Name of Unit	Medicinal chemistry
Subject Name	Medicinal chemistry-I
Course/Subject Code	BP402T
Class: B. Pharm. Semester	IV
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Learning Outcome of module I

LO	Learning Outcome (LO)	Course Outcome Code
LO1	To understand the different terms used in medicinal chemistry.	BP402.1
LO2	History of medicinal chemistry.	BP402.1
LO3	Effect of physicochemical properties on drug action.	BP402.1
LO4	Drug metabolism.	BP402.1
LO5	Factors affecting drug metabolism.	BP402.1

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Table
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INTRODUCTION TO MEDICINAL CHEMISTRY

What is medicinal chemistry? The science that deals with the discovery or design of new therapeutic chemicals and the development of these chemicals into useful medicine.

What is "medicine"? Drugs, pharmaceutics, Media distinction between drugs that are used in medicine and drugs that are abused (addiction). A compound that interacts with a biological system, and produces a biological response (ideally desired and positive)

"*Good" vs. "Bad" Drugs.* No medicine has only benefits or drawbacks. A"good" medicine would have to satisfy the following criteria, it would have to do what it is meant to do and have no toxic or unwanted side effects and be easy to take. For example, Morphine in low dose it is an Excellent analgesic, but have serious side effects such as, Addiction, tolerance (the effect of the drug diminishes after repeated doses and so we need to increase the size of the dose to achieve the same results.), Respiratory depression and it may kill if taken in excess. There is a long history of plants being used to treat various diseases. Basically, the subject of medicinal chemistry explains the design and production of compounds that can be used for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of already existing drugs, of their biological properties and their structure-activity relationships. Medicinal chemistry was defined by IUPAC specified commission as "it concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level".

Medicinal chemistry covers the following stages:

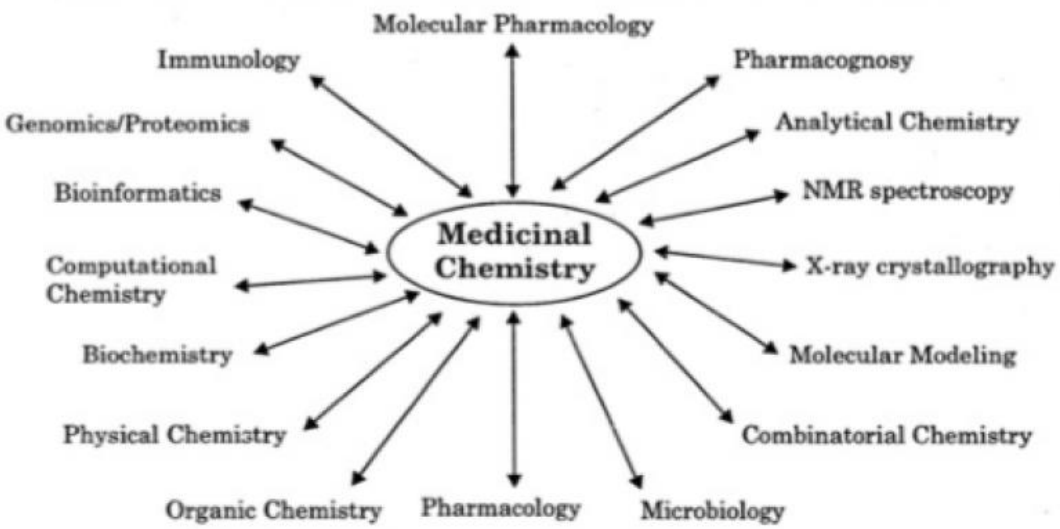
In the **first stage** new active substances or drugs are identified and prepared from natural sources, organic chemical reactions or biotechnological processes. They are known as lead molecules.

The **second stage** is optimization of lead structure to improve potency, selectivity and to reduce toxicity.

Third stage is development stage, which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it clinically useful.

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic compounds as drugs.

Medicinal chemistry is almost always geared toward drug discovery and development. Medicinal chemists apply their chemistry training to the process of synthesizing new pharmaceuticals. They also work on improving the process by which other pharmaceuticals are made. Most chemists work with a team of scientists from different disciplines, including biologists, toxicologists, pharmacologists, theoretical chemists, microbiologists, and bio pharmacists. Together this team uses sophisticated analytical techniques to synthesize and test new drug products and to develop the most cost- effective and eco-friendly means of production.



Modern Medicinal Chemistry

History and Development of Medicinal Chemistry

In the Middle Ages various 'Materia Medica and pharmacopeas brought together traditional uses of plants. The herbals of John Gerard (1596), John Parkinson (1640) and Nicolas Culpeper (1649) provide an insight into this widespread use of herbs. Exploration in the seventeenth and eighteenth centuries led to the addition of a number of useful tropical plants to those of European origin. The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry. Their development is intertwined. The isolation of a

number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud. General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)). Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery. The hypnotic activity of chloral (trichloroethanal) (1869) was also reported. Many of the developments after the 1860s arose from the synthesis of compounds specifically for their medicinal action. Although the use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin and of salicylic acid was developed in the 1860s and 1870s. p-Hydroxyacetanilide (paracetamol) and phenacetin (1886) were also recognized as pain-killers. Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899. However its mode of action was not established until 1971.The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time.Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) and procaine (1905). The barbiturates, veronal (1903) and phenobarbital (1911) were introduced as sleeping tablets. The action of acetylcholine on nerve tissue had been recognized in the late nineteenth century. Barger and Dale (1910) examined the response of various tissues to acetylcholine agonists and showed that there were different receptor sub-types; some responding to muscarine and others to nicotine.

The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins. It was also a period in which there was exposure of many Europeans to tropical diseases. The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentary and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness. Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) and later chloroquine (1943) and paludrine (1946) were introduced as quinine replacements. In 1935 Domagk observed the anti-bacterial action of the sulfonamide dyestuff, prontosil red, from which the important family of sulfonamide anti-bacterial agents was developed. The activity of these compounds as inhibitors of folic acid biosynthesis was rationalized by Woods (1940) as anti-metabolites of p amino benzoicacid. With the onset of the Second World War, there was a need for new antibiotics. In 1929 Fleming had

observed that a strain of Penicillium notatum inhibited the growth of a Staphylococcus. In 1940-1941 Chain, Florey and Heaton isolated benzylpenicillin. After considerable chemical work, the b-lactam structure for the penicillins was established. The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including streptomycin (1944), chloramphenicol (1949) and the tetracyclines such as aureomycin (1949). Several different aspects of medicinal chemistry developed in parallel through the second half of the twentieth century. Although they did not develop independantly, it is easier to follow their progression by considering them separately. The structures of the steroid hormones were established in the 1930s and 1940s.

The discovery in 1949 of the beneficial effect of cortisone in alleviating the inflammation associated with rheumatism provided the stimulus for synthetic activity in this area. A number of anti-inflammatory semi-synthetic corticosteroids such as prednisolone, betamethasone and triamcinolone became available in the late 1950s and 1960s.A number of developments took place in the 1960s, which changed medicinal chemistry. It was found that a drug, thalidomide, which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children. The consequences of this teratogenicity effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines. Unfortunately there was some tardiness in the recognition of this side-effect. Second in 1964 Hench published correlations between substituent effects (Hammett parameters) and the biological activity of some aromatic compounds. These QSAR began to provide a framework for the systematic development of drugs and for decisions to be made in the planning of a research programme.

The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine (1976) and then ranitidine (1981). The reasoning behind this work had a major impact on the development of medicinal chemistry. Paul Ehrlich was such a scientist who got fascinated by the ability of colorful dyes to interact with cellular and histological structures. He procured hundreds to thousands of dyes for his research from several chemical companies for several decades. Ehrlich found that the biological effect of a chemical compound depends on its chemical composition and the cell on which it acts. He established a connection between chemistry, biology, and medicines in a creative way. He was also inspired by his colleagues who were conducting researches in immunology including Louis Pasteur, Robert Koch, Emil Von

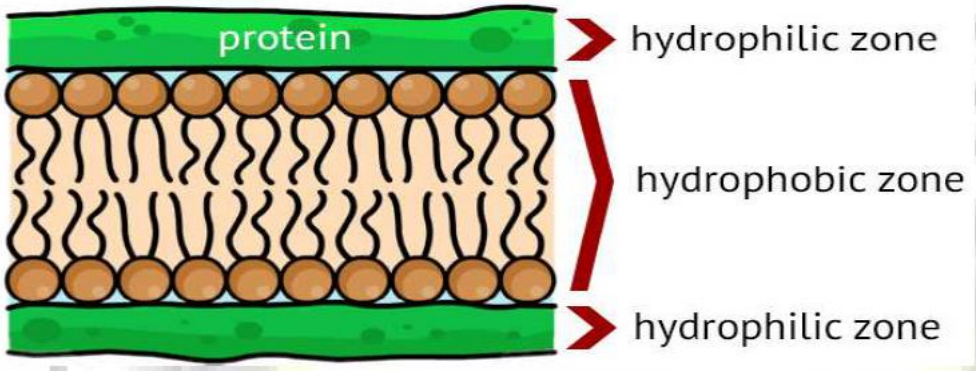
Behring, and ShibasaburoKitasato. In the 20th century, Ehrlich came up with the receptor theory; and this theory became influential to make understand how drugs bind to receptors based on their chemical structures and compositions.

Structure of Biological Membrane

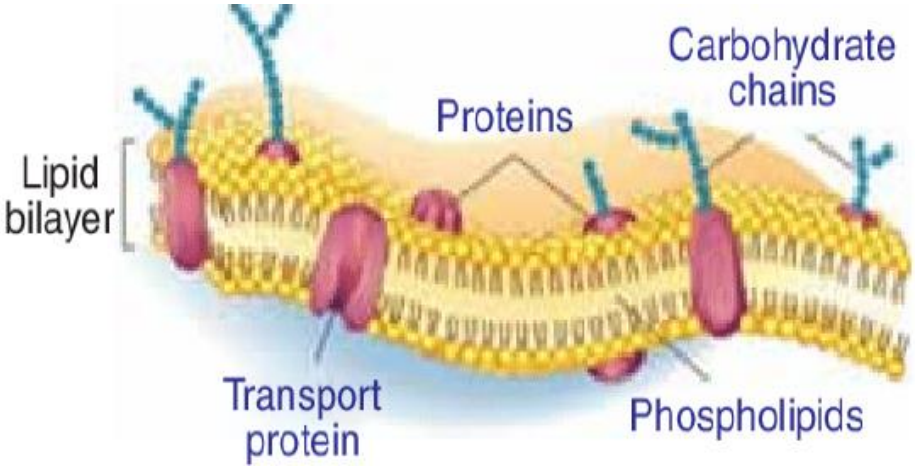
Biological Membrane (or cell membrane, plasma membrane, and plasma membrane) is a selectively permeable membrane which allows only certain substances to pass through it, and also acts as a barrier between the inner and outer surface of the cell. Celt membrane comprises of lipids and proteins along with other living molecules, which participate in the normal functioning of cells such as cell signalling, ion channel conductance, and cell adhesion. The inner cytoskeleton of the cell connects to its outer cell wall via cell membrane. Cell membrane defines the external boundaries of the cells and regulates traffic of molecule across the boundary. In eukaryotic cells, cell membrane divides the internal space into discrete compartments to segregate processes and components. It regulates the sequences of complex biochemical reactions and participates m conservation of biological energy and participates in cell-to-cell communication.

Models Depicting Structure of Cell Membrane

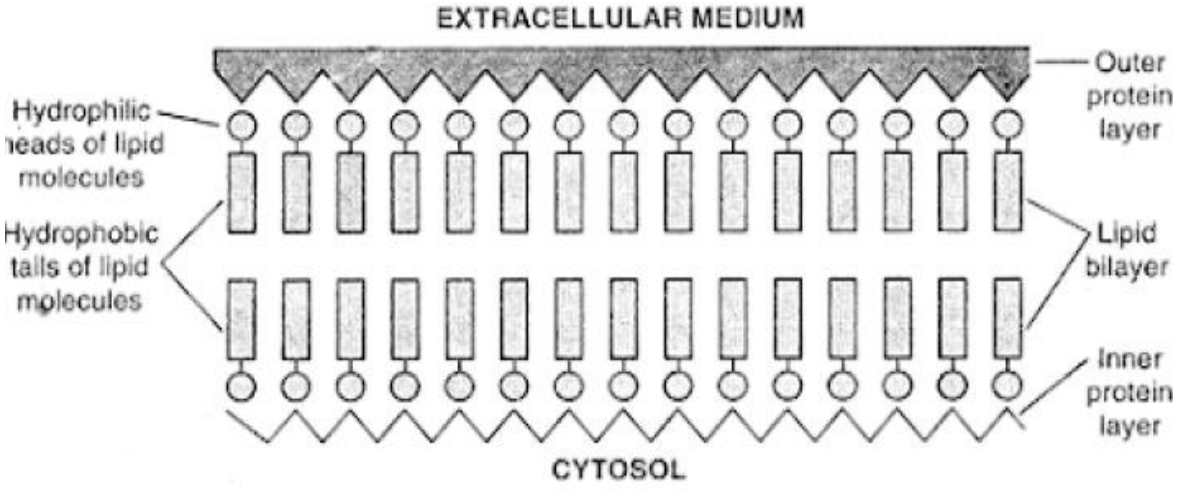
l. ***Danielli and Davson Model:*** Danielli and Davson (early 1930s-40s) have given the Lamellar theory in which they studied the arrangement of triglyceride lipid bilayer on the water surface. This model States that the plasma membrane has bimolecular phospholipids made up of two protein layers present as folded ß chains. By electrostatic bond, these protein molecules are attached to the lipid at polar hydrophilic ends.



2. *Unit Membrane Model:* According to this model, cell membrane is a continuous structure having cytoplasm on one side and extra cellular fluid on the other. Under the electron microscope, it appears as a thin, triple-layered structure with 7.5- 10 nm thickness. The membrane has two parallel dense strata each with 2.5nm thickness; these strata are separated by a light inter- zone of nearly same thickness. Isolated vesicles are formed in the cell by the folding of plasma membrane into the cytoplasm; these vesicles store extracellular material by endocytosis process.



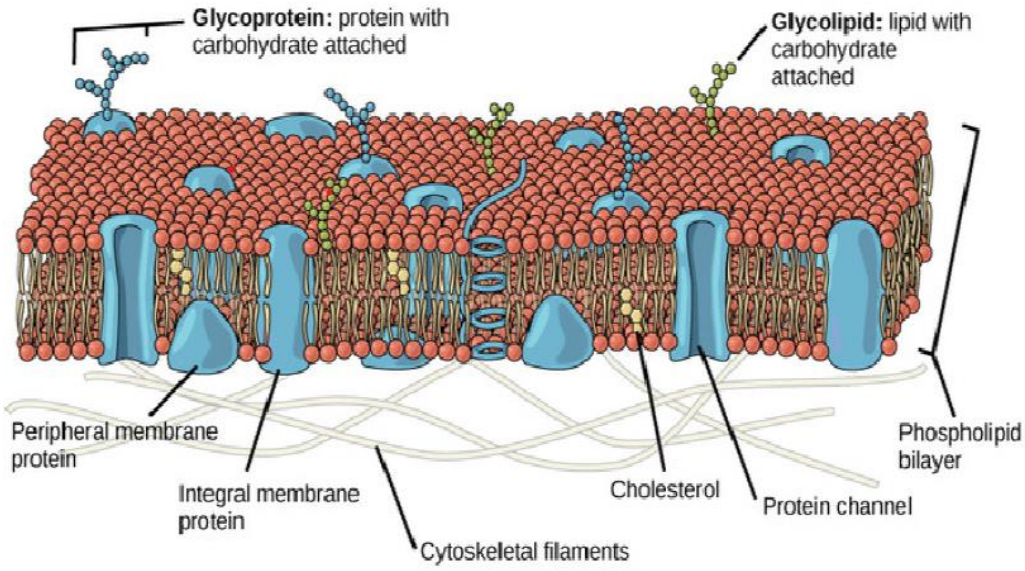
3. Robertson's Model: Through an electron microscope. Robertson revealed the tri-laminar structure of biological membrane. He observed two parallel dark hydrophilic layers (of 20-25Å width) and a middle light hydrophobic layer (of 25-35Å width) comprising the biological membrane. Organelles like nucleus, mitochondria. Endoplasmic reticulum etc. also have same tri-laminar membrane. Robertson stated that biological membrane is composed of bimolecular lipid layers sandwiched between outer and protein-layers.



4. The Fluid mosaic model– It was first proposed by S.J. Singer and Garth L. Nicolson in 1972 to explain the structure of the plasma membrane. The model has evolved somewhat over time, but it still best accounts for the structure and functions of the plasma membrane as we now understand them. The fluid mosaic model describes the structure of the plasma membrane as a mosaic of components including phospholipids, cholesterol, proteins, and carbohydrates that gives the membrane a fluid character.

Plasma membranes range from 5 to 10 nm in thickness. For comparison, human red blood cells, visible via light microscopy, are approximately 8 μm wide, or approximately 1,000 times wider than a plasma membrane. The proportions of proteins, lipids, and carbohydrates in the plasma membrane vary with cell type. For example, myelin contains 18% protein and 76% lipid. The mitochondrial inner membrane contains 76% protein and 24% lipid. The main fabric of the membrane is composed of amphiphilic or dual-loving, phospholipid molecules. The hydrophilic or water-loving areas of these molecules are in contact with the aqueous fluid both inside and outside the cell. Hydrophobic, or water-hating molecules, tend to be non- polar.

A phospholipid molecule consists of a three-carbon glycerol backbone with two fatty acid molecules attached to carbons 1 and 2, and a phosphate-containing group attached to the third carbon.



This arrangement gives the overall molecule an area described as its head (the phosphate-containing group), which has a polar character or negative charge, and an area called the tail (the fatty acids), which has no charge. They interact with other non-polar molecules in chemical

reactions, but generally do not interact with polar molecules. When placed in water, hydrophobic molecules tend to form a ball or cluster. The hydrophilic regions of the phospholipids tend to form hydrogen bonds with water and other polar molecules on both the exterior and interior of the cell. Thus, the membrane surfaces that face the interior and exterior of the cell are hydrophilic.In contrast, the middle of the cell membrane is hydrophobic and will not interact with water. Therefore, phospholipids form an excellent lipid bilayer cell membrane that separates fluid within the cell from the fluid outside of the cell.

Physiochemical properties.

The ability of a chemical compound to elicit a pharmacological/therapeutic effect is related to the influence of various physical and chemical (physicochemical) properties of the chemical substance on the bio- molecule that it interacts with.

1) Physical Properties: Physical property of drug is responsible for its action

2) Chemical Properties: The drug react extracellular according to simple chemical reactions like neutralization, chelation, oxidation etc.

Various Physico-Chemical Properties are

1. Solubility
2. Partition Coefficient
3. Dissociation constant
4. Hydrogen Bonding
5. Ionization of Drug
6. Redox Potential
7. Complexation
8. Surface activity
9. Protein binding
10. Isosterism

1. Solubility: The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute. Solubility depends on the solute and solvent as well as temperature, pressure, and pH. The solubility of a substance is the ratio of these rate constants at equilibrium in a given solution. The solubility of an organic

medicinal agent may be expressed in terms of its affinity/philicity or repulsion/phobicity for either an aqueous (hydro) or lipid (lipo) solvent.

KSOLUBILITY= KSOL/KPPT

The atoms and molecules of all organic substances are held together by various types of bonds (e.g. London forces, hydrogen bonds, dipole-dipole, etc.). These forces are intricately involved in solubility because it is the solvent-solvent, solute-solute, and solvent-solute interactions that govern solubility.

Methods to improve solubility of drugs

- Structural modification (alter the structure of molecules)
- Use of Co-solvents (Ethanol, sorbitol)
- Employing surfactants
- Complexation

Importance of solubility

- Solubility concept is important to pharmacist because it governs the preparation of liquid dosage form and the drug must be in solution before it is absorbed by the body to produce the biological activity.
- Drug must be in solution form to interact with receptors.

2. Partition coefficient: The ability of a drug to dissolve in a lipid phase when an aqueous phase is also present often referred to as lipophilicity. The lipophilicity can be best characterized by partition coefficient. Partition coefficient can be defined as the equilibrium constant of drug concentrations for "unionizable" molecules in the two phases. And for "ionizable" molecules (acids, bases, salts), where alpha (α) is the degree of ionization in aqueous solution. It is basically a constitutive property

$$P = \frac{[drug]_{lipid}}{[drug]_{water}}$$

$$P = \frac{[drug]_{lipid}}{(1-\alpha)[drug]_{water}}$$

Naturally, the partition coefficient is one of the several physicochemical parameters influencing drug transport and distribution. The contribution of each functional groups and their structural arrangement help to determine the lipophilic or hydrophilic character of the molecule. Partition coefficient majorly influence drug transport characteristics; the way in which the drugs reach the

site of action from the site of application (e.g. injection site, gastrointestinal tract, and so forth). Since the blood distributes drugs, they must penetrate and traverse many cells to reach the site of action.

Factors affecting Partition Co-efficient

- pH
- Co-solvents
- Surfactant
- Complexation

Importance of partition coefficient

- It is generally used in combination with the pka to predict the distribution of drug in biological system.
- The factor such as absorption, excretion & penetration of the CNS may be related to the log P value of drug.
- The drug should be designed with the lowest possible
- Log P, to reduce toxicity, nonspecific binding &bioavailability.

3. Ionization of drug: The accumulation of an ionized drug in a compartment of the body is known as "ion trapping". The ionization of a drug is dependent on its pKa and the pH. The pKa is the negative Logarithm of Ka. The Ka is the acidity constant of a compound, its tendency to release a proton.

$$pH - pK_a = \log([A^-]/[HA])$$
$$= \log([\text{ionized}]/[\text{non ionized}]) \quad \text{for acids}$$
$$pH - pK_a = \log([B]/[HB^+])$$
$$= \log([\text{non ionized}]/[\text{ionized}]) \quad \text{for bases}$$
$$\text{Fraction non-ionized} = [HA]/([HA]+[A^-])$$
$$= 1/1 + ([A^-]/[HA])) = 1/(1 + \text{antilog}(pH - pK_a))$$

The ratio of ionized/ non ionized drug may be determined by the Henderson- Hasselbalch relationship. This may be used to derive an Effective partition coefficient: Ex: Phenobarbital pKa

is 7.4. It is evident that phenobarbital would be predominantly in the unionized form in acidic environment.

Importance of ionization of drugs

- The lower the pH relative to the pKa greater is the fraction of protonated drug (protonated drug may be charged or uncharged)
- Weak acid at acidic pH: more lipid-soluble, because it is uncharged—the uncharged form more readily passes through biological membranes. Note that a weak acid at acidic pH will pick up a proton and become uncharged.

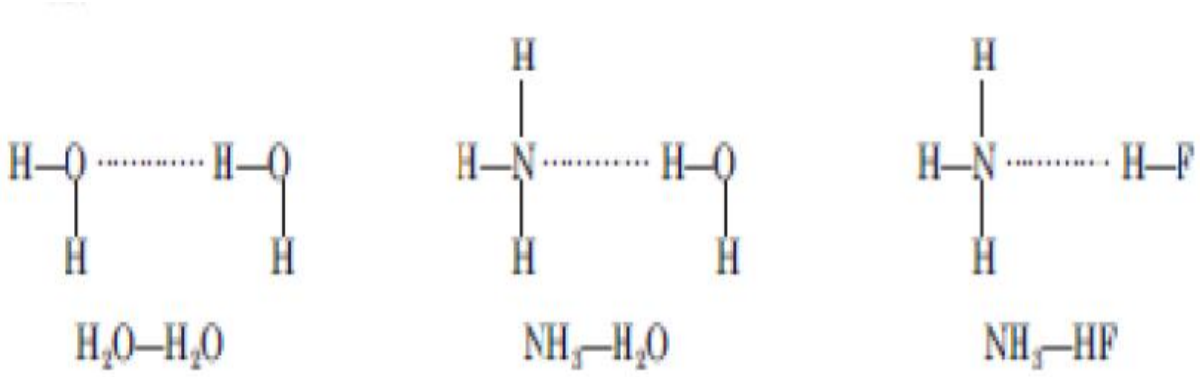
$$RCOO+H \rightarrow RCOOH$$

- Weak base at alkaline pH: more lipid-soluble, because it is uncharged—the uncharged form more readily passes through biological membranes. Note that a weak base at more alkaline pH will lose a proton, becoming uncharged

$$RNH3 \rightarrow RNH2+H+$$

4. Hydrogen Bonding: The hydrogen bond is a special type of dipole-dipole interaction between the hydrogen atom in a polar bond such as N—H, O—H or F—H and an electronegative atom O, N, or F atom. This interaction is written as A—H ⋯⋯⋯⋯B. A and B represent O, N or F. A—H is one molecule (or) part of a molecule and B is a part of another molecule; and the dotted line represents the hydrogen bond. These three atoms usually lie along a straight line, but the angle AHB can deviate as much as 30° from linearity.

Ex: Hydrogen bonding in NH3, H2O and HF.



Generally the hydrogen bonding is classified into 2 types

A. **Intermolecular hydrogen bonding**
B. **Intramolecular hydrogen bonding**

(A) Intermolecular hydrogen bonding. In this type, hydrogen bonding occurs between two or more than two molecules of the same compound and results in the formation of polymeric aggregate. Intermolecular hydrogen bonding increases the boiling point of the compound and also its solubility in water. The molecules that are able to develop intermolecular hydrogen bonding improve their solubility by the formation of intermolecular hydrogen bonding with water. Ex: Ethanol shows higher boiling point and higher solubility in water than dimethyl ether even though both have the same molecular weight.

(B) Intermolecular hydrogen bonding. In this type, hydrogen bonding occurs within two atoms of the same molecule. This type of hydrogen bonding is commonly known as chelation and frequently occurs in organic compounds.

Sometimes intermolecular hydrogen bonding develops a six or 5-membered ring. Ex:o-chlorophenol, o-nitro phenol. Intermolecular hydrogen bonding decreases the boiling point of the compound and also its solubility in water. This is because of the fact that the chelation between the ortho substituted groups restricts the possibility of intermolecular hydrogen bonding with water and thus prevents association of the molecules, which would have raised the melting point, boiling point. o-Nitrophenol.- 215°C,p-Nitrophenol-279°C,m-Nitrophenol-279°C.

Effects of hydrogen bonding. Almost all physical properties are affected by hydrogen bonding. Here only those properties that are prominently altered such as boiling points, melting point, water solubility etc., are discussed. In addition to physical properties several chemical properties like acid character, basic character, properties of carbonyl group are also affected by hydrogen bonding.

5. Protein binding: The reversible binding of protein with non-specific and nonfunctional site on the body protein without showing any biological effect is called as protein binding.

Protein + drug⟷ Protein-drug complex

Depending on the whether the drug is a weak or strong acid, base or is neutral, it can bind to single blood proteins to multiple proteins (serum albumin, acid glycoprotein or lipoproteins). The most significant protein involved in the binding of drug is albumin, which comprises more than

half of blood proteins. Protein binding values are normally given as the percentage of total plasma concentration of drug that is bound to all plasma protein.

Free drug (Df) + Free protein(Pf)→ Drug /protein complex (Dp)

Total plasma concentration (Dt) = (Df) + (Dp)

6. Complexation or chelation: Complexes or coordination compounds result from a donor acceptor mechanism (donating accepting electron or, rather, an electron pair) or Lewis acid-base reaction (donating-accepting protons). Any non-metallic atom or ion, whether free or contained in a neutral molecule or in an ionic compound, that can donate an electron pair, may serve as the donor. The acceptor, or constituent that accept the pair of electrons, can be a metallic ion or sometimes also a neutral molecule. In addition to "coordinate covalence" (i.e., bonds formed by the classical electron donor-acceptor mechanism), intramolecular forces can also be involved in the formation of complexes. Complexes may be divided broadly into two classes depending on whether the acceptor compound is a metal ion or an organic molecule.

The compounds that are obtained by donating electrons to metal ion with the formation of a ring structure are called chelates. The compounds capable of forming a ring structure with a metal atom are termed as Ligands. Most of the metals are capable of forming chelates or complexes (if the metal is not in a ring, the compound is called a metal complex), but the chelating property ís restricted to atoms like N, O and S, which are electron donating.

Applications of chelation

The phenomenon of chelation ís significantly involved in biological system andto some extent in explaining drug action.

- Dimercaprol is a chelating agent. It is an effective antidote for organic arsenical, Lewisite, but can also be used for treatment of poisoning due to antimony, gold and mercury.
- Penècillamine is an effective antidote for the treatment of copper poisoning because it forms water-soluble with copper and other metal ions.
- 8-hydroxyquinoline and its analogs act as antibacterial and antifungal agents by complexing with iron or copper.

BIOISOSTERISM

Bioisosterism is defined as compounds or groups that possess near or equal molecular shapes and volumes, approximately the same distribution of electron and which exhibit similar physical properties.

They are classified into two types.,

i) Classical biososteres

ii) Non classical bioisosters.

1.Classical Bioisosteres: They have similarities of shape and electronic configuration of atoms, groups and molecules which they replace. The classical bioisosteres may be,

A). Univalent atoms and groups:

i) Cl, Br, I

ii) CH3, NH2, -OH, -SH

B).Bivalent atoms and groups:

i) R-O-R,R-NH-R, R-S-R, RCH2R

ii) –CONHR, -COOR, -COSR

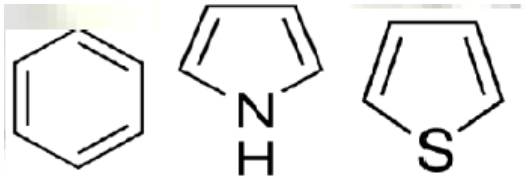
C).Trivalent atoms and groups:

i)-CH=, -N=

ii) –p=, -AS=

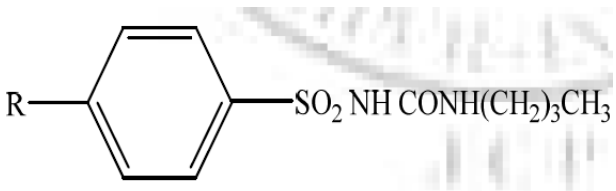
D).Tetravalent atoms and groups: =c=, =N=, =P=

E).Ring equivalent: -CH=CH-, -S-, -O-, -NH, -CH2-



Application of Classical Bioisosteres in drug design

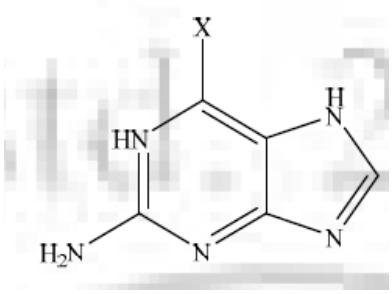
i) Replacement of –NH 2 group by –CH3 group



Carbutamide R= NH2

Tolbutamide R= CH3

ii) Replacement of –OH & -SH



Guanine= -OH

6-Thioguanine = -SH

2. Non classical Bioisosteres: They do not obey the stearic and electronic definition of classicalisosteres.Non-classical biosteres is functional groups with dissimilar valence electron configuration. Specific characteristics are

- Electronic properties
- Physicochemical property of molecule
- Spatical arrangement
- Functional moiety for biological activity.

Examples: Halogens Cl, F, Br, CN

Ether -S-, -OCarbonyl group

Hydroxyl group –OH, -NHSO2R, CH2OH

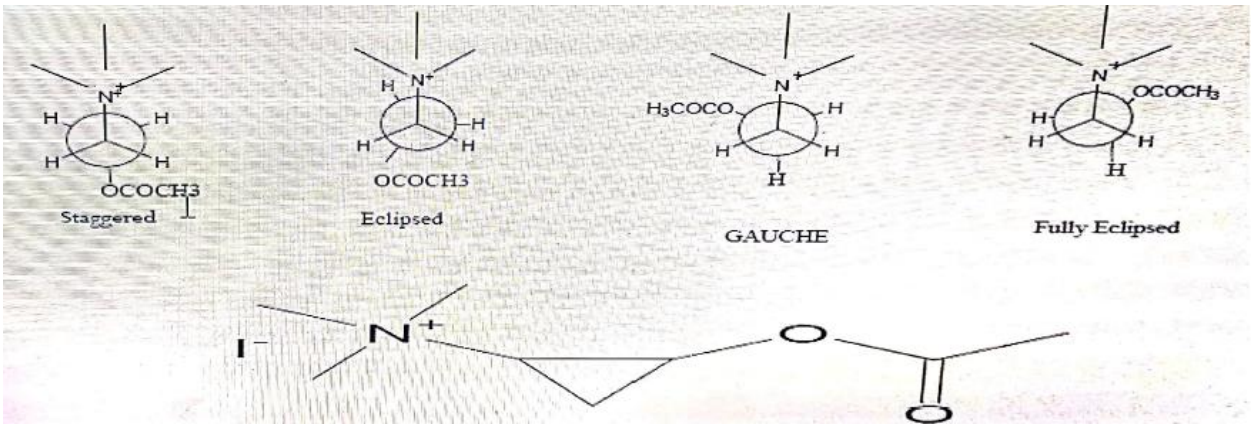
Catechol

Stereochemistry of drugs: Stereochemistry involve the study of three dimensional nature of molecules. It is study of the chiral molecules.

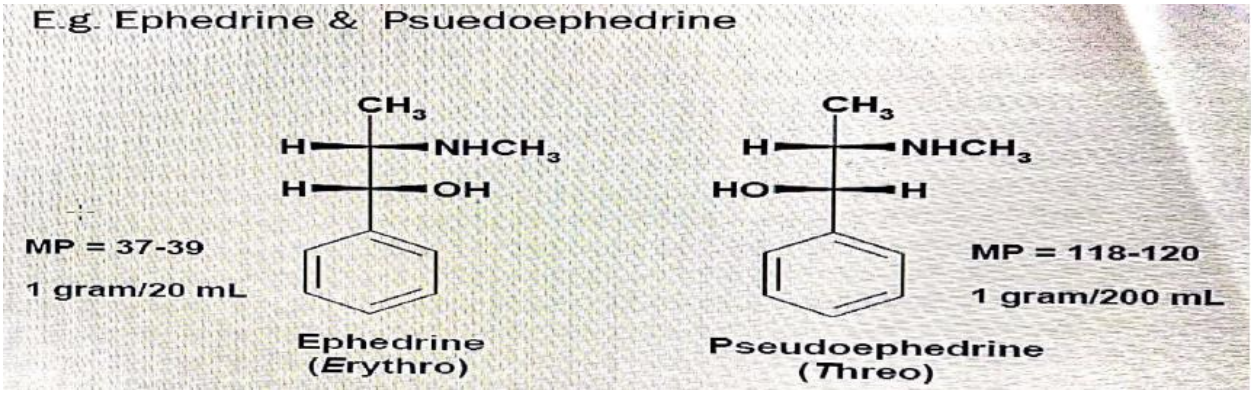
- Stereochemistry plays a major role in the pharmacological properties because;
- Any change in stereo specificity of the drug will affect its pharmacological activity
- The isomeric pairs have different physical properties (log p, pKa etc.) and thus differ in pharmacological activity.
- The isomers which have same bond connectivity but different arrangement of groups or atoms in the space are termed stereoisomer.

Conformational Isomers: Different arrangements of atoms that can be converted into one another by rotation about single bonds are called conformations. Rotation about bonds allows inter conversion of conformers.

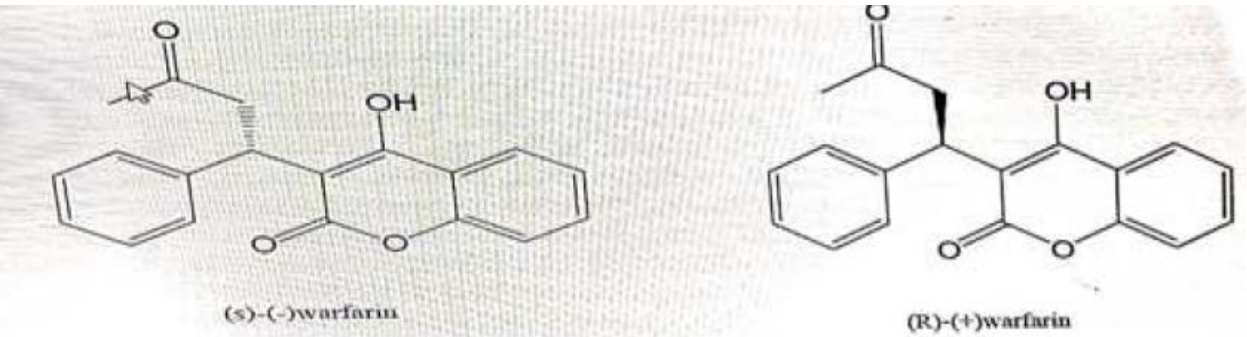
A classic example is of acetylcholine which can exist in different Conformations



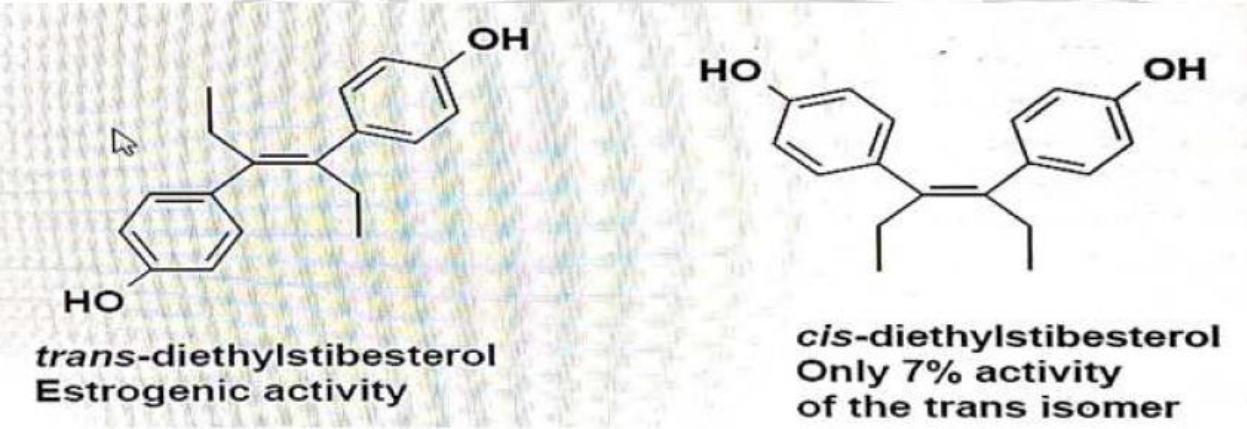
Optical Isomers: Stereochemistry, enantiomers, symmetry and chirality are important concept in therapeutic and toxic effect of drug. A chiral compound containing one asymmetric center has two enantiomers. Although each enantiomer has identical chemical & physical properties, they may have different physiological activity like interaction with receptor, metabolism & protein binding. Optical isomers in biological action are due to one isomer being able to achieve a three point attachment with its receptor molecule while its enantiomer would only be able to achieve a two point attachment with the same molecule.



The category of drugs where the two isomers have qualitatively similar pharmacological activity but have different quantitative potencies.



Geometric Isomerism: Geometric isomerism is represented by cis/trans isomerismresulting from restricted rotation due to carbon-carbon doublebond or in rigid ring system.



DRUG METABOLISM

Metabolism is the body's mechanism for processing, using, inactivating, and eventually eliminating foreign substances, including drugs. Drug exerts its influence upon the body, it is gradually metabolized, or neutralized. The liver, the blood, the lymph fluid, or any body tissue that recognizes the drug as a foreign substance can break down or alter the chemical structure of drugs, making them less active, or inert.

Drugs also can be neutralized by diverting them to body fat or proteins, which hold the substances to prevent them from acting on body organs. Once a drug is metabolized, it is the kidneys that normally filter the neutralized particles, called metabolites, as well as other waste and water, from the blood.

Drugs can also be excreted out of the body by the lungs, in sweat, or in feces. Drug metabolism is basically a process that introduces hydrophilic functionalities onto the drug molecule to facilitate excretion. Metabolism is defined as the process of polarization of a drug. This results in the formation of a metabolite that is more polar and, thus, less able to move into tissues and more able to be excreted from the body.

Drug metabolism is a detoxification function the human body possesses to defend itself from environment hostility. Metabolism is a major mechanism of drug elimination. The first human metabolism study was performed in 1841 by Alexander Ure, who observed the conversion of benzoic acid to hippuric acid and proposed the use of benzoic acid for the treatment of gout.

PHASE I : REACTIONS

Phase I metabolism is likely to be the predominant pathway of biotransformation. The enzymes involved in Phase I reactions are primarily located in the endoplasmic reticulum of the liver cell, they are called microsomal enzymes. Phase I reactions are non-synthetic in nature, and generally produce more water soluble and less active metabolite. The most common phase I reactions are oxidative processes (aromatic hydroxylation; aliphatic hydroxylation; N—, O—, and S-dealkylation; N-hydroxylation; Noxidation; sulfoxidation; deamination; and dehalogenation), reductive (azodyereduction, nitroreduction) and hydrolytic reactions

Oxidation: Oxidation is normally the first step of drug metabolism. Mixed function oxidases or monooxygenases is an important complex enzyme catalyses metabolic oxidation ofa large variety of endogeneous substances (steroidal hormones) and exogeneous substances(drugs). Some important metabolic oxidations are represented here:

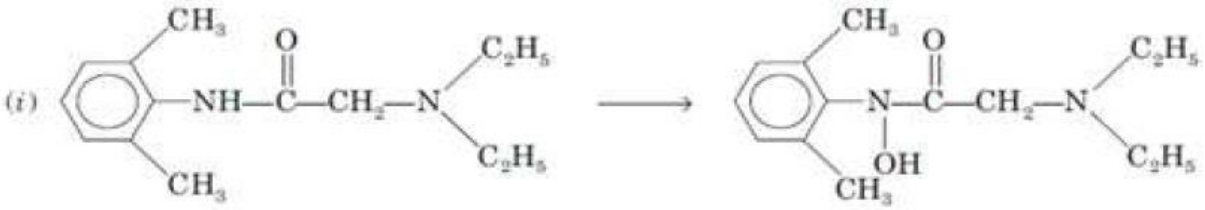
Oxidation of carbon-heteroatom systems. Carbon-heteroatom systems (N, O, S) are commonly present in many drugs. They are metabolized by any of thefollowing oxidation processes :

- Oxidation or hydroxylation of heteroatom: Ex: N-oxidation, Nhydroxylation, S-oxidation.
- Hydroxylation of carbon atom attached to the heteroatom followed by cleavage of carbon-heteroatom bond. Ex: N-dealkylation, S-dealkylation, Odealkylation.

1. Oxidation and hydroxylation of heteroatom

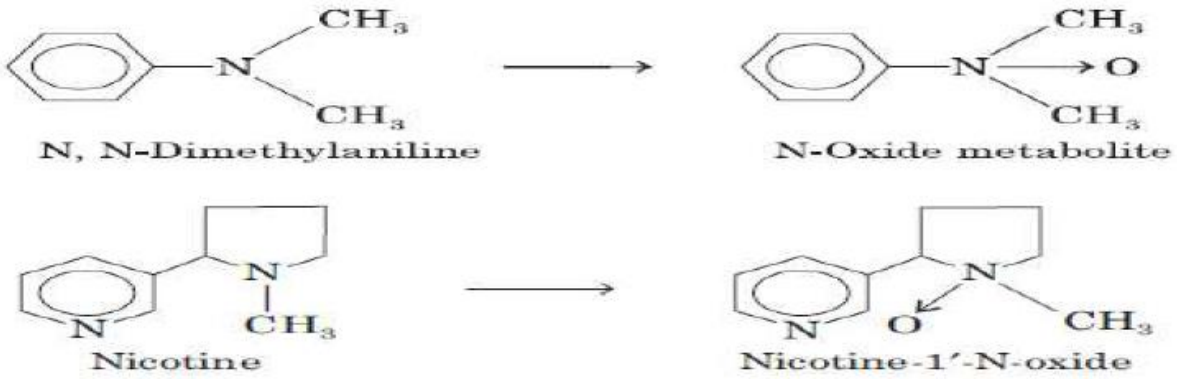
N-Hydroxylation: Drugs containing non-basic nitrogen atom (amides), non- basic aromatic amines and basicamines are metabolized by N-hydroxylation.

Ex:



Lidocaine N-Hydroxylidocaine

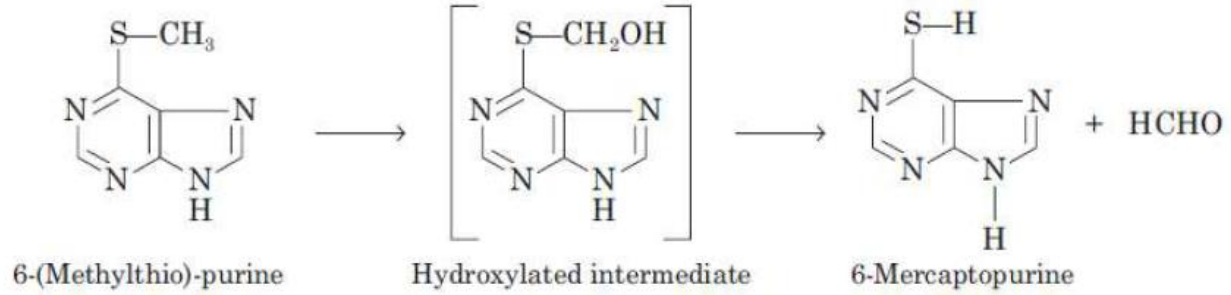
N-Oxidation: Compounds possessing of basic nitrogen are metabolized by N-oxidation process. Ex: Tertiary amines yield N-oxides.



S-Oxidation: Compounds possessing of carbon-sulfur bonds are metabolized to sulfoxides by S-oxidation.The sulfoxides may be excreted as urinary metabolites or oxidized to sulfones (—SO2—).

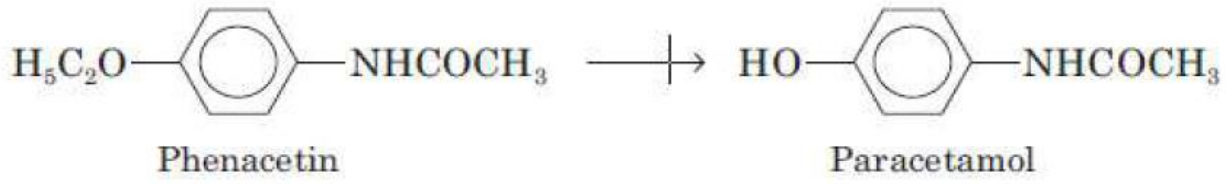
2. Dealkylations. The second type of oxidative biotransformation comprises dealkylations.

S-Dealkylation. S-Dealkylation involves oxidative cleavage of alkyl carbon sulfur Bonds



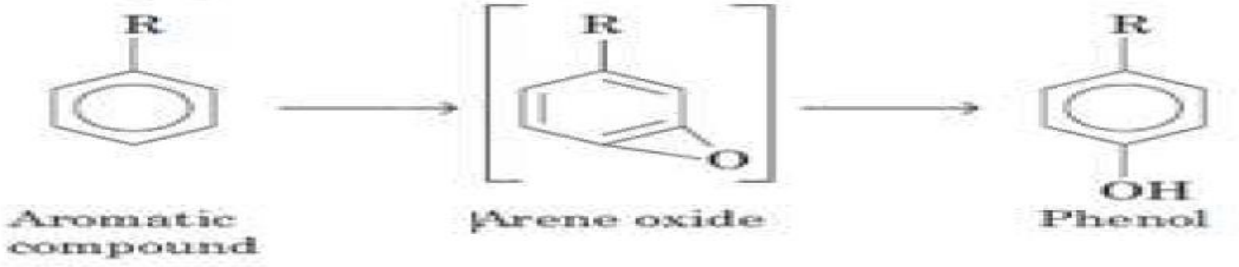
N-Dealkylation. In the case of primary or secondary amines, dealkylation of an alkyl group starts at the carbon adjacent to the nitrogen; in the case of tertiary amines, with hydroxylation of the nitrogen (ex: Lidocaine).

O-Dealkylation. O-Dealkylation of drugs possessing C—O bond involves hydroxylation of α-carbon to form an unstable hemiacetal or hemiketal intermediates. These intermediates spontaneously cleave to form alcohol and carbonyl compound.

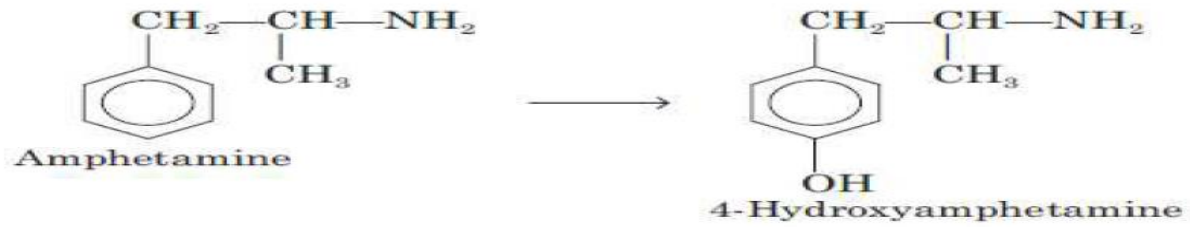


Phenacetin Paracetamol

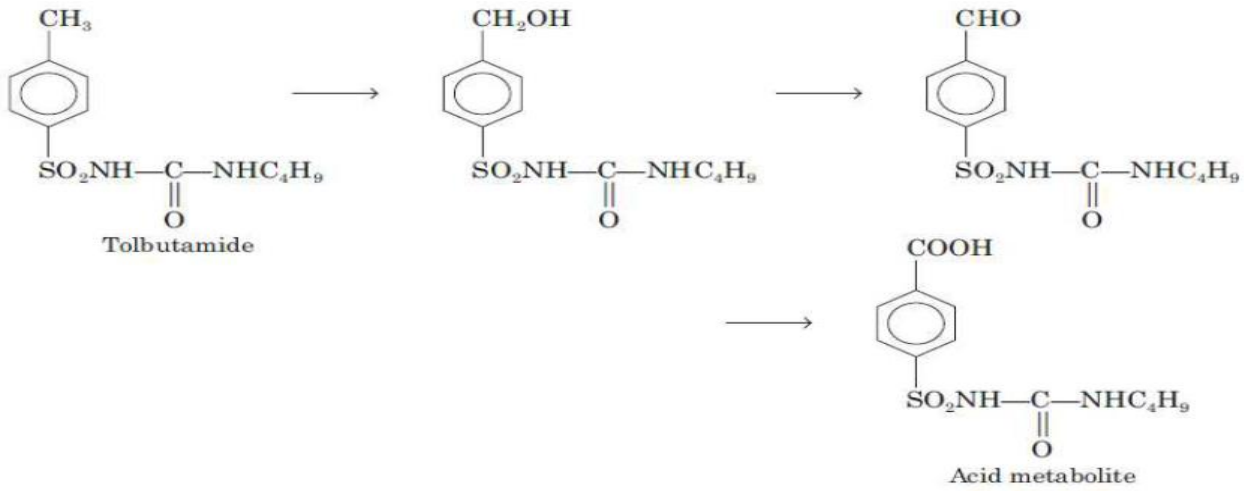
Aromatic Hydroxylation: Aromatic hydroxylation is oxidation of aromatic compounds into phenols through the intermediate formation of highly reactive immediate i.e. arene oxide



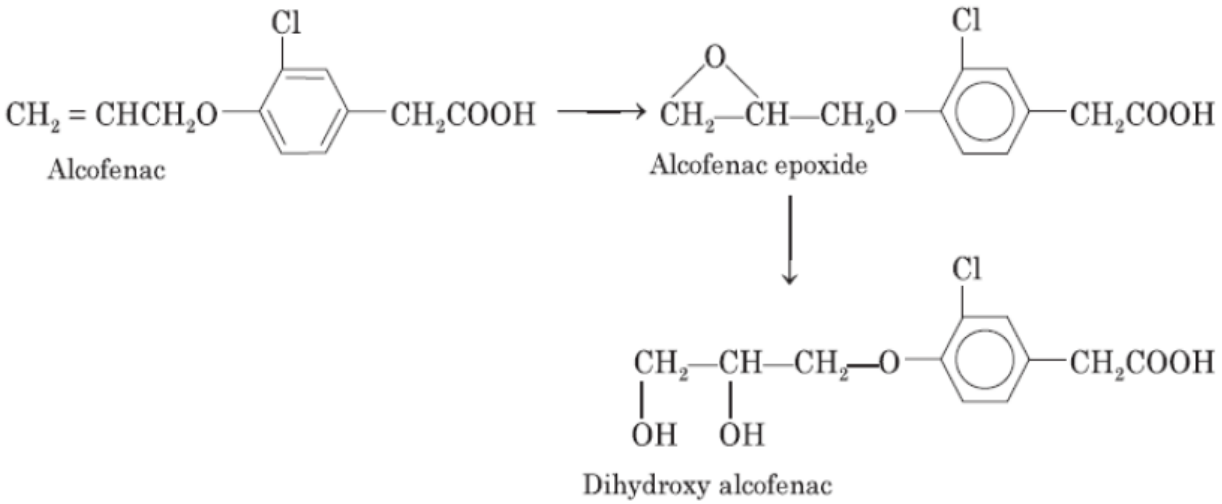
Ex: Many drugs containing phenyl groups (phenylbutazone,phenytoin, amphetamine, phenformin etc.) are metabolized by aromatic hydroxylation.



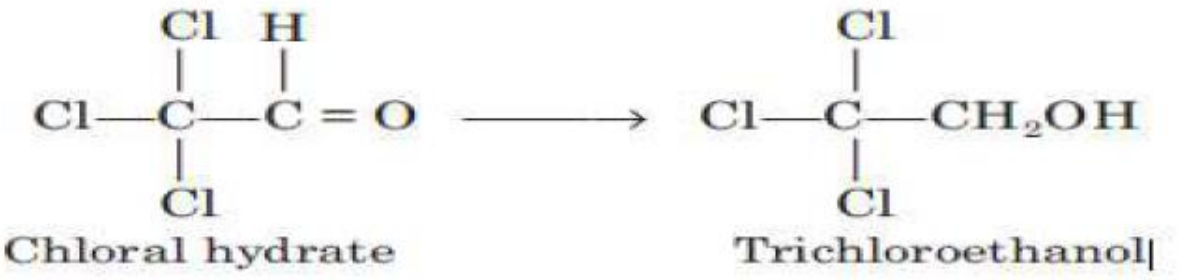
Oxidation of benzylic carbons: The carbons directly attached to aromatic rings are oxidized to aldehydes and carboxylicacids via alcohol to aldehydes and carboxylicacids via alcohols.



Oxidation of olefins: Alcofenac is oxidized to dihydroxyalcofenac.



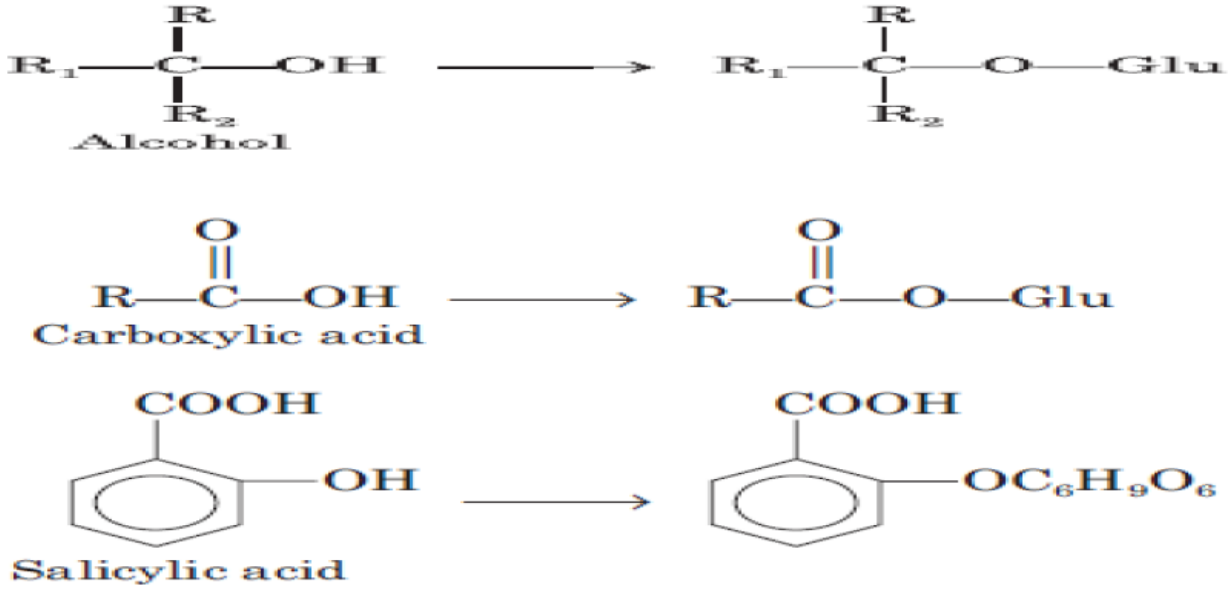
Reductive reactions: Drugs containing carbonyl, nitro, and azo groups are metabolized by reduction to alcohols and amines respectively. The reduced compounds are conjugated and eliminated from the body. Ex :



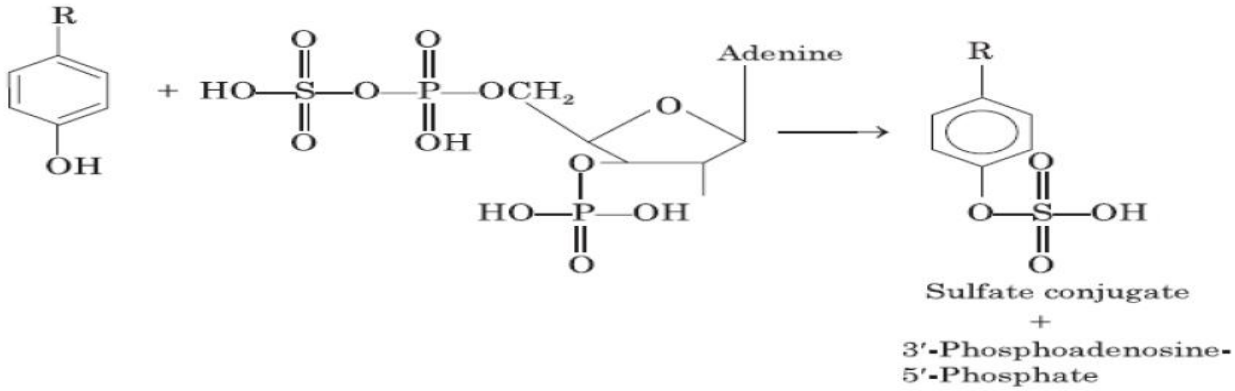
PHASE II : REACTIONS: Conjugation reactions are also known as phase-II reactions. Phase II pathways are synthetic reactions where the product or the metabolite from Phase I gets conjugated. This always produces a large, polar, metabolite that is readily excreted from the body. Some drugs are mainly conjugated and undergo very little oxidative metabolism.

Phase II occurs by glucuronidation, sulfation, aminoacid conjugation, acetylation, methylation or glutathione conjugation to facilitate elimination. Phase II conjugation introduces hydrophilic functionalities such as glucuronic acid, sulfate, glycine, or acetyl group onto the drug or drug metabolite molecules. These reactions are catalyzed by a group of enzymes called transferases. Most trasferasesare located in cytosol, except the one facilitates glucuronidation, which is a microsomal enzyme. This enzyme, calleduridine diphosphate glucuronosyl transferase (UGTs), catalyzes the most important phase II reaction, glucuronidation.

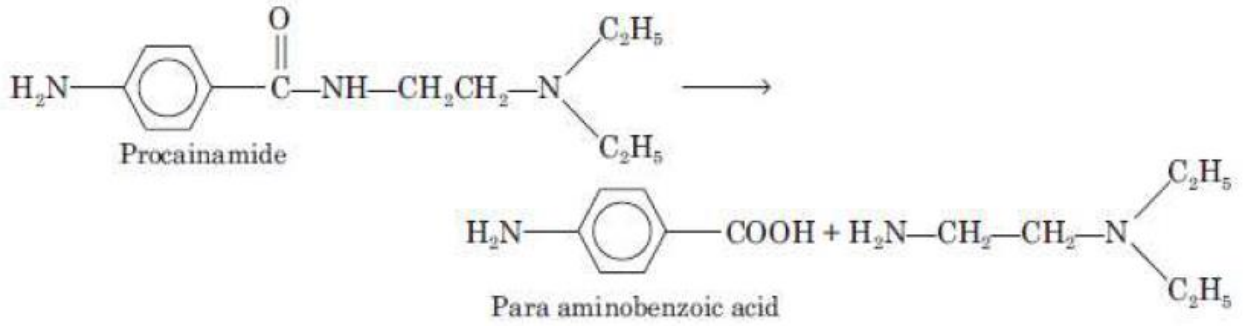
Glucuronidation. Glucuronidation involves conjugation of metabolite or drug molecule with glucuronic acid. In these reactions glucuronic acid molecule is transferred to the substrate from a cofactor (uridine-51-diphospho-α-Dglucuronic acid). Glucuronidation is catalyzed by various microsomal glucuronyl transferases. Glucuronides are generally inactive and are rapidly excreted into the urine and bile. Molecules associated with phenolic hydroxyl, alcoholic hydroxyl, and carboxylic acid groups undergo glucuronidation reaction.



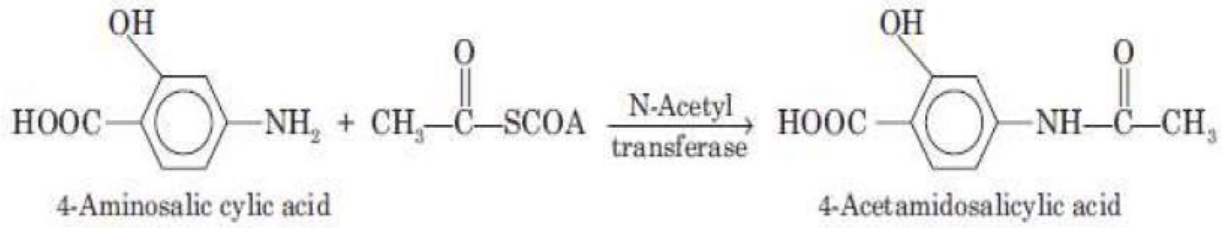
Sulfate Conjugation: Sulfate conjugation involves transfer of a sulphate molecule from the cofactor (31- phosphoadenosine-51-phosphosulfate) to the substrate (metabolite or drug moiety) by the enzymes (sulfotransferases). Sulphate conjugation is the common conjugation reactions of substrate molecules possessing of alcoholic hydroxyl, phenolic hydroxyl and aromatic amine groups. Ex:



Hydrolysis: Hydrolysis is also observed for a wide variety of drugs. The enzymes involved in hydrolysis are esterases, amidases, and proteases. These reactions generate hydroxyl or amine groups, which are suitable for phase II conjugation.



Acetylation: Acetylation is an important metabolic pathway for drugs containing primary amino groups. The acetylated conjugates are generally nontoxic and inactive. Ex: histamine, procainamide, para aminosalicylic acid (PAS), hydralazine, isoniazid.



Cytochrome p450: The cytochromes P450s [CYPs] are membrane bound proteins with an approximate molecular weight of 50 kD, and contain a heme moiety. There are about 30 human cytochrome P450enzymes out of which only six, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4are the metabolising enzymes.

FACTORS AFFECTING THE DRUG METABOLISM

A number of factors may influence the rate of drug metabolism. They are ;

1. **Physicochemical properties of drugs**. Molecular size, shape, acidity or basicity, lipophilicity, pKa, and steric and electronic characteristics of drugs influence its interaction with the active sites of enzymes.

2. **Chemical factors**. A large number of chemical substances such as drugs, insecticides etc. can increase the rate of drug metabolism due to increased rate of formation of newer enzymes or

decreased rate of degradation of drug metabolising enzymes. Ex. Alcohol enhances metabolism of phenobarbitone, phenytoin etc.

3. Diet. The enzyme content and activity is altered by a number of dietary compounds. Fat free diet depresses cytochrome P450 levels since phospholipids, which are important components of microsomes become deficient.

4. Genetic or hereditary factors. Genetic and hereditary factors are the most significant factors in drug metabolism. Genetic differences among individuals or ethnic groups can lead to an excessive or prolonged therapeutic effect or toxic overdose. Ex: The enzyme CYP2D6 metabolises a large number of drugs. The activity of this enzyme varies widely among ethnic groups. About 1% of Arabies, 30% Chinese and 7-10% caucasionsare poor metabolizers of CYP2D6 drugs.

5. Environmental factors. Environmental factors such as smoking, alcohol consumption and concomitant drug therapy also influence the outcome of drug metabolism. Ex: Cigarette smoke produces polynuclear aromatic hydrocarbons. CYP1A2 metabolises the polynuclear aromatic hydrocarbons to carcinogens responsible for lung and colon cancer.

Short Answer Type Question

1. Define medical chemistry.

2. What do you mean by GPRCs ?

3. Highlight importance of medical chemistry.

4. Highlight types of protein binding.

5. Define terms: bioisoterism, geometrical isomerism, ligands.

6. Define hydrogen bonding.

7. Define geometrical configuration.

8. Why medicinal chemistry is important to study for drug development?

9. Highlight Acetylation.

Long Answer Type Questions

1. Explain G-Protein-Coupled Receptors and their mechanism.

2. Classify heterocyclic compounds with one example.

3. Explain classifications of bioisoterism.

4. Write in details importance of bioisoterism in drug action.

5 Why solubility is important factor for drug action .

6. Describe various physicochemical properties involved in drug action.

7. Explain phase I reactions in drug metabolism.

8. Eloborate in brief factors affecting drug metabolism.

9. Explain phase II reactions in drug metabolism.