UNIT-I

INTRODUCTION TO MEDICINAL CHEMISTRY

Points to be covered in this topic

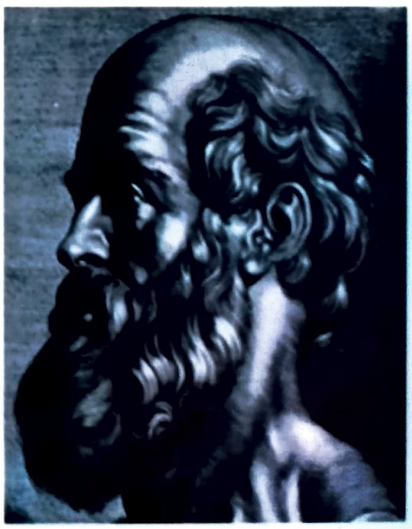
- ❑ INTRODUCTION
- ❑ HISTORY & DEVELOPMENT
- ❑ PHYSIOCHEMICAL PROPERTIES
- ❑ DRUG METABOLISM

❑ INTRODUCTION

- Medicinal chemistry is a discipline concerned with the design, development and synthesis of pharmaceutical drugs.
- The discipline combines expertise from chemistry and pharmacology that involves the identification, synthesis, and development of new chemical agents that are suitable for medical or pharmaceutical use.
- It also includes the study of existing drugs, their pharmacological properties, toxic effects, and their quantitative structure-activity relationship (QSARs).

❑ HISTORY AND DEVELOPMENT

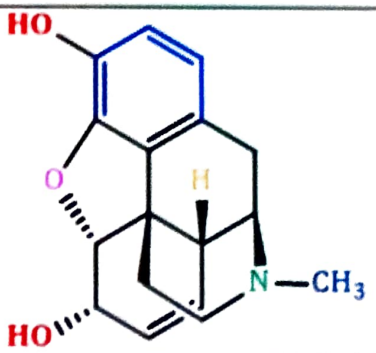
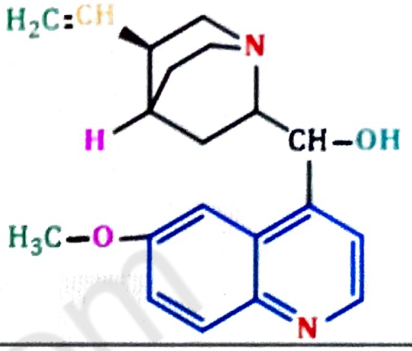
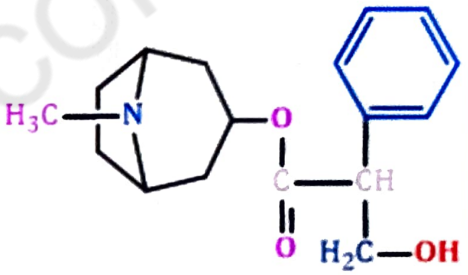
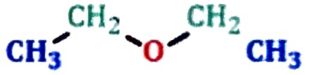
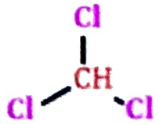
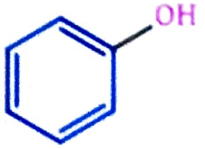
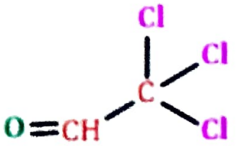
- The initial step of drug discovery involves the identification of new active compounds.
- The second step in drug discovery involves further chemical alterations on structure activity relationship (SAR) to enhance the biological and physicochemical properties of the compounds.
- The final step involves clinical trial after that the optimization of the synthetic route for bulk production and the preparation of a suitable drug formulation.



- There is a long history of plants being used to treat various diseases.
- The therapeutic properties of plants were described by the Ancient Greeks and by the Romans and are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus.

❖ Age of innovation and chemistry (19th century)

- The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry.

Year	Discovery	Structure
1805	Morphine	
1823	Quinine	
1834	Atropine	
1842	General Anesthetics (diethyl ether)	
1845	Nitrous oxide	
1847	Chloroform	
1839	Antiseptics (iodine)	
1860	Phenol	
1869	The hypnotic activity of chloral (trichloroethanal)	

❖ Age of innovation and chemistry (20th century)

- The discovery of **Penicillin by Alexander Fleming In 1929** had observed that a **strain of *Penicillium notatum*** inhibited the growth of a Staphylococcus. In 1940-1941 Chain, **Florey and Heaton** isolated **benzylpenicillin.**
- 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 teratogenic effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines.
- The development of histamine antagonist for the treatment of peptic ulcer led to **cimetidine and then ranitidine** because of major development of medicinal chemistry.

❑ PHYSIOCHEMICAL PROPERTIES

- The ability of chemical compounds to elicit a **pharmacological** or **therapeutic effect** is related to influence of various physical and chemical properties of the chemical substances on the biomolecules that interact with.

❖ Various physiochemical properties are

- Solubility
- Partition Coefficient
- Hydrogen Bonding
- Ionization of Drug
- Protein binding
- Bioisosterism
- Complexation
- Surface activity
- Optical and Geometrical isomerism.

➢ Solubility

- The solubility of a substance at a given temperature is defined as the ability of a substance to dissolve in a solvent.
- Solubility depends on the **nature of solute and solvent** as well as **temperature, pH & pressure**.
- The atoms and molecules of all organic substances are held together by various types of bonds (**e.g. hydrogen bond, dipole-dipole, ionic bond etc.**)
- These forces are involved in solubility because it is the **solvent- solvent, solute-solute, solvent-solute interactions** that governs solubility.

✓ Methods to improve solubility of drugs

1) Structural modification (alter the structure of molecules)
2) Use of Cosolvents (Ethanol, sorbitol, PPG, PEG)
3) Employing surfactants
4) Complexation

➢ Partition coefficient

- Partition co-efficient is one of the Physicochemical parameter which influencing the drug transport & drug distribution, the way in which the drug reaches the site of action from the site of application.
- Partition co-efficient is defined as equilibrium constant of drug concentration for unionized molecule in two phases.

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in water}}$$

- Since partition coefficient are difficult to measure in living system .
- They are usually determined in vitro 1-octanol as a lipid phase and phosphate buffer of pH 7.4 as the aqueous phase.
- 1-octanol as a lipid phase because,

a) It has **polar and nonpolar region.**
b) $P_{o/w}$ is **easy to measure.**
c) $P_{o/w}$ often correlates with many **biological properties.**

✓ Factors affecting Partition Co-efficient

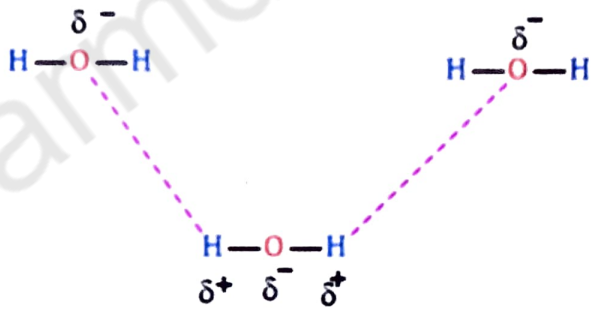
a) pH
b) Co solvents
c) Surfactant
d) Complexation

➢ Hydrogen bonding

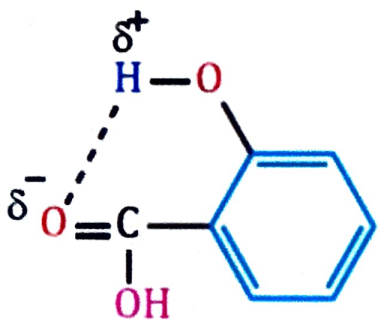
- The hydrogen bond is a special **dipole-dipole interaction** between the **hydrogen atom in a polar bond** such as N-H, O-H or F-H & electronegative atom O, N, F atom.
- The atoms capable of forming H-bonds have **at least one unshared pair of electrons.**
- The compounds that are **capable of forming hydrogen bonding** is only **soluble in water**.

✓ Hydrogen bonding is classified into 2 types:

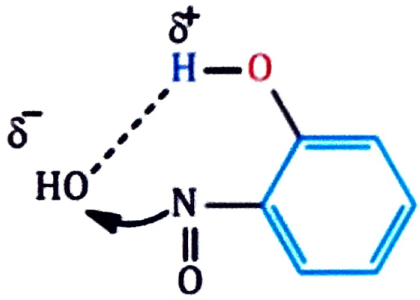
1. **Intermolecular**:- Hydrogen bonding occurs **between two or more molecules**.



2. **Intramolecular:-** Hydrogen bonding occurs **within two atoms of the same molecule.**



salicylic acid



O-Nitrophenol

✓ **Effect of H-bonding:-** All physical properties affected by H-bonding

- Boiling and Melting point
- Water solubility
- Strength of acids
- Spectroscopic properties
- On surface tension and viscosity
- Biological products
- Drug-receptor interaction

➢ Ionization of drug

- Most of the drugs are either weak acids or base and can exist in either ionized or unionized state.
- The ionization of the drug depends on its PK_a & PH.
- The rate of drug absorption is directly proportional to the concentration of the drug at absorbable form but not the concentration of the drug at the abs
- Ionization form imparts good water solubility to the drug which is required of binding of drug and receptor interaction

➢ Protein binding

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

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

- Depending on the whether the drug is a weak or strong acid, base is neutral, it can bind to single blood proteins to multiple proteins (sereum albumin, acid-gycoprotien 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.

Total plasma concentration (D_t) = (D_f) + (D_p)

➢ Bioisosterism

- Bioisosteres are **chemical substituents or groups with similar physical or chemical properties** which produce broadly similar biological properties to another chemical compound.
- Bioisosterism is used to reduce toxicity, change bioavailability, or modify the activity of the lead compound, and may alter the metabolism of the lead.

✓ Bioisosteres are classified into following two types:-

1. **Classical Bioisosteres:-** They have **similarities of shape and electronic configuration of atoms, groups and molecules** which they replace. Various examples are as follows:-

   1) Univalent atoms and groups

   i) Cl, Br, I ii) CH_3, NH_2, -OH, -SH.

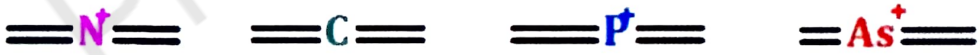
   (2) Bivalent atoms and groups

   (i) R-O-R,R-NH-R, R-S-R, RCH,R (ii)-CONHR, -COOR, -COSR

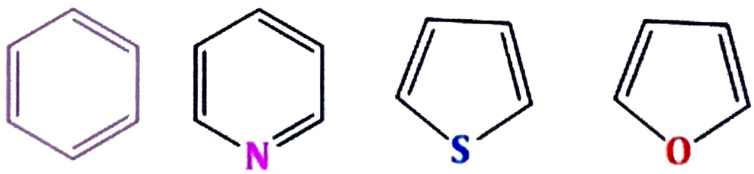
   (3) Trivalent atoms and groups

   (i) -CH=, -N=, -P=, -AS=

   (4) Tetravalent atoms and group

   (5) Ring equivalents

2. **Nonclassical Bioisosteres:-** They **do not obey the stearic and electronic definition** of classical isosteres.

- Non-classical biosteres are functional groups with dissimilar valence electronic configuration.

✓ Specific characteristics:

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

➢ Optical and Geometrical isomerism:-

1. **Optical isomerism:** Optical isomers may be defined simply as compounds that differ only in their ability to rotate the plane polarized light.

- Objects that are **not superposable** on their mirror images are **chiral.**
- Mirror image molecules are **not superimposable and are called enantiomers.**
- Stereoisomers that are **NOT mirror images** of each other is called diastereomers and they have different physical and chemical properties.

2. **Geometric isomerism:** These isomers occur where you have **restricted rotation** somewhere in a molecule. At an introductory level in organic chemistry. (examples usually just involve the carbon-carbon double bond).

- Different physical properties and Different arrangement(Different density, polarity, solubility, melting point /boiling point)
- They are in two forms *cis*- and *trans*-isomers.
- *Cis*-isomer with the hydrogens on the same side of the double bond.
- *Trans*-isomer with the hydrogens on opposite sides of the double bond.

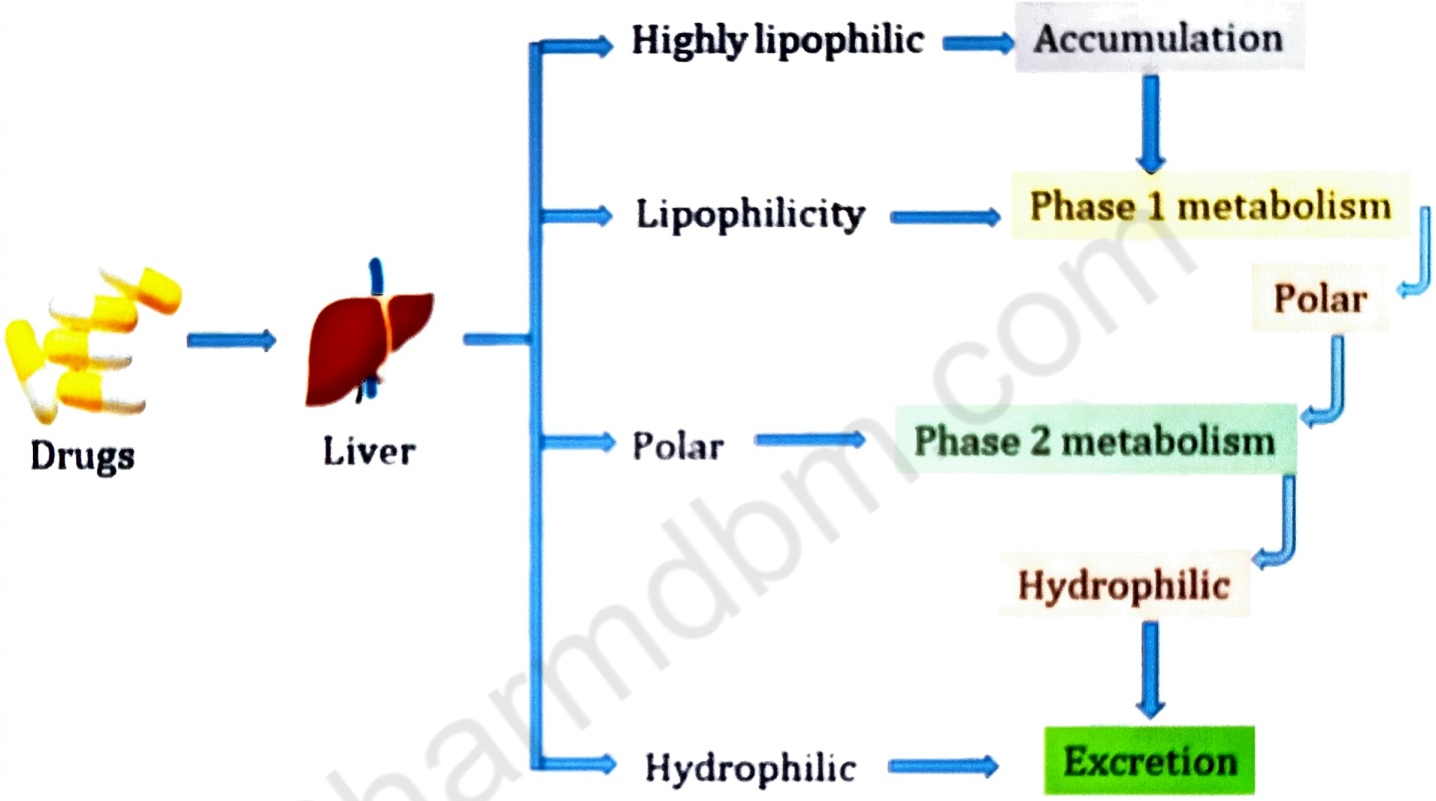
❑ DRUG METABOLISM

- Metabolism is an **essential pharmacokinetic process, which converts lipid soluble and non-polar compounds to water soluble and polar compounds** so that they are excreted by various processes.
- Drug metabolism is **the process which describes biotransformation of drugs or nonessential exogenous compounds in body so that they can be easily eliminated.** It is basically a process of introduction of hydrophilic moiety into drug molecule to facilitated excretion.

❖ Site of Metabolism

- Liver is the major site of drug metabolism.
- Liver contains many necessary enzymes required for metabolism of drugs and foreign compound (Collectively referred as xenobiotics).

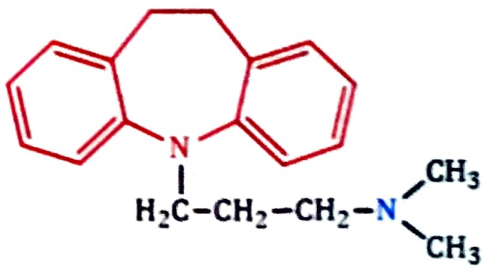
❖ Drug Metabolism Pathways



➢ PHASE 1 REACTION

- It is a predominant pathway of biotransformation.
- The most common phase 1 reactions are oxidation reaction, reduction Reduction and hydrolysis reactions.

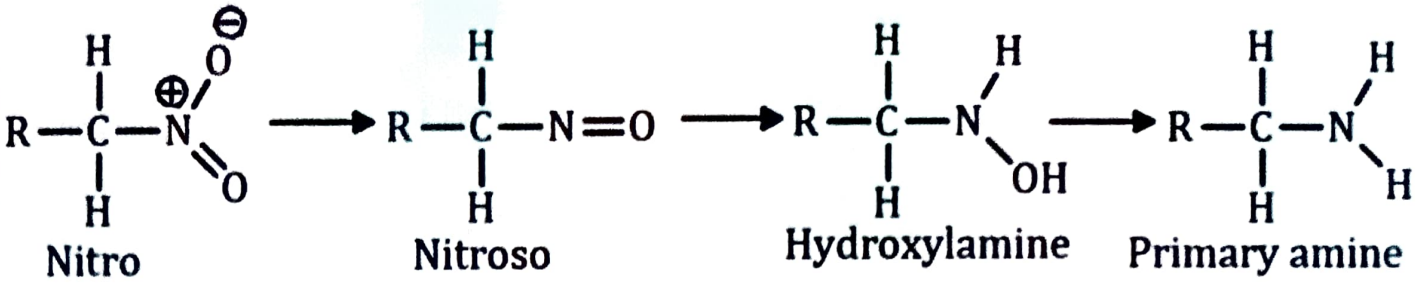
✓ Oxidation reaction (Example)

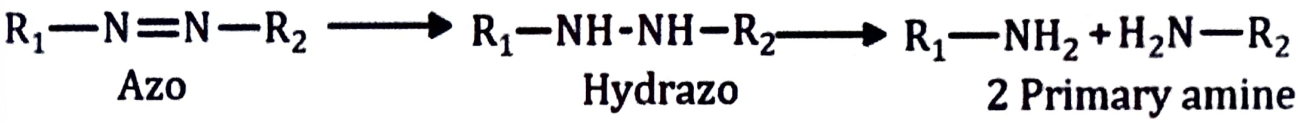


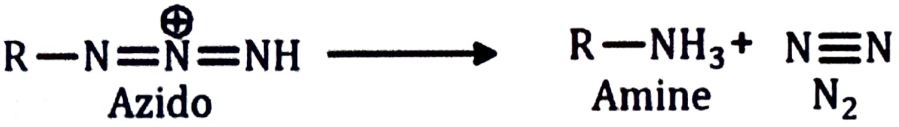
Imipramine

Imipramine N- oxide

✓ Reduction reaction (Example)







➢ PHASE 2 REACTION

- Phase II biotransformation reactions (also called ´conjugation reactions´) which generally serve as a detoxifying step in metabolism of drugs and other xenobiotics as well as endogenous substrates.
- Converted to hydrophilic & pharmacologically inactive.

✓ Examples

- Glucuronic conjugation
- Sulphonation

❖ FACTORS AFFECTING DRUG METABOLISM

➢ There are many factors which influence the rate of drug metabolism. These includes:

i. **Genetic factors** :- Differences in the expression of metabolizing enzymes and genetic polymorphism

ii. **Physiological factors**:- Including age, hormonal changes, sex differences, pregnancy and nutritional status

iii. **Pharmacodynamic factors**:- Including dose, frequency, route of administration and protein binding.

iv. **Environmental factors**:- This depends on the competition with other drugs for the metabolizing enzymes by toxic chemicals such as CO and pesticides.

v. **Environmental factors**:- This depends on the **competition with other drugs for the metabolizing enzymes by toxic chemicals** such as CO and pesticides.

vi. **Stereochemical factors** :- Many drugs **(e.g., warfarin, propranolol, hexobarbital, glutethimide, cyclophosphamide, ketamine, and ibuprofen)** often are administered as racemic mixtures in humans.

- The **two enantiomers** present in a racemic mixture **may differ in pharmacological activity**. Usually, one enantiomer tends to be much more active than the other.

✓ **For example**

- The **(S)(-) enantiomer of warfarin** is **5 times more potent** as an oral anticoagulant than the **(R)(+) enantiomer**.