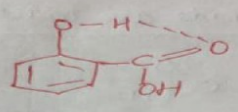
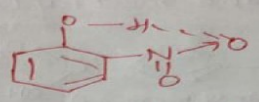
eg:-



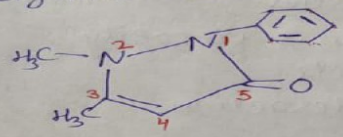
Salicylic acid



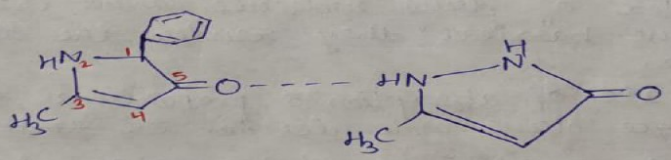
O-nitrophenol

Hydrogen bonding and biological action:

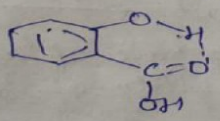
eg:-① Antipyrin i.e. 1-phenyl 2,3-dimethyl 5-pyrazolone has analgesic activity.



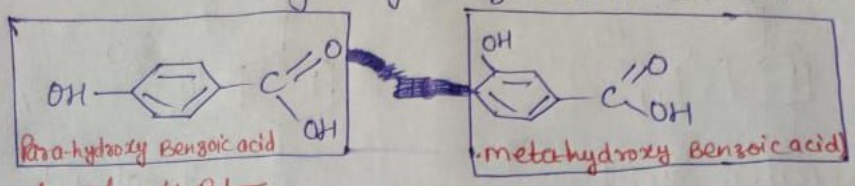
eg:-② 1-phenyl-3-methyl-5-pyrazolone is anactive.



③ Salicylic acid (o-hydroxy benzoic acid) has antibacterial activity.



g:- Para and meta hydroxy Benzoic acids are inactive:-



Effect of H.B!-

All these physical properties affected by H-bonding

1. Boiling and melting point
2. water solubility
3. Strength of acids
4. spectroscopic properties
5. surface tension & viscosity
6. Biological products
7. Drug receptor interaction

(4) Chelation/ Complexation:-

→ Complex of drug molecule cannot cross the natural membrane barriers; they render the drug biologically ineffective.

→ The rate of absorption is proportional to the concentration of the free drug molecules i.e. the ~~part~~ diffusion of drug.

→ Due to reversibility of the complexation, equillibrium b/w free drug and drug complex.

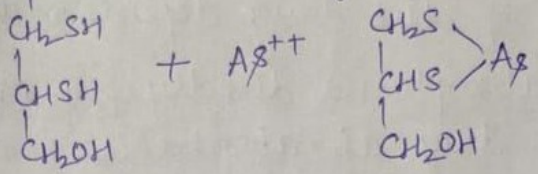
Drug + Complexing agent ⟷ Drug Complex

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

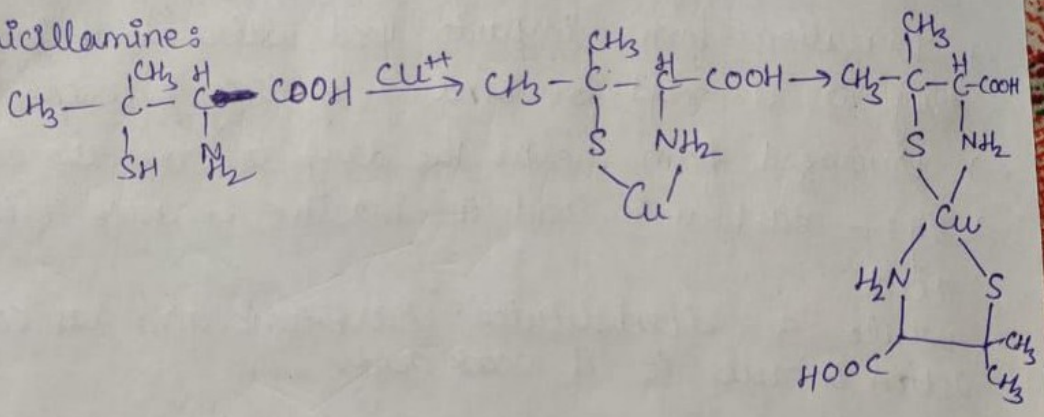
Importance of chelates in medicine :-

(1) Antidote for metal poisoning.

1. Dimercaprol is a chelating agent.



2. Penicillamine:



→ 8-hydroxyquinoline and its analogs acts as antibacterial and antifungal agent by complexing w iron or copper.

→ ~~Underside~~ undesirable side effects caused by drugs, w chelates w metals.

→ A side effect of Hydralazine, an antihypertensive agent is formation of anaemia & this is due to chelation of the drug w iron.

→ Phenobarbital forms a non-absorbable complex w polyethylene Glycol - 4000.

→ Calcium with EDTA form complex which increase the permeability of membrane.

(5) Ionization of drug:

→ Most of the drugs are either weak acids or weak

bases and can exist in either ionized or unionized 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 ∵ is reqd. for binding of drug & 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.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

Unionized acid — Conjugate acid — conjugate base

$$BH^+ + H_2O \rightleftharpoons H_3O^+ + B$$

Ionized base — Conjugate acid — conjugate base

$pKa = -\log_{10} Ka$; Ka = acid dissociation constant

According to Henderson-Hasselbalch equation

for acids $pH_{(of\ solution)} - pKa_{(drug)} = \log [ionized / unionized]$

for base $pH - pKa = \log [unionized / ionized]$

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

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-ionised form (99%).

⊙ phenytoin injections must be adjusted to pH (12) with sod. 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 ionisation 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.

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

Protein binding:-

⇒ The reversible binding of ~~protein~~ drug 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 or is neutral, it can bind to single blood proteins to multiple proteins (serum albumin, acid-glycoprotein or lipoprotein). The most significant

(16) 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 conc. of drug that is bound to all plasma proteins.

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

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

Reversible binding of drug involves weak chemical bond such as hydrogen bond, ionic bond, Vanderwal's forces, hydrophobic bond, Irreversible binding though rare, include covalent bond often reason for drug toxicity over tissues or carcinogenicity.

Stereochemistry of drug :-

⇒ Stereochemistry involve the study of three Dimensional nature of molecules. It is the study of the chiral molecules.

⇒ Stereochemistry plays a major role in the pharmacological properties because:

① Any change in stereo specificity of drug will affect its pharmacological activity.

② The isomeric pairs have different physical properties (log P, pKa etc.) & thus differ in P'cological activity.

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

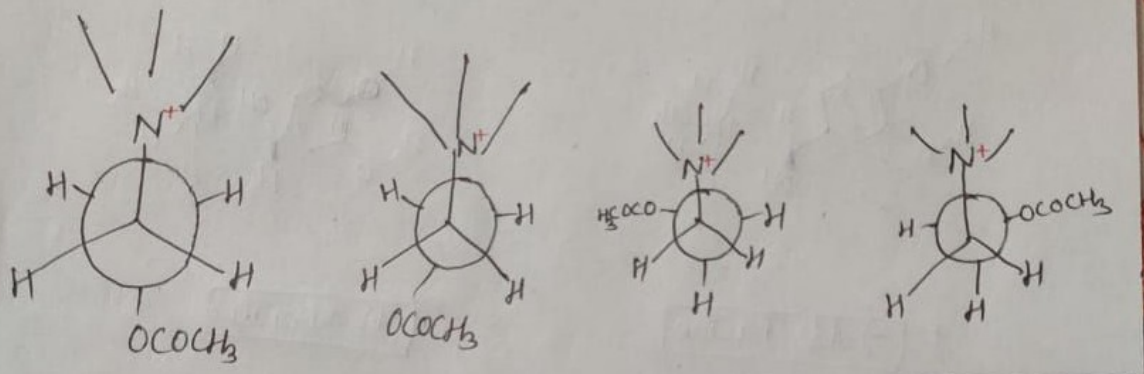
Conformational isomers :-

⇒ Different arrangement of atoms that can be converted into one another by rotation about single bonds are

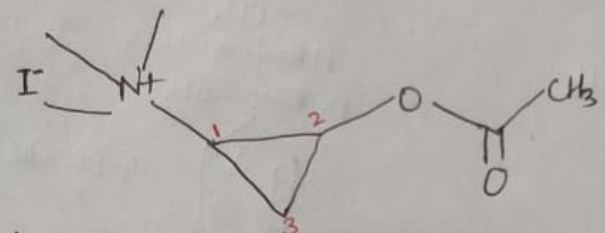
called Conformations.

⇒ Rotation about bonds allow inter conversion of conformers.

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



Staggered | Eclipsed | Gauche | Fully eclipsed



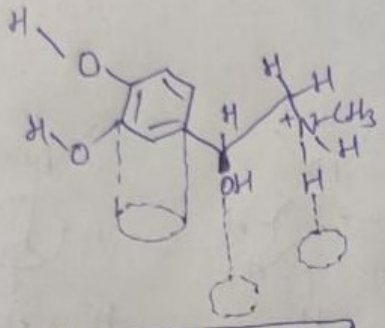
2-Acetoxycyclopropyl trimethylammonium Iodide

Optical isomers:-

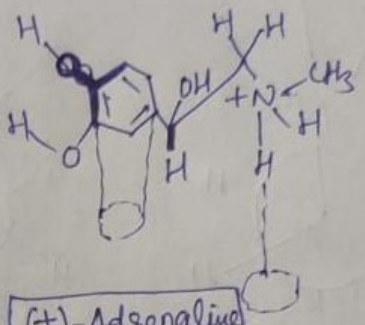
⊙ Stereochemistry, enantiomers, symmetry and chirality are imp. concept in therapeutic and toxic effect of drug.

⊙ A chiral compound containing one assymmetric Centre has two enantiomers. Although each enantiomer has identical chemical and physical properties, they may have different physiological activity like interaction to receptor, metabolism & Protein binding.

⊙ An optical isomers in biological action is due to one isomer being able to achieve a three point attachment to its receptor molecule while its enantiomer would only be able to achieve a two point attachment with the same molecule.

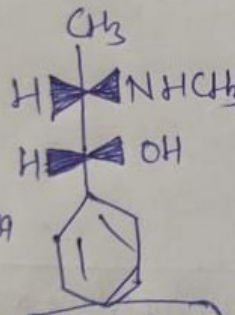


(-) Adrenaline



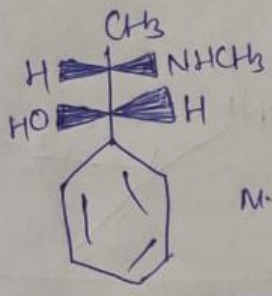
(+)-Adrenaline

eg:- Ephedrine & pseudoephedrine



M.Pt. = 37-39

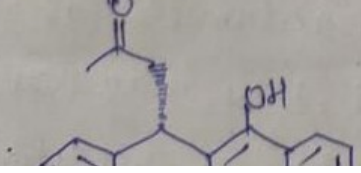
Ephedrine (erythro)

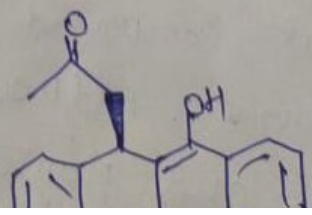


M.Pt. = 118-120

Pseudoephedrine (Threo)

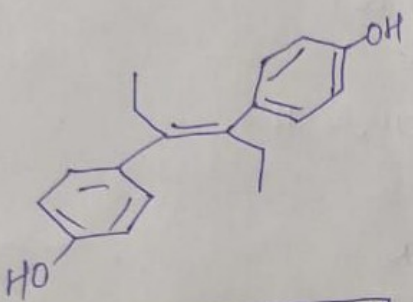
⊙ The category of drugs where the two isomers have qualitatively similar pharmacological activity but have different quantitative potencies.



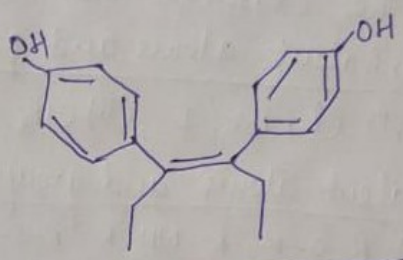


Geometric isomerism:-

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



trans-diethylstilbesterol
Estrogenic acitivity



cis-diethylstilbesterol
only 7% activity of the trans isomer

Isosterism:-

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

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

Bioisosterism

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

⇒ They are classified into two ways:-

(i) Classical bioisosteres
(ii) Non classical bioisosteres

(i) Classical bioisosteres:-

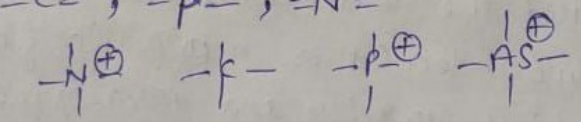
- They have similarities of shape and electronic configuration of atoms, groups and molecules which they replace.
- The classical bioisosteres may be,

⇒ 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=

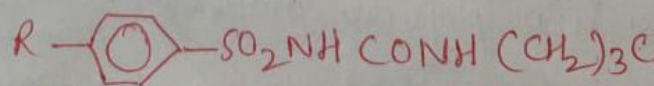
⇒ Tetravalent atoms and groups:-
=C=, =P=, =N=



⇒ Ring equivalent:-
-CH=CH-, -S-O, -O-, -NH, $-CH_2-$

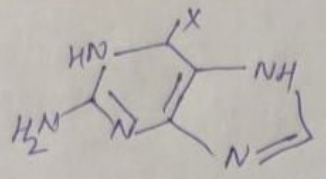
Application of classical bioisosteres in drug design:-

(i) Replacement of $-NH_2$ group by $-CH_3$ group



R = CH_3, Tolbutamide ; R = NH_2 ⇒ Carbutamide

(i) Replacement of –OH & –SH:–



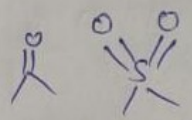
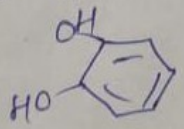
X = ↓
Guanine = OH
6-thioguanine = SH

(ii) Non- classical bioisosteres:–

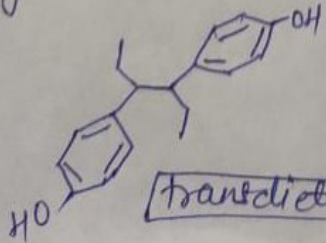
⇒ They do not obey the stearic and electronic definition of classical isosteres.

⇒ Non- classical bioisosteres are functional group of dissimilar valence electron configuration.

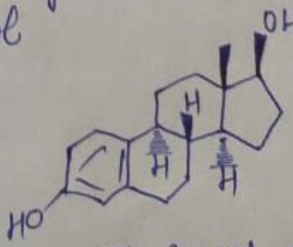
⇒ Specific characteristics:
- Electronic properties
- physicochemical property of molecule
- spatical arrangement
- functional moiety for biological activity

eg:–
1. Halogens like Cl, F, Br, CN
2. Ether –S–, –O–
3. Carbonyl group – 
4. Hydroxyl group – OH, $-NHSO_2R$, CH_2OH
5. Catechol 

6. A classical eg. of ring Vs. noncyclic structure is diethyl stilbesterol & 17-β-oestradiol



transdiethylstilbesterol



17-β-oestradiol