03/05/2018

Unit-I

medicinal chemistry :- A branch of chemistry in which the features of biological, medical, and Pharmaceutical science are studied is termed a medicinal chemistry. The study of invention, discovery, design, identification, and preparation of biological active compound their metabolism made of action at the molecular lavel and the structure activity relationship are also convered under this branch.

Medicinal chemistry also involves studing theexisting drugs their biological properties and Quantitative structure - Activity Relation ship (QSAR). The medicinal compound are basically organic compound which many include small organic molecules and biopolymers

History and development of medicinal chemistry :-
The history of medicinal chemistry consist of idea, knowleage and took having advanced moden knowledge. There are no exceptions in the remarkable advance made in the fixed of medicinal chemistry.

Drug of Antiquity :-
The therapeutic plants and minerals are in use since the ancient civilisation of the chinese the hindusthe. moyans of central American and the mediterroneom peoples of by gone days.

middle ages :- In 13th - 16th centuries the studies of Phyrice and chemistry shifted from Grerco-roman to the ambian allchemists. In abelived that chemicals could cure disease paracelsus (1493-1541) glorified antimony and site salts in elixirs.

The 19th century Age of Innovation and chemistry:-
The knowledge of chemistry expanded in the 19th century which also extended the previously estabilised Herbal Pharmacepoeia. The chemical analysis techniques were advance by the
Kolbe in 1845 synthesised acetic acid and Berthelot in 1856 synthesized methane and together they both extabilised the stage for organic chemistry.

The 20th century and the pharmaceutical Industry:-
The synthetic chemotherapeutical agent were found to be effective in protozoal and spirochental disease. Domogk stages that prontosil can cure the systemic gram-positive bacterial infections in humans and animals.

A water-soluble powder with antibacterial potency higer & toxicity lower than any know synthetic chemotherapeutic agent was made when fleming discovered Penicillin in 1929 and Florey chain examined it in 1941.

Development in the 21 century:- Our ancestors from neamaclethals, mesopotamia, egypt, greece, and ching herbal remedies for treating sick people scince then medicinal discovery has come a long was the leading manufacture such as:- F Bayer & company and farben fab-riken Hoechst. realised that their chemists can also manufacture medicines.

He was also inspired by his colleagesse who wherecondcting researchs in immonology including Louis pasteur, Robert koch Emil von. Behning and shibasaburo kitasato.

In the 20th century ennlich came up with the receptor theory and this becomes influntial to make understand how drug bind. to receptor & based on their chemical structure & compositions.

Physicochemical properties in rotation Biological Action:-
The biological Acting of targeted drug molecole is dependent on it's physicochemical characteristics essentially the nature & type of functional moieties and also the spatial arrangment of such group in the molecule modulating the structure of drug implies introduction, elimation or substitution of certain group of the drugs.

The physico chemical properties :-

1) Ionisation :- oftan the mans of a drug are responsible for it's biological activity in such cases increse in ionisation degree strengthens while something the undissociated molecules are responsible for the same in which incresein inonisation degree of active compound dse the activity.

Pka value :- The cell membrane of stomach, small intestine, mucosa, and nerveous tissue are partially dibidic in nature.
most of the drug are either weakly acidic or weakly basic
The degree of dissociation (Pka) can be calculated using Henderson Hassel bateh equation

for an acid

$$PH = Pka + \log \frac{\text{Ionised drug concentration}}{\text{unionised drug conc}}$$

Percentage of drug ionised $= \frac{10^{PH} - Pka}{1 + 10^{PH - Pka}} \times 100$

For base :-

$PH = Pka + \log = \frac{\text{unionised drug conc}}{\text{Ionised drug conc}}$

Percentage of drug ionised $= \frac{10^{Pka - PH}}{1 + 10^{Pka - PH}} \times 100$

2) Solubility :- water constitutents the major portion of living bodies. Therefore the biochemical reactions occuring with in a living body rely either on the micro molecules dispersed in the phase.

Selenally no drug molecules is completely insoluble every molecule is soluble in both are aqueous and Non-aqueous lipid compartments of a cell. How ever the solubility degree is different b/w each compartment.

3) Partition coefficient :- the equilibrium consist of drug conc in the two phase is termed as a partition cofficients are determined into vitro using n-octenol as the lipid phase and a PH 7.4 aqueous phosphate buffer as the water phase because it's standardised measurement in living systems is difficult partition cofficient (P) of a drug is expressed as :-

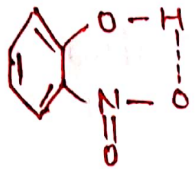
$P = (\text{drug})_{\text{lipid}} / (\text{drug})_{\text{water}}$.

(5)

4) Hydrogen bonding :- A bond in which a hydrogen atoms holds two other atom together is termed as hydrogen bonds (H- bond). This formed b/w electronegative & Hydrogen atoms. the atoms which can form H- bonds carry at least and unshared pair of electron. The atoms forming H- bonds more extent are Cl and S.

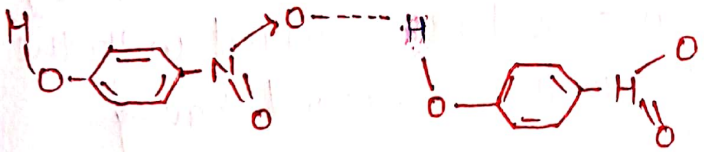
Hydrogen bonding is classified into

1) Intermolecular Hydrogen bonding :- This H- bonding occurs with in the molecules.



O-Nitrophenol

(ii) Intramolecular hydrogen bonding :- This H- Bonding occurs with in the molecule



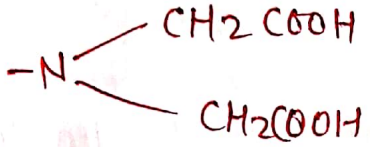
P- nitrophenyl.

5) Protein binding :- Drug distribution elimination and its Pharmacological effects get effected by binding of drug of plasma protein due to their high molecular weight. they cannot pass through capilla rise and due to their low lipid solubility they can not cross the cell membrane. Drug protein binding can occurs through ionic vander waals, and Hydrogen binding Albumin comprises nearly 50% of the total

Plasma protein and assists the drug binding in the plasma.

6) Chelation:- The reverrible binding of the digand the chelant chelater chelating agent. sequestering agent or complening agent to a metal ion to form a chelate is called chelation. This term is mostly used for complexes having metel ions bounded with two or more atom of chelating agent via combination or ionic bonds.

Chelating agent:- Ligands having more than an electron donating group are called. chelating agent. The most effective complexing agent in ligands are amino and carboxylate ions.



7) Bio Isosterism:- The formal and 3-D structure during SAR Studies and drug design should be compared with the substituent and functional group of compound having similar biological activities.

Biososterism is a medicinal chemistry approach for rotational designing of new drug applied with a lead compound (LC) using a proces of molecular modification.

Isoteres and Isosterism:-
Longmuir stated that two mains or molecule should bossess similar characteristics if they are identical in electron no. and arrangement and such peior of ions or molecule are termed 'isosteres.

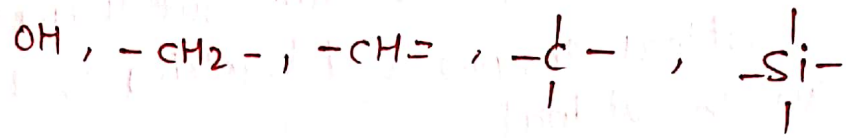
ex:- CO and N_2, CO_2 and NO_2^-, N_3^- and NCO^-

(7)

Bioisoteres:- The compound or group of almost equal molecular shapes, volumes and electron distribution and similar physical characteristic are called bioisoleres.

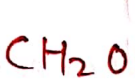
classification of Bioisteres:-

i) classical Bioisteres:- The volence electron configurations of these functional groups are similar.

ex:- 

(ii) Non-classical Bioisteres:- The volence electron configurations of there functional group are not similar.

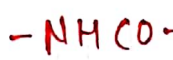
ex:-



Hydroxyl group

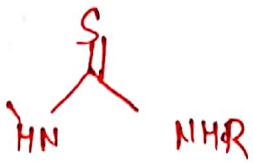
carbonyl group

carboxylic acid group

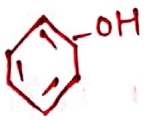


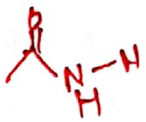
Amides

Thio ether



Thiourea

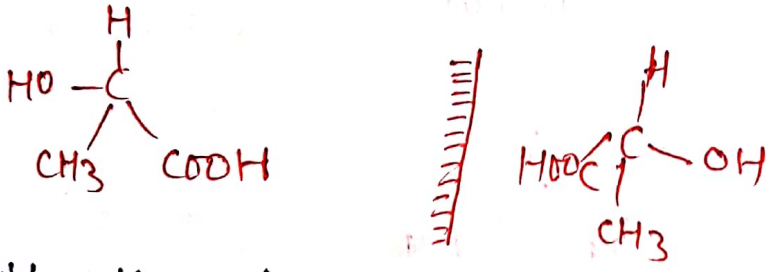




Optical isomerism :- A drug therapeutic and toxic effect can be understand by the concepts of stereo chemistry enantiomers, symmetry, asymmetry and chiracity any drug is said to be chirol if atleast one asymmetry carbon atom and two enantiomers are present in it the chemical and Physical Properties of each enantiomer are the same but their interaction with receptors enzyme and proteins in the body is different as an individual

optical isomerism are the following types :-

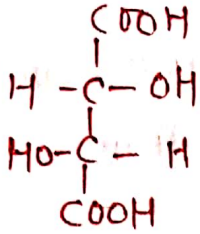
(i) Enantiomers :- A molecule becomes asymmetry and exists into two forms on attaching four different atom or groups at the pair corners of a regular tetrahedron Although the atoms in this 3-D structure are arranged in the same manner still the structure can not be superimposed an each other hence they are different.



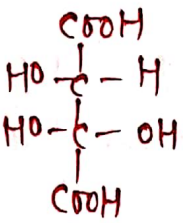
(+) Lactic acid (−) lactic acid

(ii) Diastereomers :- A compound with two similar asymmetric carbons is tartaric acid. The reason for similar asymmetric carbon atoms is that a hydrogen atom, a hydroxyl group and a carboxyl group are attached to each carbons atoms.

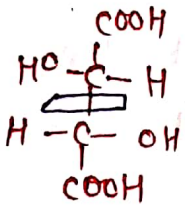
(9)



D (+) tartaric acid

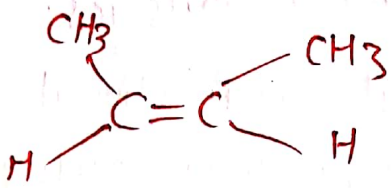


L (-) tartaric acid



meso tartaric acid

9) Geometrical isomerism :- The phenomenon of geometrical isomerism also decides the action of certain drug. A diastereoisomer occurs due to restricted rotation around a bond is a geometrical isomerism.



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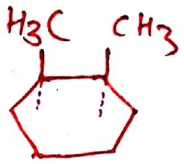

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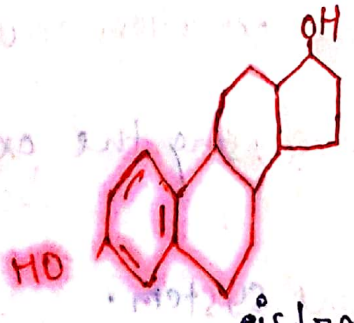
Influence of Geometrical isomerism of Pharmacological Activity :-

A compound may get varibly distributed in a living system due to the differents in the physical properties of isomers

examples :- At physiological PH one of the isomers may be highly ionised resulting in a difference in surface adsorption and membrane penetration.



eistradiol

(Drug metabolism)

The chemical alteration of a drug by the body is formed as drug metabolism also known as biotransformation.

Drug metabolism Principles:- Liver forms the organ the metabolism of a no. of a drug. There process of metabolism occurs in two parts

1) Phase I (Metabolism/Non-synthetic phase)
This is the first phase of metabolism when a drug enters the metabolism pathway. This phase yields a drug molecule with the following characteristics.

→ The molecule form a reactive site or functional group such as- (OH, -SH, or -NH_2) which further conjugates with the molecules in phase II

→ The molecule Lipophilicity (like and hydrophilicity (ryse to facilliate it's excertion.

Process of phase I metabolism:- The drug molecule may undergo any one of the following major processes during phase I metabolism.

(i) Oxidation Reaction:- Liver cells i.e hepathocytes form the most common site for oxidation of a drugs molecules with in the hepatocyte microsome is the unit where oxidation occurs.

Mixed function:- Ds the enzyme system catalysing the oxidation of drug molecules.

various system components make up the enzyme system.

a) cytochrome Oxidase enzyme :- It is generally as cytochrome P450 (CYP450)

b) NADPH :- It is another important member of this oxidative system and acts a coenzyme.

c) NADPH cytochrome Reductase :- It is another enzyme which is chemically a flavoprotein.

(ii) Hydrolysis :- In this process the drug molecule is broken down into to similar molecules by the insertion of water molecule (H_2O)

(iii) Reduction :- This reaction is associated with the introduction of H atoms eg :- chloramphenical is reduced to arylamine

(iv) Cyclisation :- This process result in the formation of a ring structure from compound arranged in a straight chain, eg :- Proguanil

(v) Decyclisation :- In this process the ring structure of the cyclic drug molecule opens up eg :- Phenytoin

2) Phase II (Synthetic Reaction) :-

The reaction is characterised by the formation of a conjugate Glycuronyl, sulphate, methyl, acetyl, glyceryl, and glutathione are the groups.

commonly involved in conjugate formation

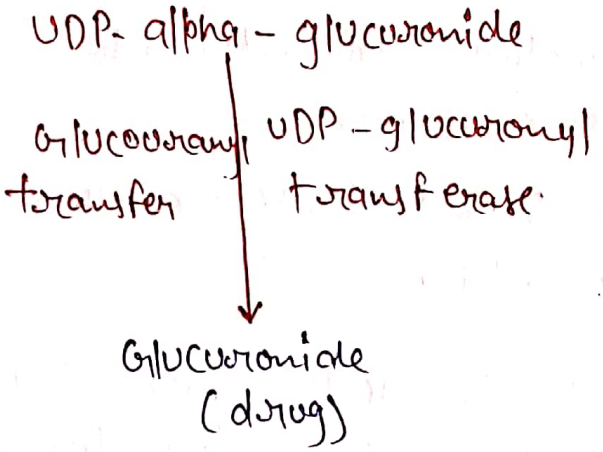
Reactions of phase II are the pathway resulting in detarification of the drug. They include

I Conjugation with Glucuronic acid :-

a) Glucuronic acid is obtained most commonly from D-glucose

b) D-Glucuronic acid is easily available for combination with functional group like amines, alcohol, acids etc.

c) Glucuronides are commonly produced by all mammals.



(ii) Conjugation with sulphate moieties:- This is a significant step in the metabolism of phenolic compound. sulphate conjugation is also referred to as enthereal sulphate synthesis.

(iii) Conjugation with Glycine moieties:- This is the major pathway involved in the biotransformation of some drugs.
ex:- in biotransformation of salicylates

(iv) Conjugation with Acetylation:- This conjugation yields amide products just like that obtained in conjugation with alpha - amino acid.

Factors affecting Drug metabolism:-
The following factors play a role in modifying drug metabol;

(i) Inhibitors:- some drug inhibit the drug metabolising enzyme & further use the drug metabolism. As a result the during of action use

(ii) stimulants:- Some drug eg. Phenobarbitone and rifamptcin the activity of drug metabolising enzyme. As a result metabolism of drug like phenytoin and warfarin use

(iii) Age :- In infants and young children drug metabolism enzymes are poorly developed thus a drug is poorly metabolism.

(iv) sex :- Drug metabolising ability in females is less than that is males.

(v) species :- Some metabolising enzymes are present only in a few mammalism species and are absent in humans. Thus drugs metabolised by these enzymes prove to be toxic to humans while they are non-toxic to others.

(vi) Genetic :- Certain individuals may inhent drug metabolism enzyme deficiency e.g. genetic deficiency of Glucose-6-Phosphate Dehydrogenase (G-6-PD) enzyme result in hoemolysis an administering primaquine.

(vii) Body temperature :- A rise in body temp. enhances drug metabolism while a decrease in body temp. reduces drug metabolism.

Stereochemical Aspects & Drug metabolism :-

→ Most only the Physiological factors effecting xenobiotic metabolism some stetaboliting

→ factor also effect drug biotransformation the xenobiotic metabolism

→ Some endogenous substance which are chiral molecules.

→ The metabolic stereochemical reactions are as follows :-

(i) substrate stereoselectivity :- In this two enantiomers of a chiral substrate gel metabolised at different rates :- example- decarboxylation of 5-α

(ii) Product stereoselectivity:- In this a new chiral centre is created in symmetric molecule and one enantiomers gets metabolism.
example:- Reduction of ketones to stereoisomeric alcohol.

(iii) Substrate - product stereo selectivity:- In this a new centre of a chiral molecule gets metabolised in so one of two diastereomers
example:- Reduction of warfarin enantiomers.

complete