Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm

Semester-IV

Subject Name: Medicinal Chemistry

Subject Code: BP402TP

Prepared by:-Ms. Foram J. Vagadia

Medicinal Chemistry

Chapter 1 Introduction

- **Medicinal chemistry** is a chemistry-based discipline, involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their **mode of action** at the molecular level and the construction of **structure-activity relationships** (**SARs**).

- **Drug** is any substance presented for treating, curing or preventing disease in human beings or in animals. It may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.

The important role of drugs in human society

- Drugs have irrevocably changed the fabric of society by improving both the individual quality of life and life expectancy.
- Some examples are shown as follows:

1. Bacterial and virus infections: polio, smallpox, tuberculosis and related diseases have, to a very major extent, become minor public health concerns.

2. An increase in life expectancy resulting from drug therapy has also led to a shift in population demographics toward a more healthy, elderly population.

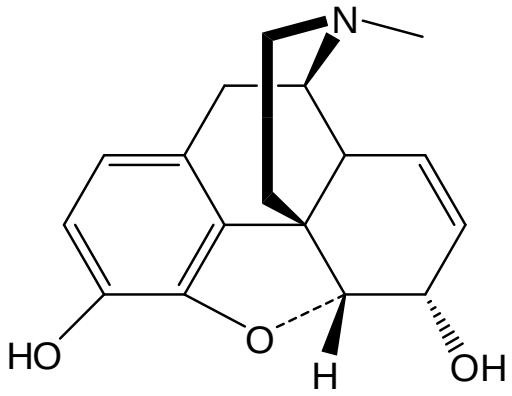
3. Drug regimens for birth control have improved individual life choices and the quality of life.

4. HIV protease and reverse transcriptase inhibitors for the treatment of HIV infections have changed a disease with a fatal prognosis to a potentially chronic one.

5. Cancer is also being viewed as a potentially chronic, rather than fatal disease with newer, non-cytotoxic approaches.

Origins of Medicinal Chemistry

1. Early investigations of natural products

- Natural products having a history as folk remedies were in use. Fore examples, opium, belladonna, cinchona bark, etc. Many drugs originally used as folk remedies, nowadays, have been abandoned.
- *1.2. In the late eighteenth and early nineteenth centuries, chemical experimentation led ultimately to its use in the discovery of new drugs.*
- **In 1853,** Henry How conceived the idea that functional groups in natural products might be modified by chemical reagents.
- *He heated morphine with methyl iodide, hoping to convert the alkaloid to codeine. He obtained, however, a new substance of the quaternary salt of morphine.*
- 

- **In 1898**, the first commercially available semisynthetic morphine derivative (ethyl ether) was introduced as a cough sedative in preference to codeine or other opiates.
- Meanwhile, diacetylmorphine was introduced as a safer pain reliever than morphine. It quickly became popular throughout the world.
- Four years passed before its addictive properties of heroin were recognized. Laws were later passed by governments to restrict its use.
- **During the 1840s**, the first use of synthetic organic chemicals were introduced for anesthesia during a tooth removal, such as nitrous oxide, ether, and chloroform.
- **In 1864**, barbituric acid had been synthesized as a useful hypnotic.
- **In 1875**, salicylic acid was introduced as a possible cure for *typhoid fever*. It was found to be an effective antipyretic.

- **In 1899**, Aspirin was marketed as an antipyretic without the unpleasant side effects. This indicated that the chemical structures from natural products were changed into better drugs.
- **Medicinal Chemistry began.**

2. Fast Development from 1900's to 1960's

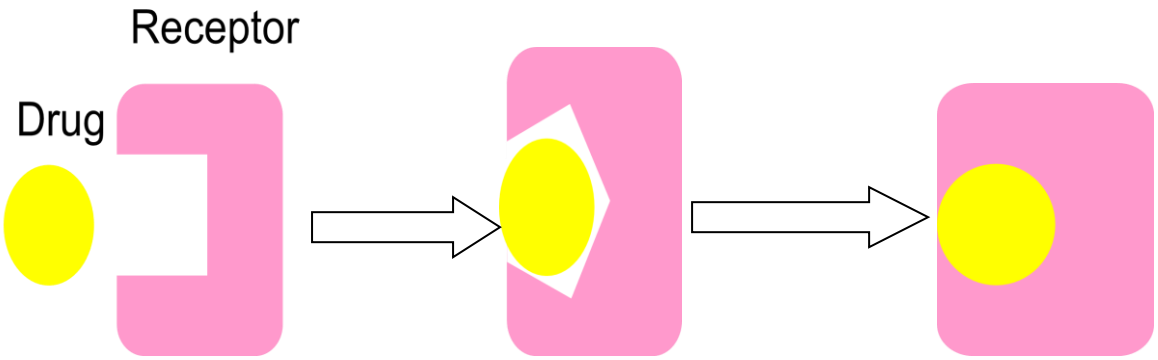
- **1920's~1930's**: Anesthetics, Hypnotics, Analgesics were used extensively. In research for functional "pharmacophore", structure-function relationship was investigated gradually.
- **After 1930's**: The development of new drugs was speeded greatly by the close combination of Medicinal Chemistry and Experimental Pharmacology.
- **Theory of antimetabolite** was formed by using metabolic products as lead compounds.
- Discovery of **penicillin** which is the first antibiotics is an epoch-making achievement.
- *Afterward, tetracycline, streptomycin, chloramphenicol, erythromycin were introduced one after another.*
- **In 1940's**, the first drug used for treating cancer as a biological alkylating agent was nitrogen mustard, which began tumor chemical therapy.
- **In 1960's**, oral steroidal contraceptive agents were discovered. Corticosteroids have become an important drugs.
- **After 1950's**, aging disease, cerebrovascular and cardiovascular diseases became first reason for human death. New drugs design based on enzymes or receptors as drug targets.
- **In 1964**, first β-Adrenergic blocking agent, Propranolol, was marketed.
- **In 1979**, Nifedipine, Calcium Channel Blocker was marketed.
- **In 1981**, Captopril, Angiotensin Converting Enzyme (ACE) Inhibitor was launched.

3. Drug Target and Drug Design

- Mechanism based drug design
- Structure based drug design
- Known targets: 480, receptors: 45%; enzymes: 28% (See p5~6)

Receptor Used as Drug Target

- **Receptors**: M acetylcholine receptor; adrenergic receptor; angiotensin receptor; dopamine receptor; serotonin receptor; opioid receptor etc.
- Drugs effecting on receptors：
- **Agonist；Antagonist**



- **Agonist** is an endogenous substance or a drug that can interact with a receptor and initiate a physiological or a pharmacological response (contraction, relaxation, secretion, enzyme activation, etc.).
- **Antagonist** is a drug or a compound that opposes the receptor-associated responses normally induced by another bioactive agent.
- **Partial agonist** is an agonist which is unable to induce maximal activation of a receptor population, regardless of the amount of drug applied.

Enzyme Used as Drug Target

- **Enzyme**: Angiotensin Converting Enzyme (ACE), Cycloxygenase（COX_2）, β-Lactamase, Acetylcholine Esterase etc.
- Drugs effecting on enzyme: **Enzyme Inhibitor**

Ion Channal Used as Drug Target

- **Ion Channal**: Calcium Ion Channal, Potassium Ion Channal, Sodium Ion Channal, Chloride Ion Channal, etc.

Drugs effecting on Ion Channal: Calcium Channal Blocker, Potassium Channal Blocker, Sodium Channal Blocker, etc.

Nucleic Acid Used as Drug Target

- Nucleic Acid: RNA, DNA
- Drugs: antiviral agent, quinolone agent, etc.

❖ **Nomenclature of Drug Substances**

✓ **INN:** International Non-proprietary Names for Pharmaceutical Substance, that is, common names by national or international nomenclature commissions

✓ **Chemical Name** by international union for pure and applied chemistry (IUPAC) and international union of biochemistry (IUB)

✓ **CADN:** Chinese Approved Drug Names

✓ **English Chemical Name** based on nomenclature of chemical abstracts (CA)

✓ **Trade Name**

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Physicochemical Properties of Drug

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 reacts 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 solventsolvent,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 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.
2. Drug must be in solution form to interact with receptors.

2. Partition Co-efficient

- Drug (aqueous) PC 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] = [drug]lipid
  [drug]water

For i o nized (acids, bases and salts)
P[Ionized molecule] = [drug]lipid
[1-a][drug]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

im portance 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,

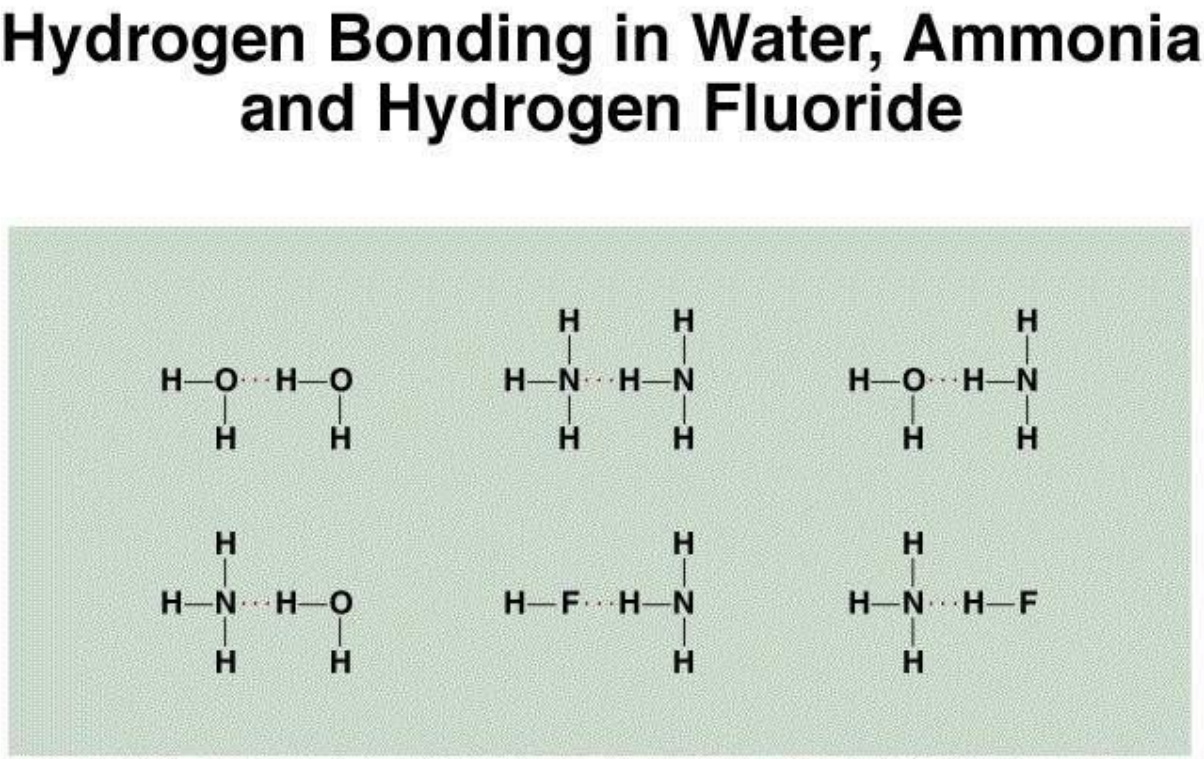
The compounds that are capable, of forming hydrogen bonding is only soluble in water.

Hydrogen bonding is classified into 2 types:

1. Intermolecular
2. Intramolecular

Intermolecular hydrogen bonding

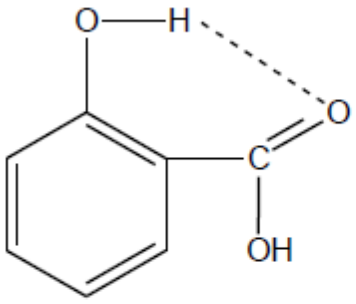
- It is occur between two or more than two molecules of the same or different compound.
- Due to this increase the boiling point of the compound & increase the molecular weight of compound hence more energy is required to dissociate the molecular for vaporization.



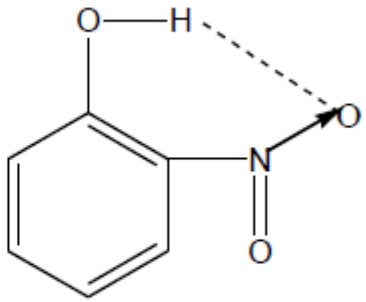
Intramolecular Hydrogen bonding

- H- bonding occurs within two atoms of the same molecules.

- This type of bonding is known as chelation and frequently occurring organic compounds.
- Sometimes h-bond develop six or five member rings Due to decrease the boiling point



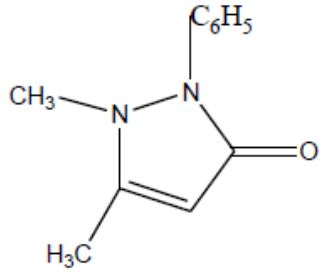
salicylic acid



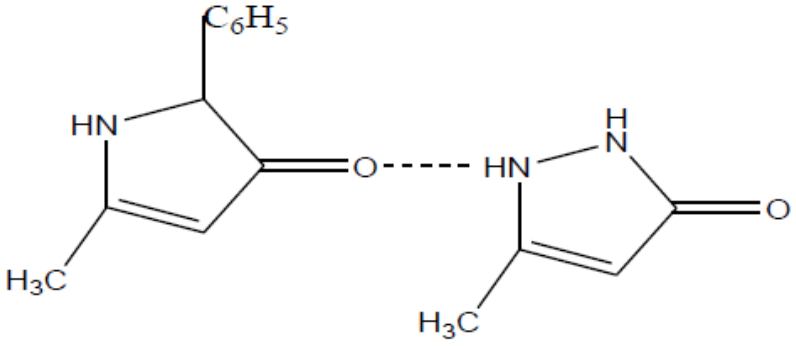
o-nitrophenol

Hydrogen Bonding and biological action

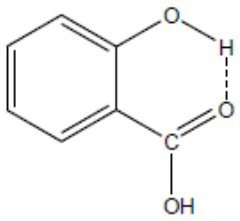
Eg. 1) Antipyrin i.e. 1- phenyl 2,3- dimethyl 5- pyrazolone has analgesic activity.



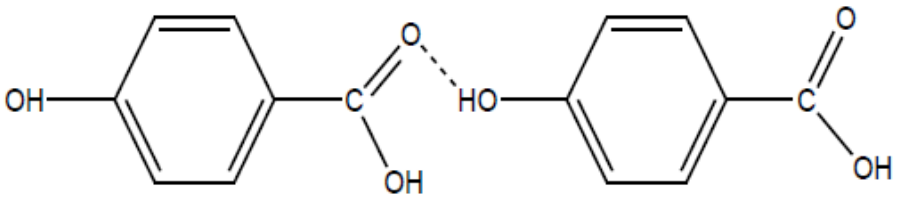
1-phenyl-3-methyl-5-pyrazolone is inactive.



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



Para and meta Hydroxy Benzoic acids are inactive.



- ✓ **Ef fect 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

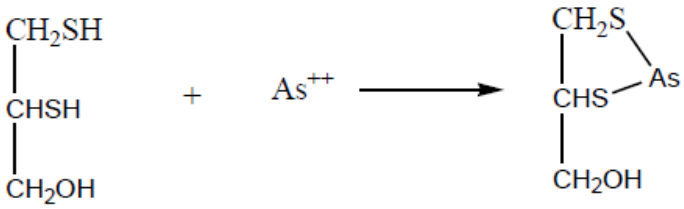
Drug + complexing agent ⟷ Drug complex

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

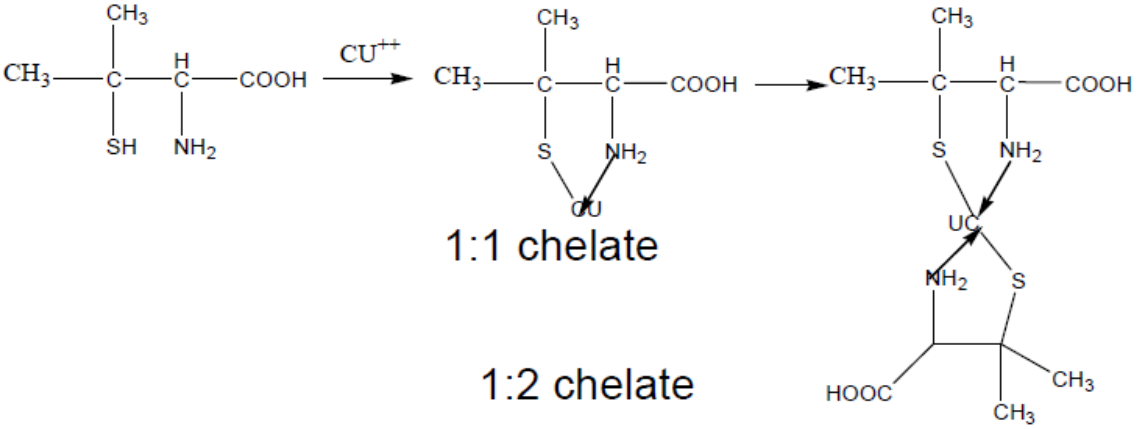
Importance of chelates in medicine:

a)Antidote for metal poisoning

1.Dimercaprol is a chelating agent.



2.Penicillamine

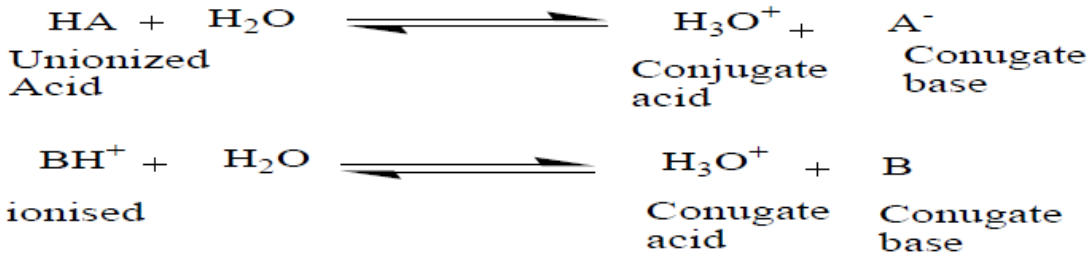


- 8-Hydroxyquinoline and its analogs acts as antibacterial and anti fungal agent by complexing with iron or copper.

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

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 pka 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. 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 (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.

$$\text{Free drug}(D_f) + \text{Free protein}(P_f) \rightleftharpoons \text{Drug /protein complex } (D_p)$$

$$\text{Total plasma concentration } (D_t) = (D_f) + (D_p$$

7 Stereochemistry of drugs

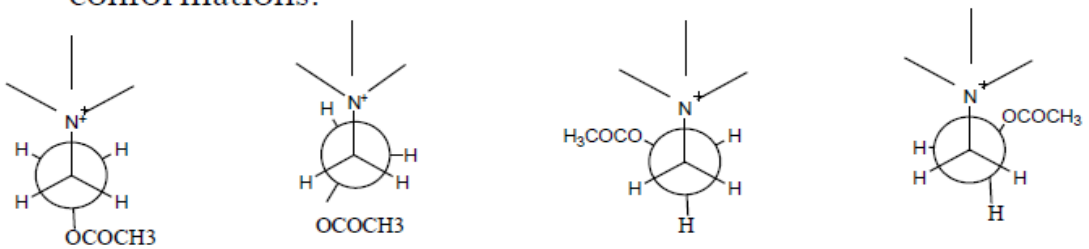
- ✓ stereochemistry involve the study of three dimensional
- ✓ nature of molecules.
- ✓ It is study of the chiral molecules.
- ✓ Stereochemistry plays a major role in the pharmacological properties because;

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.

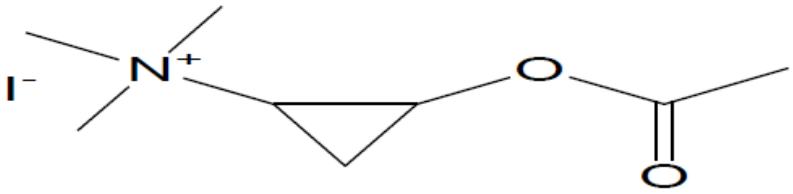
- ✓ The isomers which have same bond connectivity but different arrangement of groups or atoms in the space are termed stereoisomer.

- ✓ 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 Eclipsed GAUCHE Fully Eclipsed

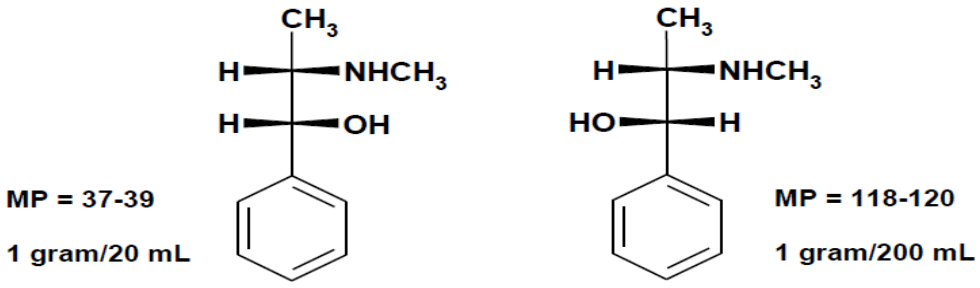


2-Acetoxycyclo propyl trimethyl ammonium iodide

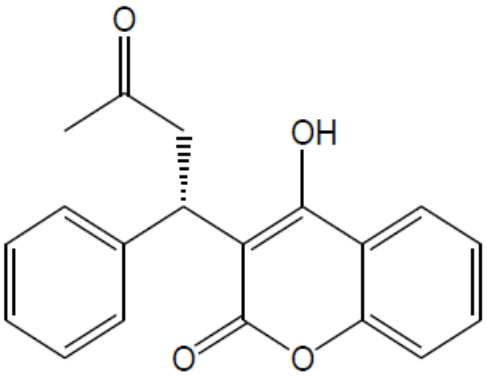
Optical Isomers

- ✓ 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.

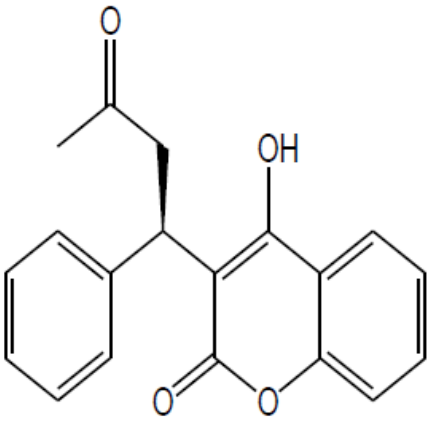
E.g. Ephedrine & Psuedoephedrine



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



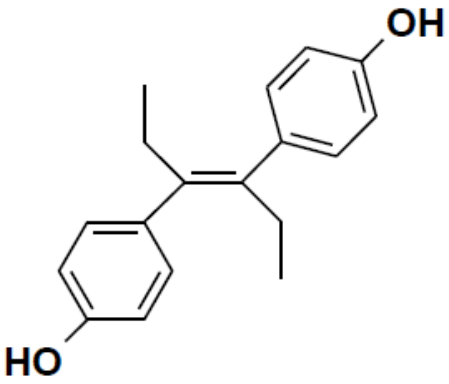
(s)-(-)warfarin



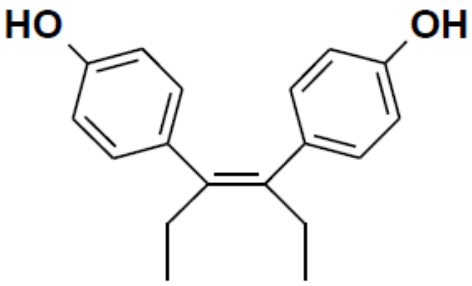
(R)-(+)warfarin

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

8. 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) CH_3, NH_2, -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

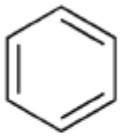
i)-CH=, -N= ii) –p=, -AS=

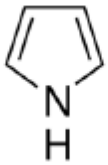
Tetravalent atoms and groups

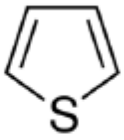
=c=, =N=, =P=

Ring equivalent

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

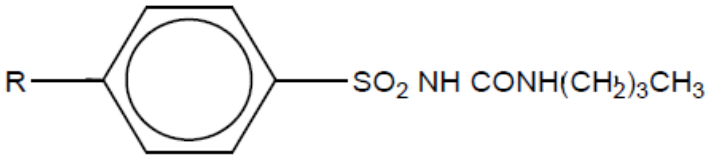






- Application of Classical Bioisosteres in in drug design

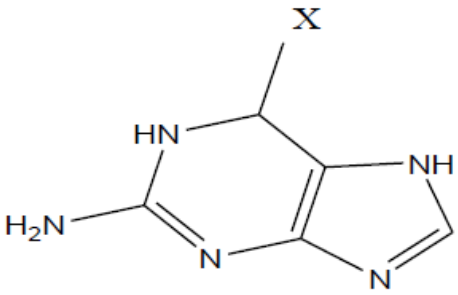
i) Replacement of –NH 2 group by –CH3 group.



Carbutamide R= NH2

Tolbutamide R= CH3

ii)Replacement of –OH & -SH



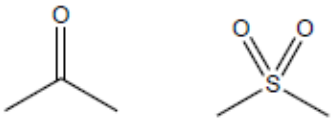
Guanine= -OH

6-Thioguanine = -SH

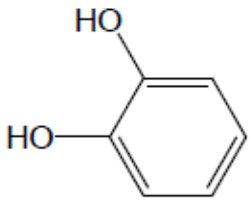
Non classical Bioisosteres

- ✓ 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:
    1. Electronic properties
    2. Physicochemical property of molecule
    3. Spatical arrangement
    4. Functional moiety for biological activity

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

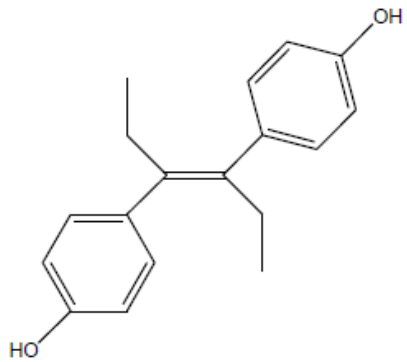


- Hydroxyl group –OH, -NHSO2R, CH2OH
- Catechol

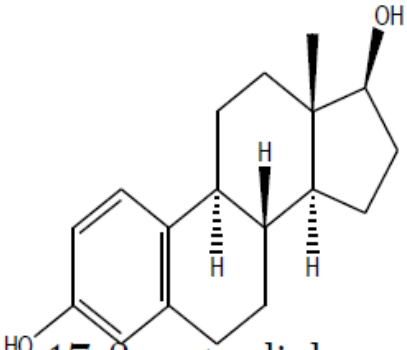


Catechol

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



***trans*-diethylstibesterol**



17-ß oestradiol.