaginase, an enzyme that removes the amino group from asparagine and is present in blood plasma and leukemic cells, is administered in massive quantities. About 50% of children with acute leukaemia experienced complete recovery after receiving this medication. Intravenously administered asparginase causes the release of acute lymphatic leukaemia. Although asparagine may not cause bone marrow depression, hair loss, or effects on the intestinal mucosa, it has many other important toxicities in people, especially in organs that contain a lot of protein.

**(f) Interferon**

A naturally occurring protein-based substance that infected cells release. Leukocytes, a component of human white blood cells, are interferon's original source, but more recently, the DNA recombinant approach has been employed to augment this important discovery. lymphokines and natural killer cells: White blood cells, in modest quantities, are the building blocks of glycoprotein lymphokines. Lymphokines control the body's own immunological response. Few lymphokines inhibit or stimulate B-cell or T-cell proliferation. Antibodies, which identify and penetrate foreign cells, must be produced by B-cells. It is thought that T-cells can activate the development of cytotoxic or deadly cells that attack foreign bodily cells.

**(g) Mitotic Inhibitors**

These belong to the alkaloid family that Vinca rosea Linn contains. These alkaloids include, for instance:

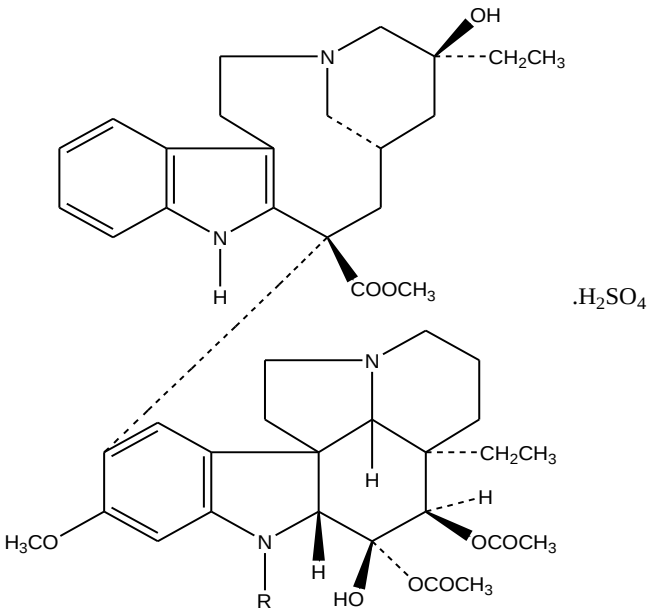
(1) Vincristine

(2) Vinblastine

These substances, known as mitotiv inhibitors, bind to the microtubular protein tubulin and prevent it from polymerizing. This results in mitotic spinning and cytoskeletal dysfunction.

(1) **Vincristine**

This medication is injected intravenously. It is a quick-acting medication that is useful in treating paediatric neoplasms, lymphomas, breast cancer, sarcomas, and acute leukaemia in children. Vincristine sulphate is discovered to be utilised in the treatment of Hodgkin's disease, Burkitt's disease, and the Wilmil tumour in conjunction with other antineoplastic drugs.




R= -CHO : Vincristine, R= -$CH_3$ : Vinblastine

Vinca alkaloids are "*spindle poisons*".They bind to the microtubule protein "*tubulin*"and causes depolymerisation of microtubules, which are essential for formation of *mitoticspindle**.

**Uses:**

Vincristine is used to treat Hodgkin's and non-lymphomas, Hodgkin's Ewing's soft-tissue sarcoma, and Wilm's tumour in children with acute lymphoblastic leukaemia. Vinblastine is used to treat systemic Hodgkin's and non-lymphomas, Hodgkin's as well as metastatic testicular cancer when combined with bleomycin and cisplatin.

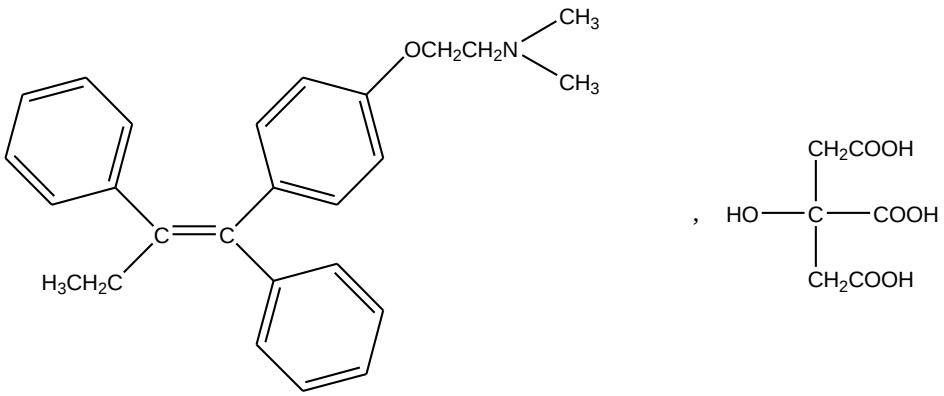
## 3.5.6 Hormones

Prostate and breast cancer are both commonly treated with hormones. Androgens promote the spread of metastatic prostate cancer whereas estrogens inhibit it. As a result, oestrogen therapy is utilised both before and after surgery to treat prostate cancer. There is no established mechanism of action for oestrogen treatment. Ethinyl oestradiol, dimestrol,

oestradiol propionate, diethylstilbestrol, and estrogenic chemicals collectively are the most often utilised estrogenic compounds in the treatment of breast cancer.

**Estrogens:** Estrogens are the primary sex hormone found in females. It causes puberty, gets the body ready for pregnancy, and even controls the menstrual cycle. During menopause, oestrogen levels fluctuate, which causes many unpleasant symptoms in women. An androgen-dependent plant called carcinoma prostrate responds satisfactorily to estrogens. Recurrence eventually happens but lengthens life when hormone reliance is gradually removed. Male breast cancer has been treated palliatively with estrogens in the past. Estrogen receptors are present in the cells of some breast tumours. Both oestrogen and antiestrogens make these react. Only in cases where surgery or radiotherapy are not options is hormonal treatment employed. Only women who have been menstruating for more than 5 years and who do not respond to tamoxifen should utilise estrogens.

**Tamoxfen (Antiestrogen):** Chemically, tamoxifen is composed of (z) 2 [4. (1, 2-diphenyl but- 1-enyl) phenoxy] -N-N-dimenthy ethyl amine. As it is effective against oestrogen receptor positive and negative breast cancer in both women before and after menopause, it is administered orally and is legally accessible in its citrate form. After mastectomy, it is the first line of defence against breast cancer.




Tamoxifen citrate

**Antianddrogen:** Flutamides have antiandrogen properties and have an early healing effect on metastatic situations in prostrate malignancy. It has been noted that steroid hormones, such as estrogens, androgens, progestins, and glucocorticoids, respond favourably to human cancer. At the writing level, hormones are typically said to work on particular target tissues.

**Progestins:** These provide short-term alleviation for a number of developmental, recurring disorders (after surgery and radiation therapy), and metastatic endometrial malignancy.

Additionally, they're employed to treat metastatic breast cancer that is resistant to tamoxifen. Reductase 5-a Finasteride is an inhibitor, preventing the body from converting testosterone to dihydrotestosterone for use in the prostate and other tissues. It demonstrates the impact on advanced prostate cancer.

**Glucocorticoids**: According to some reports, glucocorticoids prevent lymphatic tissue from producing proteins and absorbing glucose. Most often used in childhood acute leukaemia and lymphomas, lymphocytic activity. They ask for forgiveness, but after a short while it happens again, and eventually the answer fades. Protein receptors that are closely related to hormone receptors can be found in the cytoplasm of target cells. The structure of the receptors is altered by hormones that bind to them. In order to alter the writing phase, the complex then travels to the nucleus where it collides with the receiving site. While some neoplastic cells are independent and do not respond to hormone therapy, others are hormone-dependent and do. Dromostandolone is another androgenic drug used to treat metastatic breast cancer in postmenopausal women.

## *3.6 RECENT DEVELOPMENTS IN CANCER CHEMOTHERAPY*

For the control of cancer, there are numerous therapy options. Below are some examples.

**1. Chemotherapy:** Anti-cancer drugs or chemotherapy both involve substances that prevent cell division and antimetabolites that prevent nucleotide production.

(a) Mercapto purine: A purine analogue used to treat leukaemia. It interferes with replication by converting into nucleotides in vivo, incorporating into nucleic acids.

(b) Fluoro uracil, a pyrimidine analogue that is used to treat colorectal cancer and which invivo transforms into fluorodeoxy uridine phosphate to prevent recurrence.

(c) Methotrexate: A drug used to treat choriocarcinoma that is a folic acid analogue.

(d) Azaserine: An anticancer drug that is a glutamine analogue. By preventing glutamine-dependent processes, it prevents nucleic acid biosynthesis (replication).

(e) Acivicin: Another glutamine analogue utilised as an anti-cancer medication. It makes advantage of the enzyme as a competitive glutamine inhibitor.

Anti-metabolites like methotrexate, azaserine, and acivicin are used to treat cancer. They are known as anti metabolites because they interfere with nucleic acid binding by competing with glutamine's metabolic function.

**2. Radiotherapy:** Radiation can interfere with DNA's interaction with phosphodiesters, which can harm the reproductive system. As a result, the proliferation of cancer cells may slow down. This idea underlies the use of radiation to heal plants.

**3. Photochemotherapy:** A recently developed cancer treatment. To kill cancer cells, it employs laser light along with a medication that is light-sensitive.

## *3.7 GENE THERAPY*

A number of catastrophic genetic illnesses brought on by hereditary predisposition or genetic deficiency are frequently untreatable. There is hope for a cure for this fatal condition thanks to genetic treatment. Genetic treatment refers to the use of genes as therapeutic agents or to treat genetic diseases.

### 3.7.1 Vector used in genetic therapy

Retroviruses mainly in the urine leukemia virus (MLV) are used as a gene carrier. When a virus infects a host cell, recombinant retroviral RNA is rewritten and randomly synthesized into the host cell's DNA. Even though genetic therapies were originally designed to treat genetic predisposition, they were not used to treat cancer, neurological and infectious diseases. Cystic fibrosis, an autoimmune disease (SCID), familia hyper cholesterolemia, hemophilia and Duchenne muscular dystrophy (DMD) are genetic diseases that are treated using genetic therapy.

Infectious diseases are treated with genetic predisposition to cancer, heart disease, Alzhemer's, Parkinson's disease and AIDS. Retroviruses, particularly the urinary leukaemia virus (MLV), are employed as a gene carrier in genetic treatment. Recombinant retroviral RNA is randomly generated into the DNA of the host cell when a virus infects it. Hereditary therapies were not employed to treat cancer, neurological disorders, or infectious diseases even though they were initially intended to treat genetic predisposition. Genetic treatment is used to treat genetic disorders such cystic fibrosis, an autoimmune condition called SCID, familial hypercholesterolemia, haemophilia, and Duchenne muscular dystrophy (DMD). Genetic susceptibility to cancer, heart disease, Alzheimer's, Parkinson's disease, and AIDS is treated in infectious illnesses.

### 3.7.2 Family Measures Hyper Cholestrolemia Gene Therapy

1. Modification of the retrovial vector containing the LDL receptor gene

2. Patients' livers are used to isolate hepatocytes.

3. The virus that carries the LDL gene transmits to hepatocytes.

4. The patient's portal blood is given modified hepatocytes.

Contrary to the examples given above, the cystic fibrosis gene therapy protocol is unique. The cystic fibrosis transmembrane regulator (CFTR) gene is directly injected into the nasal or bronchial epithelium, where it is expressed following integration into the host DNA. Patients who have genetic cancer are given tumour cells that contain genetic cytokines as a form of treatment. Genetic compression is a component of other genetic treatments for cancer that are administered to the patient.

## *3.8 SUMMARY*

The summary of the present chapter are:

1. Antineoplastic agents are used in tumor, cancer or neoplasm. Tumor indicates any abnormal mass or growth of tissues. Cancerous tumor is a malignant neoplam with potential danger. The tumors have a rapid growth of cells but the rate of cell death is less.
2. The role of alkylating agents, antimetabolites, carcinolyte antibiotics, mitotic inhibitors, and combinations of mechlorethabamine, cyclophosphamide, melphalan, Uracil, mustard, and 6 - mercaptopurine with the most recent developments in cancer chemotherapy, hormones, and natural products are discussed in the current chapter's research on cancer chemotherapy.
3. A class of anticancer medications known as alkylating agents interferes with DNA to stop the growth of cancer cells.
4. Alkylating agents are among the first class of substances shown to be helpful in chemotherapy for cancer.
5. Cancer chemotherapy compounds that block replication of cells and antimetabolites that block nucleotide biosynthesis are used as anti cancer agents or in chemotherapy of cancer.
6. Genetic treatment refers to the use of genes as therapeutic agents or to treat genetic diseases.

## *3.9 REFERENCES*

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## *3.10 TERMINAL QUESTIONS*

1. What is Cancer chemotherapy?
2. What are Antineoplastic agents and its role?
3. Discuss role of hormones and natural products in cancer chemotherapy?
4. Sythesis of mechlorethabamine, cyclophosphamide, melphalan, Uracil, mustard and 6-mercaptopurine?
5. What is gene therapy?

# UNIT 4: CARDIOVASCULAR DRUGS

## Contents:



## *4.1 INTRODUCTION*

Cardiovascular drugs are a class of medications that have a significant effect on the heart or blood vessels. They can also be termed as those drugs that are used primarily to treat cardiovascular disorders. These drugs oftenregulate the total functioning of the heart as well

as helps incirculating the blood to specific parts of the system. Cardiovascular drugs are used to treat heart failure, hypertension, and many other cardiovascular disorders.

Medications that have effect on the cardiovascular system are among those that are most utilised in medical practise and research. These drugs have three main mechanisms of action on the heart: they affect the strength with which the heart muscle contracts (inotropic effects), they affect the frequency with which the heart beats, or the rate at which the heart beats (chronotropic effects), and they affect the regularity with which the heart beats (rhythmic effects). Drugs that effect on blood vessels normally do so by modifying the state of contraction of the smooth muscle in the vessel wall, which in turn varies the diameter of the vessel and, as a result, controls the amount of blood flowing through the channel. High blood pressure (hypertension), a kind of chest discomfort known as angina pectoris, heart failure (insufficient output from the heart muscle), and arrhythmias (disturbances of cardiac rhythm)are just few conditions in which cardiovascular medicines may be beneficial.

There are many kinds of cardiovascular drugs, which are classified as follows:

## *4.2 OBJECTIVES*

After that unit learners will be able to

- Introduction of cardiovascular drugs & diseases and drug inhibitors.
- Synthesis of cardiovascular drugs e.g. amyl sitrate, sorbitrate, diltiazem, guinidine, verapamil, methyedopa, aterolo & oxyprenolol

## *4.3 TYPE OF THE CARDUOVASCULAR DRUGS*

There are many kinds of cardiovascular drugs, which are classified as follows:

1. Cardiac Glycosides
2. Anti-Anginal Drugs
3. Calcium Channel Blockers
4. β-Adrenergic Blocking Agents
5. Vasodilators
6. Anti-Arrhythmic Agents
7. Anti Hypercholesterolemic Agents

8. Sclerosing Agents


Fig. 4.1 cardiovascular drugs

## 4.3.1 Cardiac Glycosides

The Cardiac Glycosides are thefamily of naturally occurring drugs whose activity causes toxic as well as cardiotonic effects on the body. Cardiac glycosides are derived from variety of sources, including plants such as Digitalis and Strophanthus as well as animals such as the venomous toad. Cardiac glycosides have been utilised as both medicines and poisons throughout the history.

Steroids with cardioactive properties, as well as their glycosides, are abundant in nature and have distinct effects on the contractility and electrophysiology of the heart. Their finding is an example of folk medicine, which was known to ancient civilizations such as the Romans and the Egyptians. Most glycosides are derived from the leaves of the foxglove (Digitalis purpurea or Digitalis lanata), which are available in abundance. Cardiac glycosides are a mixture of an aglycone or genin and one to four sugars units that were discovered by William Withering (1785) and have been used since then to treat heart disease. The steroidal aglycone of glycosides is responsible for cardiac activity, while sugars facilitate solubility and dispersion, which affects the strength and duration of action of the glycosides in the body. These glycosides are being utilised less commonly these days. Calcium channel blockers (such as verapamil), Acetyl Choline Esterase Inhibitors (ACEIs), and diuretics are often used to treat patients with this condition.

Cardiac glycosides are harmful because they impede the $Na^+$, $K^+$, and ATP pumps of the heart, resulting in elevated intracellular levels of calcium ions. The elevated amounts of $Ca^{++}$ in the blood are mainly responsible for the occurrence of cardiac arrhythmias, which indicates glycoside poisoning.

Table.1. Common cardiac glycosides

| Source | Structure | Aglycone | Glycoside |
|---|---|---|---|
| Leaf of Digitalis Lanata | Glucose-3 acetyldigitoxose-digitoxose$_2$-aglycone | Digitoxigenin<br>Gitoxigenin<br>Digitoxigenin | Lanatoside-A<br>Lanatoside-B<br>Lanatoside-C |
| Leaf of Digitalis Purpurea | Glucose-digitoxose$_3$-glycone | Digitoxigenin<br>Gitoxigenin | Purpurea Glycoside A<br>Purpurea Glycoside B |
| Leaf of Strophanthus Gratus | Rhamnose-Aglycone | Quabagenin | g-Strophanthin |
| Seed of Strophanthus Kombe | Glucose-glucose-cymarose-aglycone | Strophanthidin | k-Strophanthosi de |

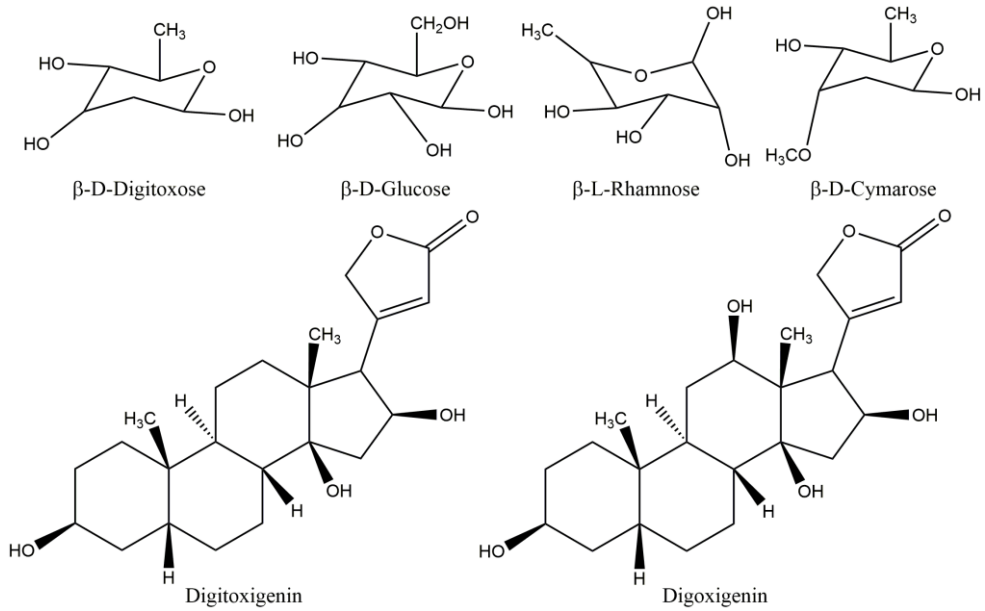



Fig.4.2 Structure of few cardiac glycosides and aglycones

### 4.3.2 Anti-Anginal Medications

When someone have angina pectoris, a sudden, acute pain in chest is felt that typically radiates to the left shoulder, and then moves down from the shoulder to the arm. The source of this kind of pain is thought to be the temporary condition of myocardial ischemia. This condition of myocardial ischemia occurs due to reducing of coronary blood flow and increasing need of myocardial oxygen. The increased energy demand caused by activity, emotion, eating, or coitus is known to cause attacks (stable angina), which then reduce when the increased energy demand is removed. Significant arteriosclerosis of the major coronary arteries (conducting vessels), which flow epicardial and send perforating branches to serve the deeper tissue, is the underlying pathology in this case. The coronary occlusion is 'fixed'; blood flow does not rise in response to increased demand, despite dilatation of resistance arteries mediated by local causes, and ischemic discomfort is experienced as a result. The end diastolic left ventricular pressure rises from 5 to approximately 25 mm Hg because of the inadequacy of the ischaemic left ventricle, which causes subendocardial 'crunch' during diastole and aggravates the ischaemia in this region. A sort of quickly developing and rapidly reversible left ventricular failure results, which can be alleviated by resting and lessening the stress placed on the myocardium.All the organic nitrates undergo fast first-pass metabolism, which occurs in extrahepatic tissues such as blood vessels and liver because of the activity of the glutathione-nitrate reductase enzyme.Glyceryl trinitrate is the most often prescribed medication for the relief from acute anginal discomfort. In just less than two minutes, this medication is absorbed from the lingual, sublingual, and buccal mucosae, thusproviding immediate relief to the patient having angina pectoris.

Long-acting organic nitrate medications, such as orally givenisosorbide, dinitrate, pentaerythritol tetranitrate, and erythrityl tetranitrate, are used to avoid recurrent anginal discomfort. Also, orally given sustainedrelease formulations such as glyceryl trinitrate ointment, buccal pills, and transdermal patches are all utilized for treating the condition of angina pectoris.

Angina may be relieved by three types of medications: organic nitrates, calcium channel antagonists (for both spasmatic and chronic stable angina), and beta-adrenergic antagonists (for both exertion-induced and non-exercise-induced angina). Anti-anginal medicines are primarily effective in relieving pain by lowering the oxygen demands of the heart, which in turn reduces the sensation of anginal discomfort. Each type of anti-anginal

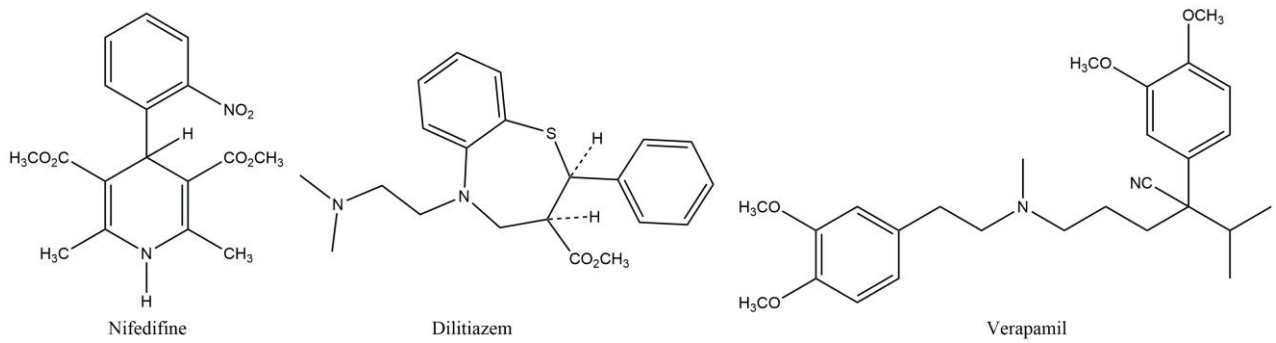
drug employs a separate method for lowering cardiac strain, and as a result, many classes of anti-anginal agents may be used in conjunction to maximise the therapeutic impact.

### 4.3.3Calcium Channel Blockers

Calcium Channel Blockers are medications that prevent calcium channels from opening. There are a variety of calcium channel blockers available, and they are particularly effective in treating myocardial insufficiency. Inhibiting calcium ion invasion into cardiac cells is beneficial in inhibitinganginal discomfort. Physiologically, calcium is present in the human body both intracellularly and extracellularly. Many medicines have been discovered to influence the transport and availability of calcium. When medicinal drugs exert their effects by blocking calcium-dependent actions, they often achieve this blockage by lowering the levels of free calcium in the cytoplasm of the cell.

It is possible to prepare the hydrochloride salt of each calcium channel blocker, which is delivered as oral tablets and capsules, by adding an amine group to the compound. Additionally, these medicines have a mainly hydrophobic nature, which accounts for their quick and full absorption upon oral administration. Around 75-95 percent of the medicine is detected in the bloodstream.

Most of these agents are found in the plasma primarily in the protein-bound (80-95 percent) state, even though they are active in the free form. The length of action for most agents is between 4 and 8 hours, except for amlodipine, which has 24-hour duration of action owing to the presence of the chlorine atom in the compound.




Nifedifine Dilitiazem Verapamil

Fig.4.3 Structure of some Calcium Channel blocker

**Mechanism:** These medications work by selectively inhibiting calcium ion influx into heart muscle while also inhibiting calcium ion inflow into vascular smooth muscle, among other things. It dilates the main coronary arterioles, and by inhibiting coronary artery spasm, it increases myocardial oxygen delivery in patients with Prinzmetal's angina (Chronic Coronary Artery Disease).

### 4.3.4 β-adrenergic receptor blockers

These are the agents that blocks the action of the beta-adrenergic receptor. When it comes to the therapy of exertioninduced angina, beta-adrenergic blocking medications are utilised. These medications can be taken single as well, but they are mostly used in conjunction with calcium channel blockers, nitrates, or can be combination of both the drugs. Propranolol is a medication that serves as a prototype for this class.

Adrenergic nervous system plays a significant role in maintaining blood pressure, heart rate, bronchial tone, and gastrointestinal motility. Norepinephrine is generated and stored in granules inside the nerve terminals from where it is released as required. During neuronal depolarization, it is released into the synaptic vesicle in small quantities. Myocardial contraction is caused by an interaction with the β-receptor, which also leads to increase in blood flow via vasodilation, relaxation of the bronchi, and enhanced glycolytic activity. β-adrenoreceptor stimulation is reduced or prevented in the presence of beta-adrenoreceptor blocking drug, which has the primary impact of lowering cardiac activity. They are used for the treatment of angina pectoris and cardiac arrhythmias as they help in reducing the heart's oxygen consumption while also boosting its tolerance to physical activity.

Propranolol is a nonselective adrenergic receptor antagonist that is often used to treat heart failure and bronchitis. It is commonly used for the treatment of exertion-induced angina, which is caused by coronary atherosclerosis. As a result, medications with beta-blocking activity lower the heart rate and reduce the power of muscle contraction, making them effective in the treatment of hypertension and cardiac arrhythmias, as well as angina and other cardiovascular diseases. The anti-anginal effectiveness of propanolol is often enhanced using organic nitrates or calcium channel blockers in conjunction with other medications.

**Mechanism:** It is believed that the β-Adrenergic Antagonist works by decreasing sympathetic activation of the heart, which lowers the heart rate and lessens the contractibility

of the heart muscle. These actions, in turn, lower the oxygen needs of the myocardium, which is beneficial both during exercise and during resting state.

### 4.3.5 Vasodilators

Vasodilators are a class of medications that influence the circulatory system and are used to treat various medical conditions. Their therapeutic activity is attributed to its capacity to widen coronary arteries, and are also used to treat coronary artery disease, notably angina discomfort, among other conditions. It is a naturally occurring vasodilatory chemical that is secreted by the myocardium during hypoxia-induced events. Inhibition of adenosine absorption byred blood cells (RBCs) and the vasculature is said to be the mechanism through which dipyridamole produces its long-lasting and selective coronary vasodilation. These medications are used to treat or prevent many conditions such as hypertension, Pulmonary hypertension, heart failure, high blood pressure during pregnancy and chest pain caused due to reduced blood flow to the heart.

**Mechanism:** A single unifying mechanism does not exist; instead, different vasodilators may operate at different points in the cascade of events that link excitatory signals to contractions in vascular smooth muscle cells. For example, the vasodilators known as calcium channel antagonists prevent or limit the entry of calcium into vascular smooth muscle cells through voltage-dependent channels in the membranous membrane of these cells. Calcium channel blockers work in this fashion by limiting the amount of free intracellular calcium that is accessible to interact with smooth muscle contractile proteins in the body.

Some other vasodilators, such as diazoxide and minoxidil, induce blood arteries to dilate by activating potassium channels in the vascular smooth muscle. An increase in potassium conductance causes hyperpolarization of the cell membrane, which results in relaxation of the smooth muscle of the vascular system.

### 4.3.6 Antiarrhythmic Agents

When it comes to the therapy of cardiac arrhythmias, antiarrhythmic medicines are quite helpful. Cardiac arrhythmias are characterised by a disruption in the conduction of impulses across the heart because of disturbances in the production of impulses.

**Mechanism:** Cardiac arrhythmias may arise because of a disruption in the origin of the impulse, which are the pacemaker cells. Those cells may have impaired automaticity, which is the rhythmic trait that allows them to depolarize their membranes at the appropriate pace.

Disruption of the automaticity of pacemaker cells may be caused by underlying disorders such as hypertension, atherosclerosis, hyperthyroidism, or lung disease, among others. The genesis of impulses in cells other than pacemaker cells may result in the development of several types of arrhythmias. Ectopic arrhythmias are what they are referred to as. Excessive myocardial catecholamine production, myocardial ischemia, and the toxicity of cardiac glycosides are all potential causes of ectopic arrhythmias.

Additionally, arrhythmias may be created when the electrical impulse does not fully die down before the beginning of phase 0 of the heartbeat. Consequently, a part of the previous impulse that remains at the end re-enters and re-excites the cardiac muscles prematurely, resulting in the phenomenon known as asynchronous depolarization. Pre-mature heartbeats are distinguished by the presence of this distinctive shape. Re-entrant arrhythmias are prevalent in patients with coronary artery disease.

These drugs are further classified into four different types:

**(a) Class I Drugs:** Class I antiarrhythmic medicines are often local anaesthetics that act on the myocardial membrane and nerve to slow the conduction of electrical impulses in the heart. These medications also slow down the pace of depolarization without altering the resting potential of the brain. Quinidine is an example of this kind of medication.

**Quinidine** is a drug that is used to treat a variety of ailments. Quinidine is a medication that is commonly used for the acute and chronic treatment of ventricular and supraventricular arrhythmias, especially supraventricular tachycardia, in both adults and children. Cinchona bark contains a group of alkaloids that are known as cinchona alkaloids. It has a close relationship to the drug quinine.

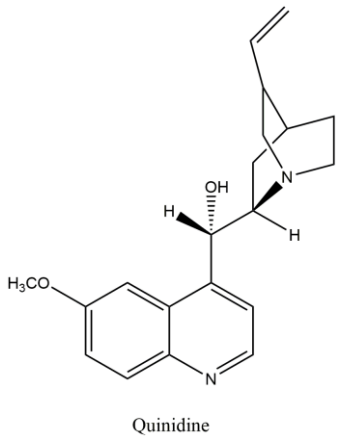



Fig.4.4. Structure of Quinidine

(a) **Class II drugs:**β-adrenergic receptor blockers are used to treat arrhythmias in the class II category. They go through the process as described below:

i) Specifically, they reduce adrenergic ally enhanced phase 4 depolarization by inhibiting B receptor function.

ii) At typical therapeutic levels, these drugs have been shown to reduce neurologically induced automaticity.

iii) These medicines produce excitability when used in greater dosages.

As an example, **Propranolol** is a beta-adrenergic receptor antagonist that is used to treat heart failure.

(b) **Class III drugs:** Antiarrhythmic medications of class III produce a homogenouslengthening of the duration of action potential throughout the body.

**Bretylium** is a genus of plants that includes the species Bretylium.

(c) **Class IV drugs:** Class IV antiarrhythmic pharmaceuticals work by inhibiting the sluggish inward current carried by calcium.Supraventricular arrhythmias are treated extremely well by blocking the conduction of premature impulses at the AV-node, which is accomplished by the actions described above.

(d) **Verapamil** is a calcium channel blocker that is used in the treatment of angina pectoris and supraventricular arrhythmias (supraventricular tachycardia).

Table.2. Classes of Antiarrhythmic Drugs

| **Class** | **Antiarrhythmic Drugs** | **Pharmacological Effects** |
|---|---|---|
| IA | Quinidine, Procainamide, Disopyramide | Duration of action potential is also decreased; Rate of depolarization is decreased |
| IB | Lidocaine, Phenytoin, Tocainide Mexiletine | Rate of depolarization is decreased; Duration of action potential is also decreased |
| IC | Flecainide | Rate of depolarization is decreased; No change in duration of action potential is observed |
| II | Propranolol | Sympathetic activity is inhibited |
| III | Bretylium, Amiodarone | Duration of action potential is prolonged |
| IV | Verapamil | Inward calcium current is inhibited |

### 4.3.7 Anti-Hypercholesteraemic drug

Coronary artery disease is one of the most common causes of death throughout the world. High cholesterol levels in the blood are one of the major causes of this disease. High cholesterol levels are caused by a variety of genetic abnormalities that are related with the accumulation of specific classes of lipoprotein particles in the bloodstream. Several medications, including statins, fibrates, bile acid sequestrants, niacin, ezetimibe, omega-3 fatty acids, and natural extracts are used to treat hypercholesterolemia. Statins are the most prescribed medication. It has been noted that these medications produce a wide range of responses in various people.

Atherosclerosis is a condition in which fat deposits in the inside walls of arteries developed in humans. High blood pressure and heart attack may be caused due to cholesterol buildup in the arteries, which can further lead to high blood pressure and heart failure. The amount of cholesterol may be controlled by using the following anti-hypercholesteromic medications i.e.Aluminium Nicotinate also called as Niclex, Clofibrate also known as Atromid-S and D-Thiroxine Sodium.

### 4.3.8 Sclerosing Agents

These drugs are those substances that cause scarring.They cause irritation of the intimal layer of the vessel wall, resulting in the formation of a thrombus. It induces endothelium to adhere to one another and occludes the arteries. These medications are used in the treatment of varicose veins or commonly termed as dilated veins.

Creasing chemicals produce irreversible endothelial injury, which results in inflammation and thrombosis of the vessels, which ultimately results in the creation of fibrous tissues. Sclerosing chemicals, when injected into blood arteries or lymphatics, cause the walls of the vessels to shrink and eventually obliterate the vessel. Pleural effusion is another condition that can be treated with sclerosing drugs. As a result of their injection, these drugs cause inflammation of the pleura, which results in adhesions of the pleural membranes and the closure of the cavity, preventing the build-up of fluid in the pleura again.

## *4.4 CARDIOVASCULAR DISEASES*

Diseases affecting the human heart and other organs of the circulatory system are referred to as cardiovascular diseases. A set of conditions affecting the heart and blood arteries is referred to as cardiovascular diseases (CVDs). It is a group of diseases that affect the blood

vessels that supply the heart muscle, brain, and arms and legs. Heart attacks and strokes are sudden and severe events that are primarily caused by blockage in supply of blood to the heart or brain. It is most often caused by a build-up of fatty deposits on the inner walls of the blood arteries that supply the heart or the brain. Stroke can be caused by bleeding from a blood artery in the brain or by blood clots clotting the blood vessels in the brain. Several other common cardiovascular diseases occur in human beings, some of them are discussed below:

### 4.4.1 Cardiac Failure

Cardiac failure, also known as congestive heart failure, is characterised by a reduction in the contractility of the ventricles, resulting in a decreased cardiac output that is insufficient to meet the metabolic needs of the body. Greater blood volume, end-diastolic volume, and venous return are all associated with increased cardiac failure, resulting in a reduction in systemic blood pressure as the degree of cardiac failure rises. A typical heart would attempt to raise the force with which it contracts in response to these modifications. Therefore, it leads to a rise in heart rate, systemic vascular resistance, and venous load, among other things. When sympathetic tone is elevated, it is possible that myocardial contractility will be raised as well. As the severity of cardiac failure increases, the heart gets dilated, which may result in swelling and ascites in the lungs, among other complications.

It can also be termed as a medical disorder in which the heart is unable to adequately pump blood to the rest of the body's organs. The "failing" heart continues to beat, but it does so at a lower rate than it should. People who suffer from heart failure are unable to exercise because they get short of breath and exhausted. The slowing of blood flow out of the heart results in a back-up of blood returning to the heart through the veins, which causes congestion in the tissues. Swelling is a common side effect. It is most common to see swelling in the legs and ankles, but it can manifest itself in other places of the body as well. Occasionally, fluid accumulates in the lungs and interferes with breathing, resulting in shortness of breath, particularly when a person is lying down. Heart failure impairs the kidneys' ability to excrete salt and water, as well as their overall function.

### 4.4.2 Ischemic Heart Disease

Ischemic heart disease is a kind of heart disease that occurs because of advanced atherosclerosis. Angina pectoris is a common side effect of this medication. Angina pectoris is a kind of myocardial ischemia characterised by a sudden, acute pain that originates in the

myocardium and is caused by a reduction in coronary blood flow and an increase in myocardial oxygen demand.

Angina pain is caused in certain people by atherosclerotic constriction of the coronary blood arteries, which is caused by atherosclerosis. Specifically, in these individuals, the reduction in myocardial oxygen demand, which is caused by nitrate administration, happens as a direct consequence of changes in the systemic circulation. In these patients, the administration of nitrates results in dilatation of both resistance and capacitance vessels in the chest, with symptoms often extends to the left shoulder and down the left arm.

Angina may be classified into two types:

(1) Typical

(2) Variant

This categorization is based on the causes that precipitated the attack as well as the electrophysiologic alterations that were seen during the assault. It doesn't matter which angioplasty is used since the underlying reason is myocardial ischemia, which is caused by a reduction in coronary blood flow and an increase in myocardial oxygen demand. In the treatment of acute angina pain, organic nitrates, calcium channel blockers, and B-adrenergic blocking medications are used. According to the labour load of the heart, which comprises the function of the heart rate, systolic pressure, thickness of the ventricular heart muscle, and diameter of the heart, the oxygen need of the myocardial tissues is determined.

Myocardial ischemia occurs when there is insufficient oxygen available to satisfy the demands of the myocardium. Depending on the cause, this might be caused by atherosclerotic constriction of the coronary circulation or by vasospasm of the coronary veins. Angina pain is caused in certain people by atherosclerotic constriction of the coronary blood arteries, which is caused by atherosclerosis. Specifically, in these individuals, the reduction in myocardial oxygen demand, which is caused by nitrate administration, occurs as a direct consequence of changes in the systemic circulation. In these patients, the administration of nitrates results in the dilatation of both resistance and capacitance capillaries.

### 4.4.3 Cardiac Arrhythmias

Cardiac Arrhythmias are irregular heartbeats. Various reasons, including a disruption in the conduction of impulses via myocardial, problems of impulse production, or a combination

thereof, may produce cardiac arrhythmias. There are a variety of variables that alter the natural rhythm of electrical activity inside the heart.

Arrhythmias may develop for a variety of causes, the most common of which are:

(a) Pacemaker cells are unable to perform their functions adequately.

(b) The transmission via the AV-node is prevented from proceeding.

Arrhythmias may be triggered by a variety of conditions including pulmonary illness, hyperthyroidism, and atherosclerosis. Ectopic arrhythmias are among of the most prevalent types of arrhythmias. Ectopic electrical signals develop when electrical signals spontaneously emerge in areas other than the pacemaker and then compete with the regular electrical impulses. Ectopic foci are also induced by myocardial. Another factor that contributes to the development of arrhythmias is a process known as re-entry. During this process, the electrical impulse does not terminate once it has been fired, but instead continues to circulate and excite resting cardiac cells into depolarizing.

### 4.4.4 Thrombosis

Thrombosis is a kind of blood clot. Thrombosis, which includes coronary, embolic, venous, and traumatic thrombosis, is responsible for a significant number of fatalities each year under the category of cardiovascular illnesses, according to the American Heart Association. In addition to vascular damage, blood stasis and blood hypercoagulability may all contribute to thrombosis (intravascular clotting). When the subendothelial cells of a blood artery or the cells of tissue are wounded, a vasoconstrictive reflex is triggered, which lowers the volume of blood flow and causes the platelets to stick to the injured cells of tissue. In response, platelets release ADP and prostaglandin peroxide molecules and aggregate into a plug-like structure, which is formed by the platelets. Platelets release and platelets aggregation are the terms used to describe these two processes, respectively. It is possible that the release of biochemicals from platelets will result in the production of thromboxane A2, which is synthesised by the platelets and promotes platelet aggregation, or the production of prostacyclin (PGI2), which is synthesised by the blood vessel cells and inhibits platelet aggregation.

### 4.4.5 Platelet aggregation

It has been implicated in the production of thrombi, notably in the arterial system, as well as in the pathophysiology of atherosclerosis in general and in specific. Atherosclerotic illness is caused by the accumulation of platelets. Because it acetylates cyclo-oxygenase, a platelet

enzyme, aspirin functions as an anti-platelet medication by decreasing platelet aggregation, thus preventing blood clot formation. This prevents the production of thromboxane A2, which is a potent vasoconstrictor as well as an inducer of the platelet release response and platelet aggregation in the bloodstream. The irreversible impact lasts for the duration of the acetylated platelet's life, which is typically 4-7 days after injection. According to recent clinical research conducted by the Food and Drug Administration of US (FAO), taking a aspirin tablet each daydecreases the risk of having a second heart attack by almost 20% for those people who have previously had one heart attack.

### 4.4.6 Kawasaki Disease

Kawasaki illness is a condition that affects children between the ages of 6 months and 4 years that causes coronary aneurysms and may result in heart attack and death. The results of a recent clinical investigation suggest that aspirin, taken in large dosages, may be useful in the treatment of the complications of Kawasaki illness.Due to the enlargement of glands (lymph nodes) and mucous membranes within the mouth, nose, eyes, and throat, Kawasaki illness was originally referred to as Mucocutaneous Lymph Node Syndrome (MCLNS).

Children who have Kawasaki illness experience high fever, swollen hands and feet with skin peeling, red eyes and tongue. However, Kawasaki illness is frequently curable, and most children who receive therapy within 10 days ofonset of the condition recover without experiencing any serious complications.

The complications due to this disease include inflammation of the blood vessels and coronary arteries. Usually the coronary arteries, that supplies blood to the heart and heart muscle is affected which can also lead to weakening and bulging of the artery wall (aneurysm). This increases the risk of blood clotting, which could further lead to a heart attack or cause life-threatening internal bleeding.

### 4.4.7 Atherosclerosis

Atherosclerosis is a disease of the arteries. Atherosclerosis is a condition characterised by the accumulation of fat in the inner linings of arteries. When it comes to the development of atherosclerosis in humans, cholesterol is a critical factor to consider. This may cause high blood pressure and a heart attack by interfering with the flow of oxygen to the body. Among healthy individuals, blood cholesterol levels vary from 190 to 250 mg percent, with around 70% of the total being in the form of cholesterol esters and 30% being in the Free State.

There are many approaches that may be used to put the blood cholesterol level within the normal range:

a) suppressing cholesterol production in the liver.

b) cholesterol metabolism and biliary excretion both are increased.

c) reduce cholesterol absorption from the gastrointestinal system

The fat in the human body is the primary source of the precursor to cholesterol synthesis in the body. As a result, reducing the amount of fat in the diet may help to lower the production of serum cholesterol in the body. The consumption of unsaturated fats derived from vegetable source seems to be associated with a reduction in the build-up of blood cholesterol in arteries.

## *4.5 DRUGS FOR CARDIOVASCULAR DISEASES*

### 4.5.1 Amyl Nitrate

The use of amyl nitrate has been shown to be useful in both treating and reducing the pain associated with angina pictoris. The most apparent activity of this medication is exerted on the smooth muscle of the vascular system. In contrast to arteries, nitrate expands veins more than arteries, causing secondary pooling of the blood. This lowers the preload on the heart as well as the diastolic size and pressure, resulting in reduction in cardiac workload.

**Synthesis:** Amyl nitrate may be made by esterifying simple amyl alcohol with nitric acid ($HNO_3$) or sodium nitrite in conc. $H_2SO_4$.

### 4.5.2 Diltiazem

Diltiazem is a type of calcium channel blocker that is used to treat heart failure. $Ca^{++}$ (calcium ion) influx into myocordial cells is prevented in the therapy of myocardial insufficiency and angina discomfort, respectively. Since 1960, it has been recognised that calcium ions play a key role in a wide range of physiological activities. Calcium may be present in several locations in the body, including both the extracellular and intracellular spaces. Diltiazem prevents the entry of $Ca^{++}$ ions into the cell by interfering with their mobility.

It works by relaxing the vascular muscle and lowering blood pressure, among other things. This is connected to the long-term therapeutic effects of decreasing blood pressure, as lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, with the

majority of these being strokes and myocardial infarctions as the result. In response to depolarization, diltiazem reduces the inflow of extracellular calcium ions across the membranes of cardiac and vascular smooth muscle cell membranes. Diltiazem is classed as a negative inotrope (a force that is reduced) and a negative chronotrope (a time that is increased) (decreased rate). It is also referred to as a "rate-control medication" because it lowers the heart rate.

### 4.5.3 Verapamil

Verapamil is a coronary dilator that was first created in Germany in 1962 for the treatment of angina. In the treatment of angina, it is a calcium channel blocker that is administered intravenously. A chemical derivative of papaverine, verapamil is effective and commonly used for the treating supraventricular arrhythmias. It was initially developed as a vasodilator for the treatment of anginal symptoms. This medication inhibits the sluggish inward flow of $Ca^{+2}$ ions, resulting in a slowing of the conduction process. This is used in controlling atrial and paroxysmal tachycardias which is tightly linked to plasma proteins in high concentrations.

With antiarrhythmic, analgesic, and hypotensive properties, verapamil is a calcium channel blocker of the L-type. Verapamil is an immediate-release medication with a limited duration of action, necessitating dose 3 to 4 times daily; however, extended-release formulations are available that allow for once-day administration of the medication. Patients with severe left ventricular dysfunction or hypertrophic cardiomyopathy should avoid taking verapamil because it is a negative inotropic medication (i.e., it decreases the strength of myocardial contraction). The decrease in contractility caused by verapamil may increase the risk of exacerbating these pre-existing conditions.

### 4.5.4 Methyldopa

Methyldopa is methyl analogue of dopa, which acts as a precursor for the neurotransmitter dopamine. It is one of the most extensively used and oldest antihypertensive medications in the market. It is an α-methyl derivative of dopa (3,4-dihydroxyphenly)-2-methyl-L-alanine sesquihydrate. Because of the transfer of blood from the arteries to the tissue’s capillaries and vein, the central nervous system is overstimulated. This has the potential to promote arteriole contraction as well as increase marginal resistance to the flow of blood in the body.

It is a fine powder that ranges in colour from white to yellowish-white and may include friable lumps. It is just a marginally soluble compound in water. The amino acid active transport system is responsible for the absorption of methyldopa when it is taken orally. After 2 to 3 hours, plasma concentrations reach their maximum levels. It has a half-life of about 2 hours and is removed. It undergoes considerable metabolization and is eliminated in the urine as both the unmodified drug and the O-sulphate conjugate form of the drug. Benzodiazepines such as methyldopa are used in the treatment of moderate to severe hypertension in combination with diuretics. Its efficacy is limited by its adverse effects and toxicity.

### 4.5.5 Atenolol

In addition to being an antiarrhythmic medication, atenolol is also recognised as a β-adrenoceptor blocking agent. Its half-life is between 6-9 hours. Its primary impact has been shown to be the reduction of heart activity via the inhibition or prevention of beta-adreno receptor activation. The polarization-repolarization phase of the action potential, as well as its excitability and refractoriness, as well as impulse conduction and membrane responsiveness within cardiac fibres, may be influenced by these agents. Furthermore, this medication is used in the treatment of angina pectoris, where it helps to reduce oxygen consumption while improving cardiac endurance during physical activity. Long-term therapy of hypertension with atenolol is also beneficial.

### 4.5.6 Sorbitrate

Also known as isosorbide dinitrate, this medication is used to treat a variety of conditions. Both the treatment and prevention of painful anginal events are accomplished with the help of sorbitrate. It has a lengthy duration of action as an antianginal agent. This medication may be taken sublingually, as well as by the transdermal and buccal modes of administration. In certain cases, the effect of sorbitrate might persist up to six hours. Sorbitrate is largely metabolised in the liver by an enzyme known as glutathione-nitrate reductase.

It is an oral organic nitrate with a moderate to long duration of action that is used for the alleviation and prevention of angina pectoris (chest pain). Relaxation of the vascular smooth muscle results in dilatation of peripheral arteries and veins, particularly those in the lower extremities. Diastolic blood pressure and pulmonary capillary wedge pressure are both reduced because of dilatation of the veins, which promotes peripheral pooling of blood and

diminishes blood return to the heart (preload). Systolic arterial pressure, mean arterial pressure, and systemic vascular resistance are all reduced because of arteryol relaxation.

### 4.5.7 Quinidine

Quinidine is an alkaloid that is found in the bark of the cinchona tree (Cinchona officinalis L.) and is close to the quinine drug. The drugs quinidine and quinine are diastereomers of each other and have same structure. Quinidine and quinine are structurally related compounds, and quinidine is the dextro isomer of quinine. In its most basic form, quinidine is made up of two rings: one being a quinoline ring and the other being bicyclic quinuclidine ring system, with a hydroxy methylene bridge linking the two rings with other. Quinidine is mostly metabolised in the liver. Its excretion via the kidneys is also substantial. It is not tolerated well by a considerable proportion of individuals, and it cannot be administered beyond the test dosage in most cases.

Quinidine is available as a sulphate, gluconate, or polygalacturonate, depending on the formulation. Each has somewhat different physical and bio absorption characteristics than the other. Quinidine sulphate is an oral medication that may also be administered intramuscularly if necessary. It is quickly absorbed from the GI tract, and the commencement of action occurs in around 30 minutes after ingestion. Due to its water solubility, quinidine gluconate is primarily utilised in situations when a speedy reaction is required, and oral administration of quinidine sulphate would be ineffective due to the nature of the situation. Quinidine polygalacturonate provides more stable and consistent quinidine blood levels than quinidine monogalacturonate.

### 4.5.8 Oxyprenolol

A medication known as oxyprenolol is a β-adrenergic blocking agent. Known as the adrenergic nervous system, it is a part of the nervous system in which norepinephrine serves as a neurotransmitter between the nerve terminal and the effector muscle. An essential role in the regulation of numerous physiological activities is played by the adrenergic nerve system. These include the regulation of heart rate and force, blood pressure, bronchial tone, and gastrointestinal motility.

Oxyprenolol is a lipophilic molecule, which means that it can pass the blood-brain barrier without being destroyed. Due to its hydrophilic nature, it has been linked to a higher incidence of CNS-related side effects when compared to other hydrophilic ligands such as

atenolol, sotalol, and nadodrol. Oxyprenolol is a powerful beta-blocker that should not be taken to asthmatics since it has the potential to cause irreversible airway dysfunction as well as inflammation.

## *4.6 SUMMARY*

The summary of the present chepter are :

- Cardiovascular medications influence the heart, blood vessels, and circulatory system, either directly or in a secondary manner. Cardiovascular pharmaceuticals are generally defined as medications that influence the cardiovascular system. They are divided into eight main categories.
- A few of the disorders in which cardiovascular drugs may be effective include high blood pressure (hypertension), a kind of chest pain known as angina pectoris, heart failure (insufficient output from the heart muscle), and arrhythmias (disturbances in the heart's rhythm).
- Cardiovascular illnesses are defined as diseases that affect the heart and other organs of the circulatory system in humans. Cardiovascular illnesses refer to a group of ailments that affect the heart and blood vessels in the body (CVDs).
- The synthesis of certain cardiovascular medications, such as amyl nitrate, diltiazem, verapamil, methyldopa, sorbitrate, and quinidine, among others, is being investigated.

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## *4.8 TERMINAL QUESTIONS*

1. What is Cardiovascular Drugs?
2. What are drugs for Cardiovascular Diseases?
3. Discuss different types of Cardiovascular Diseases?
4. What is Anti-Hypercholesteraemic drug?