Introduction to Medicinal Chemistry

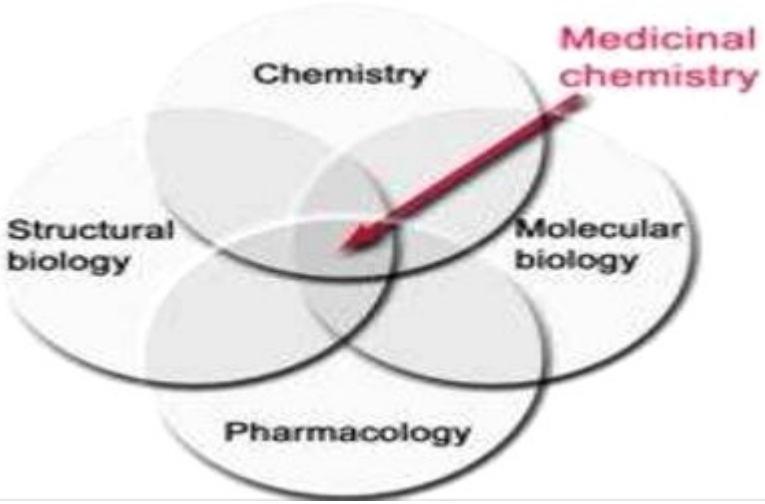
Medicinal chemistry is best to be defined as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery).

In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

Generally Medicinal Chemists can:

- Make new compounds
- Determine their effect on biological processes.
- Alter the structure of the compound for optimum effect and minimum side effects.
- Study uptake, distribution, metabolism and excretion of drugs.

Medicinal chemistry is the chemistry discipline concerned with the design, development and synthesis of pharmaceutical drugs. The discipline combines expertise from chemistry and pharmacology to identify, develop and synthesize chemical agents that have a therapeutic use and to evaluate the properties of existing drugs



Primary objective of medicinal chemistry

Generally, we can identify the following stages in drug discovery, design and development

Drug discovery-finding a lead

- Choose a disease.
- Choose a drug target.
- Identify a bioassay.
- Find a lead compound.
- Isolate and purify the lead compound if necessary.
- Determine the structure of the lead compound if necessary.

Drug design

- Identify structure-activity relationships (SARs)
- Identify the pharmacophore.
- Improve target interactions (pharmacodynamics).
- Improve pharmacokinetic properties,

Drug development

- Patent the drug.
- Carry out preclinical trials (drug metabolism, toxicology, formulation and stability test, pharmacology studies, etc).
- Design a manufacturing process (chemical and process development).
- Carry out clinical trials.
- Register and market the drug.
- Make money.

History and Development of Medicinal Chemistry

3500 BC - Sumerians report use of opium

3000 BC - Chinese report use of ma huang (ephedra)

Greek culture:

Hippocrates- followed the teachings of Aristotle; focus is on the soul.

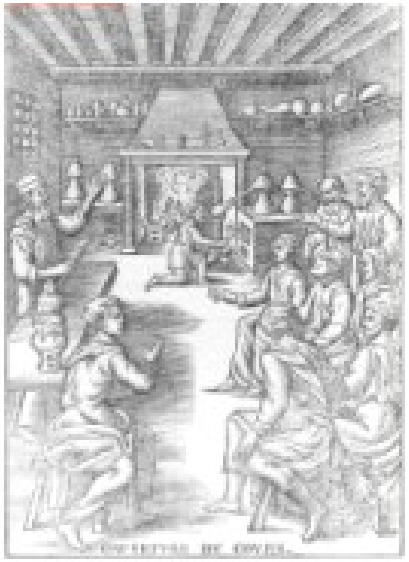
Galen- followed the teachings of Plato; focus is on experiment- believed the whole could be explained by the parts

Renaissance period:

Doctors were humanists- followers of Hippocrates- treat the soul and the body will heal. Initially, there were no relationships with alchemy.

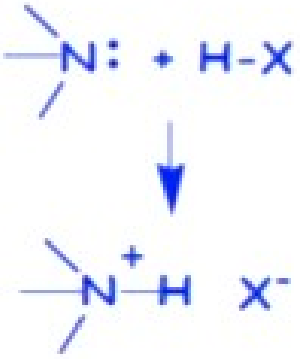
History and Development of Medicinal Chemistry

In 1793, Faureroy & Vauquehin split from the monarchy-controlled bodies and establish the Ecole Supurieure de Pharmacie- 1st to incorporate chemistry into the pharmacy curriculum. Develop research to find the active principles in plant-based drugs.



1803 - Derosome isolates a crystalline salt from opium

1817 - Sertürner publishes work demonstrating that the narcotic principle of opium is basic (alkaline) and, thus, it will form salts with acids- names the principle "morpheus"

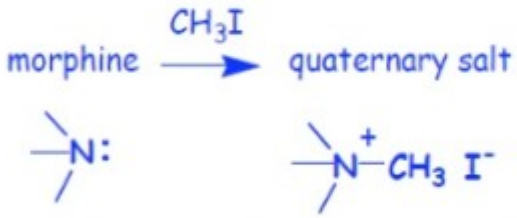


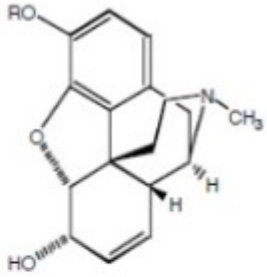
Gay-Lussac predicts that other alkaline plant extracts will have useful medical properties- changes name of morpheus to morphine

1818 - Meissner proposes the general term alkaloids

History and Development of Medicinal Chemistry

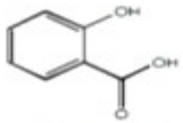
1853 - Henry How proposes that there are "functional groups" that can be chemically modified to alter reactivities….





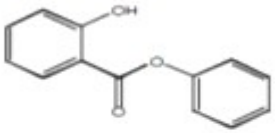
morphine R = H
codeine R = CH_3

Fraser and Brown make quaternary salts of many different alkaloids (i.e, morphine, strychnine, nicotine) and find that all exhibit curare-paralyzing activities- propose that quaternary salts have curariform activity



salicylic acid

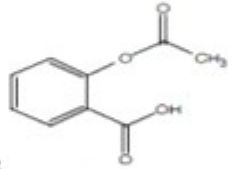
1875- Carl Buss isolates salicylic acid from *Spirea ulmaria* and shows that it is an effective antipyretic- however, it is unpalatable and causes gastric distress.



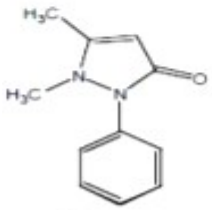
salol (phenyl salicylate)

1883- von Nencki makes a salicylate ester with phenol, salol- it has very poor solubility but it is better tolerated. It is hydrolyzed slowly in the small intestine to give salicylic acid- the first sustained release drug

1890s - Hoffman at Bayer tests acetyl salicylic acid and finds it to be better tolerated- names it aspirin as in "a" for acetyl and "spirin" for *Spirea*. It is rapidly hydrolyzed in the gut to give active salicylic acid- it is a "pro-drug"



acetyl salicylic acid



phenazone

Phenazone was synthesized in 1884 and was the most popular drug world-wide until it was taken over by aspirin in the early 1900s- in addition to being an antipyretic, it also cured headaches- a new market was born…

Drug Classification

Pure organic compounds are the chief source of agents for the cure, mitigation or the prevention of disease. These remedial agents could be classified according to their origin:

- **Natural compounds**: materials obtained from both plant and animal, e.g. vitamins, hormones, amino acids, antibiotics, alkaloids, glycosides…. etc.).
- **Synthesis compounds**: either pure synthesis or synthesis naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) to reduce their cost.
- **Semi-synthesis compounds**: Some compounds either can not be purely synthesized or can not be isolated from natural sources in low cost. Therefore, the natural intermediate of such drugs could be used for the synthesis of a desired product (e.g. semi synthetic penicillins).

Since there is no certain relation between chemical structure and pharmacological activity therefore, it would be unwise to arrange all drugs on the basis of their structures or origin.

Thus, it is better to arrange the drugs according to their medicinal use. Drugs can be classified according to their medicinal uses into two main classes:

I-Pharmacodynamic agents: Drugs that act on the various physiological functions of the body (e.g. general anaesthetic, hypnotic and sedatives, analgesic etc.).

II-Chemotherapeutic agents: Those drugs which are used to fight pathogenic (e.g. sulphonamides, antibiotics, antimalarial agents, antiviral, anticancer etc.).

Drug Classification

Drugs can be classified depending heir use to treat different types of diseases:

1-Infectious diseases: Born (transmitted) from person to person by outside agents, bacteria (pneumonia, salmonella), viruses (common cold, AIDS), fungi (thrush, athletes foot), parasites (malaria)

2-Non-infectious diseases: disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc. (e.g. diabetes, heart disease, cancer. Haemophilia, asthma, mental illness, stomach ulcers, arthritis).

3-Non-diseases: mitigation of pain (analgesic), prevention of pregnancy (contraception), anesthesia.

Physico-chemical properties in relation to biological action

Drug action results from the interaction of drug molecules with either normal or abnormal physiological processes. Drugs normally interact with targets (which they are proteins, enzymes, cell lipids, or pieces of DNA or RNA). The ability of a chemical compound to elicit a pharmacologic /therapeutic effect is related to the influence of its various physical and chemical (physicochemical) properties.

The most pharmacologically influential physicochemical properties of organic medicinal agents (OMAs) are:

1. Solubility
2. Ionization
3. Partition Coefficient
4. Hydrogen bonding
5. Protein binding
6. Chelation
7. Bioisosterism
8. Optical and Geometrical isomerism

DEFINITION:

- 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 extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc.

Various Physico-Chemical Properties are,

- ✓ Solubility
- ✓ Partition Coefficient
- ✓ Dissociation constant
- ✓ Hydrogen Bonding
- ✓ Ionization of Drug
- ✓ Redox Potential
- ✓ Complexation
- ✓ Surface activity
- ✓ Protein binding
- ✓ Isosterism

1. Solubility:

- The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equillibrium with the solid solute.
- Solubility depends on the nature of solute and solvent as well as temperature , pH & pressure.
- The solubility of drug may be expressed in terms of its affinity/philicity or repulsion/phobicity for either an aqueous or organic solvent.
- 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

- Importance of solubility

1. Solubility concept is important to pharmacist because it govern 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.
2. Drug must be in solution form to interact with receptors.

2. Partition Co-efficient

- $Drug_{(aqueous)} \rightleftharpoons Drug_{(lipid)}$

- 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.
- $$P_{[Unionized\ molecule]} = \frac{[drug]_{lipid}}{[drug]_{water}}$$

For ionized (acids, bases and salts)

$$P_{[\text{Ionized molecule}]} = \frac{[\text{drug}]_{\text{lipid}}}{[1-a\,][\text{drug}]_{\text{water}}}$$

a = degree of ionization in aqueous solution.

- Partition coefficient affects the drug transfer characteristics.
- The contribution of each functional group & structural arrangement help to determine the lipophilic or hydrophilic character of drug molecules.
- It is widely used in QSAR.

- Factors affecting Partition Co-efficient

- pH
- Co solvents
- Surfactant
- Complexation

- Partition Co-efficient 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,
  - It has polar and nonpolar region
  - Po/w is easy to measure
  - Po/w often correlates with many biological properties
  - It can be predicted using computational mode

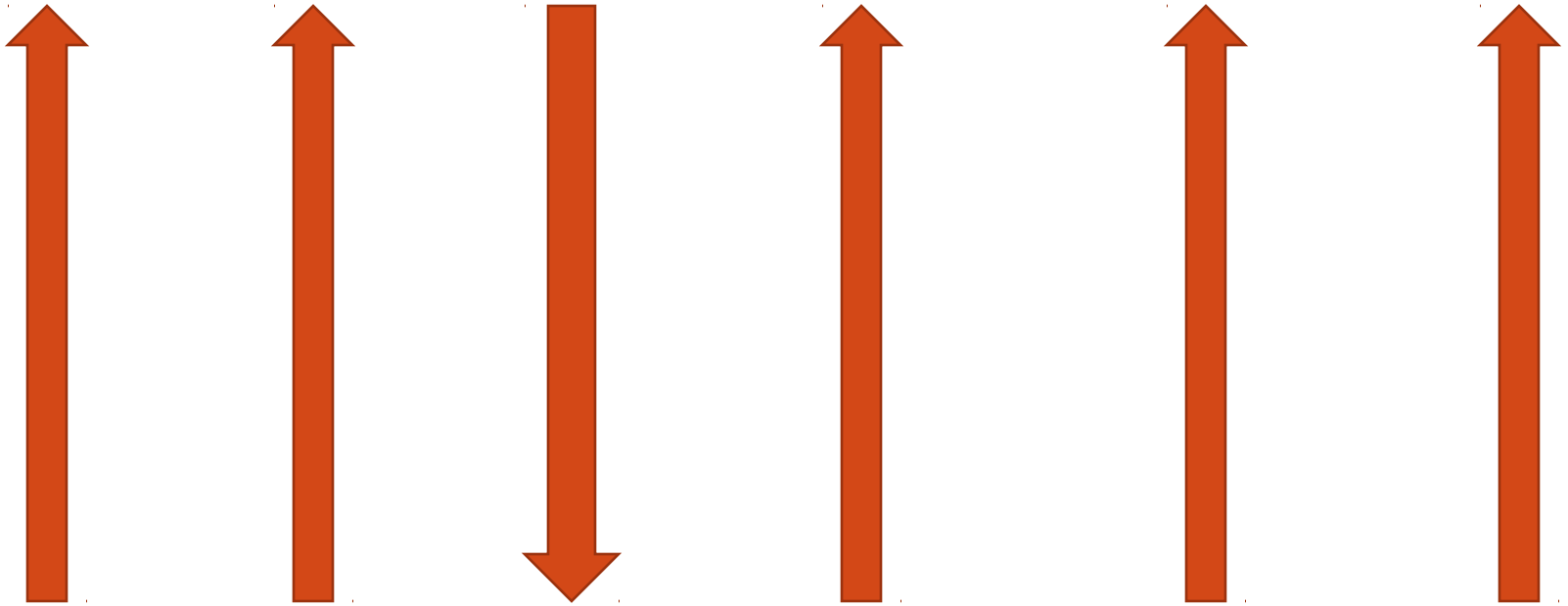
- The Partition co-efficient, P is dimensionless and its logarithm, log P is widely used as the measure of lipophilicity.

- The log P is measured by the following methods.

1) Shake flask method
2) Chromatographic method (HPLC)

- Phenobarbitone has a high lipid/water partition coefficient of 5.9. Thiopentone sodium has a chloroform/water partition coefficient of about 100, so it is highly soluble in lipid.
- Hence, thiopentone sodium is used as ultra-short acting barbiturates.

What else does lopP affects?



log P

Binding to enzymes /receptor

Aqueous solubility

Binding to P_{450} metabolising enzymes

Absorbance through membrane

Binging to blood/tissue proteins

Importance of partician 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. Hydrogen Bond

- 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.
- Dipoles result from unequal sharing of electrons between atoms within a covalent bond.

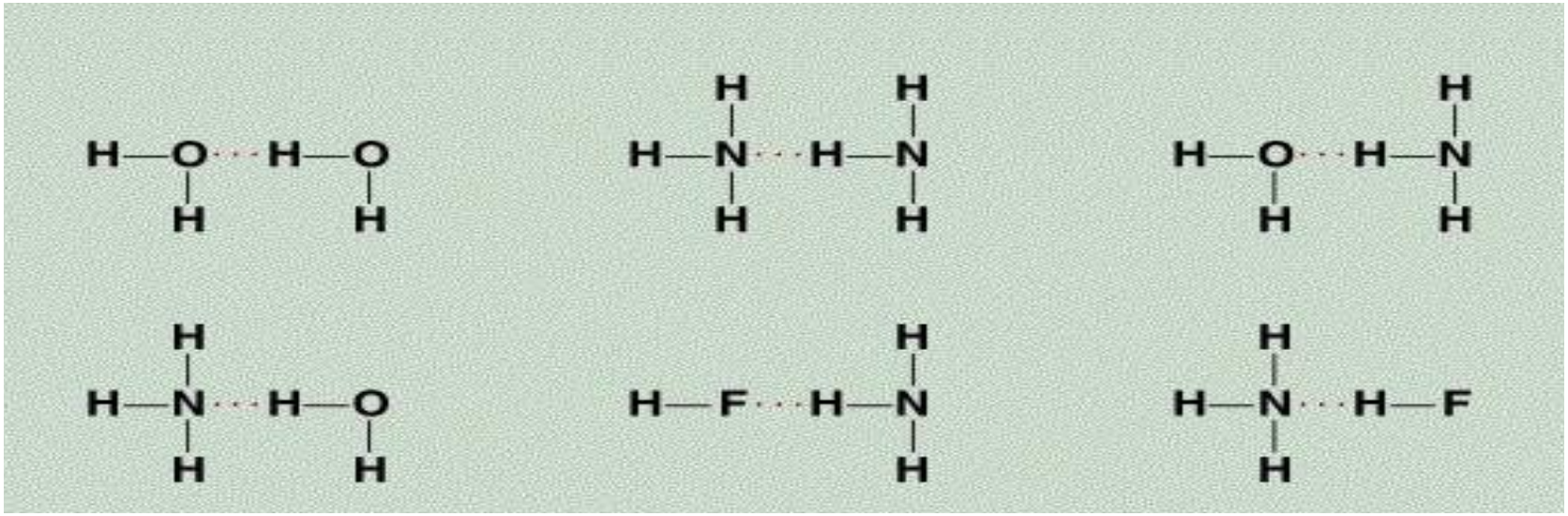
These are weak bonds and denoted as dotted lines.

O-H…….O, HN-H…….O,

- The compounds that are capable, of forming hydrogen bonding is only soluble in water.
- hydrogen bonding is classified into 2 types:
  1. Intermolecular
  2. Intramolecular

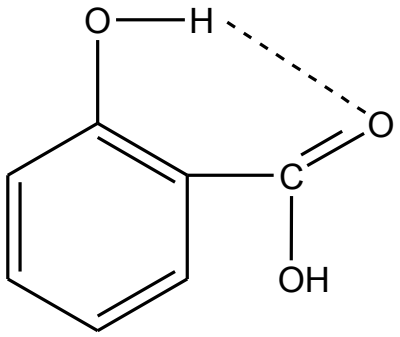
1) Intermolecular hydrogen bonding

- It is occur between two or more than two molecules of the same or different compound.
- Due to this increase the boiling point of the compound & increase the molecular weight of compound hence more energy is required to dissociate the molecular for vaporization.

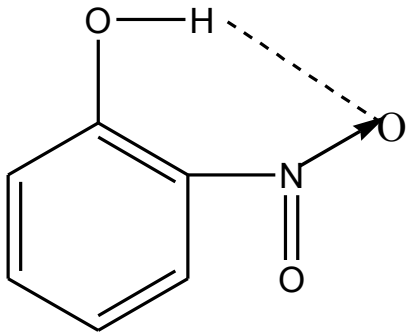


2) Intramolecular Hydrogen bonding

- H- bonding occurs within two atoms of the same molecules.
- This type of bonding is known as chelation and frequently occurs in organic compounds.
- Sometimes h-bond develop six or five member rings
- Due to decrease the boiling point



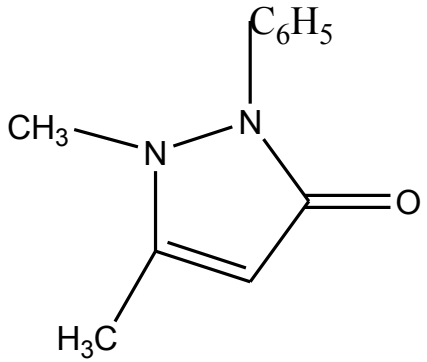
salicylic acid



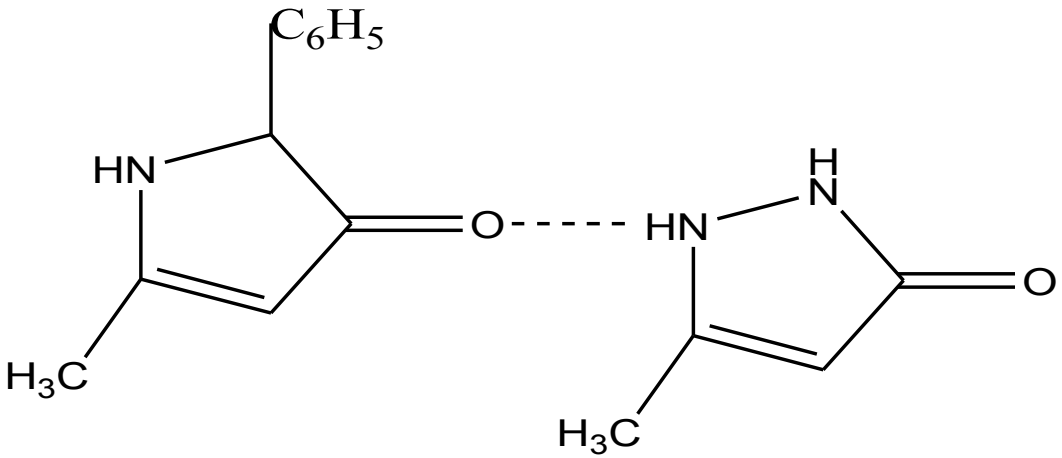
o-nitrophenol

Hydrogen Bonding and biological action

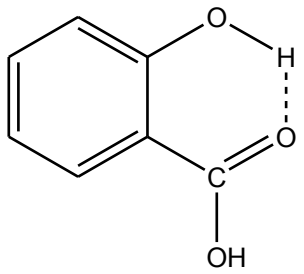
Eg. 1) Antipyrin i.e. 1- phenyl 2,3- dimethyl 5- pyrazolone has analgesic activity.



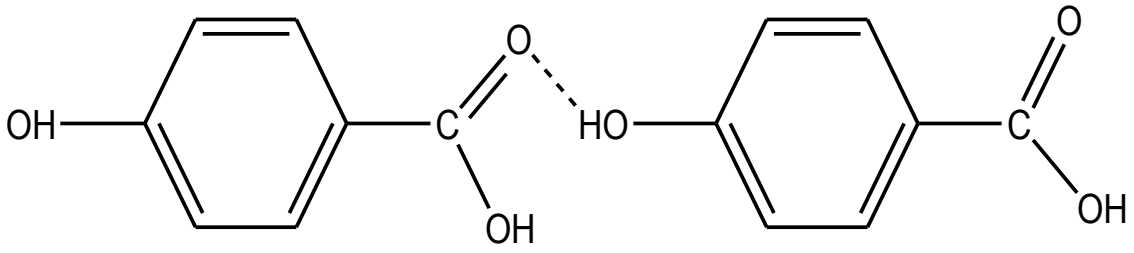
1-phenyl-3-methyl-5-pyrazolone is inactive.



Salicylic acid (O-Hydroxy Benzoic acid) has antebacterial activity



Para and meta Hydroxy Benzoic acids are inactive.



Effect of H-bonding

All physical properties affected by H-bonding,

1. Boiling and Melting point
2. Water solubility
3. Strength of acids
4. Spectroscopic properties
5. On surface tension and viscosity
6. Biological products
7. Drug-receptor interaction

4. Chelation /Complexation

- Complex of drug molecules can't cross the natural membrane barriers, they render the drug biological ineffectivity.
- The rate of absorption is proportional to the concentration of the free drug molecules i.e. the diffusion of drug.
- Due to reversibility of the Complexation, equillibrium between free drug and drug complex

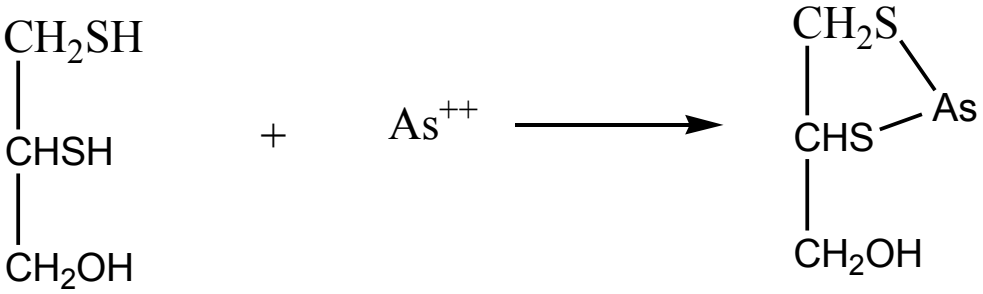
Drug + complexing agent $\longleftrightarrow$ Drug complex

- Complexation reduce the rate of absorption of drug but not affect the availability of drug

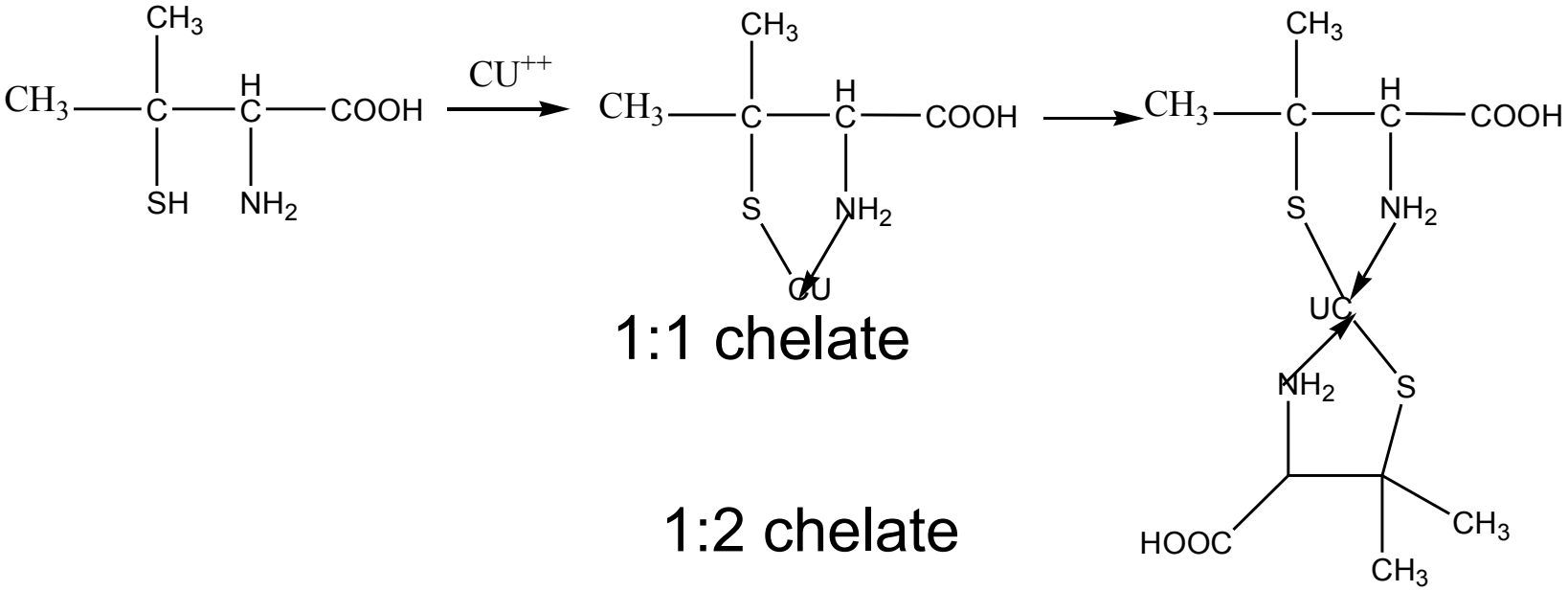
Importance of chelates in medicine:

a)Antidote for metal poisoning

1.Dimercaprol is a chelating agent.



2.Penicillamine



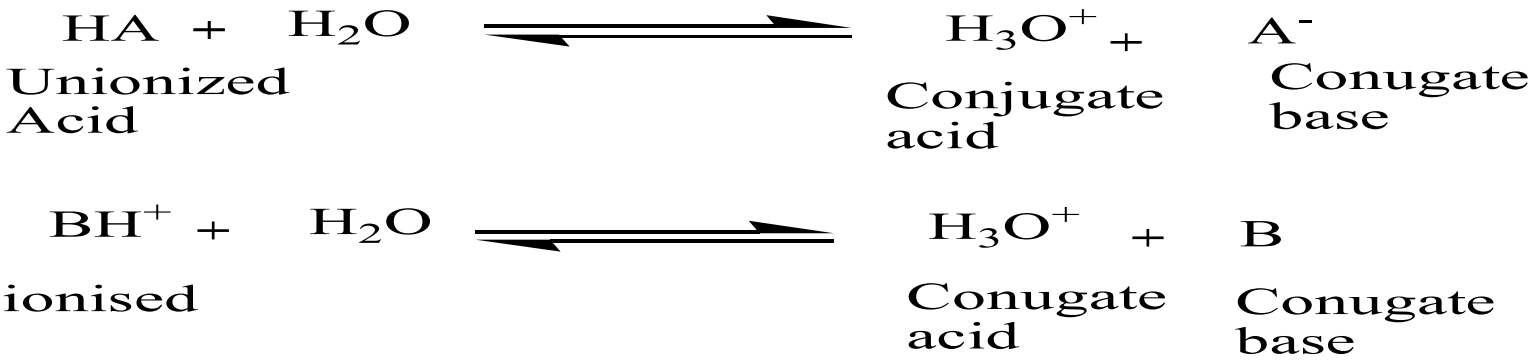
- 8-Hydroxyquinoline and its analogs acts as antibacterial and anti fungal agent by complexing with iron or copper.

- Undesirable side effects caused by drugs, which chelates with metals .
  - A side effect of Hydralazine a antihypertensive agent is formation of anemia and this is due to chelation of the drug with iron.
- Phenobarbital forms a non-absorbable complex with polyethylene glycol-4000.
- Calcium with EDTA form complex which is increase the permeability of membrane.

5. Ionization of drug

- Most of the drugs are either weak acids or base and can exist in either ionised or unionised state.
- Ionization = Protonation or deprotonation resulting in charged molecules.
- The ionization of the drug depends on its pKa & 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 absorption site.
- Ionization form imparts good water solubility to the drug which is required of binding of drug and receptor interaction
- Unionized form helps the drug to cross the cell membrane.
- Eg; Barbituric acid is inactive because it is strong acid.

  while, 5,5 disubstituted Barbituric acid has CNS depressant action because it is weak acid.



According to Henderson-Hasselbalch equation

for acids pH-pKa = log [ionized/unionised]

for base pH-pKa = log [unionized/ionised]

% ionisation = 100\[1+10 $^{(pH-pka)}$]

When an acid or base is 50% ionised: pH = pKa

Eg: the solution of weak acid Aspirin in stomach (pH-1.0) will get readily absorbed because it is in the un-ionosed form(99%).

- Eg:Phenytoin injection must be adjusted to pH 12 with Sodium Hydroxide to obtain 99.98% of the drug in ionised form.
- Tropicamide eye drops an anti cholinergic drug has a pk_a of 5.2 and the drug has to be buffered to pH 4 to obtain more than 90% ionisation.
- Importance of Ionization of drug

- Weak acid at acid pH: more lipid soluble because it is uncharged, the uncharged form more readily passes through the biological membranes.

$$RCOO^- + H^+ = RCOOH$$

- Weak base at alkaline pH: more lipid soluble because it is uncharged, the uncharged form more readily passes through the biological membranes.

$$RNH^+ = RNH^2 + H^+$$

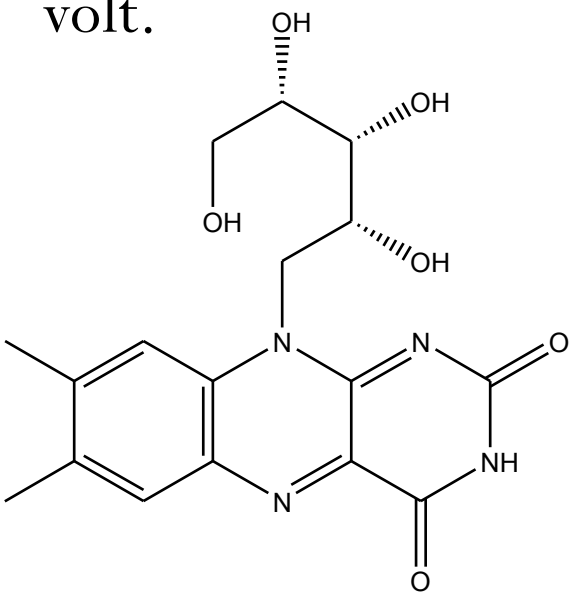
6. Redox Potential

- The oxidation-reduction potential may be defined as a quantitative expression of the tendency that a compound has to give or receive electrons.
- The correlation between redox potential and biological activity can only be drawn for the compound of very similar structure and properties.
- The redox potential of a system may be calculated from the following equation.
- $E=E_0+0.0592/n \log[\text{conc. of reductant} / \text{conc. of oxidant}]$

Examples,

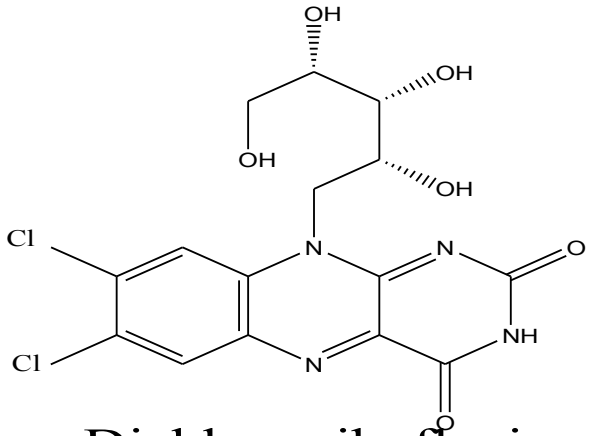
1) Riboflavin analogues

The biological activity of riboflavin is due to E =-0.185 volt.



riboflavin

Riboflavin E_0 = -0.185 V



Dichloro riboflavin

Riboflavin analogue E_0 = -0.095V

2).The optimum bacteriostatic activity in quinones is associated with the redox potential at +0.03 volt, when tested against Staphylococcus aureus.

7. Surface Activity

- Surfactant is defined as a material that can reduce the surface tension of water at very low concentration.
- Surface active agents affect the drug absorption which depends on:
  1. The chemical nature of surfactant
  2. Its concentration
  3. Its affect on biological membrane and the micelle formation.
- In lower conc. of surfactant enhanced the rate of absorption because amphiphilies reduces the surface tension and better absorption.
- In higher conc. of surfactant reduced the rate of absorption.

Applications:

1. The antihelmentic activity of hexylresorcinol
2. Bactericidal activity of cationic quaternary ammonium compounds.
3. Bactericidal activity of aliphatic alcohols.
4. Disinfectant action of phenol and cresol.
5. Bile salt solutions of approximately physiological concentration greatly enhance the dissolution rate of poorly water soluble drugs like grasiofulvin, hexestrol by micellar solubilization effect.

8. 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.

  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 (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 $(D_t) = (D_f) + (D_p$

9. Stereochemistry of drugs

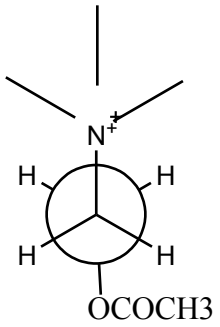
- Stereochemistry involve the study of three dimensional nature of molecules. It is study of the chiral molecules.
- Stereochemistry plays a major role in the pharmacological properties because;
  1. Any change in stereo specificity of the drug will affect its pharmacological activity
  2. The isomeric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

Conformational Isomers

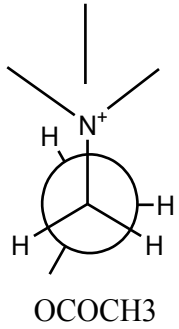
- Different arrangement of atoms that can be converted into one another by rotation about single bonds are called conformations.

- Rotation about bonds allows inter conversion of conformers.

- A classical example is of acetylcholine which can exist in different conformations.



Staggered



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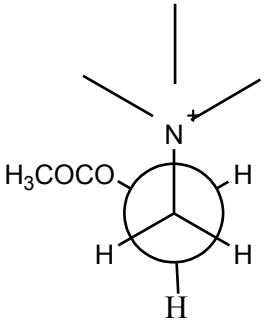
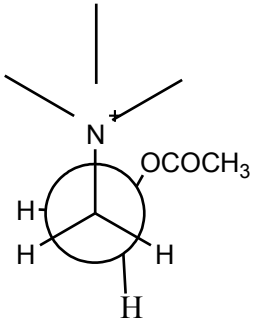
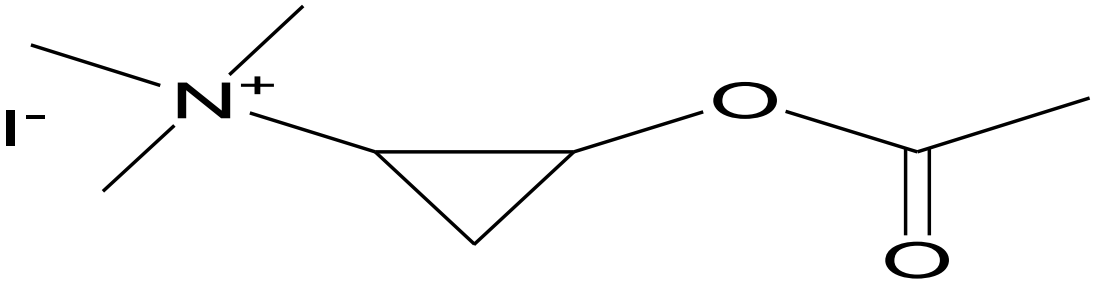


GAUCHE



Fully Eclipsed



2-Acetoxycyclo propyl trimethyl ammonium iodide

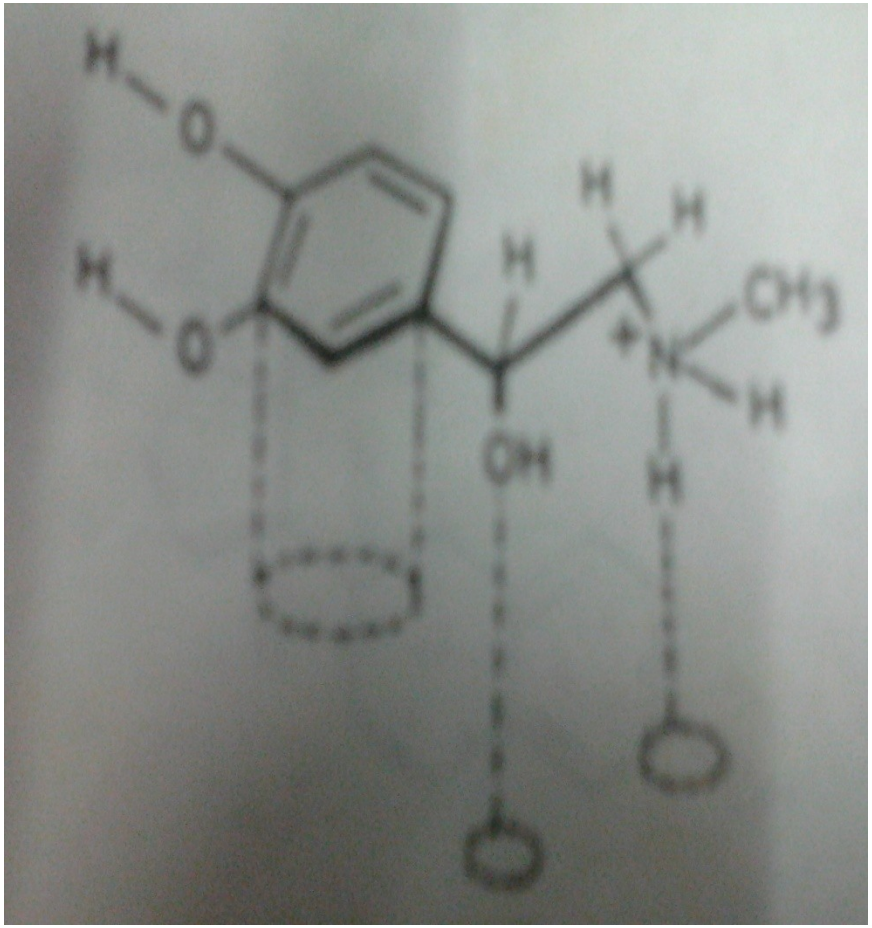
Optical Isomers

- Stereochemistry, enantiomers, symmetry and chirality are impotant concept in therapeutic and toxic effect of drug.

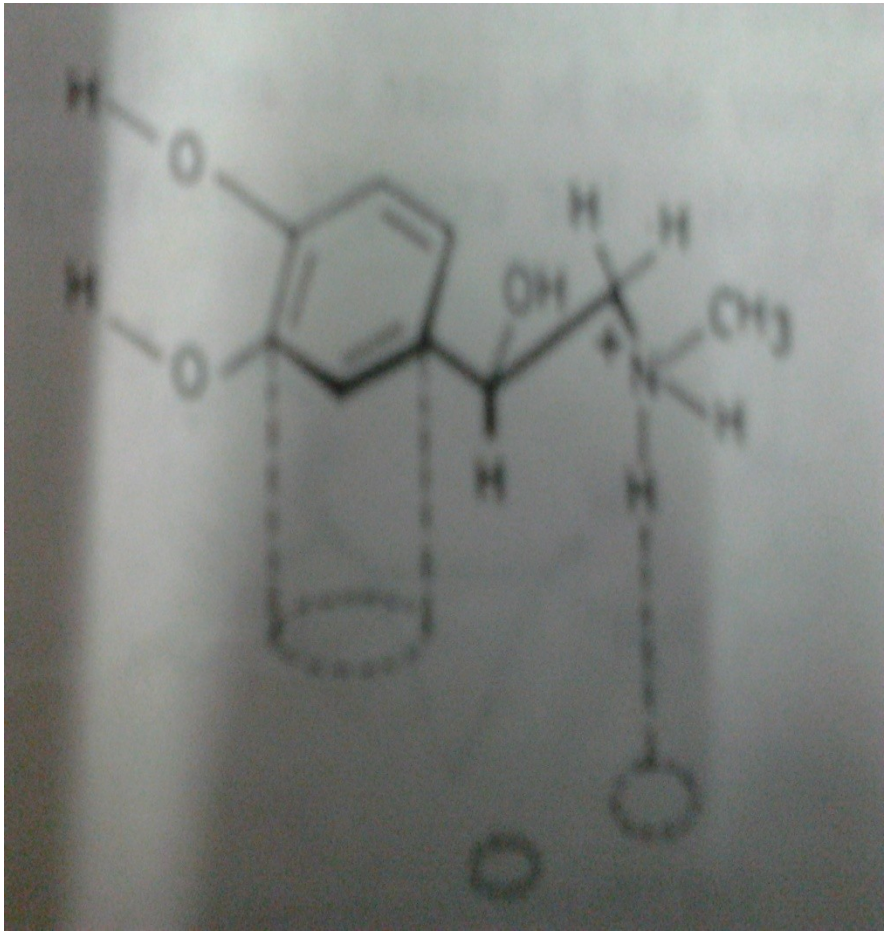
- A chiral compound containing one asymmetric centre has two enantiomers. Although each enantiomer has identical chemical & physical properties, they may have different physiological activity like interaction with receptor, metabolism & protein binding.

- A optical isomers in biological action is 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.

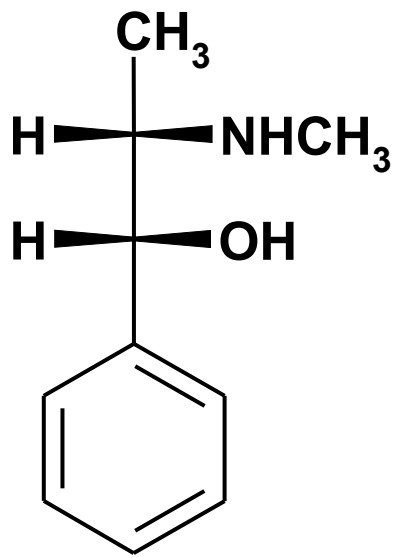
(-)-Adrenaline



(+)-Adrenaline



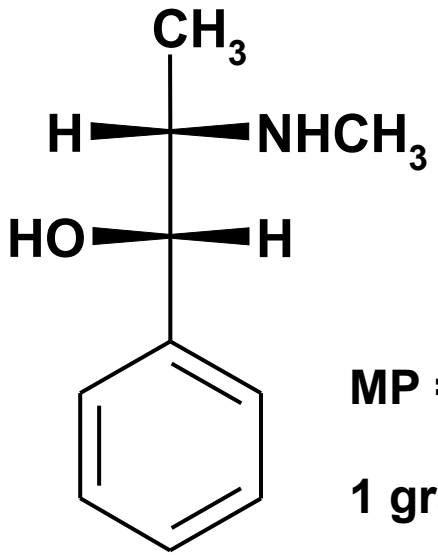
E.g. Ephedrine & Psuedoephedrine



MP = 37-39

1 gram/20 mL

Ephedrine
(*E*rythro)

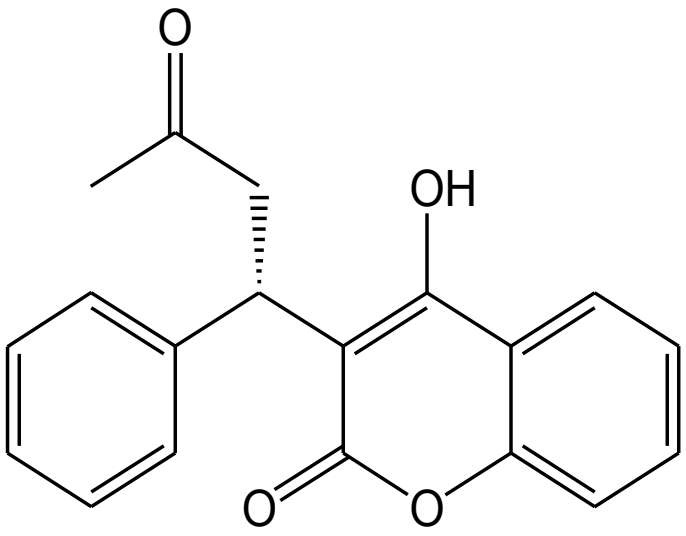


MP = 118-120

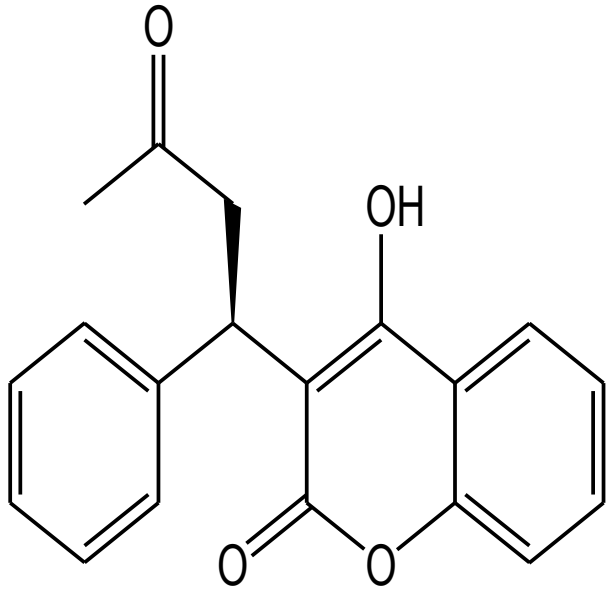
1 gram/200 mL

Pseudoephedrine
(*T*hreo)

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



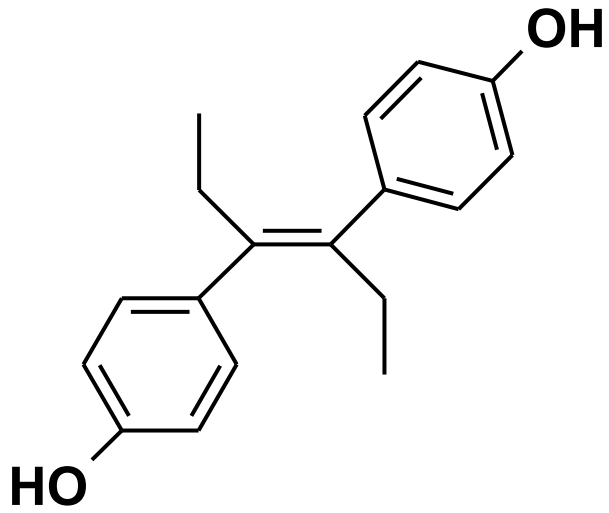
(s)-(-)warfarin



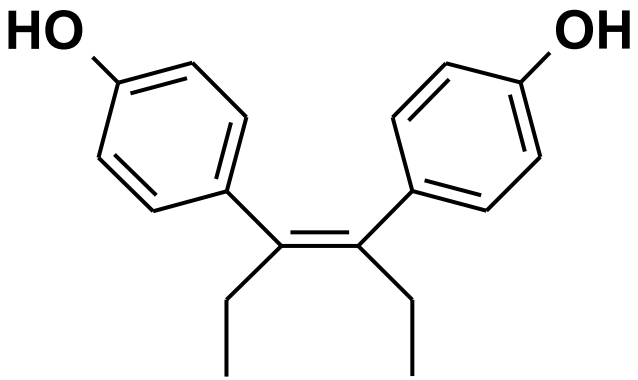
(R)-(+)warfarin

• Geometric Isomerism

Geometric isomerism is represented by cis/trans isomerism resulting from restricted rotation due to carbon-carbon double bond or in rigid ring system.



***trans*-diethylstibesterol**
Estrogenic activity



***cis*-diethylstibesterol**
Only 7% activity
of the trans isomer

10. Isosterism

- Longmuir introduced the term isosterism in 1919, which postulated that two molecules or molecular fragments containing an identical number and arrangament of electron should have similar properties and termed as isosteres.

- Isosteres should be isoelectric i.e. they should possess same total charge.

- 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.

Classical Bioisosteres

- They have similarities of shape and electronic configuration of atoms, groups and molecules which they replace.

- The classical bioisosteres may be,

Univalent atoms and groups

i) Cl, Br, I ii) CH3, NH2, -OH, -SH

Bivalent atoms and groups

i) R-O-R,R-NH-R, R-S-R, RCH_2R

ii) –CONHR, -COOR, -COSR__

- Trivalent atoms and groups

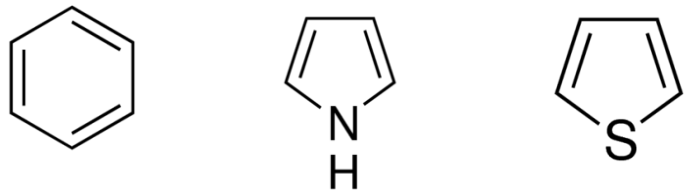
  i)-CH=, -N= ii) –p=, -AS=

- Tetravalent atoms and groups

  =c=, =N=, =P=

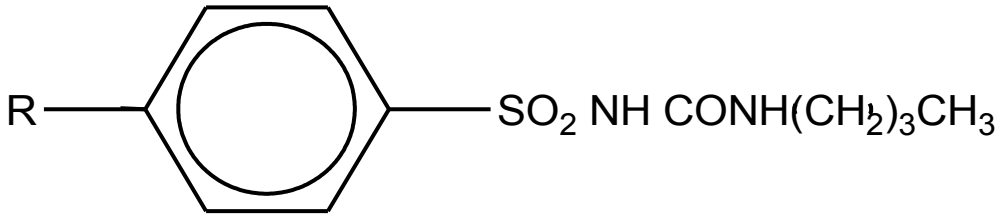
- Ring equivalent

  -CH=CH-, -S-, -O-, -NH, -CH_2-



- Application of Classical Bioisosteres in in drug design

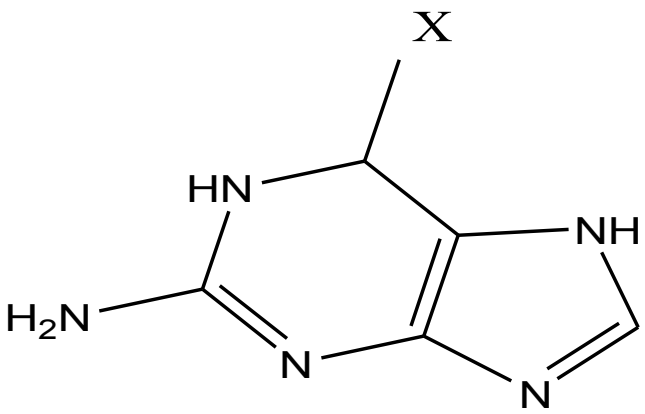
i) Replacement of –NH 2 group by –CH3 group.



Carbutamide R= NH2

Tolbutamide R= CH3

ii)Replacement of –OH & -SH



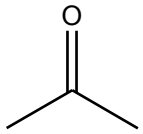
Guanine= -OH

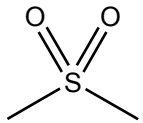
6-Thioguanine = -SH

Non classical Bioisosteres

- They do not obey the stearic and electronic definition of classical isosteres.
- Non-classical biosteres are functional groups with dissimilar valence electron configuration.
- Specific characteristics:
  - Electronic properties
  - Physicochemical property of molecule
  - Spatical arrangement
  - Functional moiety for biological activity

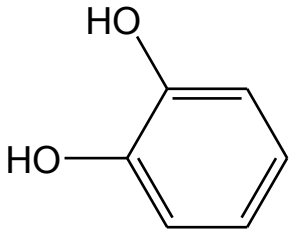
- Examples
- Halogens Cl, F, Br, CN
- Ether -S-, -O-
- Carbonyl group





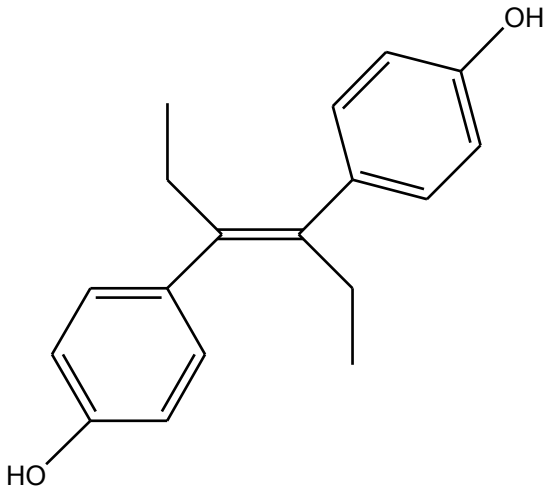
- Hydroxyl group –OH, -NHSO2R, CH2OH

- Catechol

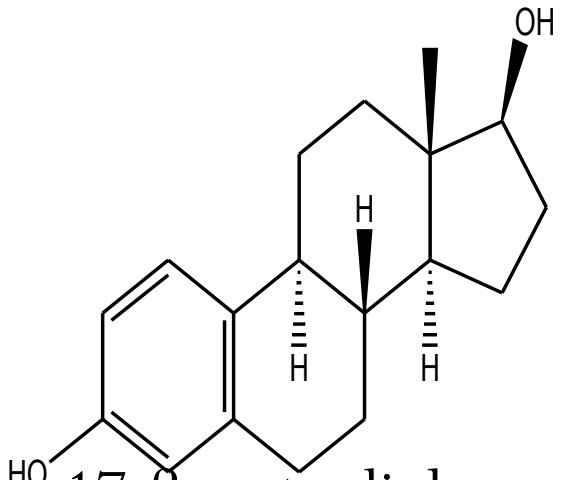


Catechol

- A classical e.g. of ring Vs. noncycclic structure is Diethylstilbosterol & 17-ß oestradiol.



***trans*-diethylstibesterol**



17-ß oestradiol.

Drug Metabolism

Introduction

- Biotransformation: Chemical alteration of the drug in body that converts nonpolar or lipid soluble compounds to polar or lipid insoluble compounds
- Consequences of biotransformation
  - Active drug → Inactive metabolite : Pentobarbitone, Morphine, Chloramphenicol
  - Active drug → Active metabolite: Phenacetin
  - Inactive drug → active metabolite: Levodopa

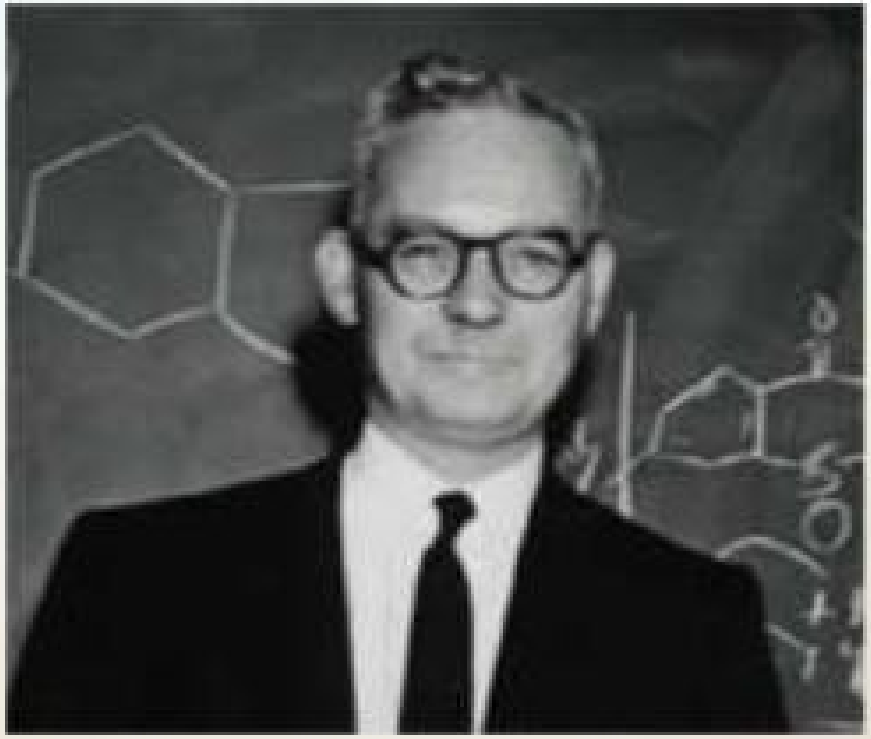
Prodrugs

- Inactive drug is converted to active metabolite
- Coined by Albert in 1958
- Advantages:
  - Increased absorption
  - Elimination of an unpleasant taste
  - Decreased toxicity
  - Decreased metabolic inactivation
  - Increased chemical stability
  - Prolonged or shortened action

History

- Welsh biochemist
- Metabolism of sulfonamides, benzene, aniline, acetanilide, phenacetin, thalidomide and stilbesterol
- Metabolism of TNT (Trinitrotoluene) with regard to toxicity in munitions (1942)

Richard Tecwyn Williams

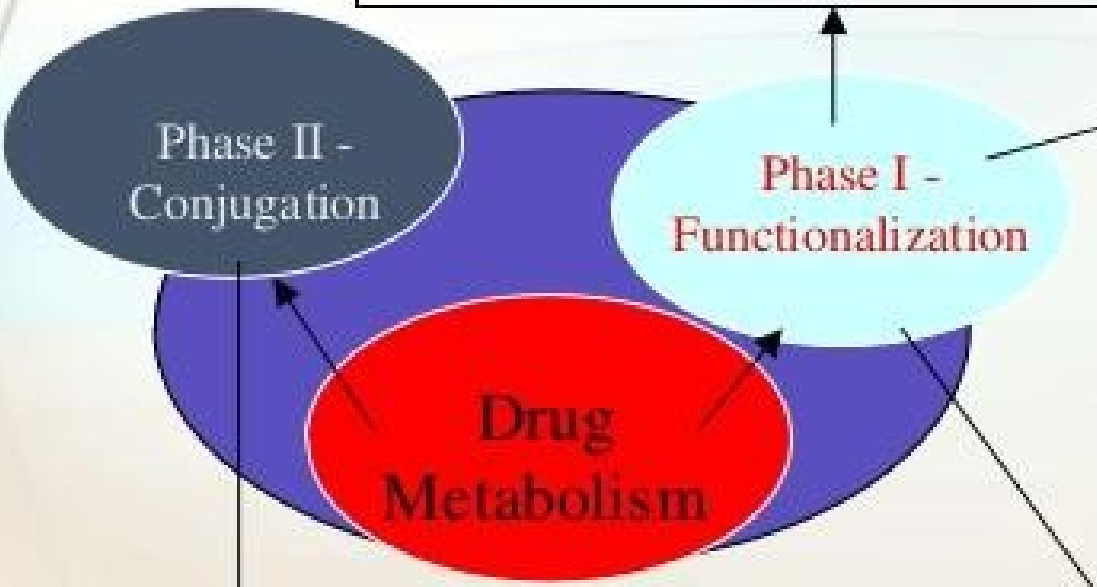


1909 - 1979

Phases of Metabolism

- **Phase I**
  - Functionalization reactions
  - Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2, -SH).
- **Phase II**
  - Conjugation reactions
  - Subsequent reaction in which a covalent linkage is formed between a functional group on the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid

Phases of Metabolism



Hydrolytic Reactions

Esters, amides, epoxides and arene oxides by epoxide hydrase

Oxidation

- Aromatic moieties, Olefins
- Benzylic & allylic C atoms and a-C of C=O and C=N
- At aliphatic and alicyclic C
- C-Heteroatom system
  - C-N (N-dealkylation, N-oxide formation, N-hydroxylation)
  - C-O (O-dealkylation)
  - S-dealkylation
  - S-oxidation, desulfuration
- Oxidation of alcohols and aldehydes, Miscellaneous

- **Conjugation**
  - Glucuronic acid
  - Sulfate, Glycine and other AA
  - Glutathione or mercapturic acid
  - Acetylation, Methylation

Reduction

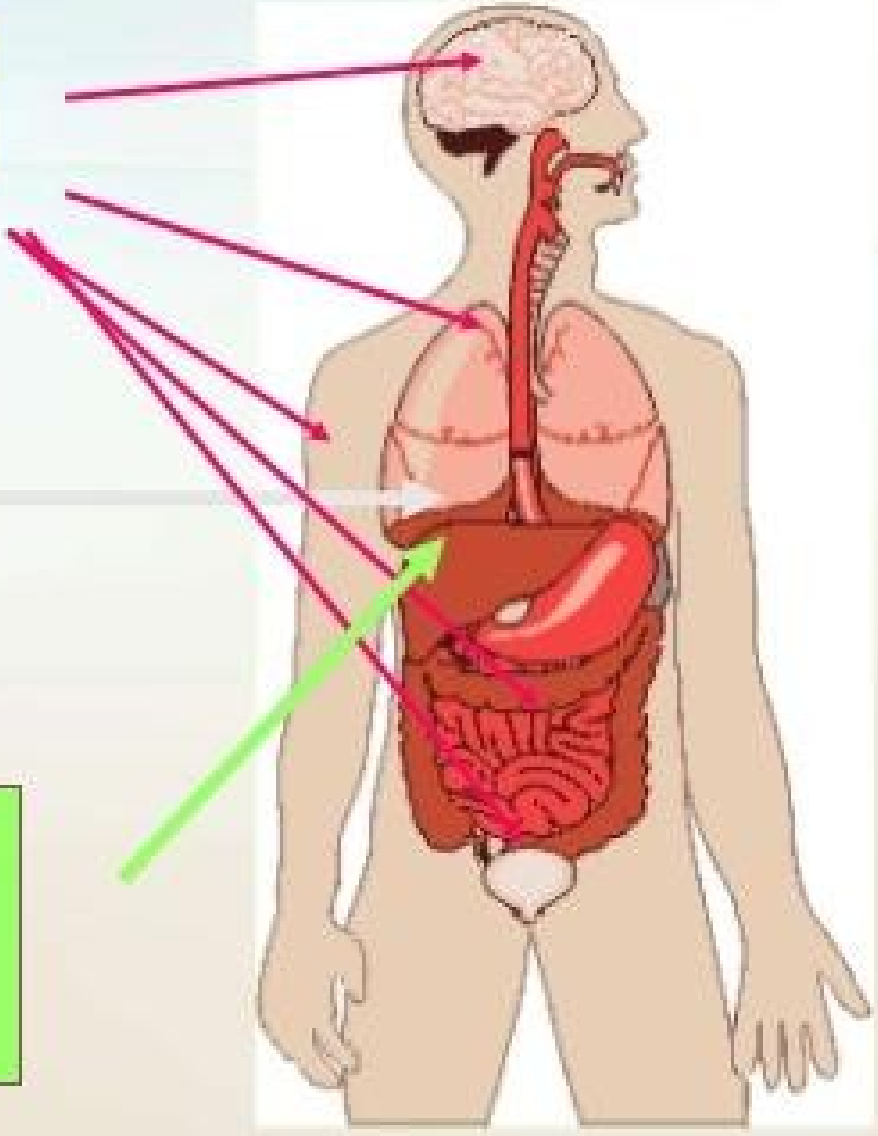
- Aldehydes and ketones
- Nitro and azo
- Miscellaneous

Sites of Drug Metabolism

Extrahepatic microsomal enzymes (oxidation, conjugation)

Hepatic microsomal enzymes (oxidation, conjugation)

Hepatic non-microsomal enzymes (acetylation, sulfation,GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)



Phase I / Non Synthetic Reactions

Oxidation

- Addition of oxygen/ negatively charged radical or removal of hydrogen/ positvely charged radical.
- Reactions are carried out by group of mono-oxygenases in the liver.
- Fianl step: Involves cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and O2

Cytochrome P450 enzymes

- Monooxygenase enzyme family
- Major catalyst: Drug and endogenous compound oxidations in liver, kidney, G.I. tract, skin and lungs
- Oxidative reactions require: CYP heme protein, the reductase, NADPH, phosphatidylcholine and molecular oxygen
- Location: smooth endoplasmic reticulum in close association with NADPH-CYP reductase in 10/1 ratio
- The reductase serves as the electron source for the oxidative reaction cycle

Non-CYP Drug Oxidations

- Monoamine Oxidase (MAO), Diamine Oxidase (DAO)
  - MAO (mitochondrial) oxidatively deaminates endogenous substrates including neurotransmitters
  - Dopamine, serotonin, norepinephrine, epinephrine
- Alcohol & Aldehyde Dehydrogenase
  - Non-specific enzymes found in soluble fraction of liver
  - Ethanol metabolism
- Flavin Monooxygenases
  - Require molecular oxygen, NADPH, flavin adenosine dinucleotide (FAD)

Reduction

- Converse of oxidation
- Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane.

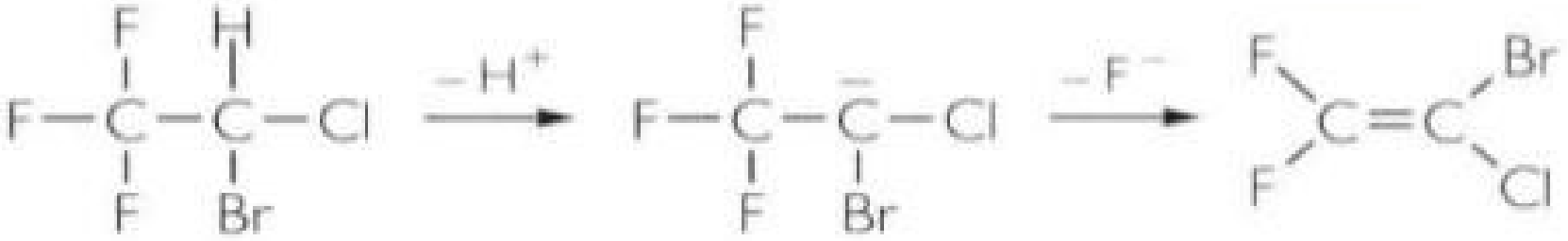


Figure 1.25 Reductive defluorination of halothane.

Hydrolysis

- Cleavage of drug molecule by taking up a molecule of water.

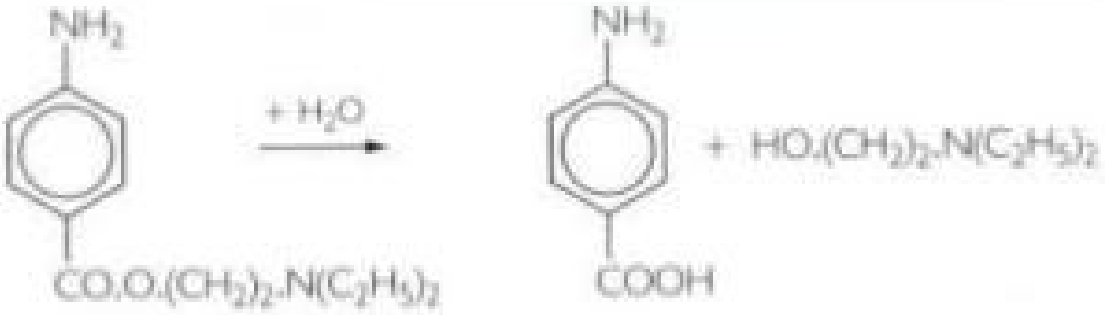


Figure 1.26 Hydrolysis of procaine.

- Sites: Liver, intestines, plasma and other tissues
- Examples: Choline esters, Procaine, Isoniazid, pethidine, oxytocin.

Cyclization and Decyclization

- **Cyclization**
  - Formation of ring structure from a straight chain compound
  - E.g. Proguanil
- **Decyclization**
  - Opening up of ring structure of the cyclic drug molecule
  - E.g. Barbiturates, Phenytoin.

Phase II/ Synthetic reactions

- Conjugation of the drug or its phase I metabolite with an endogenous substrate to form a polar highly ionized organic acid

- Types of phase II reactions
  - Glcuronide conjugation
  - Acetylation, Methylation
  - Sulfate conjugation, Glycine conjugation
  - Glutathione conjugation
  - Ribonucleoside/ nucleotide synthesis

Glucuronide Conjugation

- Conjugation to α-d-glucuronic acid
- Quantitatively the most important phase II pathway for drugs and endogenous compounds
- Products are often excreted in the bile
- Requires enzyme UDP-glucuronosyltransferase (UGT)
- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose

Glucuronide Conjugation Continued..

- Enterohepatic recycling may occur due to gut glucuronidases
- Drug glucuronides excreted in bile can be hydrolysed by bacteria in gut and reabsorbed and undergoes same fate.
- This recycling of the drug prolongs its action e.g.Phenolpthalein, Oral contraceptives
    - Examples: Chloramphenicol, aspirin, phenacetin, morphine, metronidazole

Acetylation

- Common reaction for aromatic amines and sulfonamides
- Requires co-factor acetyl-CoA
- Responsible enzyme is N-acetyltransferase
- Important in sulfonamide metabolism because acetyl-sulfonamides are less soluble than the parent compound and may cause renal toxicity due to precipitation in the kidney
- E.g. Sulfonamides, isoniazid, Hydralazine.

Sulfate Conjugation

- Major pathway for phenols but also occurs for alcohols, amines and thiols
- Sulfate conjugates can be hydrolyzed back to the parent compound by various sulfatases
- Sulfoconjugation plays an important role in the hepatotoxicity and carcinogenecity of N-hydroxyarylamides
- Infants and young children have predominating O-sulfate conjugation
- Examples include: a-methyldopa, albuterol, terbutaline, acetaminophen, phenacetin

Amino Acid Conjugation:

- ATP-dependent acid: CoA ligase forms active CoA-amino acid conjugates which then react with drugs by N-Acetylation:
  - Usual amino acids involved are:
    - Glycine. Glutamine, Ornithine, Arginine

Glutathione Conjugation:

- Glutathione is a protective factor for removal of potentially toxic compounds

- Conjugated compounds can subsequently be attacked by g-glutamyltranspeptidase and a peptidase to yield the cysteine conjugate => product can be further acetylated to N-acetylcysteine conjugate

  E.g. Paracetamol

Hofmann elimination

Inactivation of the drug in the body fluids by spontaneous molecular re arrangement without the agency of any enzyme

e.g. Atracurium.

Inhibition of Metabolism

- Competitively inhibit the metabolism of another drug if it utilizes the same enzyme or co factors.
- A drug may inhibit one isoenzyme while being itself a substrate of another isoenzyme

e.g. quinidine is metabolized by CYP3A4 but inhibits CYP2D6

- Inhibition of drug metabolism occurs in a dose related manner and can precipitate toxicity of the object drug.
- Blood flow limited metabolism

e.g. Propranolol reduces rate of lignocaine metabolism by decreasing hepatic blood flow.

Microsomal Enzyme Induction

- Certain drugs, insecticides and carcinogens increase the synthesis of microsomal enzyme protein.
- Different inducers are relatively selective for certain cytochrome P-450 enzyme families e.g.
  - Phenobarbitone , rifampin, glucorticoids induce CYP3A isoenzymes
  - Isoniazid and chronic alochol consumption induce CYP2E1
- Induction takes 4-14 days to reach its peak and is maintained till the inducing agent is present.

Consequences of Induction

- Decreased intensity or Increased Intensity of action of drug
- Tolerance- autoinduction
- Precipitation of acute intermittent porphyria
- Interfere with adjustment of dose of another drug
- Interference with chronic toxicity

Possible Uses of Induction:

Congenital non hemolytic anaemia

Cushing's Syndrome

Role of Metabolism in pediatric and elderly

- New born has low g.f.r and tubular transport is immature, so the t1/2 of the drug like streptomycin and penicillin is prolonged
- Hepatic drug metabolising system is inadequate in new borns e.g. chloramphenicol can produce gray baby syndrome
- In elderly the renal function progressively declines
- Reduction of hepatic microsomal activity and liver blood flow
- Incidence of adverse drug reactions is much higher in elderly

Role of Metabolism in Drug discovery

- In drug development it is important to have an information on the enzymes responsible for the metabolism of the candidate drug
- Invitro Studies can give information about
  - Metabolite stability
  - Metabolite profile
  - Metabolite Identification
  - CYP induction/Inhibition
  - Drug/Drug interaction studies
  - CYP isoform identification