UNIT 1 INTRODUCTION TO MEDICINAL CHEMISTRY

→ The discipline of Medicinal chemistry is devoted to discovery & development of new agents for treating diseases

→ Compound can be new natural or synthetic organic.

→ As defined as IUPAC, "It is a branch of chemistry that deals with aspects of biological, Medicine & P'ceutical sciences."

→ It is concerned with invention, discovery, design development, identificat^{n} & Preparation of Biological active compound.

→ It includes study of their Metabolism, interpretation of their Mode of Action, & Construction of Structure Activity relationship (SAR).

→ It deals with Pharmacokinetics of Drug.

A D M E

→ Medicinal chemistry involves three Major stages:-

1) DISCOVERY - Choice of Target, Identificat^{n} of LEAD

2) OPTIMIZATION - Optimizat^{n} of P'codynamic & P'cokinetic properties

3) DEVELOPMENT - Preclinical & clinical studies.

① DISCOVERY :-

The process of drug discovery begin with identification of new previously undiscovered, Biologically active compound, called as "HITS or TARGETS", which are found by Screening of many compounds.

② Optimizat^n :-

Hits are converted to leads, to further optimize, various properties.

HIT
↓
Chemical or funct^n group modificat^n
↓
Lead compound
↓
Lead optimizat^n.

It is done to Enhance the lead to improve its Effectiveness, diminish toxicity or ↑ absorpt^n.

Optimization results into drug molecule which is safe & Effective, also suitable for use in human clinical trials.

③ Drug Development :-

The compounds that clear optimization, undergo,

- Patenting
- Preclinical
- clinical trials,
- Marketing of Drug.

HISTORY OF MEDICINAL CHEMISTRY & DEVELOPMENT..

- MEDICINE IN THE ANTIQUITY
- MEDICINE IN MIDDLE AGE
- 19th century
- MODERN CHEMISTRY

1) DRUGS/MEDICINE OF ANTIQUITY :-

The oldest record of using therapeutic plants & Minerals were derived from ancient- civilizat^n of chinese, Hindus & Mediterraneans.

In ancient 'Greek Apothecary' were found for opium & cocoa leaves.

- Roman Medicines (approx 200 BC), gave invention to hospitals

② Medicines in MIDDLE AGES (400 - 1500 A C).

- Era of horrible Pandemics & Epidemics (POX, TB)..
- Arabic Medicine come into Existence :- Development of Medical Procedure for drug Prpt^n (distillation).
- Antimony & its salts used as Medicines.

③ The 19th Century / Innovation Era / Golden Period of chemistry :-

→ 1828 - urea & 1845 - Acetic acid by kolbe, gave rise to organic compounds to be Extracted.

The Isolation of MORPHINE in 1853, in pure form, brought a revolution for compound as pure substance to be used as therapeutic agents.

→ In 1932, Med. chem recieved formal recognizat" in academic pharmacy.

→ Various other discovery in this era include,

Digitalis For stimulat" of heart-

Emetine from Bark of ipecac, for diarrhoea.

1899 Aspirin for fever & Pain.

With Discovery of penicillin in 1928 by Alexander Fleming, the first class as Antibiotic, came into Existence.

In 1940, Nitrogen Mustards as alkylating agent, to treat- cancer was discovered.

In late 70's, Doulopment of recombinant-drugs, development of Biotechnology.

Further development of various classes of Medicinal agents like psycological agents, hormones, steroids, Anaesthetics & analgesics, hypnotics & sedatives, anticonvulsants, etc came into action.

SINCE then, 2000's the Period of 4) Modern chemistry exists :=

Early 2000's - Deciphering human Genome,
Gene therapy,
Molecular Diagnosis,
3D Modeling.

Future chemistry := Personalized Medicine ? (may be).

PHYSICOCHEMICAL PROPERTIES.

The Biological activity of targeted drug Molecule is solely dependent on its physicochemical properties, essentially nature & type of functional Moieties, its spatial arrangements

Modulating a structure of drug implies introduction, elimination or substitut^n of certain groups in drug.

Physicochemical properties play an important role in modyfying the biological activities of many compounds. Thus, Pharmacological or therapeutic effect of a Drug relates to its biodistribution & certain Parameters like.

- Ionization
- solublity
- Partition co-efficient
- Hydrogen Bonding
- Protien Bonding
- Chelation.
- Bioisosterism.
- Stereochemical Aspects.

Medicinal chemistry has its main focus on broad-based variations. Embracing influence of numerous possible Manipulations with regard to chemical structure on biological activity.

FERGUSON'S PRINCIPLE :-

According to Ferguson's, it is unnecessary neither to define the nature of Biophase or receptor, or nor to measure conⁿ of drug at site of action, Based on mode of action, drugs can be divided as,

Structure Specific Drugs

Their Biological Actⁿ does not depend on Variatⁿ of Structure or thermodynamic activity.

- They have same structural characteristics to produce same Biological response.

Structure non specific drugs.

Their Biological Actⁿ depends on thermodynamic activity.

Chemical Structure are diffrent, but produce Similiar Biological response.

E.g. $CHCl_3$, $C_2H_5O-C_2H_5$ } all 3 are General Anaesth

↓

For such drugs, Physicochemical Parameters are to be importantly studied..

1) IONIZATION

Most of the Drugs are either weak acids or base & Can be exist in either ionized or unionized state.

→ Ideally, a drug should be equal Balance of ionized & unionized state to cross the lipid bilayer of cell & enter Blood circulation that is water soluble.

The ionizat° of drug depends on its Pka & PH.

→ The rate of drug absorption is directly Proportional to Cont° of drug in solut° form.

→ Ionization imparts good water Solubility, that is required for binding of Drug & receptors.

→ Unionized form helps drug to cross cell Membrane.
Eg. Barbituric ā is inactive °.° it is strong acid.
while, 5,5 disubstituted Barbituric ā has CNS depressant action, because it is weak ā.

Ionization can be determined by Handersan Haselbach Eqn as,

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

unionized — conjugate ā — Conjugate base

°.° For acids, $PH - PKa = \log \frac{[ionized]}{[unionized]}$ —(1)

% Ionizat^{n} can be calculated, as,

$$\% I = \frac{100}{[1+100^{(PH-Pka)}]} \quad \text{——(2)}$$

When acid & base is 50% ionized, PH = Pka.

Eg. sol^{n} of Aspirin in stomach (PH = 1.0) will get readily absorbed bez it is in unionized form (99 %).

Importance of Ionization :-

- To understand Lipid & water solubility of Drug.
- To understand which membrane drug will pass.
- To understand the distribution of Drugs, in body.

1) Ionizat^n = PH = PKa + log [unionized] / [ionized]

2) Solubility 3) Partition coefficient.

(2) * Solubility

↓

Max amt of solute p'cle that can be dissolved in 100ml of solvent is solubility of Drug at given temp.

Drug + Solvent → sat soln → Max solids of Drug.

↳ Depend on Nature of Solute
Temp., PH, Pressure.
- Bonds (H-Bond, dipole-dipole, Ionic Bond) etc.

Method to ↑ Solubility :=
- Alter structure
- use of Co-Solvent (ethanol)
- Addn of surfactants.
- complexatn.

Rl^n to B.A (Importance of solubility)

↳ B.A of drugs depends on their solubility in given solvent system.

Actual drug at site of Action ↳ Drug must be in soln bf it can be absorbed by membrane to give its activity

↳ Must be in soln to interact with receptor

Where lipid solubility is imp / first req of drug to be transported to Membrane surface, the diffusn across Membrane is dependent on drug's lipid solubility.

3) Partitn coefficient

n-octanol / water system.

⇒ Ratio of cont^n of Drug in water phase & liquid phase / Ratio of cont^n of drug in 2 Phases at Eqllm

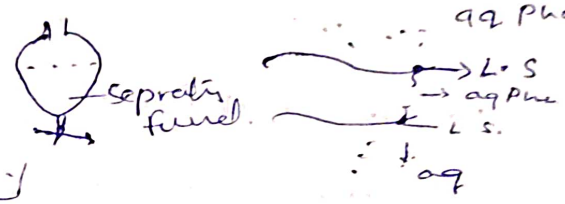
$K = \frac{C_o}{C_w}$ = $\frac{\text{Cont}^n \text{ in organic Phase (Lipophilic)}}{\text{Cont}^n \text{ in aq. Phase (Hydrophilic)}}$

↓

Partn coefficient.

R/n to Biological Activity.

oil + water or Phenol + water



↓

Nature of drug canbe understood

Measured by separatn methods

K > 1 Lipophilic

< 1 Hydrophilic

Eg

↑ the Partn coff

↑ the Lipid solubility

→ Affects drug absorptn & distributn.

→ Generally used in combinatn with PKa to Predict distributn of Drug.

→ Since Membrane is Lipophilic, so rate of transfer can be noted.

(Transport Eg Diffusn)

Partitn coefficient - Canbe defined as Eqllm const (P), of drug cont^n in Lipid phase & water phase.

P = drug(lipid) / drug(water)

Difficult for B.S, so done in vitro by Sat wat - oct or Sat oct - wat systems

oct → Adsorpt of lipid fluids

↓

Lesser H$_2$O water aq phase

(Phosphate Buffer pH 7.4) → aq phase

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3)

PARTITION CO-EFFICIENT

Partition co-efficient is one of physicochemical parameter, which influence Drug transport & Distribution, the way in which Drug reaches site of action from site of application.

Partition co-efficient is defined as ratio of conc^n of drug in organic phase & aqeous phase.

OR

Equillibrium Constant of Drug Concentrat^n for unionized Molecule in two phases.

$$P_{[unionized\ molecule]} = \frac{Drug_{(lipid)}}{Drug_{(water)}} \quad or \quad K = \frac{C_o}{C_{aq}}$$

IF $K > 1$, Drug is Lipophilic, whereas
$K < 1$, Drug is hydrophilic.

The contribut^n of each functional group & structure arrangement help to determine Nature of Drug.

* Factors affecting Part^n coefficient :=

1) PH 2) COsolvents 3) Surfectants 4) complexation

* Partition co-efficient is difficult to Measure in living systems So, they are usually determined by invitro n-octanol/sat. water System.

→ n Octanol has a property similar to phospholipid layer & thus used as lipid phase.

IMPORTANCE :-

- It is generally used in combination ō PKa to Predict distribut" of Drug in B. System.

- The factors such as absorpt", Excret" & Penetrat" through CNS, May be related to P. coffiog value of drug.

- As the Part" co-efficint increase, lipophilicity of Drug increases.

4) HYDROGEN BONDING

The H-Bond is a Special dipole-dipole interact" b/w hydrogen atom in Polar Bond such as N—H, O—H, or F—H & Electronegative atom O, N, F rarely S, & Cl.

Dipole results from unequal sharing of electrons b/w atoms in a covalent Bond.
Such bonds are weak bonds & denoted by dotted lines

O—H ..... H , HN - H .... O,

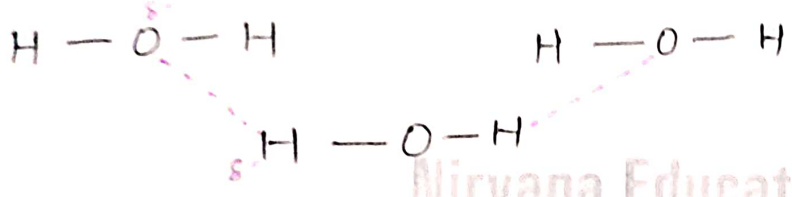
The compounds that are capable of forming h-Bond is only soluble in water.

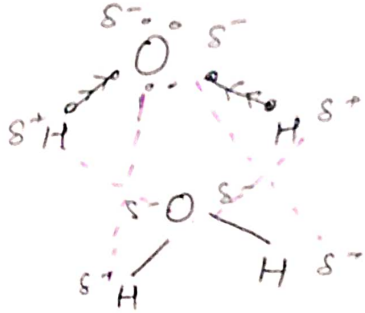
- H-Bonding can be classified as
  (i) Inter molecular
  (ii) Intra Molecular.

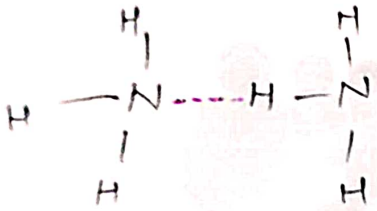
(i) Intermolecular

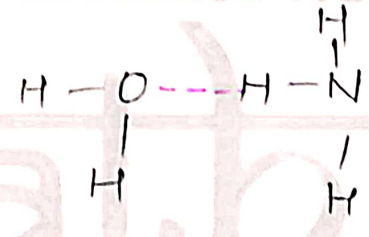
It occurs b/w two or more than two molecules of same or different compound.

→ This causes increase in Boiling point of compound, ↑ increase Mwt of compound, hence more Energy is reqd to dissociate the molecule for vapourization.









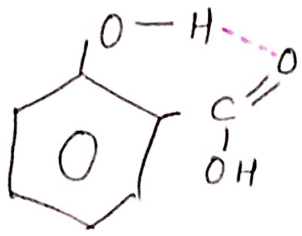
2.5 - 2.7 A°

> 3 A° very less or no interaction

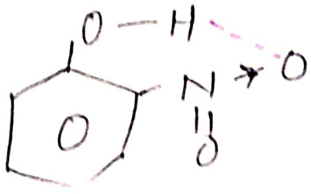
(ii) Intramolecular

- H-Bonding occurs, within two atoms of same molecule,
- this may lead to develop 5- or 6 membered ring like structure
- Due to this Boiling point decreases.

Ex



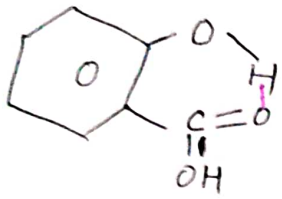
Salicylic Acid

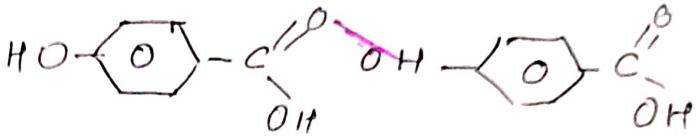


O-nitrophenol.

Hydrogen Bonding & Biological Action.

1) S.a (o-hydroxy Benzoic a) 2) p/m hydroxy Benzoic acid





- has Anti Bacterial Activity
- Intra Molecule Bonding
- Less Mpt

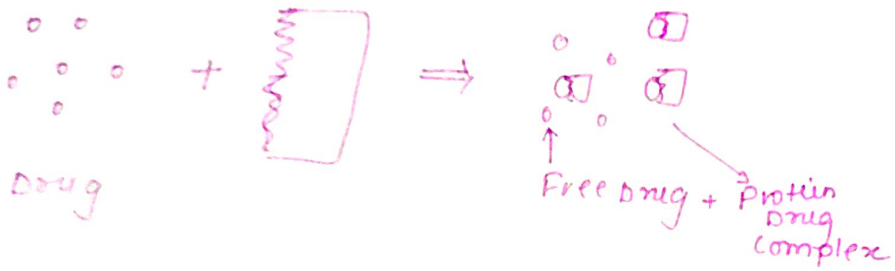
Inter Molecule Bonding are inactive & no Anti Bacterial effect.
↓
↑ Mpt.
(Results in DIMER format that doesn't pass Membrane easily.)

Factors affecting
(i) physical state
(ii) Temp & PH
(iii) Solvent.

Effects of H-Bonding
→ To determine & Prove basis of α helical structure of Protien in DNA, that are held by H-Bond.
→ Base Pairing of nucleic acid.
→ Physical state of water, DNA, Prot^n & Drug Molecules are Maintained by H Bonding.

5) PROTIEN BONDING.

- It is a Process in which Drug Molecule bind with Protien, it forms complex & this is known as Protien Binding.
- Protien usually fnt in Blood system.



After Absorption of Drug, when drug reaches into Systemic Circulatn, it binds with plasma protien, which is fnt in Blood & form Plasma Protien Drug Complex.

Plasma Protiens include :- Albumin (90% attaches to albumin)
Globulin
Glycoprotn
Lipoprotn.

The form Drug-Protn complex can be
1) Reversible
2) Irreversible.

(i) Reversible :- Here drug binds ~ weak forces or bonds like Vanderwals or H-Bond, & thus easily detach & it become free at site of action to Provide its therapeutic effect.

ii) Irreversible :- Here Drug binds with Protien with strong bonds like covalent or ionic bond, so they cannot easily detach & not become free to give its effect.

Importance to B. system

- It influence Bioavailability & Distribution of active drug.
- Both complex & free drug are important for complete Pharmacological action.

COMPLEXATION / CHELATION :-

Since Complex Drugs Cannot cross natural Membrane Barriers, they reduce Rate of absorption of Drug.

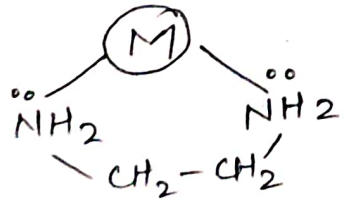
- The compounds that are obtained by donating electron to Metal ion, with formation of ring structure are called "Chelates"
- The Compounds that are capable of forming ring Structure with Metal ions are 'Ligands'.

→ Biological Molecules & Medicinal Agents May develop chelate Structure by forming ring with Metal through Co-ordinate Bonds (Bonds in which e⁻ pair are from same atom)

→ Ligand can be Unidentate (single group capable of Binding) Ex - NH_3

Multidentate (More than one group capable of Binding) Eg. EDTA.

* "A substance containing two or more ligands (lone pair of electron (donor) group), may combine with Metal ion to form complex, known as 'chelates' & the phenomenon is called 'chelation'.



EDTA.

Importance :-

EDTA is a powerful chelating agent, it can displace toxic heavy Metals, such as lead & Mercury from cellular layer.

But EDTA is not highly selective in its action; bcz it tightly binds $\overset{+2}{C}$ calcium & creat loss of calcium.

∴ to avoid Excess loss of calcium from the body, during EDTA therapy, it is necessary to administer this antidote as disodium calcium salts.

→ Iron deficiency Anameia can be treated with EDTA complex $\overset{+3}{iron}$.

& on Other Band Deferoxamine is highly selective antidote, that chelates iron in iron Poisoning.

→ Dimercaprol (BAL) – lead Poisoning works with same Phenomenon.

→ Numerous Antimicrobial & Neoplastic agents exert their action by complex formation with DNA base Pairs.

7) BIOISOSTERISM :-

Isosterism is of vital importance in Medicinal chemistry bez Biological characteristic of isosters appear to be similiar; more frequently than physical & chemical characteristics.

BIOISOSTERS, are group of chemical substituents which have similiar physical or chemical property with similiar Biological activity.

Isosters simply means compounds ī same e⁻ configuration.

Example :- CO_2 & N_2O , CO & N_2, etc.

Friedman Proposed a defination of Bioisosterism as "the phenomenon by which compound usually fit with similiar functional group & posses same type of Biological activity.

Replacement - May increase biological activity,
Sometimes decrease " or
remain Neutral / No effect.

Types of Bioisosterism

i) Classical
ii) Non classical..

1) Classical Bioisosters

They have similiar shape & configwral" of atom (same valence e⁻). when one bioisoster is replaced or substituted by other, it give similiar response.

Further it can be classified as;

i) Monovalent / univalent :- (one valency left to be attached) $-H, F$ $-CH_3$; $-NH_2$, $-BR$, I .

ii) Bivalent / Divalent :-

$-CH_2-$, $-NH-$ / $-COCH_2-$, $-CONH-$

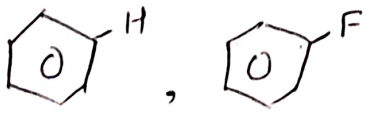
iii) Trivalent :-

$>CH-$, $>N-$

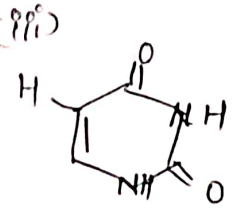
(iv) Tetravalent :-

$=N^+=$, $=C=$

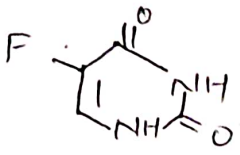
v) Ring Equivalent :-

i) 

ii) 

(iii) 

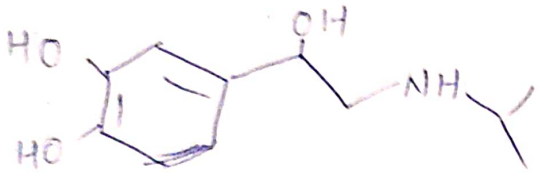
uracil



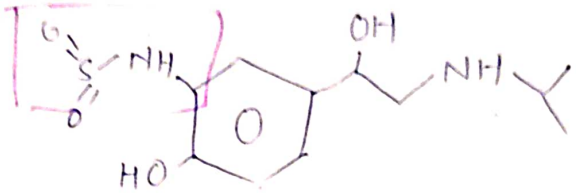
5-Fluorouracil

ii) Non classical Bioisosters :-

They donot have same steric or electron configuration, but have same properties, due to this they give similar biological properties (activity)



Isoprotenol



Sotenol

Importance :-

↳ It is used to develop potent compound, reduce toxici & change Bioavailability.

→ During drug design, exchanging one bioister for another is used to enhance desired effect without changing much of structure.

- Helps to produce safe & More Effective Drug.

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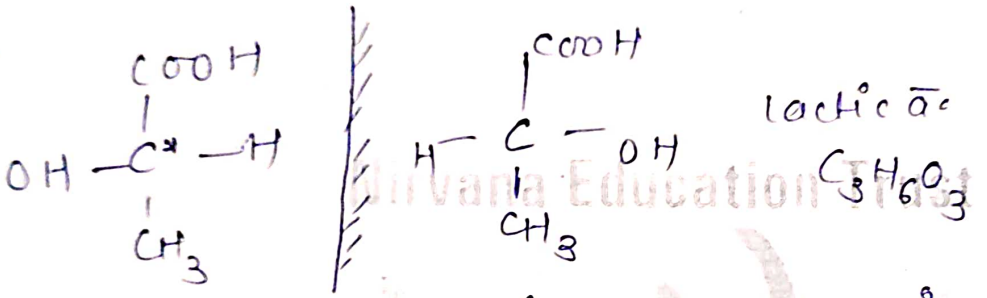
8)

Stereochemistry

optical iso

- Those Molecule s have same Molecular, Structural formula & same Properties, but differ in behaviour towards light
- Such Molecules, which rotate plane pol light are optically Active
- Such Molecule contain chiral carbon
  Four differ group/atoms



lactic ac
$C_3H_6O_3$

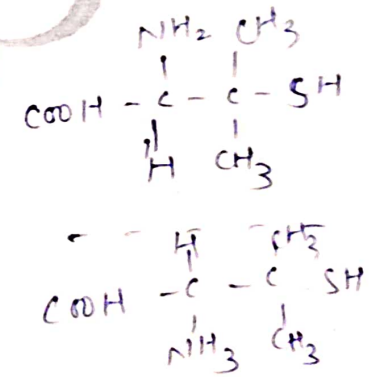
Enantiomers → super imposable Mirror image
Diastereomers - Non " "

Rotating light-com

- dextro clockwise ↑
- ↓ Mixture not opt Act.
- levo Anticlo ↑

- adrenaline is more active than (+)

D - Penicil



D - used for Antimicro
L - toxic.
due to Drug receptor specificity.

L Penicillin

METABOLISM ≅ BIOTRANSFORMATION.

- Humans are exposed to variety of drugs & nonessential exogenous (foreign) compounds, collectively called xenobiotics.
- Metabolism plays a central role in elimination of drugs & other compound from body.
- Most organic compound entering the Body are Lipophilic, To be absorbed through membrane, Once in blood stream, Molecules can diffuse passively other membranes & distributed to each site of Action, to exert P'cological Effect.
- Being Lipophilic, they get reabsorbed from Renal tubule & again circulate into Body. Thus it is necessary to transform such molecule to hydrophilic nature or polar form.
- Once, they are Sufficiently polar, it can be easily Excreted through Body.

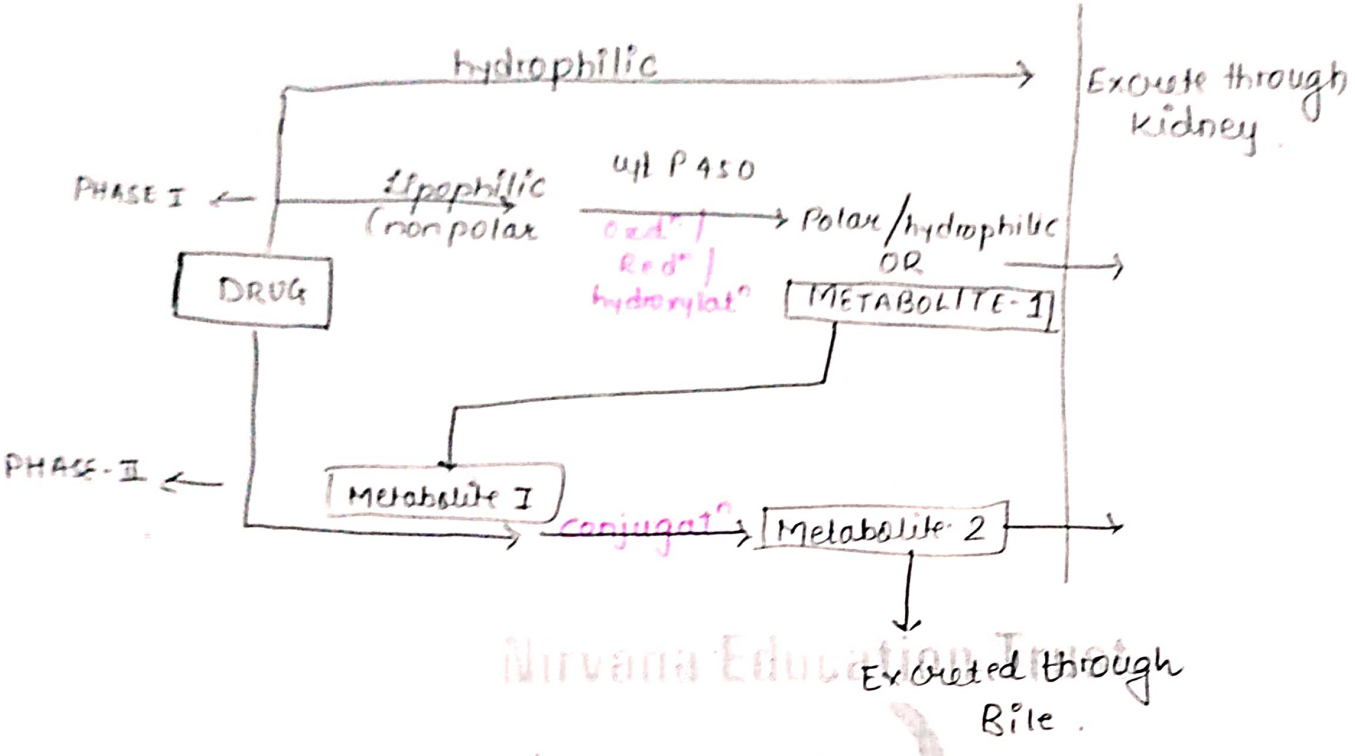
Drug Metabolism Rxn can be divided into two phases :=

PHASE I – Functionalization rxns (oxidation, Reduction & hydrolytic Biotransformation)

PHASE II – CONJUGATION rxns

→ Metabolism renders the drug to be - inactive or
- toxic or
- active (prodrug).

Brief Overview of Metabolic pathways.



PHASE I.

The purpose of these reactions is to introduce functional polar group Eg (OH, COOH, NH_2, SH) into xenobiotic molecule to produce a more water soluble compound.

This can be achieved by direct introduction of functional group (aromatic or aliphatic hydroxylation) or Modifying existing functional groups (Red^n of ketones & aldehydes to alcohols; oxid^n of alcohols to acids)

Although Phase I rxn may not sufficiently Produce hydrophilic or inactive Metabolite, they generally undergo phase-II rxn, to conjugate further.

Phase I rxn

- Also known as Non Synthetic or functionalizat° reaction.
- Phase I rxns include :- (i) oxidative Biotransformat°
  (ii) Reductive "
  (iii) Hydroxylation / Hydrolysis rxn's.

by Far, oxidative biotransformat° is most common & imp in drug Metabolism.

General Stoichiometry include that describe oxid° of xenobiotic (R-H) to convert it into oxidated metabolite as (R-OH).

Can be given as,

$$R\text{-}H + NADPH + O_2 + H^+ \xrightarrow{\text{(in the of P450)}} ROH + NADP^+ + H_2O$$

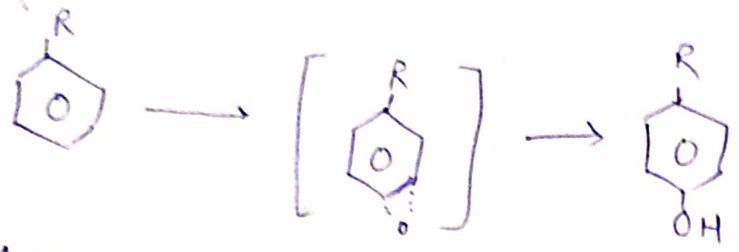
The enzyme system carrying out this Metabolism as reffered as, Mixed-function oxidase or Monooxygenase.

(i) Oxidative Rxn's (add° of oxygen).

↳ (a) Oxid° of Aromatic Moieties :-

Aromatic oxid° refers to oxid° of Aromatic compounds to their corresponding phenolic Metabolites (arenols).

- All aromatic oxid°, Proceds by initially forming 'epoxide' intermediate, that changes instantly to 'arenol' form.



Arene Epoxide Arenol.

Example include,

Acetanilide PCM.

(More Soluble).

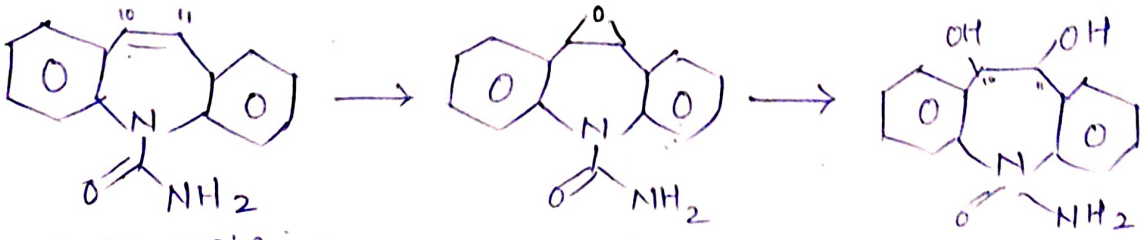
Other drugs that follows this Path include, Propranolol, Phenytoin, Phenobarbitol, Atorvastatin, Warfarin.

In compounds ☡ with two aromatic rings, Oxidⁿ occurs in more electron rich ring.

(ii) Oxidatⁿ of olefins :- (double bond C=C)

The Oxidⁿ of olefinic carbon-carbon double bond leads to corresponding epoxide. Epoxides formed from olefins are more stable & Aromatic epoxides.

Example of olefinic Metabolism is drug Carbamezepines.



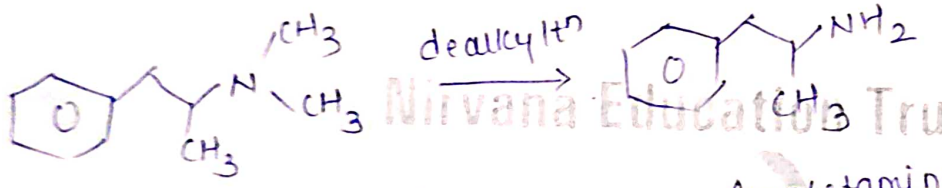
carbamezipine 10,11 Epoxide Dihydroxy carbamezipine.

(iii) oxidⁿ of Hetero atom

- Oxidⁿ of Carboratom attached to Hetero atom
- Oxidⁿ of Hetero atom (S, N, O)

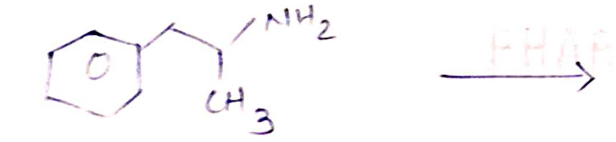
- Dealkylatⁿ
- oxidative deaminatⁿ

(i). dealkylation - Removal of alkyl group.

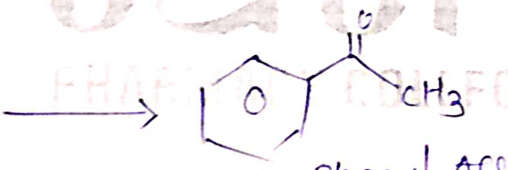


Methamphetamine — Amphetamine.

(ii) oxidative deamination = Removal of amino group

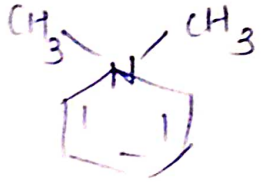


Amphetamine

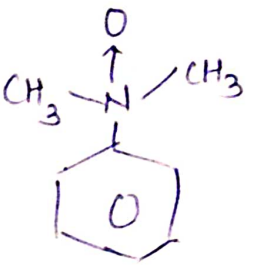


Phenyl Acetone.

(iii) Oxidatⁿ of Hetero atom :-



Dimethyl Aniline



N-Oxide Metabolite.

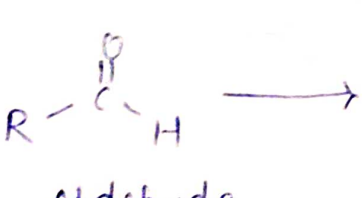
2) REDUCTION (Add^n of hydrogen / Removal of oxygen).

Reduction plays an imp role in metabolism of many compounds containing carbonyl, nitro & azo groups.

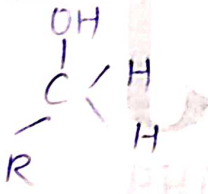
Red^n of carbonyl gives alcohol derivates,
nitro & azo generate amino derivatives.

The hydroxyl & amino moieties of Metabolites are more susceptible to conjugation than functional group of parent-compounds. Hence, Reductive Process, as such, faciliate conjugation.

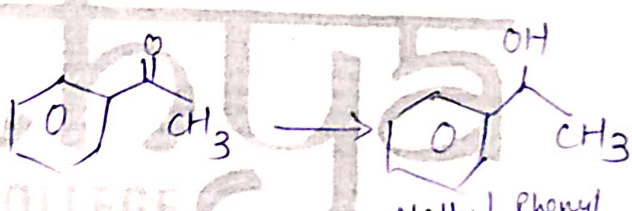
General Reactions include,



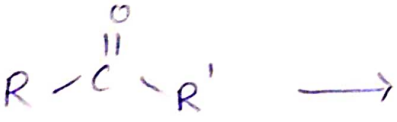
Aldehyde



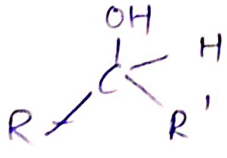
Primary of Alcohols.



Acetophenone → Methyl Phenyl carbinol.



Ketone



Secondary Alcohols,

Alcohol metabolite arising from reduct^n of carbonyl compounds; generally undergo further conjugation.

(3) Hydrolysis :- (Breakdown in the presence of water)

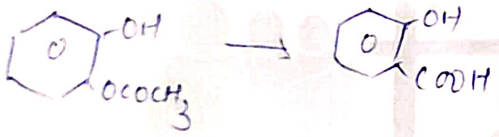
The metabolism of ester & amide linkage is catalyzed by hydrolytic enzymes

The Metabolite Products can be (carboxylic acids, alcohols, Phenol & amines).

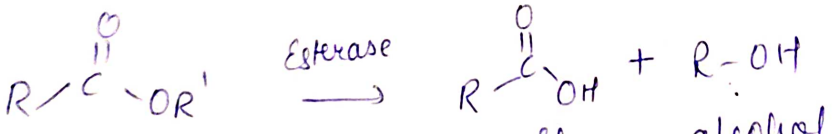
- This Products are More Susceptible to conjugation & Excretion than Parent drug.

- A classical Example of hydrolysis Pathway is

Aspirin ⟶ Salicylic acid



→ General Ester's conversion include



MISC Rxn

(i) cyclizatn - ring struc. from straight chain Eg. Proguanil

(ii) Decyclizatn - cyclic ⟶ straight. Eg. Phenytoin.

PHASE - II METABOLISM :-

The purpose of phase II rxn is to attach small, Polar & ionized endogenous compound such as glucoronic acid, Sulfate, glycine & other amino acid to functional handles of Phase I Metabolite or Parent compound that already have suitable functional group to form as s. Products.

- Conjugated Metabolites are readily excreted in urine & generally devoid of Pharmacological activity & toxicity in humans.

Phase I rxn donot always Produce hydrophilic inactive Metabolite Various phase II / conjugatn rxns, however can convert these Metabolites to more polar & water soluble products.

Types of phase II rxn's :-

(i) Glucoronic acid conjugation.
(ii) Sulfate conjugation
(iii) Conjugatn with glycine, glutamine or other amino acids.
(iv) GSH or Mercapturic acid conjugation.
(v) Acetylation.
(vi) Methylation.

(i) Glucuronic Acid Conjugation

It is most common Pathway. bcz of easily available of D-glucuronic acid (derived from D-glucose) & when attached to xenobiotic, greatly increase water solubility of Product.

It includes two steps:-

(i) synthesis of activated co-enzyme UDPGA (uridine 5' diphospho α D glucomic a).

(ii) Subsequent transfer of glucoronyl group from UDPGA to appropriate substrate, by the of UDP glucoronyl transferase enzyme.

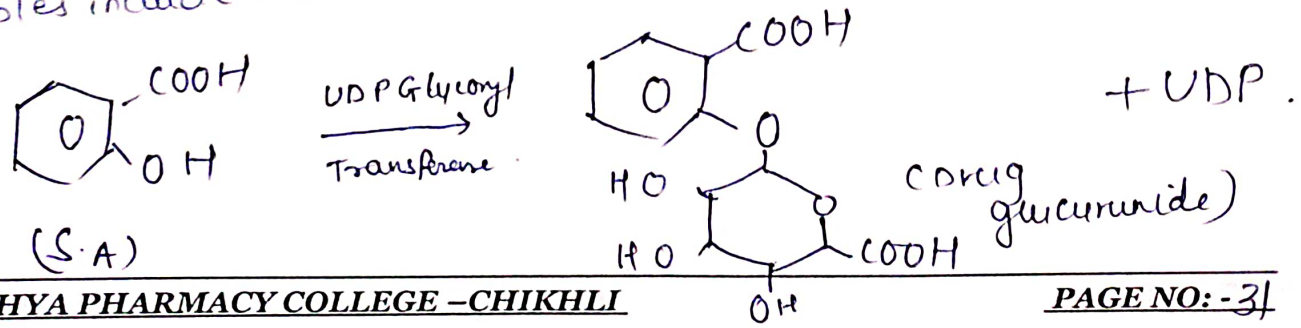
All glucoronide conjugates have β-configuration or β-linkage at C-1, so called as β-glucuronides.

This Metabolite products are excreted through Bile.

Glucuronidation increases MWt of drug & thus favours excretion through bile.

This drug can further be hydrolyzed in gut & reabsorbed to undergo recyling of Drug.

→ Examples include - oral contraceptives, chloramphenicol, Metronidazole.



2) Sulfate Conjugation

Conjugation of xenobiotics with sulfate primarly occurs with phenols & occasionaly with alcohols & aromatic amines & N-hydroxy compounds.

- Here amt of sulfate is limited.

- Process involves activat^n of inorganic sulfate to coenzyme 3'phosphoadinosine - 5' phospho sulfate (PAPS) sulfotransferase enzyme is used as catalysis.

Sulfate conjugation generally leads to w.s & inactive metabolite
Ex. = α methyl dopa, Terbutaline.

(iii) Acetylation :-

Acetylation constitutes an imp metabolic route for drug containing Primary Amino groups. & hydrazine group

- Reqd factor is Acetyl CO.A, & enzyme responsible is N-Acetyl transferase.

$$R-NH_2 \xrightarrow[CO.A]{Acetyl} R-NHCOCH_3$$

- This route is imp in sulfonamides, as this are less soluble than Parent Compound & May cause renal toxicity due to ppt^n in kidney.

(iv) Amino Acid Conjugation

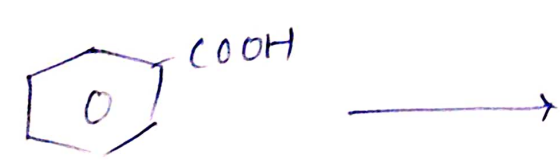
The Amino acids like Glycine & Glulomine are used primarily, to conjugate carboxylic acids, specifically Aromatic & aryl alkyl acids.

The quantity of Amino ā conjugation is very minute, as less availablity of amino ā, compared to D-glucuronic ā.

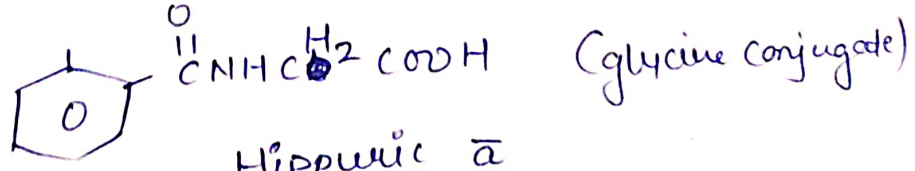
Here, Carboxylic acid substrate is activated with "ATP" & "CoA", to form Acyl-CoA Complex.

This complex later acylates glycines or glutamines, under influence of specific glycine or glutamine N-Acyltransferase enzyme

Amino Acid Conjugates, being Polar & water Soluble, are Excreted mainly renally & sometimes in Bile.

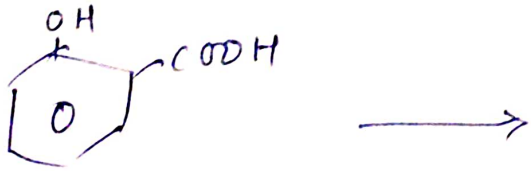


Benzoic ā

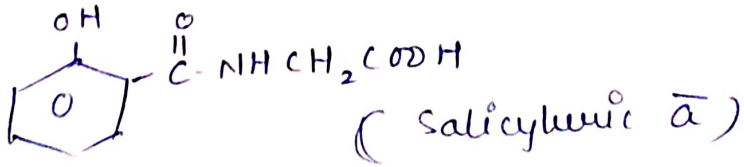


(Glycine conjugate)

Hippuric ā



S. ā



(Salicyluric ā)

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FACTORS AFFECTING DRUG METABOLISM

Drugs & xenobiotics are metabolized by either phase I or phase II pathways, to give several metabolites.

The relative amt of any Metabolite is determined by conc^n & activity of enzyme, responsible for Biotransformat^n.

Many factor may affect this Metabolism, such as Age, species, Strain, Genetic & Heredity factors, enzyme induct^n & inhibition, etc.

→ BIOLOGICAL FACTORS

(i) AGE DIFFRENCE :-

In Most fetal & newborn animals, undeveloped or deficient oxidative & conjugative Enzyme are responsible for reduced Metabolic capacity.

In humans, oxidative & conjugat^n capabilities are low in newborns than in adults.

Example, the oxidative Metabolism of Tolbutamide appears to be markedly low in newborns.

→ Neonates & newborns (upto 2 months – 1yr)
  ↳ Metabolism is slow due to less development of Microsomal enzyme.

→ childrens (1-12yr) → Metabolism is rapid compared to adults.

→ Elderly → slow Metabolism.

(ii) DIET :=

The enzyme content & activity is affected by dietery components.

Eg low Prot^n Diet → slow Metabolism
High " " → Rapid ".

BCZ Prot^n stimulate enzyme Synthesis.

(iii) SEX DIFFRENCE :-

The Rate of Metabolism, Varies according to gender

Eg Benzodiazepines { Metabolize slow in women, / Rapid in men.

Some factors may affect due to pregnancy, hormonal imbalance.

II) CHEMICAL FACTORS :-

a) Enzyme induction
b) enzyme inhibition.

A) ENZYME INDUCTION :-

The Process by which, activity of drug Metabolizing enzymes is increased is called Enzyme Induction. & agents are called "inducers".

Enzyme induction increases rate of drug Metabolism & decreases duration of Action.

→ It occurs due to increased stability of Cyt P450 enzymes.

Eg ORAL CONTRACEPTIVE $\xrightarrow{CyP_3A4}$ Inactive, → Elimination.

induction

RIFAMPIN → enzyme inducer

B) ENZYME INHIBITION :-

Several drugs & other xenobiotics, have ability to inhibit Drug metabolism, such agent are called "Inhibitors"

With decreased Metabolism, a drug often accumulates, leading to Prolonged drug action & several adverse Effects.

Inhibition
- Direct - Interaction at Enzyme site, to change activity
  - Competitive
  - Non competetive.
- Indirect
  - ↓
  - Due to fall in rate of enzyme synthesis (repression)
  - OR
  - Due to Nutritional deficiency
  - OR
  - Hormonal Imbalance.

Eg TERFENADINE $\xrightarrow{CYP3A4}$ Active Antihistamine.

⊖ Inhibits

Erythromycin, Ketoconazole

Eg → Metabolism of phenytoin is inhibited by drugs such as Chloramphenicol, Disulfiram.

(III) PHYSICOCHEMICAL PROPERTIES :-

↳ Pka, solublity, Polarity, size, shape, etc. also effect drug Metabolism.

IV) STEREOCHEMICAL ASPECTS OF DRUG METABOLISM :-

Many Drugs like Warfarin, Propranolol, hexobarbital, ketamine, ibuprofen, etc are often administered as racemic mixture in humans,

The two enantiomers present in mixture may differ in their p'cological Effect.

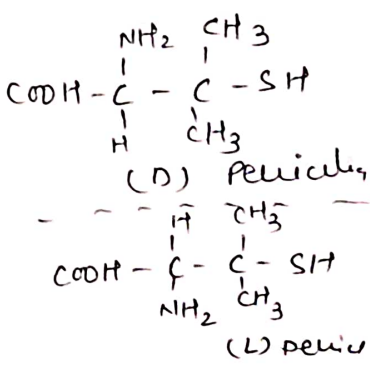
usually, one enantiomer is more active than the other.

Eg (S)(-) enantiomer of warfarin is 5 times more Potent as an oral anticoagulant than (R)(+) enantiomer.

In other instance, two enantiomer have totally diffrent activities

for Eg - (+) Propoxyphene is analgesic, whereas (-) Propoxyphene is an antitussive.

Eg D Penicillinase → arthritis, L - toxic.



Eg (-) quinine → treat Malaria
(+) quinine → No effect on Malaria.

This is due to, Metabolizing enzyme has preference for one enantiomer of the drug, than other.

Eg D(+) glucose easily metabolised than L(-) glucose.