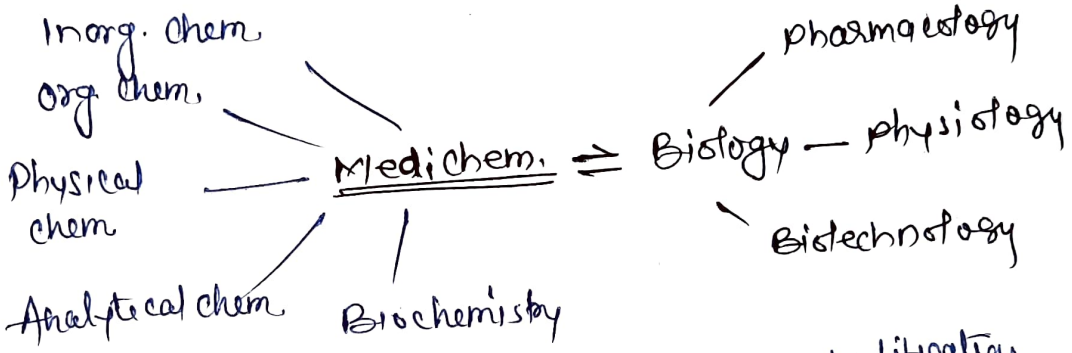
MEDICHEM

INTRODUCTION

Medicinal Chemistry :→ is the sciences which interlinked in the branches of chemistry to Biology. It is a chemistry-based discipline, which involves ~~the~~ aspect of Biological, medical & pharmaceutical Sciences.



It Concern with → Invention, Discovery, design, identification, preparation of biological active compound. In respect to Chemistry, study their ADME, interpretation of their mode of action at the molecular level & Construction of structural-activity relation ship

Basic Concern →

According to recommendation of International Union of pure and Applied chemistry (IUPAC), it concern with the discovery, the developement, the identification, and the interpretation of the mode of action of Biologically active compounds at the mol. level. It involves

- ↳ Synthesis
- ↳ SAR
- ↳ Receptor Interaction
- ↳ A, D, ME

Importance :->

- Isolation, Synthesis, Characterization of Biological active chemical compounds
- understating the MOA, activity, Potency, of ~~of~~ Chemical analouge
- differentiate the stereo-isomeric form & their activity
  e.g. L-DOPA is active used in parkinson disease
- Analyse the physio-chemical properties & ~~relate~~ relate their activity

History & Development

A large no. of plants were used to treatment of many disease & recorded by Hippocrates, Galenous & Dioscorides"
17th & 18th Centuries — exploration of plants
Greek ~~Physician~~ Physician, Hippocartes (450 BC) → Foundation of Modern medicine & According to him, a disease is a pathological process & its treatment with a drug is not a magic
Hippocartes - introduce the medicine System.
Medical Preparation is documented in — Rigveda (India)
Materia Medica (China)
(2500-3000 BC)
Ayurveda (~~1200-1000 BC~~), more than 5000 Ago in Sanskrit discribed by physician " Charak, Sushruta, ~~Vag~~ Vaagbhatt & other.
19th Century — " Modern Medicinal Chemistry "— introduction of Side chain theory of drug action in 1885 by " Ehrlich"

SUMMARY OF DRUG DEVELOPEMENT

3500 BC → Sumarians reported use of opium
3000 ~~BC~~ → Chinese reported use of Ephedra
1818 → Meissner proposed the term Alkaloid
1820 → Isolation of morphine, quinine & atropine
1842 → General anesthesia were introduced, antiseptic like Iodine & phenol were used in surgery
1853 → Henrey proposed relationship btw functional group, modifiers & their reactivities
1884 → Local anesthetic action of cocain was reported
1890 → Hoffman named acetyl Salicylic acid as aspirin
1894 → Ehrlich reported Lock-key theory
1899-1901 - Meyer & Overton related distribution coefficient with Biological activity
1910 - Barger & ~~Mayer~~ Dale - examine the tissue response of Muscarine & nicotine
~~1920~~ - 1921 → Barbiturates were introduced as Sedative
1935 → Domagk = Sulfonamide dye (~~proto~~prontosil red) as antimicrobial
1944-1949 → Isolation of antibiotics - Streptomycin, Chloramphenicol, Tetracycline

PHYSIOCHEMICAL PROPERTIES IN RELATION TO BIOLOGICAL ACTION

1 IONIZATION / ACID-BASE / pK_a & pH

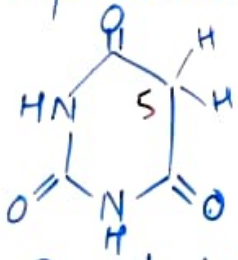
Union are better absorbed than ion form of drug
Weak acids are absorbed in gastric pH & weak base are absorbed in intestine

For WA $pH - pK = \log \frac{Ion}{Union}$ — $pH \propto$ Ionization

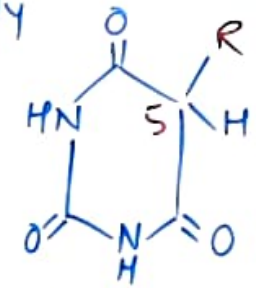
For WB $pH - pK = \log \frac{Union}{Ion}$ — $pH \propto \frac{1}{Ionizatn}$

Also imp for formulation - to adjust pH
e.g Indomethacin Suspension is buffered at pH 4-5, (unstable in alkaline media)

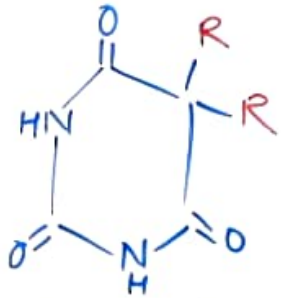
Imp for activity



Barbituric ā



5-mono-substituted



5,5-di Sub.

Strong Acid → No Activity

Weak Acid → CNS depressant

2. SOLUBILITY

* In oral formulation, drug must be disolved in media for absorption
* lipid solubility of drug → ↑ absorptn → ↑ Activity

Polar nonionic comp (-NH, -SH, -OH, >=O) make H-bond with water → Hydrated → Dissolution
Non polar comp. interact with lipids by hydrophobic bond and get dispersed
Solubility can changed by simple derivetization

Phenobarbitone (water insoluble) → Phenobarbitone Sod. (Water Soluble)

Chloramphenicol (Slightly Solu) → Chloramphenicol palmitate (water insoluble)

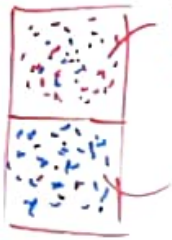
Mask the Bitter taste

3 PARTITION COFFICIENT (P)

A equilibrium constant of drug conc in lipid phase & water phase

$$P = \frac{\text{Drug Conc. in lipid phase}}{\text{Drug Conc. in water phase}}$$

$P_{o/w} \propto$ diffusion rate (at cell mem)



Water Saturated Octanol → Polar property of lipid layer

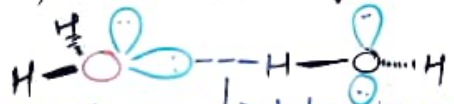
Octanol Saturated water → physiological aqueous components

e.g., → Mode of actn of GA
Barbiturates → Hypnotic
Disinfaction at microbial cell mem

PHYSIOCHEMICAL PROPERTIES IN RELATION TO BIOLOGICAL ACTION

4. Hydrogen Bonding :-

Result from electrostatic interaction b/w non bonding e^- pair of hetero atom like N, O, & S and e^- deficient H-atom of -OH, -NH & -SH



↳ Weak bond

H-bonds are directional in nature

Imp. for → Drug - Target protein Interaction
(Site specific interaction with cellular Receptors, Enzymes & Protein)

→ Stabilizing the structure by intramolecular bond formation. e.g., -α-halical structure of protein and base-pair of DNA

5. Protein Binding :→

Drug - Plasma protein Binding → "Storage"
↳ ↑ Duration, ↓ Elimination, ↓ Vd

Drug - Tissue Protein Binding → "Toxicity"
↳ ↑ Vd, ↑ Tissue accumulation

Drug - Cellular Transporter/Target proteins
↳ helps in drug Absorption (by Carrier protein)
↳ Helps in Uniform drug Distribution
↳ Solubility - water insoluble + lipoprotein
→ Circulate & Distributed

6. Chelation - Complexes

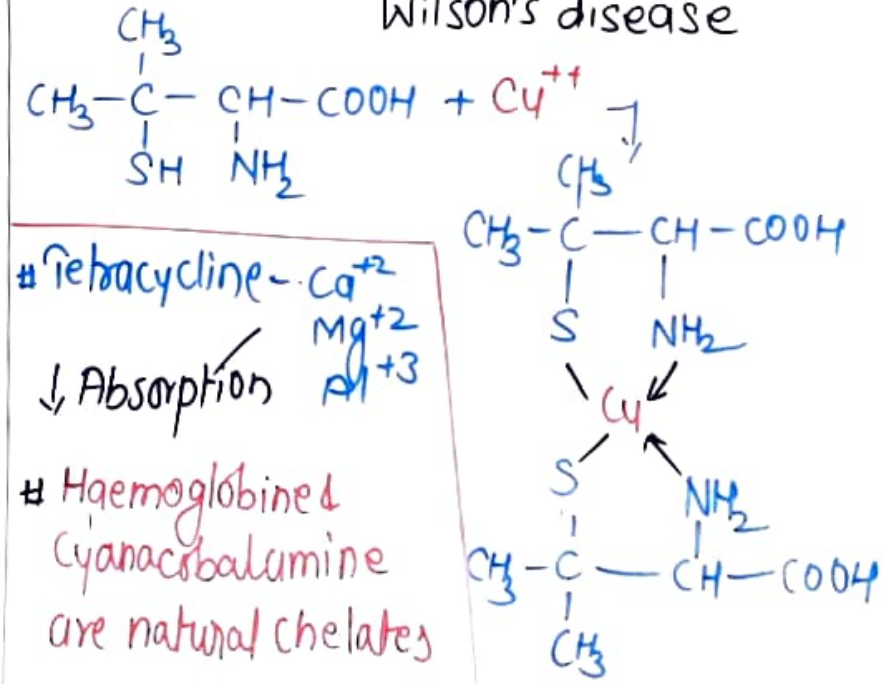
Metal ion (Incomplete Velency Cell) —— (Ligand) e^- donating molecule or ion (Amines, Imines, Ketone, Sulphide) N, O, & S

Complexing Agent →

EDTA → Antidote for Pb^{++}, Vd^{++} → ↑ water solubility → ↑ Excretion

Dimercaprol (BAL) — Antidotes for As^{++}, Hg^{++}, Au^{++}

Penicillamine → Chelates the Serum Cu^{++} in Wilson's disease



Tetracycline - Ca^{+2}, Mg^{+2}, Al^{+3} ↓ Absorption

Haemoglobine & Cyanacobalamine are natural chelates

BIOISOSTERISM

~~Bioisoter~~

Bioisosteres– Certain drugs, chemicals, and functional group having same physical & chemical properties & produces similar biological effect or properties are known as Bioisosters & the relation b/w Bioisosteres are known as Bioisosterism.

* This was introduce by I. Langmuir in 1919, who defined isosteres as compound or group of atom having the same number & arrangement of e^-

According ly those compound having same total charge as well as same no. of e^- (Isoelectric) would process similar physical properties & Such isosteres when produces same Biological effect are knows as "Bioisosteres"

Isosteres

ex : N_2 & CO = both have same 14 e^-
= both are uncharged
= ~~Same~~ Similar physical property

eg. → CO_2 & N_2O, N_3^- & NCO^-, $-CH=CH-$ & $-S-$

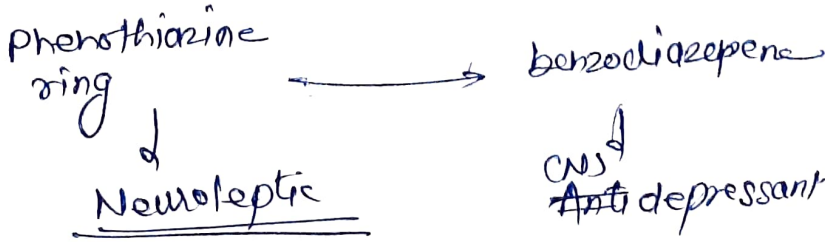
$-COO^-$ & $-SO_2NHR$, $-Cl$ & $-CF_3$

Langmuir had introduced this concept to explain similarities in physical properties for nonisomeric molecules

ex  benzene & Thiophene  - having Similar properties

$-C=C-$ & $-S-$ = Ring equivelent

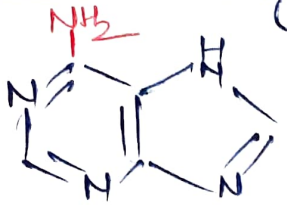
ex:



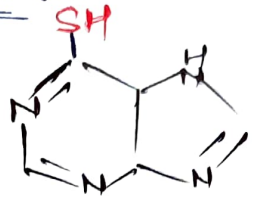
Pharmaceutical Application

① Structural analogue Design

(I)

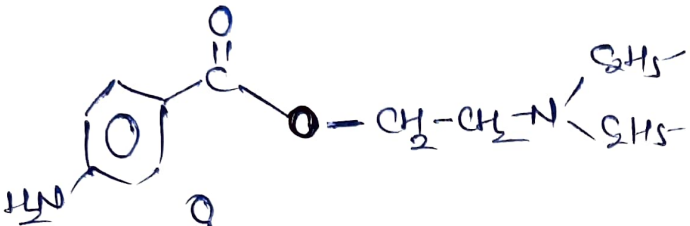


Adenine
(DNA Base pair)

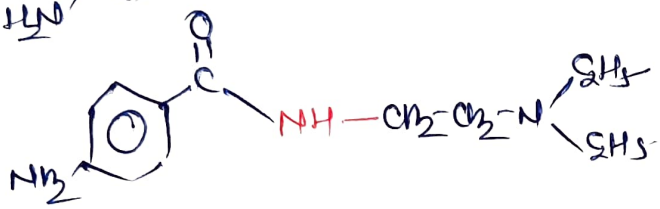


Mercaptopurine
anticancer (Antimetabolite)

(II)

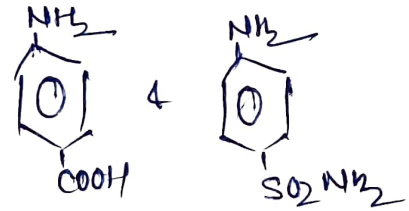


Procain (local Anesthetic)

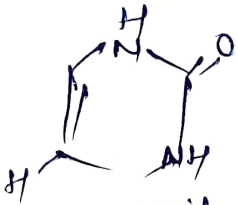


Procainamide (Local Anesthetic)
(Longer duration)

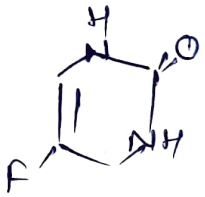
(III)



PABA



Uracil



5-Fluro uracil

STEREOISOMERISM ASPECTS DRUG ACTION

The Significance of Stereochemistry on—

- # Drug Disposition
- # Drug - Protein / Receptor Interaction
- # Biological Activity.
- # P'kinetic & P'Dynamic profile

Stereoisomers may have similar qualitative activity but differ in quantitative activity due to differ in 3D arrangement of atom & thus differ in stereo structural specific Drug interaction.

‼ Importance is observed from Thalidomide Tragedy in early 1960, & later on observed teratogic action by its "S-enantiomers"

L. Pasteur (1860), observed that mould & yeast can differentiate the (+) & (−) tartarate by utilization on isomer more than other

In 1888, J. Lewkowitch demonstrate that Penicillium glaucum selectively oxidised (+) mandelic acid, (+) lactic & (+) glyceric

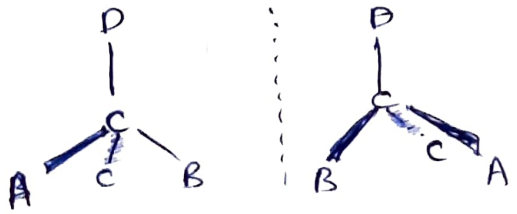
OPTICAL ISOMERISM

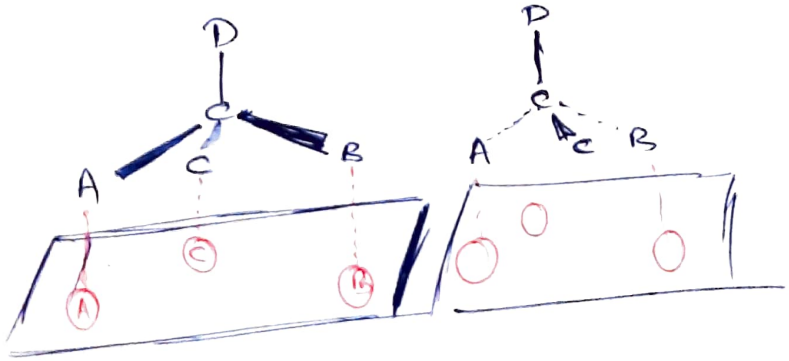
Found mostly in chiral-carbon containing compounds

OA = due to ~~dys~~ dissymmetry of molecules

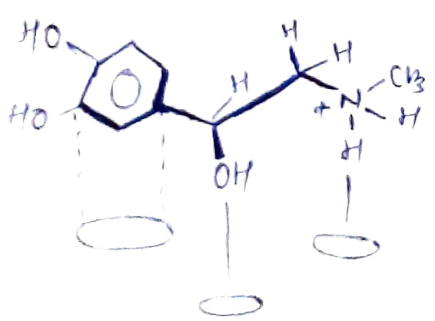
Enantiomers (mirror image) - d/l, R/S, D/L

L.H. Easson & E. Steadmann (1933) - hypothesized that stereospecificity of optical isomer in biological action is due to one isomers being to ~~achieve~~ achieve a three point attachment with its receptor molecule while other isomer is achieve two point attachment with the same receptor.

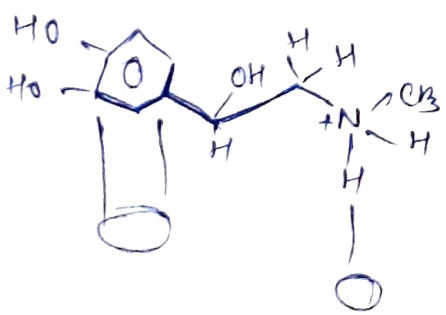




ex. Adrenaline



(−) Adrenaline



(+) Adrenaline

ex. (1) (−) adrenaline is more active than (+) isomer

(2) S(−) warfarin 5 times more potent than R(+)

(3) S(+) propranolol is more potent than (+)

(4) S(+) Amphetamine is 3-4 times more active than (+)

(5) l-dopa is active than d-dopa

(6) (S) L-Thyroxine has thyroid activity but

R D-Thyroxine has antihypercholesterolemic activity

(7) D-Penicillamine is used in arthritis while

L-Penicillamine is high Toxic

(8) 1S 2R Propoxyphene – analgesic while

1R 2S P-H ——— – Antitussive

(9) Labetelol = Commercially – only 4 isomers Diastereomer

– α+β blocker

RR – β_1 & β_2 blocker

SR – α_1 blocking

SS & RR → contribute to drug activity

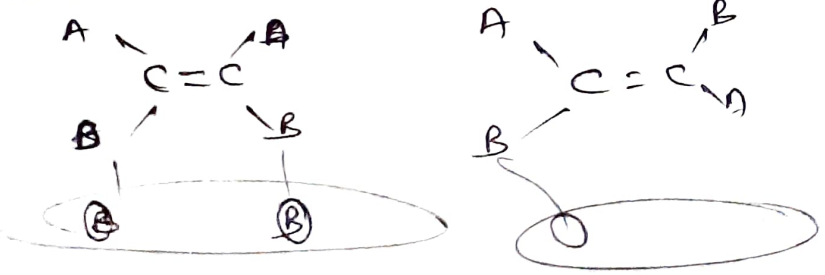
(10) SS Ethambutol → antitubercular

RR Ethambutol → ocular toxicity

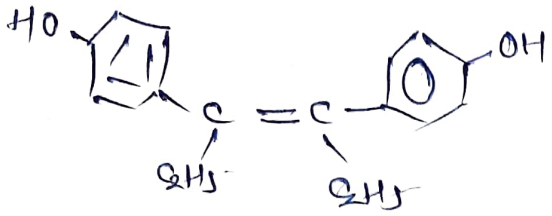
Geometrical Isomerism

Also known as Cis-Trans System & occurs due to restriction of rotation on C=C double bond or in ring system

- These isomers have significant difference in physicochemical properties, which affect significant biological action & distribution pattern
- Similar as optical isomers, they have differ in Drug-receptor interaction.

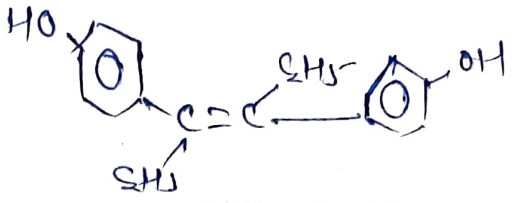


ex ① Trans (E) diethyl stilbesterol is more potent than cis (Z)



cis-isomer

(-)- Active



Trans isomer

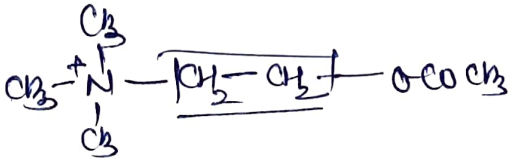
↓

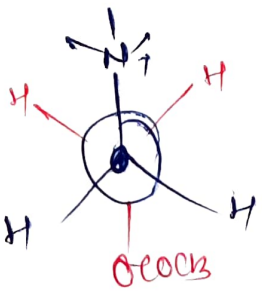
more estrogenic activity

② Cis-2 phenylcyclopropylamine (↔ 1R,2S) is less active as MAO Inhibitor than trans (1S,2R) (+) isomer

③ while ↔ 1R,2S cis form more effective as blocker of amine uptake mechanism

Conformational Isomer

ex. Acetylcholine 



θ = 180

Staggered Anti

→ Stable
— lowest energy (interact)
— Trans / Transoid form

↓

fully interact with M-Receptor

eclipsed

θ = 120

→ unstable
— lowest interact energy
— cis/cisoid

fully eclipsed

θ = 0°

Gauche (Staggered) θ = 60° → Interact with N-receptor

DRUG-METABOLISM

BIOTRANSFORMATION :- Chemical alteration of the drug / Xenobiotic within the biological System (body)

Major Alteratn
- Chemical nature (↑polarity) → For Excretion
- Biological Activity → depends on Metabolite

- Xeno-Biotic - Xenos (Stranger) for Biological System, also know as Exogenous Substance (Drugs, Foods, Chemicals, Antigens, Carcinogens, etc)
  - ↳ They may have
    - # P'cological Response
    - # Toxicological Response
    - # Immunological Response

Nutritional Value

MAJOR SITES: → # Liver, Kidney, Lungs, GI, Blood

BIOCHEMICAL ALTERATION

1. Enhance Polarity For Easy in Excretion

Lipid Soluble → Water Soluble (−OH −NH− −O− −SH−)

e.g.
- Phenyl Butazone —Oxdn→ Oxy Phenyl butazone
- Hexobarbital —Oxdn→ 3-hydroxy Hexobarbital

2. Biological Inactivation (Terminate Drug Action)

- Phenobarbitone → Hydroxy Phenobarbitone
- Phenytoin → p-hydroxy phenytoin
- Salicylic acid → Salicyluric acid

3. Biological Activation

Prodrug (Inactive) → Active

- L-DOPA → Dopamine
- Enalapril → Enalaprilate
- α-me.dopa → α-me. norepinephrine

Active → Active Metabolite

- Amitryptilline → Nortryptilline
- Codeine → Morphine

4. P'cological Alteration

- Iproniazid → Isoniazid
  (Antidepressant) (Anti-TB)

5. Toxicological Alteration

- Paracetamol → Imidoquinone der. (Liver Damage)
- Halothane → Trifluro acetic ā (Liver damage)

DRUG

Highly Polar (Streptomycin, Neostigmine) → (Lipid Soluble Drug)

P-I
- # Functional group change
- # attached −OH −SH− −NH−
- # change Biological Activity
- # (Hydroxylatn, Oxdn, Redn)

P-II
- # Conjugation Reactn
- # attached endogenous polar molecular
- # Facilitate Excretion
- # Detoxification

Polar drug (−OH −SH− −O− −NH−) → P-II → # Terminate drug Action

ELIMINATION

DRUG METABOLISM - PHASE-I REACTION #PART-1

Metabolic Enzymes

① Microsomal Enz. / Cyt P450 Dependent - Found in lipophilic mem. of Smooth Endoplasmic reticulum
PI → Oxdⁿ, Reductⁿ, Hydroxylation
PII → Glucuronic Conjugation

2) Non-Microsomal → Found in cytoplasm & attached to mitochondria (Oxidase, peroxidase, dehydrogenase, esterase, etc)
↳ # act on water soluble xenobiotic (Alcohol)

PHASE I REACTION

Non-Synthetic / Functionalizatⁿ Reaction
Mainly depends on Cyt P450 Enz (Monooxygenase) also known as Cyt P450 Mixed Function Oxidase, a microsomal mem. bound enz.

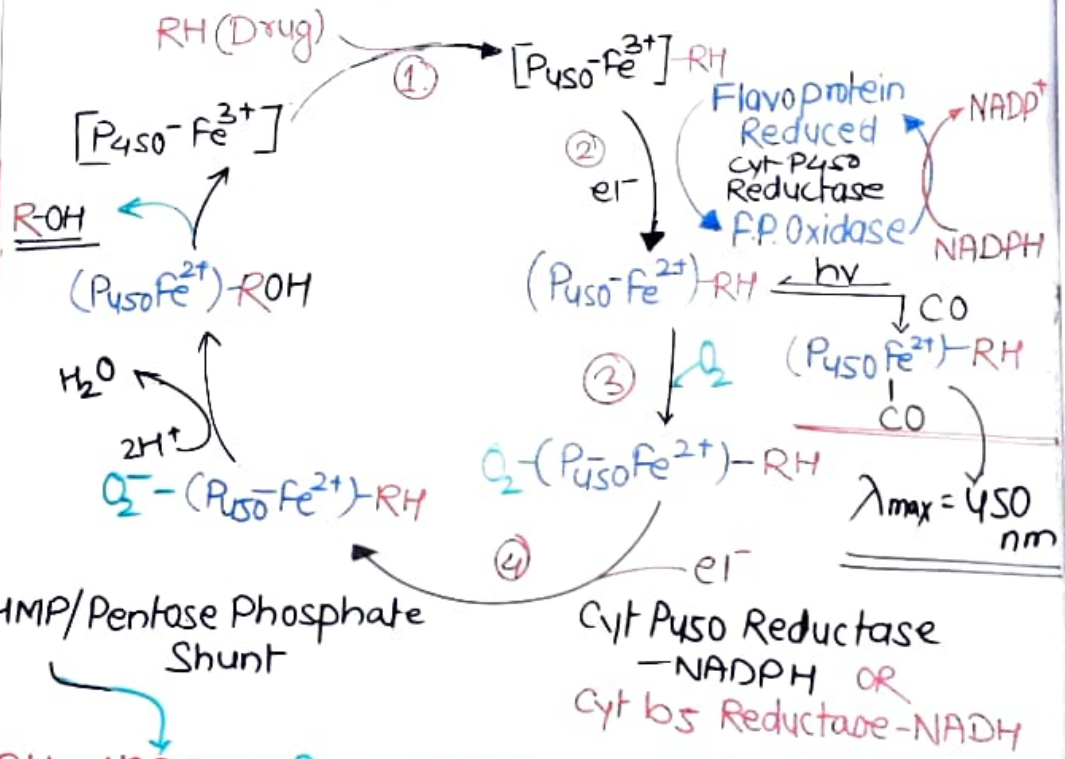
Non-Microsomal - Flavin Mono-oxygenase (Ziegler's Enzyme, Amine Oxidase, Dehydrogenase)

Key Role : ① Alteratⁿ of Functional Group

Drug ⟶ Drug (-OH, -O-, -SH-, -NH-)

② Enhance polarity
③ Change in Biological Activity (Inactivatⁿ, Activatⁿ, P'ological Alteratⁿ, Toxicological Alteration)

Oxidative Biotransformation



RH + NADPH + O_2 ⟶ R-OH + H_2O + $NADP^+$

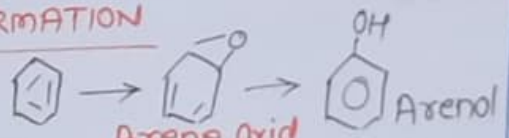
Enzyme → Mixed Function Oxidase (MFO)

- Proteins → Haem Protein → Cyt P450, Terminal Oxidase
  → Flavoprotein → Cyt P450 Reductase NADPH₂-Dependent
  → Cyt b5 Reductase-NADH₂ dependent

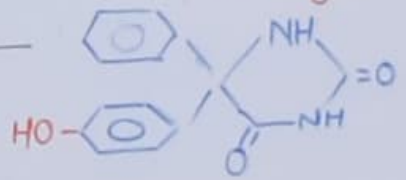
PHASE 1 REACTION OF DRUG METABOLISM #PART 2

1 OXIDATIVE BIOTRANSFORMATION

i) Aromatic Hydroxylation



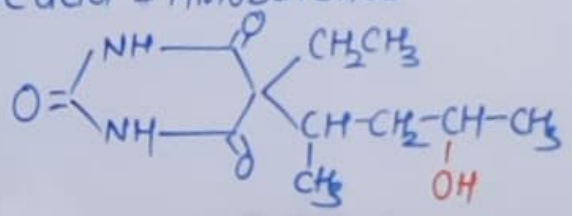
* Phenylbutazone → Oxy—
# Acetinilide → Paracetamol
# Phenytoin → p-hydroxy⁺—



ii) Alephetic

$R-CH_2-CH_2-CH_3 \rightarrow R-CH_2-\underset{OH}{CH}-CH_3$

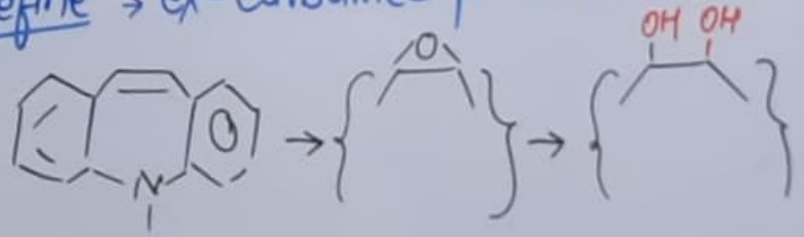
Ibrufen # Velproic acid # Amobarbital
Pentobarbital⁺



iii) Epoxidatⁿ

$R-CH=CH \rightarrow R-\underset{O}{CH-CH}$ Aldrin

iv) Olefine → ex- Carbamezapine derv.

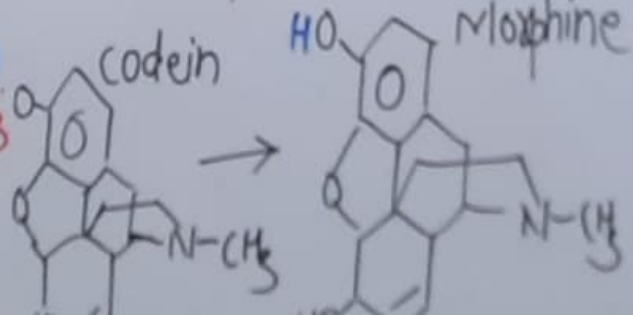


Carbon-heteroatom C-N, C-S, C-O

v) Oxd. Dealkylation

a) O-dealkylation

R-O-R → R-OH

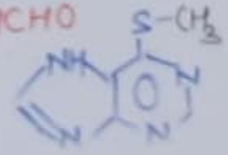


b) N-dealkylatⁿ $>N-R \rightarrow >N-H + HCHO$

Morphine, # Caffeine # Adrenaline # Diazepam

c) S-dealkylatⁿ $-S-R \rightarrow -SH + HCHO$

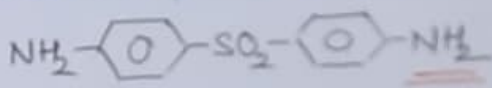
6methyl mercaptopurine



vi) N-Oxdⁿ/Hydroxylatⁿ

$R-NHR \rightarrow R-\underset{OH}{NR}$ (1°/2°) $R_3N \rightarrow R_3N\rightarrow O$ N-oxide

Lidocaine, Nicotein, Acetamenophen, Dapsone

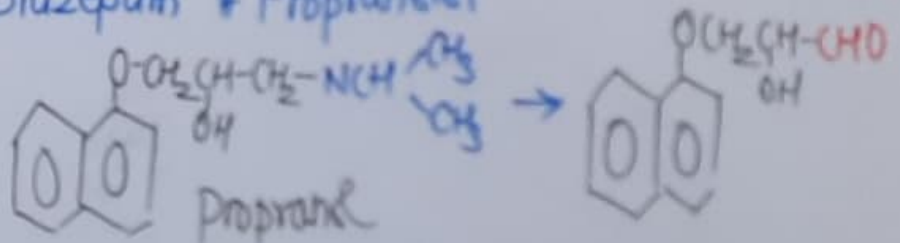


vii) S-Oxidⁿ $R-S-R \rightarrow R-\overset{O}{S}-R$

Phenothiazene # chlorpromazine

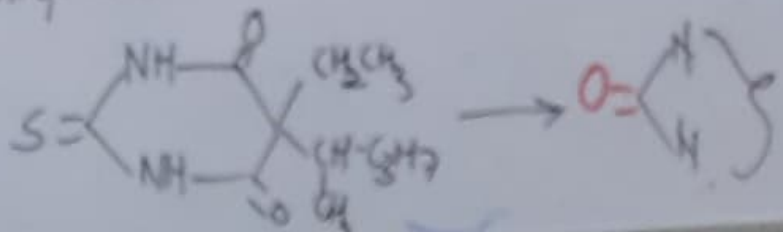
ix) Deamination $RCH_2-N< \rightarrow RCHO + HN<$

Diazepam # Propranolol



x) Desulfuration $>=S \rightarrow >=O + SH_2$

Thiopentone



PHASE-2 DRUG METABOLISM

Synthetic / Anabolic / Detoxification Reaction
↑ Polarity of drug by conjugatn with polar moiety
Terminate Biological Action
* Microsomal - Glucuronyl & GSH-S-transferase

1 GLUCURONIDATION → Glucuronyl transferase

UDP-Glucuronic ā + RXH ⟶ RX-GA + UDP-H

XH = -OH, -COOH, $-SO_2NH_2$, -NHOH

Morphine # Acetaminophene # Diazepam # Digoxin

* Enz → Liver, Intestine, kidney, Skin, lungs, Brain

2. ACETYLATION :- N-Acetyl transferase

R-CO-S-CoA + $ArNH_2$ ⟶ Ar-NH-COR

Acetyl CoA → Isoniazid, Sulfonamide, Dapsone

* Non Micro → REC liver, G.mucosa, blood, lungs

3. METHYLATION - Transmethylase

RXH + S-adenosine Methionine → $RX-CH_3$

Catecholamines, # Histamine

4. SULPHATE CONJUGATION - Sulfotransferase

RXH + Phospho-Adenosy-phospho sulfate → $RX-SO_3$

RXH → phenols, Aromatic amines etc (Liver, kidney, Intestine)

Salbutamol, Terbutaline, Me-dopa

5. GLUTATHIONE - GSH-S-transferase (Microsomal & Non-M

$RX + GSH \longrightarrow R-GS + X^- + H^+$ (Free Radical eliminatn)

Epoxide, Arene oxide, paracetamol, ethacrynic acid

6. AMINO ACID (GLYCENE & GLUTAMINE) - transferas

(Microsomal)

Aromatic ā, Arylalkylacid,
Haloperidol, phenylacetic acid, Salicylic acid

7. WATER

Epoxide hydrolase (Microsomal) → Arene Oxide
↳ Benzopyrane, Carbamezapine

Cytosol - Alkene Oxides, Fatty ā epoxide
↳ Leukotriene A_4

FACTORS AFFECTING DRUG METABOLISM

1. Enzyme Induction & Inhibition

Drug → Unchanged + Metabolite → Inactive / Active / Toxic

(+) Enz Inducer

(−) Enz inhibitors

* **Enz Inducers** – Phenytoin, Carbamezapine, Barbiturates, Alcohol, Rifampicin, Griseofulvin
* **Enz Inhibitors** – Cimetidine, Omeperazole, ketokonazole, Erythromycin, Protease inhibitors

2. Physiochemical Properties of Drugs

pKa, Solubility, Polarity, size, shape, etc

3. Environmental factors :– pressure, Temp., atomosphere, humidity, etc → "Alter physiology"

4. Biological Factor :-

ⓐ Age →

Oldage → ↓ Metabolism

child → ↑ BMR → ↑ Metabolism

ⓑ Liver Disease → ↓ Metabolism

ⓒ Pregnancy → ↓ absorption by Progesterone
↓ Conc. of plasma proteins
↑ Renal clearance

Metabolism → ↑ Activity of CyP2D6 & CyP3A4
↓ Activity of CyP1A2

5. Stereochemical Aspect drug Metabolism

Structural Specific Drug–Protein Interaction

↓

Stereo selective Metabolism

ex① (−) Quinine treat maleria but (+)Q. doesnot

② D(+) Glucose easily metabolised → $CO_2 + H_2O$
L(−) Glucose not metabolised & excrete

③ Some bacterias ferment the dextro form of a compounds without affecting levo form