Date: _____ Page: _____

Unit - I

Introduction to medicinal chemistry —!

Medicinal chemistry explains the designe and productio of compounds that can be used for the prevention, treatment or cure of human and animal diseases.

Medicinal chemistry includs the study of already existing drugs, of their biological property and their structure activity relationship.

Medicinal chemistry was defined by IUPAC specified commision as —

"It concerned the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds".

Medicinal chemistry covered or can be completed or done under following steps—

Step-1 → The development or synthesis of lead compound or molecules.

Step-2 → Optimization of lead structure.

Step-3 → Development and modification of pharmaco-kinetic and pharmaceutical properties.

Date: _____ Page: _____

Step-1 → The development and synthesis of lead compound or molecules :-

In this stage new active substances or molecules or drugs are identified and prepared from natural sources, organic chemical rxn's or biotechnological processes.

The compounds synthesized are k/as lead molecule or lead compound.

This compound represent the activity of all drugs of this class.

Step-2 → Optimization of lead structure :-

In this stage lead structure is optimized to improve potency, selectivity and lessen toxicity.

Step-3 → Development and modification of pharmaco-kinetic and pharmaceutical properties :-

In this stage optimization of synthetic route bulk production and modification of pharmacokinetic and pharmaceutical properties of active substances should be done to render the compound chemically useful.

Date: _____ Page _____

Medicinal chemistry is the application of chemical research technique to the synthesis of pharmaceutical

History of medicinal chemistry

During the early stages of medicinal chemistry development, scientist word concerned with the isolation of medicinal agent found in plants, but today scientist in this feed are also equili concerned with the creation of new synthetic drug compounds.

Medicinal chemistry is almost always geared towards drug discovery and development.

Historical development in medicinal chemistry

S.N.	Era/Date	Historical developments
1-	3000 B.C.	The emperor sheng ning listed the crood drug chang shang for malaria
2-	1500 B.C.	Squill was discribed as cardiac tonic.
3-	50 A.D.	Pliny was introduced for Helminthiasis
4-	180 A.D.	Galen were used small quantity of natural product to treat diseases, all though today this preparations are considered useless.

Date: _____ Page: _____

5-	1820	Isolation of quinine and colchicine was done and first U.S. pharmacopoeia was published.
6-	1839	Iodine was used as topical antiseptic.
7-	1860	Phenol was used as in disinfactent.
8-	1874	Heroin was prepared from morphin
9-	1899	Aspirin was introduced.
10-	1908	Sulphanilamide was synthesized as antibiotic.
11-	1909	Ehrlich coined the turm chemotherapy.
12-	1910	Barger & Dale descrite the structure activity relationship of sympathomimetic drugs.
13-	1911	Stable analogues of acetyl coline were used as parasympathomimetic.
14-	1912	The turm vitamine was coined.
15-	1922	Insulin was isolated.
16-	1929	ⓐ Peniciline was discover. ⓑ Vit-k was shown to be an essential for the biosynthesis of blood clotting factor.

Date: _____ Page _____

17	1939	Dapsone was found to supress experimental tuberculosis.
18	1939-1968	Clinically useful sulphonamides were introduced.
19	1968	Dapsone was used in treating leprosy in humans.
20	1949	Purine analoges were used as anticancer agent.
21	1955	Prednisone and prednisalone were used as antiinflametry agent.
22	1957	5-Fluro uracil was used as anticancer agent.
23	1959	some Vinca alkalaids were used in cancer chemotherapy
24	1977	Captopril was discovered as an antihypertensive
25	1993	Zidovudine was discovered as anti HIV aget.
26	1994	Gene therapy was introduced.
27	1998	Nitric oxide was used as vasodilator.
28	2002	Drug designed was introduced.
29	2006	Use of computational technique in medicine was started.

Date: _____ Page: _____

Physiochemical properties in relation to biological action

The ability of a chemical compound to elicit (produce) if pharmacologic or therapeutic effect is relative to the influence of various physical and chemical properties of the chemical substance on the biomolecule or the body, is called as physiochemical properties of organic medical or medicinal agents (OMAs).

There are so many physiochemical properties of an organic medicinal agent, some of them are as following —

→ Solubility.
→ Partition coefficient.
→ Dissociation constant (pK_a).
→ Ionization.
→ Hydrogen bonding.
— Molar refractivity.
— Drug shape.
→ Complexation and chelation.
— Surface activity.
— Protein binding.
— Bioisosterism.
— Geometrical and optical isomerism.

Solubility :-

The solubility of a substance at a given temperature is defined as the concentration of the dissolve solute which is

equilibrium with solid - solute.

* Solubility depends upon the nature of solute and solvent as well as the temperature, pressure and pH.

* The solubility of a substance is the ratio of rate constant at equilibrium in a given solution.

$$K_{solubility} = \frac{K_{solubilized}}{K_{ppt}}$$

* On the basis of affinity or phillicity and repulsion or phobicity for aqueous or lipid solvent, the OMAs are divided or categories in following categories —

1- Hydrophillic ⟶ Water loving.
2- Hydrophobic. ⟶ water hating.
3- Lipophillic. ⟶ Lipid loving.
4- Lipophobic. ⟶ Lipid hating.

(binding) Forces involve in the solubilization —!

They are so many types of attractive forces which involve the solubilization process but only 3 are mainly active forces which are as following —

Date: _____ Page: _____

① Vander waals attraction force :-

These are weakest intermolecular force which occur b/w non-polar groups —

② Dipole - Dipole binding - [Dipole - Dipole attraction forces) :-

These forces occur when electronegative atom element are attach to carbon.

They are stronger and occur electrostatically b/w electron deficient and electron rich atoms ((Dipole).

Eg :- Hydrogen banding (only for substance containing high electronegative atom).

③ Ionic banding :-

It is basically electrostatical force b/w cations and anions.

These ionic attraction are common in inorganic compounds and salts of organic compounds.

They are relatively strong forces.

Date: _____ Page: _____

Methods to improve solubility of drug

There are some modification or changes in structure by which we can improve the solubility of drugs —

1- Alterations in structure -:

(i) Addition of some polar groups like carboxylic acid, ketones and amines can increase the solubility of our drug.

(ii) By changing the acidic or the basic groups into esters, the solubility can enhance.

2- Addition of co-solvent -:

By the addition of co-solvents, the solubility of our drug can improve.

Ex -: The commonly used co-solvent in p'ceutical industry are propylene glycol, poly ethylene glycol, ethanol and sorbital.

3- Addition of surfectant -:

Surfectant can also be used to ↑ solubility of the drug.

A surfactent or surface active agent is amphipratic in nature that is one part

is of polar nature and other part is of non polar nature. When a surfactant is place in water it will form micelles so the drug will dissolve properly.

4- Complexation →

There are so many types of complexing agent, by addition of these agent the solubility of our drug can increase.

Importance of solubility in pharmaceutical chemistry

(i) The concept of solubility is important for a pharmacist beco2 it governed the preparation of liquid dosage form and the drug drug must be in solution before it can be absorbed by the body to have any biological activity.

(ii) Drug must be in solution to interapt with receptor.

(iii) Drugs must some degree of solubility in aqueous compartment as well as in lipid compartment.

Date: _____ Page _____

2- Partition coefficient :-

It is the ratio of concentration of a compound in the two phases of a mixture of two immiscible liquids at equilibrium.

$$K = \frac{C_1}{C_2}$$

C_1 = lipid

C_2 = water

Importance

- For drug delivery, the lipophillic / hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption
- Since biological membranes are lipodal in nature the rate of drug transfer for passively absorbed drug is directly related to the lipophilicity of the molecule.

3- Dissociation constant :-

It is the ratio of molar concentration of substance in ionized form to the molar concentration of unionized form is K/as dissociation constant.

Importance

Date: Page:

4- Complexation and chelation →

- When simple molecules are combine together by any physical or chemical attraction force then they form a complex and the process of formation of complex is known as complexation.

Importance of complexation

* Solubility enhancement.
* Bioavailability enhancement.
* Modifying drug release.
* Taste masking.
* Administration of therapeutic agent.
* In the treatment of poisoning.

- Complexes may be divided broadly into 2 classes depending on whether the acceptor compound is a metal ion or an organic molecule.

- The compound capable of forming a ring structure with a metal atom are called ligand.

- The compound that are obtained by donating electron to metal ion with formation of ring structure are called chelate.

Application of chelation

* Dimercaprol is a chelating agent. It is an efficient antidote for organic arsenical

Date: _____ Page: _____

But can also be used for treatment of poisoning due to antimony, gold and mercury.

* 8-hydroxiquroline and it's analoges act as antibacterial and antifungal agent by comparing with iodine or copper.

5- Ionization of drug :-

The accumulation of a ionized drug in a compartment of body is known as ion trapping.

The ionization of drug is dependent on it's pK^a and the pH.

The pK^a is the negative logarithm of ka. The ka is the activity constant of a compound, it's tendency to release a proton.

The ratio of ionized / non-ionized drug may be determined by henderson-hasselbalch relationship —

$$pH - pK^a = \frac{\log [A^-]}{[HA]}$$

$$= \log \frac{[\text{ionized}]}{[\text{non-ionized}]} \longrightarrow \text{For acid}$$

Date: Page:

$$pH - pK_a = \log \frac{[B^-]}{[HB]}$$

$$= \log \frac{[\text{non-ionized}]}{[\text{Ionized}]} \longrightarrow \text{For base}$$

Importance

* The lower the pH relative to the pK_a, greater is the fraction of protonated drug.

* Weak acid at acidic pH → More lipid-soluble, because it is uncharged — the uncharged form more readily passes through biological membrane.

$$RCOO^- + H^+ \longrightarrow RCOOH$$

* Weak base at alkaline pH → More lipid-soluble, because it is uncharged — the uncharged form more readily passes through biological membrane.

$$RNH_3^+ \longrightarrow RNH_2 + H^+$$

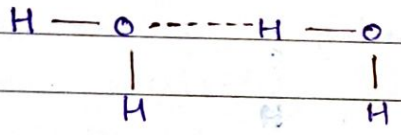
Date: _____ Page: _____

6- Hydrogen banding :-

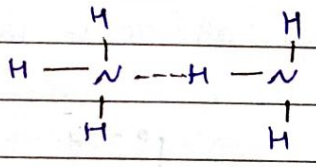
The hydrogen banding is type of dipole - dipole interaction b/w the hydrogen atom in a polar bond such as N-H, O-H or F-H and an electronegative atom O, N, F.

* It is written as A—H----B.

eg :-



$H_2O - H_2O$

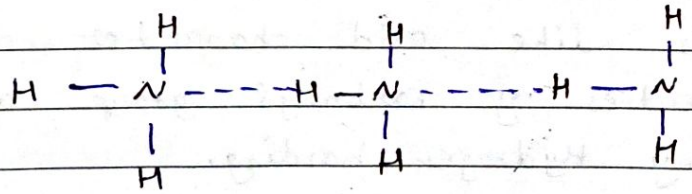


$NH_3 - NH_3$

Types of hydrogen banding

(a) Intermolecular hydrogen banding :-

In this type, hydrogen banding occurs b/w two or more than two molecules of the same compound and results in the formation of polymeric aggregate.



Date: _____ Page: _____

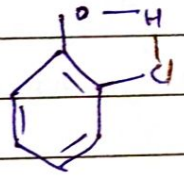
ⓑ Intramolecular hydrogen bonding :-

* In this type, hydrogen bonding occurs with in two atoms of the same molecule.

* This type of hydrogen bonding is commonly has chelation and frequently occurs in organ compound.

* Some times intramolecular hydrogen bonding develop a 6 or 5 - membered ring.

Eg →



orthochlorophenol

Effect of hydrogen bonding

Almost all physical properties are affected by hydrogen bonding.

Here only those properties that are prominently altered such as boiling point, melting point, water solubility etc.

Chemical properties like acid character, basic character, properties of carbonyl group are also affected by hydrogen bonding.

— Boiling and melting point →

Inter molecular H bonding ↑es the boiling point of the compound

Date: _____ Page: _____

due to association of several molecules of the same compound.

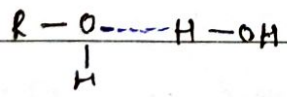
As a result the intermolecular forces are ↑ed and hence more energy (large amount heat) is required to dissociate the molecules for vapourization.

Intramolecular hydrogen bonding ↓es the boiling point of the compound becoz of the fact that chelation b/w the groups of ~~Sa~~ same molecule restricts the possibility of intermolecular hydrogen bonding and thus prevents the association of the molecule which result in the ↓es of boiling point.

— Water solubility →

The solubility of a compound ↑es with the hydrogen bonding b/w the solvent and the solute.

Ex →; Ethanol or methanol with water.



— Strength of acid →

Any structural feature that contributes the greater stability of anion is comparision to free free acid will shift the ionization equilibrium to the right.

Thus if the anion of acid work stablised

Date: _____ Page: _____

due to intramolecular H bonding, there would be the marked ↑ in the strength of acid.

Effect, importance and advantages of partition co.

Partition coefficient is very useful parameter and it may be used in combination way the pka or dissociation constant. To predict the distribution of a drug compound in a biological system.

All the factors like absorption, excretion and penetration of the CNS is related with the log p value of a drug.

Date: _____ Page: _____

Bioisosterism :-

* Langmuir suggested that any two ions or molecules having an identicle number and arrangement of electrons must exhibit similar characteristics and all such pairs be named as '*isosters*'.

Eg :- (i) CO (4+2) and N_2 (3×2)

(ii) CO_2 (8) and N_2O (8)

(iii) N_3^- (10) and NCO^- (10)

* It is point quite evident that such isoster which are isoelectric in nature must show similar activity and similar properties.

* Isosterism is of vital importance to a medicinal chemist becoz it is assumed that the groups which are having the similar physical and chemical properties should compasss the similar biological activity.

* Friedman proposed the following definition of biosterism —

"The phenomena by which compound usually fit the broadest definition of isosters

and posses the same type of biological activity".

* Burger defined the bioisosterism as following —

The compounds or groups that essentially possess the equal molecular shape and volume, approximetly the same distributies of electron and exhibit physical characteristic like hydrophobicity, pka etc. are called as bio isosters and the phenomena is called as bio isosterism.

He also suggested that if any compound or molecule which are isostere in nature that is having same member of electrons and some physical and chemical properties, should compasses same biological activity.

Classification of bioisosterism

There are 2 mains type of bio isosterism which are as following —

(i) Classical bioisosterism.
(ii) Non-classical bioisosterism

(1) Classical bio isosterism —

Classical replacement is "like for like". In terms of number of atoms,

Date: _____ Page: _____

valency, degree of unsaturation and aromaticity.

The compound which follow all these conditions of classic replacement are called as classical bioisosteres and the phenomena is called as classical bioisosterism.

eg → The classical bioisosteres may be ——

(i) Monovalent or univalent →

(a) $-CH_3$, $-NH_2$, $-OH$, $-F$
(b) $-Cl$, $-NH_2$, $-SH$
(c) $-Br$, $-I$

(ii) Bivalent or divalent →

(a) $-CH_2-$, $-NH-$
(b) $-COCH_2-$, $-CONH-$

(iii) Trivalent →

$>CH-$, $>N-$

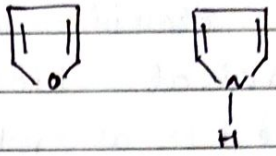
(iv) Tetra valent →

$=\overset{+}{N}=$, $=C=$

Date: _____ Page: _____

(v) Ring equivalent :-

(a) 

(b) 

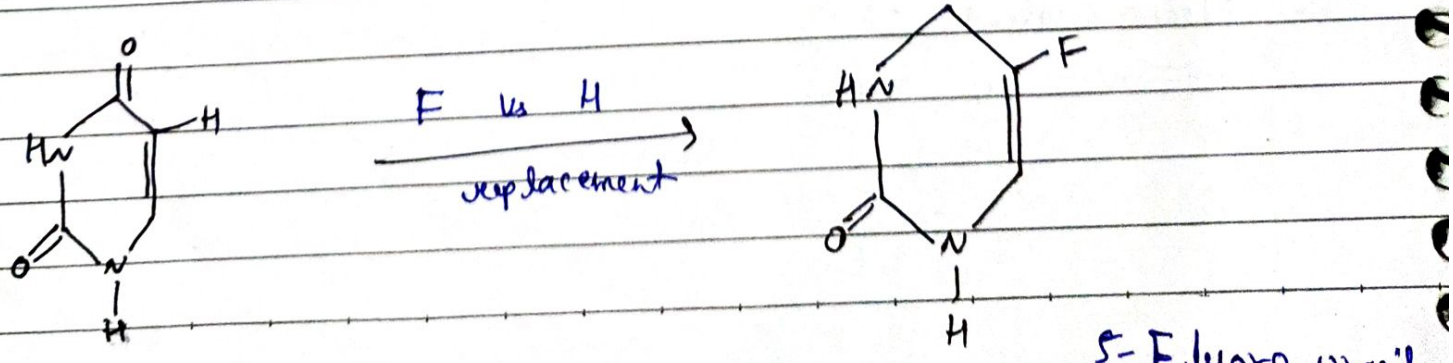
Application of classical bioisosterism

There are so many types of drug where the concept of classical bioisosterism has been applied some of them are as following —

1- Fluorine Vs Hydrogen replacement :-

The substitution of hydrogen by fluorine is one of the most commonly applied mono valent isosteric replacement.

This results in the formation of 5-Fluoro uracil which is an antineoplastic drug or anticancer drug which is obtained by the hydrogen substitution of uracil.



Uracil

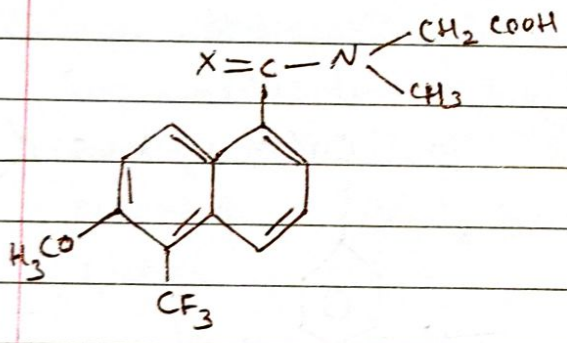
5-Fluoro uracil

Date: _____ Page: _____

2- Di valent replacement involving double bond :-

The replacement of C=S with C=O in tolrestat is under study for the treatment of human diabetes.

If we substitute C=S with C=O :- with antidiabetec resulted is more active and more potent than the previously produced drug.



Tolrestat

(i) X = S

(ii) X = O

(ii) Non - Classical bioisosterism :-

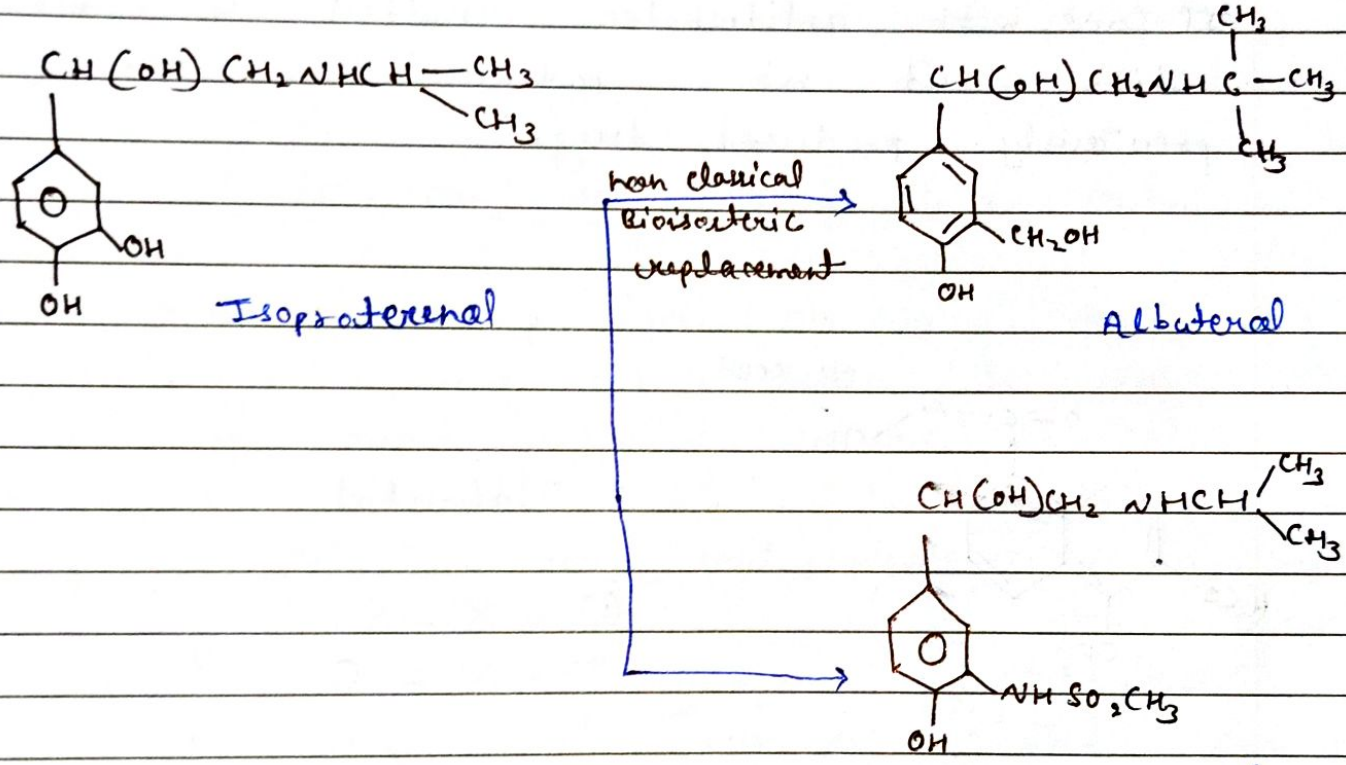
The non - classical bioisosters comprise the groups which are structurally similar but do not meet the electronic and steric requirements.

These isosters retain activity by the retention of their properties like pK^a, electrostatic potential etc.

Date: _____ Page: _____

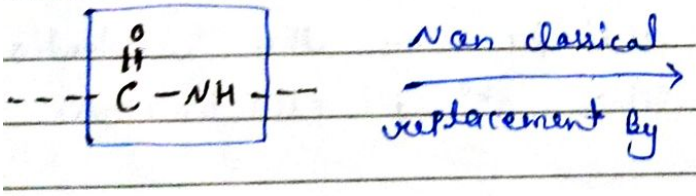
Ex → (1) – Attemps to ↑ the duration of action of this class of agents by preventing the route of metabolism has resulted the potent and more selective agent.

– β - Adrenergic agents –



(ii)

– Peptide bond and peptide fragments have been replace with a ~~white~~ wide variety of structural maiety in ~~atom~~ to convert peptides into chemically stable and orally available molecules.



Date: _____ Page: _____

Applications of bioisosterism

1- Bioisosterism is very important aspect of medicinal chemistry for medicinal chemist becoz it can help into the production of more safer and more clinically effective agents.

2- Bioisosterism has been proved in resolving so many biological problesm effectively.

Drug metabolism

Drug metabolism may be defined as the biochemical modification of one chemical form to another, occuring usually through specialized enzymetic system.

It often involves the conversion of lipophillic chemical compounds (drugs) into highly polar derivative that can be easily excited from the body.

Drug metabolism or detoxification rxn's can be divided into two broad categories —

1- Phase I rxn or functionalization.
2- Phase II rxn or conjugation.

Date: _____ Page: _____

1- Phase - I rxn or functionalization -!

- These rxn are termed as the non synthetic rxn.
- It includes oxidation, reduction, hydrolysis, cyclization and decyclization rxn.
- These rxn's are carried out mostly by mixed functional oxidases usually cytochrome 450 (cyp 450) which occur usually in liver.
- In these rxn a polar group is either introduced or unmasked if already present.
- These rxn's are succeeded by phase II rxn's.
- Most of the phase I product are not eliminated directly instead they undergo phase II rxn.
- Various phased I rxn's are as following —

(a) Oxidation →

It is the most commonly occuring rxn by which hydrophillicity of drug is led by the introduction of -OH group.

(I) Oxidation at carbon centre -!

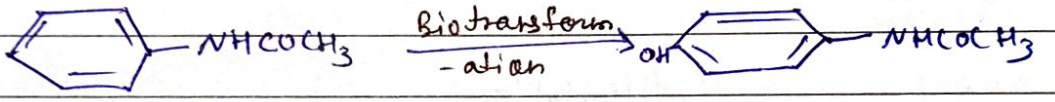
This include oxidation at aromatic ring, olefins centre and aliphatic group.

Date: _____ Page: _____

* Important drug undergoing metabolism by this rxn include.

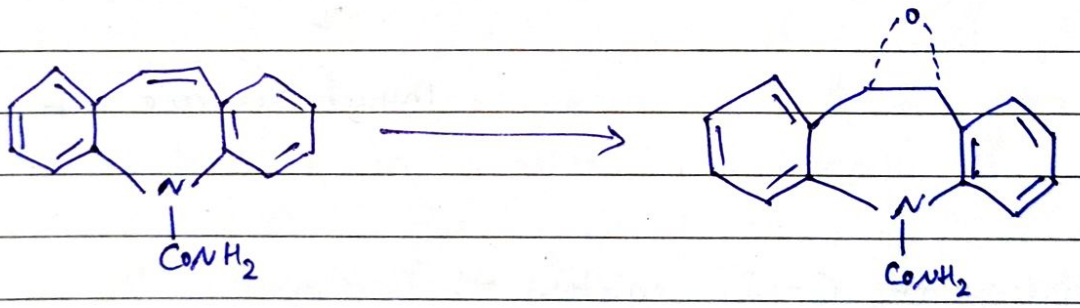
Eg → Acetanilide (Analgesics).
Phenyl butazone (Analgesics).
Valpecoic acid (antiepileptic) etc.

* Acetanilide —



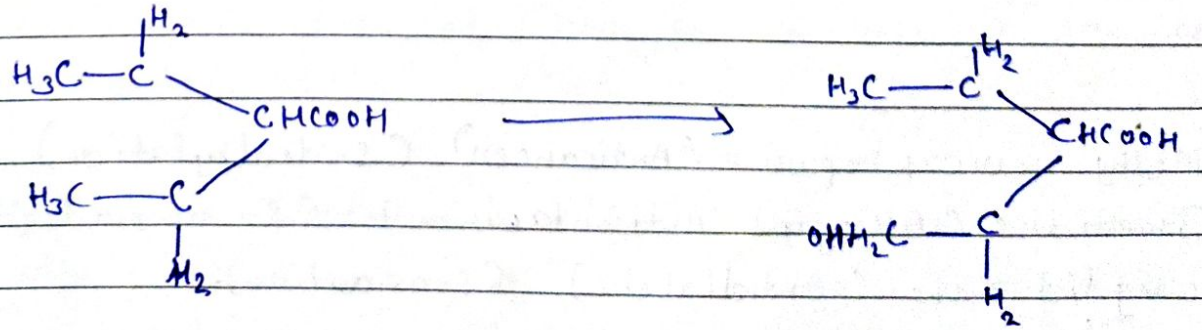
PCM

* Carbamazepine —



Carbamazepine epoxide

* Valproic acid —



4-hydroxy valproic acid

Date: _____ Page: _____

Oxidation at carban heteroatom centre →

* In C-N →

* This involves oxidation on C-N, C-S and C-O system.

* The oxidation rxn's on C-N system comprise of N-dalkylation and N-deamination, formation of N-oxide and N-hydroxylation.

Eg → Eg. of C-N system.

Methamphetamine —(N-dealkylation)→ Amphetamine —(oxidative deamination)→ Phenyl acetone + NH_3

(Antidepressant)

* Oxidation at C-S system →

It may involve S-dealkylation, desulfuration and S-oxidation.

Eg →

6-Methyl mercaptopurine (Anticancer) (S-dealkylation)
Cimetidine (Allergy) (Antihistaminine) (S-remove)
Roriglitazone (Antidiabetic) (S-oxidation).

>C=O ⊢ aldehyde / ketone

Date: _____ Page: _____

* Oxidation at C–O system :-

When C–O system is present then important oxidation processes includes oxidative dehalogenation, oxidative aromatization or O-dealkylation.

Eg → Halothane (General anaesthetic).

(b) Reduction →

The reduction rxn's results in the generation of polar functional group such as hydroxyl and amino etc.

* These rxn's may occur on several functional group such as carbonyl, hydroxyl etc.

* The reduction can also be done for unsaturate aliphatic group (alkene and alkyne).

Eg → Nitrazepam (Hypnotic and antianxiety agent).
Prontosil (Antibiotic).

(c) Hydrolysis :-

These rxn's generally involve a large chemical changes in the substrate or drug.

* Hydrolysis occurs when esters are present in the structure of the drug. or amide containing drugs.

Date: _____ Page: _____

Ex → Ester containing drug → Aspirin (Analgesic).
Amide containing drug → Procainamid (Antiarrhythmic drug).

2- Phase II metabolism (conjugation action) -:

* The phase II rxn follows phase I rxn and occur mostly in the product of phase I rxn.

* In these rxn's a suitable moity such as glucuronic acid, glutathione, sulphate, glycine etc. get conjugated to the metabolized of phase I rxn.

* The phase II rxn's are the basically reeal drug detoxification rxn.

* These are also term as conjugation rxn's becoz moity which are attached are large in size and strongly polar in nature.

* These rxn's are catalysed by a variety of transferase enzyme like UDP (uridine di phosphate) glycoronyel transferases, sulphotransferases and glutathiane transferases etc.

Glutathione → Cysteine
→ Glutamic acid
→ Glycine

Date: _____ Page: _____

Example

S.N.	Conjugated group	Endogenous cofactor	Enzyme	Drug
1-	Glucoronidation	UDP- glucoronic acid	UDP- glycoronosyl transferase	Chloroamphenicol Salicylic acid.
2-	Sulphation	Sulphate	sulphotransferase	PCM Salbutamol
3-	Glycine/ Glutamine	Glycine/ Glutamine	N- Acyl transferase	cholic acid, Phenylacetic acid, Nicotinic acid.
4-	Glutathione		Glutathione -S- transferase	PCM, N- ethacrynic acid
5-	Methylation	S- adenosyl L- methionine	methyl transferase	Morphine, Nicotine, Histidine, Propyl thiouracil
6-	Acetylation	Acetyl coenzyme A	Acetyl transferase	Dapsone, Isoniazid, Procainamide, Hydralazine

Date: _____ Page: _____

Factor affecting drug metabolism

There are so many factors which can affect the drug metabolism. Some of them are as following—

1- Genetic factors :-

Genetic factors are responsible for the variation in drug metabolism due to the difference of metabolizing enzyme.

2- Physiological factors :-

It includes the factors like age, sex differences or gender, harmonal changes, body weight, pregnency and nutritional status.

3- Pharmacodynemic factors :-

It include dose, frequency, route of administration and protein binding.

4- Environmental factors :-

It is an important factor which can affect the drug metabolism due to the intake of some chemicals or the changes of metabolizing enzymes by toxic chemical such as pesticides and CO. etc.

5- Stereo chemical accepts of drug metabolism :-

The stereo chemical factor may also play an

Date: _____ Page: _____

important role in bio transformation or metabolism of drug becoz most of the metabolizing enzyme show stereo selectivity. that is one stereo isomers can show the better bio transformation than other.

* They can show the substrate stereoselectivity that is both enentiomers of a chiral substrate are metabolized at different rates.