DEPTH OF BIOLOGY

MEDICINAL CHEMISRTY

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UNIT-1ST

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Introduction to medicinal chemistry

- Medicinal chemistry involves **the creation and refinement of molecules for the purpose of creating or improving drugs**
- It is based on synthetic organic chemistry, a discipline in which scientists combine small molecules to create new ones.
- It also deals with the study of existing drugs , their biological activity and structure activity relationship [SAR]
- - mechanism of action
- -Uses of drugs
- -Synthesis of drugs
- -SAR
- CHEMISTRY BEHIND DRUGS

- The ancient civilization of the Chinese, the Hindus found to be that they used therapeutic plants and minerals for treatment
- They chewed coca leaves that contained cocaine and used mushrooms as hallucinogens

- Cinchona bark and opium were also used
- The 19th century known as the age of INNIVATION AND CHEMISTRY
- In 1853 morphine was heated with methyl iodide by henry and created new substance of quaternary salt of modified morphine

- In 1898 morphine derivative was used as cough sedative
- During the 1840's first use of organic chemicals were introduced , anesthesia during a tooth removed like nitrous oxide, ether and chloroform.
- 1864- barbituric acid synthesized as a useful hypnotic
- 1875-salicyclic acid for typhoid fever

- 1899- aspirin marked as antipyretic without any side effects

- The combination of experimental pharmacology and medicinal chemistry speeded up the development of drugs after the 1930's
- The greatest achievement was the discovery of penicillin by alexander Fleming in 1928 , which was used as first antibiotics
- Nitrogen mustard was the first drug used for beating cancer in 1940
- In 20th century , Paul Ehrlich and john Lang by introduced the receptor theory that drug bind to receptor based on their composition & chemical structure.

Physicochemical properties in relation to biological action

1. IONIZATION- the property of any atom or molecule losing /gaining electrons and acquiring + or – charge

A → (IONIZATION) A^+/ A^-

Unionized ionized

Non-ionic ionic

e.g.: **NaCl→ Na^+ Cl^-**

$CH_3COOH \rightarrow H^+$ $CH3COO^-$

DRUG- unionized = lipophilic

Ionized= hydrophilic

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DURING INTAKE- drug should be unionized

ABSORPTION- drug reaches into ***blood (hydrophilic)***

DRUG should be hydrophilic

(for this it must be ionized)

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DISTRIBUTION- drug reaches to site of action

Drug need to cross the cell membrane which is made of phospholipids which in turn is lipophilic in nature

So hence drugs should be lipophilic

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Drug should be lipophilic **(for this it must be unionized)**

RELATION TO BIOLOGICAL ACTION

- Plays important role in pharmacokinetics
- Pharmacokinetics involve ADME i.e. absorption, distribution, metabolism and excretion

- Good balance of ionized-unionized form is better for pharmacokinetics
- Unionized form of drugs- LIPOPHILIC & also helps to cross cell membrane
- Ionized form of drugs- HYDROPHILIC imparts better water solubility for drugs which is necessary for binding interaction of drug with its receptor.

- For example- drug must be weakly acidic or basic
- Degree of dissociation/ ionization can be determined by Henderson hassilbalch equation

For a weak acid

$$pH - pK_a = \log \frac{[Ionized]}{[Un-ionized]}$$

For a weak base

$$pH - pK_a = \log \frac{[Un-ionized]}{[Ionized]}$$

2. SOLUBILITY- maximum amount of solute that can be dissolved in 100ml/gm of solvent at a given temperature is called solubility of drugs

It depends upon

a. Nature of solute and solvent
b. Temperature
c. pH
d. Pressure

Various types of bonds like hydrogen, dipole-dipole, ionic bond hold together the atoms and molecules in organic substances

Methods to improve drug solubility

1. Altering the structure of molecule
2. Complexation
3. Addition of surfactants
4. Use of co-solvents

Important relation to biological action

- ✓Drugs must be in solution and interact with receptors
- ✓Drugs must be in solution before it can be absorbed by biological membrane and show its activity
- ✓Bioavailability of drugs mainly depend on their solubility in the given solvent system

3. PARTITION COEFFICIENT-

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The partition coefficient is defined as the ratio of unionized drug distributed between organic phase and aqueous phase at equilibrium.

FORMULA

$$K = \frac{C_o}{C_w}$$

OR

$$\text{Partition coefficient (k)} = \frac{\text{conc. of Drug in org. phase.}}{\text{conc. of Drug in aq. Phase.}}$$

IMPORTANCE-

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- Affects drug absorption and distribution
- Helps to know whether the drug is lipophilic or hydrophilic

Can be measured through separation method. If,

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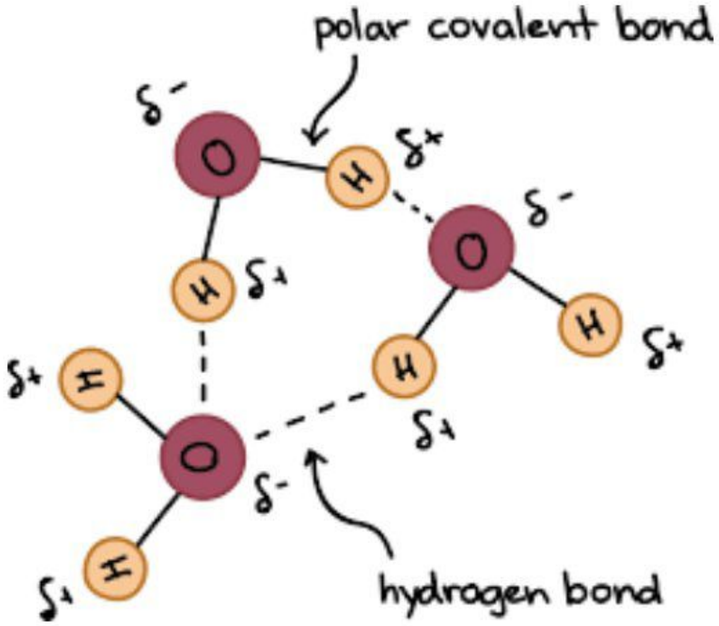
K>L then lipophilic and if K<L then hydrophilic

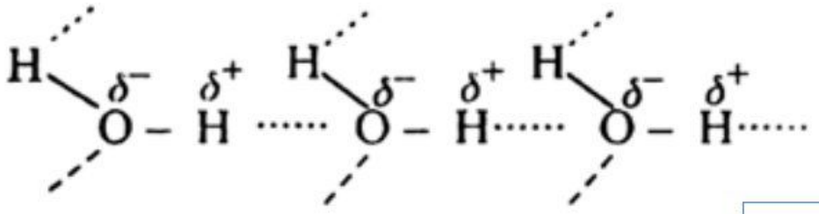
- Rate of drug transfer is directly related to the lipophilicity of drug because biological membranes are lipophilic

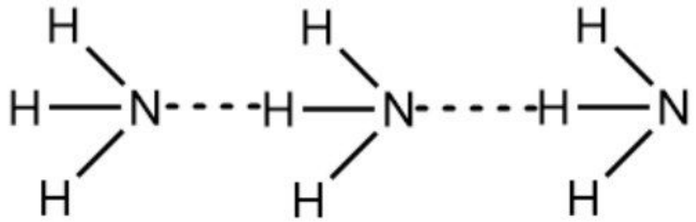
4. HYDROGEN BONDING - **a special type of dipole-dipole attraction between molecules, not a covalent bond to a hydrogen atom**. It results from the attractive force between a hydrogen atom covalently bonded to a very electronegative atom such as a N, O, or F atom and another very electronegative atom.

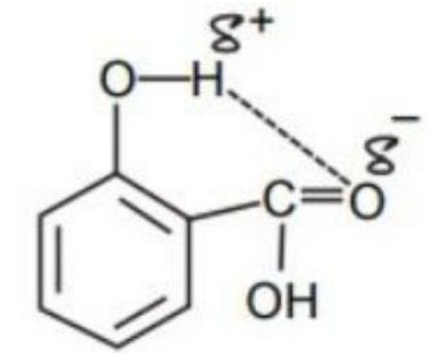


- It is of 2 types-
  - Intermolecular
  - Intramolecular

1. INTERMOLECULAR hydrogen bonding- When hydrogen bonding takes place between different molecules of the same or different compounds







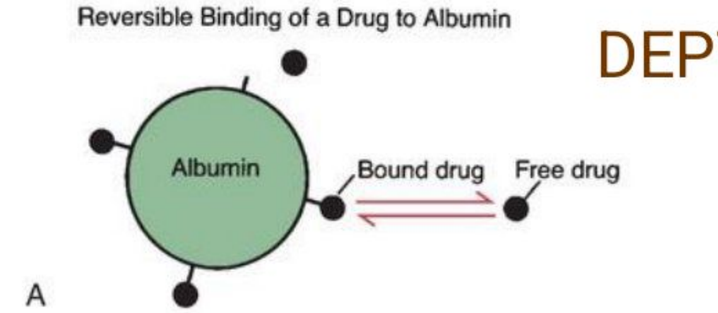
Salicylic acid

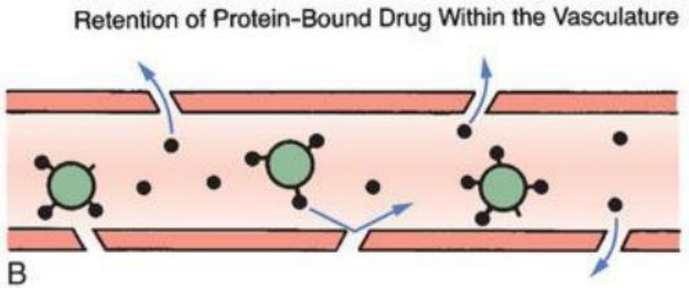
2. INTRAMOLECULAR hydrogen bonding- The hydrogen bonding which takes place within a molecule itself is called **intramolecular hydrogen bonding.**

IMPORTANCE-

- ✓Intramolecular hydrogen bonding decrease the melting –boiling point and solubility
- ✓Intermolecular hydrogen bonding increase the melting –boiling point and solubility
- ✓Important for drug receptor interaction
- ✓Very important in chemistry of genetic code- DNA

6. PROTEIN BINDING- process by which drug molecule gets attached to the protein molecule and forms a complex





After the absorption of drugs, when drug reaches into systematic circulation, it binds with plasma protein and forms a plasma protein drug complex

Proteins present in blood-

- Albumin
- Globulin
- Lipoprotein
- Alpha acid glycoprotein

2 types of complex are formed

- Reversible
- Irreversible

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1. REVERSIBLE- in this the bonding between protein and drug is very weak like van-derwaals force or hydrogen bonding which can detach easily. Drug become free and then this drug bind with receptor and give its pharmacological action.
2. IRREVERSIBLE- in this the bonding between protein and drug is very strong like covalent which does not detach easily . So that drug does not become free hence no binding occurs resulting to no pharmacological action.

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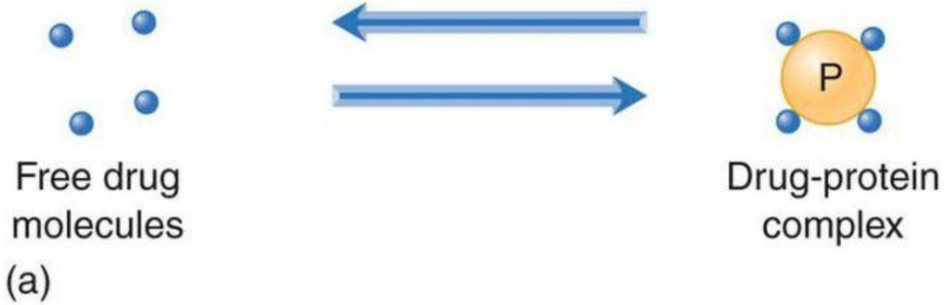
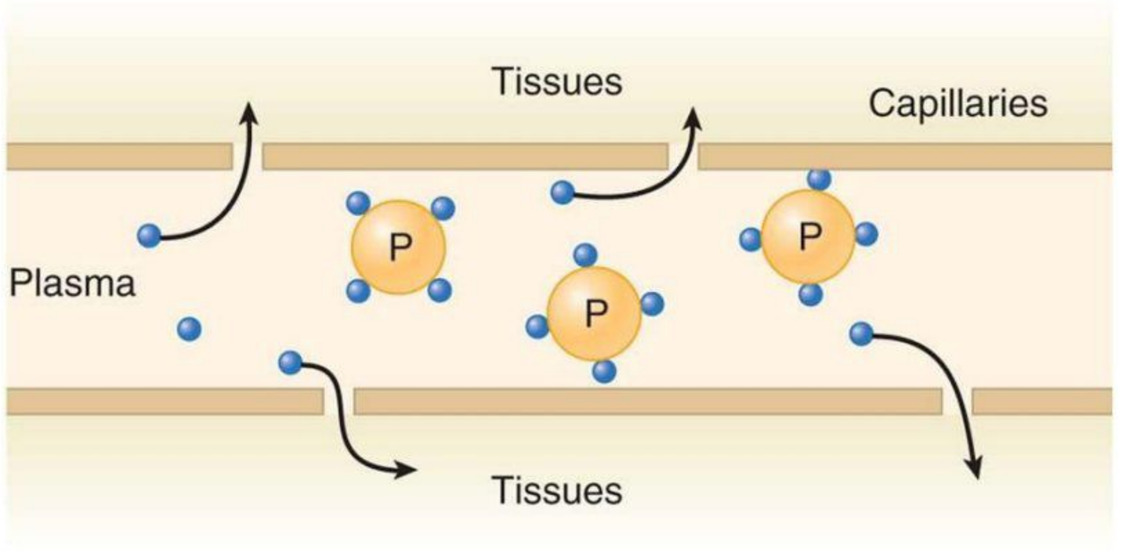
- IMPORTANCE-

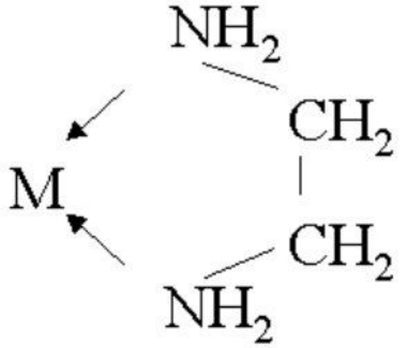




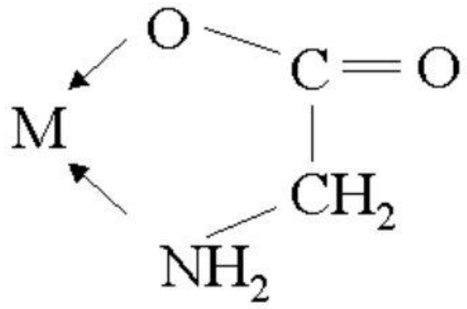
- ❑Influence the bioavailability and distribution of active compounds
- ❑Complex and free drug form are important for complete pharmacological action

6. CHELATION- type of bonding of ions or molecules to metal ion.

Compound containing 2 or more ligand groups may combine with a metal ion to from complex known as chelate



ethylenediamine



glycinato

IMPORTANCE

EDTA is injected into the bloodstream then this bind with heavy metal & make chelates then remove heavy metals from body

Used in poisoning

When heavy metals like Pb, Hg, Fe and arsenic build up in the body they can be toxic and are treated by chelation therapy

BIOISOSTERISM

- Here bio = same and sterism means same electronic configuration
- Example- N_2 and CO both have same electronic configuration i.e. 6 while N_2O and CO_2 have 8

- There are 2 types of bioisosterism- classical and non classical

1. CLASSICAL BIOISOSTERISM- electronic configuration, physical , chemical and pharmacology properties are same.

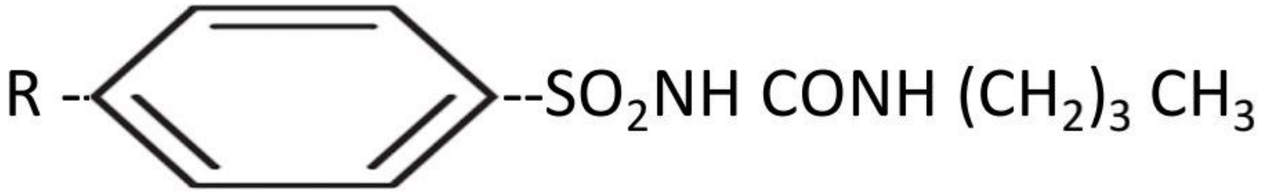
It may be univalent- H, Cl, Br , -CH2

Bivalent –CH-, -NH-

Trivalent –CH=

Tetravalent =CH= or ring structure equivalent

APPLICATION- replacement of NH_2 group by CH_3



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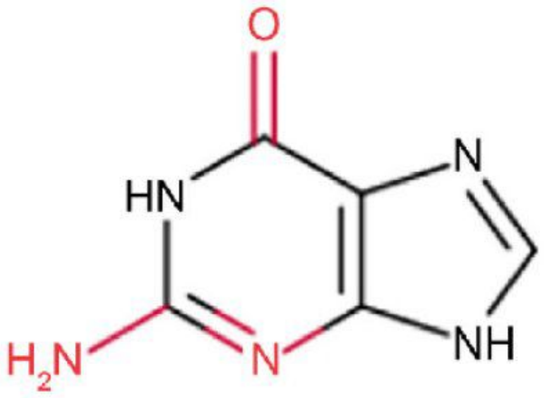
If this R is replaced by R-NH2= carbutamide and if by CH3 then tolbutamide

Replacement of OH group by SH

Guanine



Thioguanine

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2. NON- CLASSICAL BIOISOSTERISM: only electronic configuration change other things approx. same

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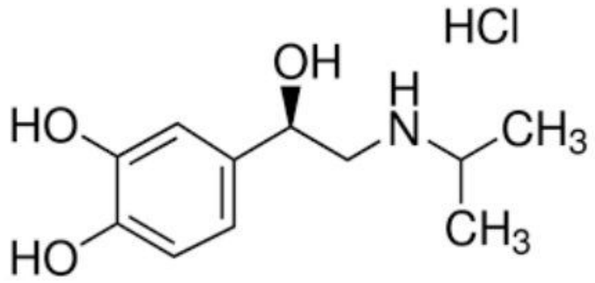

ISOPROTERENOL

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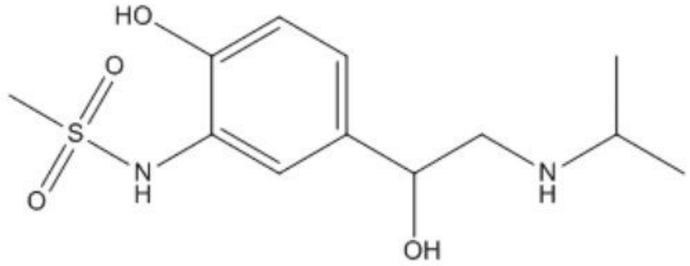


SOTERENOL

IMPORTANCE-broadly used in pharmaceutical science

- Used to change bioavailability and reduce toxicity
- In drug design, the purpose of exchanging one bioisosters for another is to enhance the desired properties without change in their structure
- It has solved many biological problems

OPTIC AND GEOMETRIC ISOMERISM [STERIOCHEMISTRY]

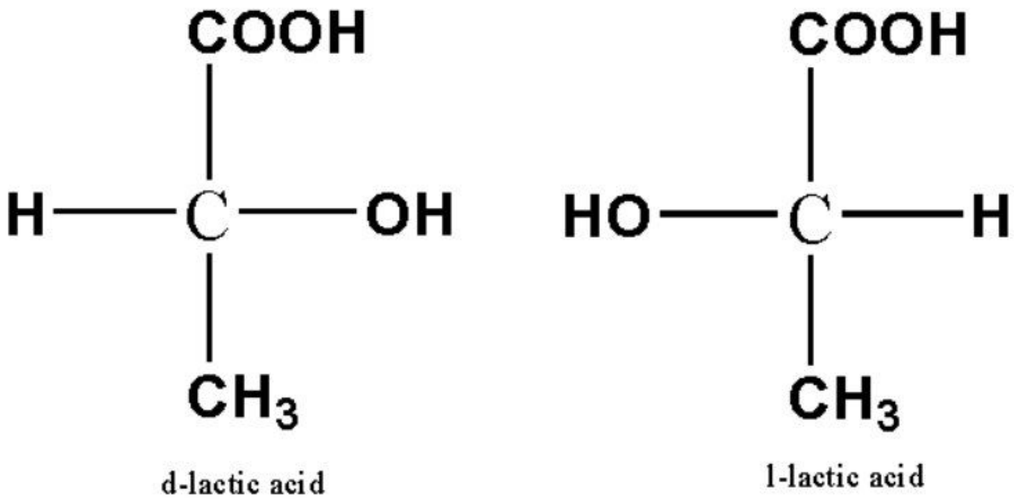
1. OPTICAL ISOMERISM- molecules with same molecular, structural formula and same properties but differ in behavior towards light

Compounds which rotate plane polarized light are known as ***optically active compounds***

They contain chiral carbon [4 different group/atom]

Enantiomers- non super imposable mirror image

Diastereomers- non superimposable non mirror images



d-lactic acid

l-lactic acid

- Clockwise- dextrorotatory [+]
- Anticlockwise- levorotatory [-]

#ROLE IN BIOLOGICAL ACTION

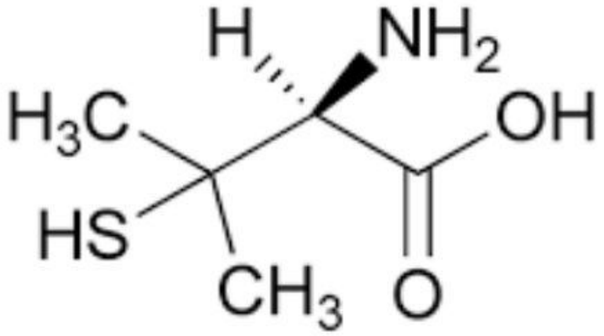
In some cases 1 enantiomer is active while others may be toxic

[-] adrenaline is more active than [+] adrenaline

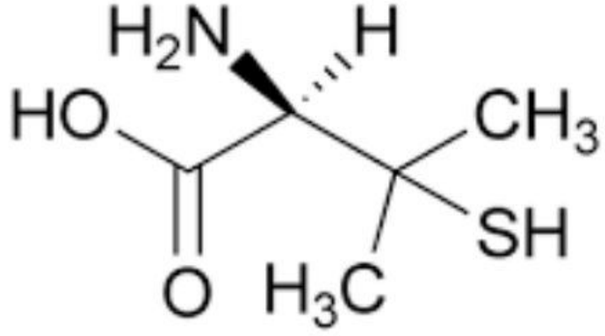
The [+] & [-] enantiomers may have different biological responses.

d penicillamine-used to treat arthritis

l penicillamine- very toxic



D-penicillamine



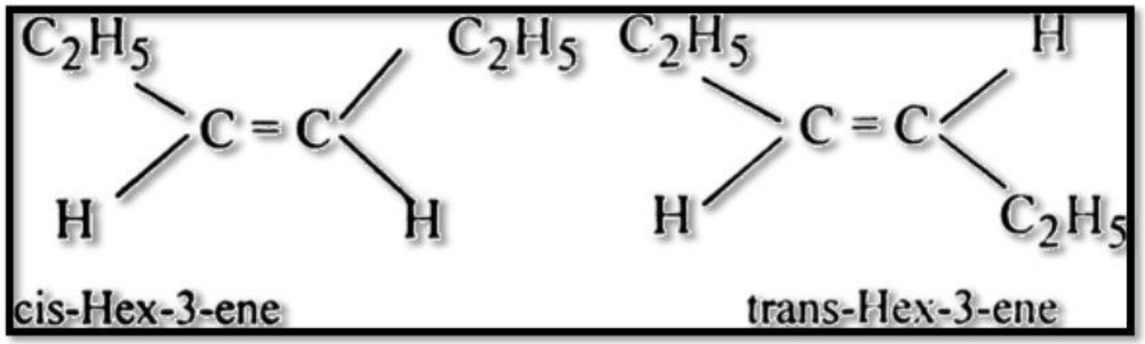
L-penicillamine

This happened because of change in structure of drugs hence it cannot bind with receptor

2.GEOMETRICAL ISOMERISM- also known as cis-trans isomerism

Different spatial arrangement but same number and types of atoms and bonds

Eg-



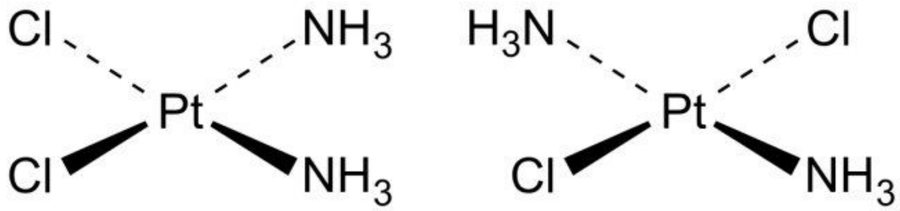
#IMPORTANCE-

Affects the biological activity of drugs

Trans diethyl stilbestrol is more potent than cis form

Cis-platin has anti cancer activity

While trans-platin is toxic



DRUG METABOLISM

- A drug has to be removed from the body after it has produced its effect i.e. it has to be excreted out
- This is possible due to metabolism only, it is the process of metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems.
- It leads to detoxification.

- Drugs get orally absorbed goes to systematic circulation and passes through the liver.
- Drugs are generally polar or lipid soluble.
- When a polar drug is absorbed by human body it is excreted unchanged through the kidneys

- But most of the drugs are lipid soluble, metabolism helps in creating more polar and less lipid metabolites which can be easily excreted

- Metabolism is performed by various enzymes present in GIT, liver, kidney, lungs . It causes alternation in chemical structure of drugs and this process is called as ***enzymatic transformation*** DEPTH OF BIOLOGY
- Drug metabolism takes part in 2 phases

PHASE 1 REACTION- also called functionalization reactions. In this type of reaction, a functional polar group [i.e. OH, COOH, NH2, 5H] is introduced in drug or in zenobiotics to convert them into more water soluble compounds so that they can be easily excreted out from body. DEPTH OF BIOLOGY

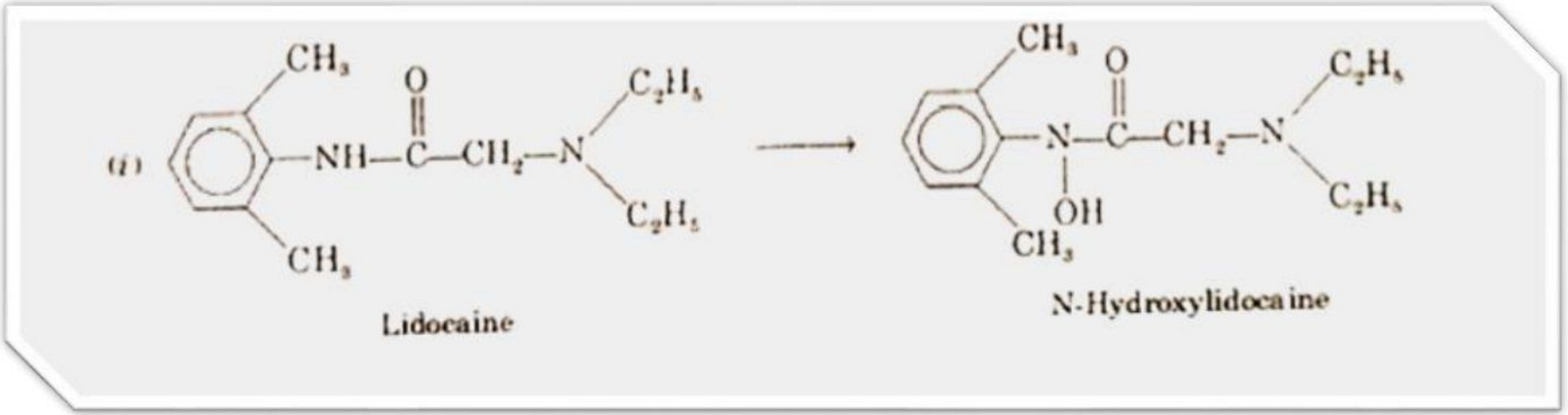
Various reactions like oxidation, reduction, hydrolytic biotransformation are involved in phase 1 reaction. DEPTH OF BIOLOGY

- OXIDATION- addition of oxygen or removal of hydrogen. It is the main process in metabolism. Reaction is carried out by group od mono-oxygenase in the liver [cyctochrome P450 enzyme]

1.HYDROXYLATION OF HETEROATOM

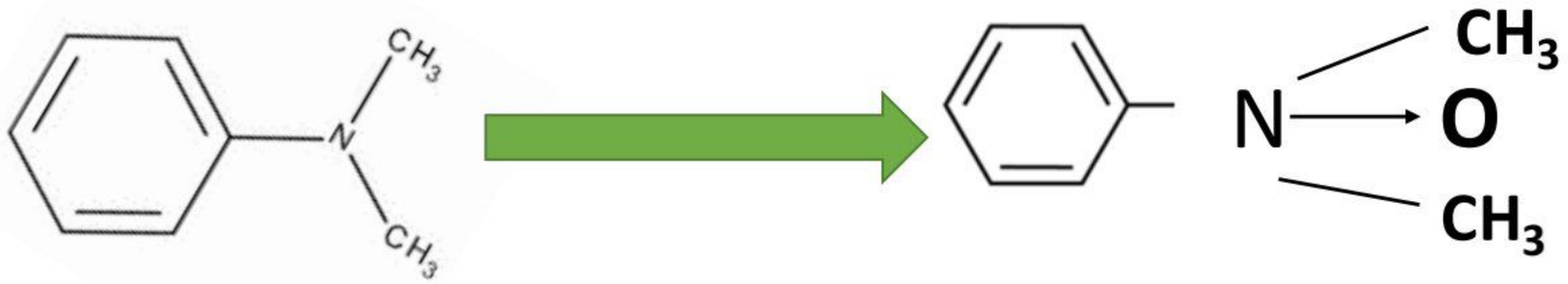
N-hydroxylation- drugs containing non-basic nitrogen atom (amides), non-basic aromatic amines and basic amines are metabolized by N-hydroxylation

Example-



2. OXIDATION

a. N- oxidation- compounds containing simple nitrogen atom are metabolized by N-oxidation process. Ex- tertiary amines yield N-oxides



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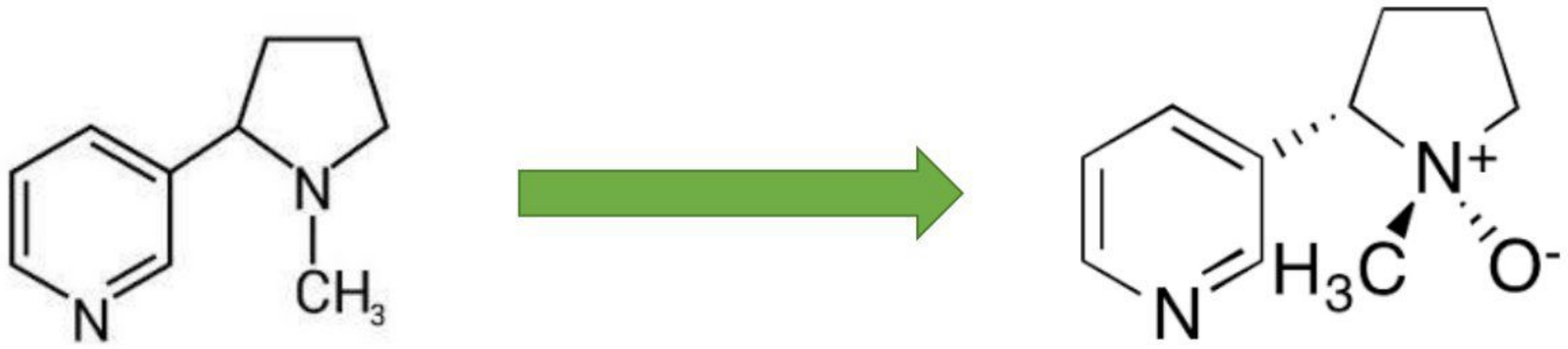

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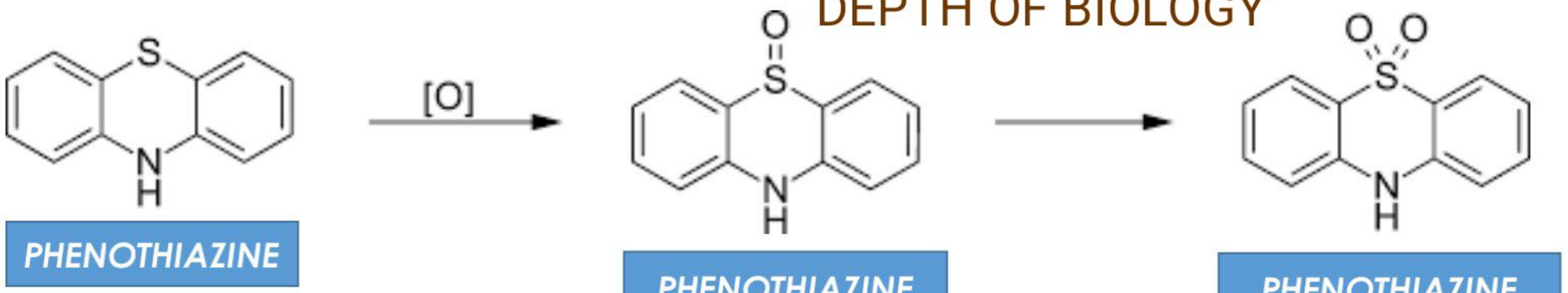
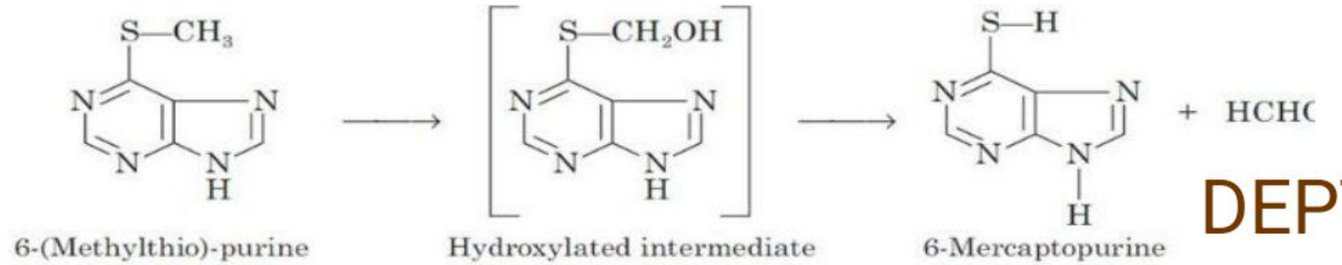
b. S-oxidation- compounds containing carbon- sulphur bond are metabolized to sulfoxides by this. The sulfoxides may be excreted out as urinary metabolites or may be oxidized as sulfones ($-SO_2-$) .



3. DEALKYLATION

The second type of biotransformation comprises dealkylation.

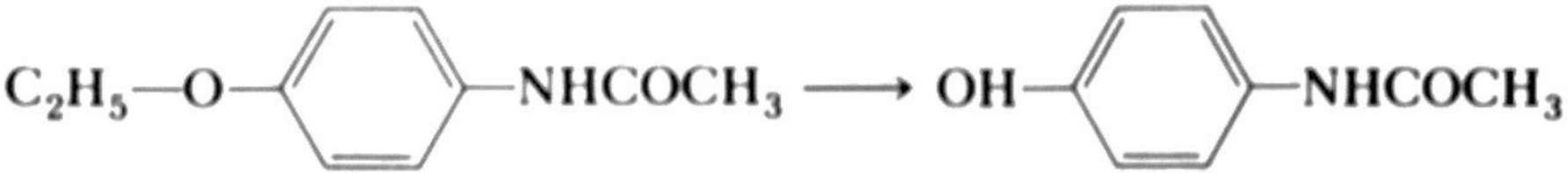
a. S- dealkylation- involves oxidative cleavage of carbon sulfur bonds



b. N- dealkylation- dealkylation in case of primary or secondary amines start from the carbon adjacent to nitrogen while in case of tertiary amines it starts with hydroxylation of nitrogen

c. O- dealkylation- o dealkylation of compounds containing C-O bond involves hydroxylation of alpha carbon forms an unstable hemiacetal or hemiketal intermediate

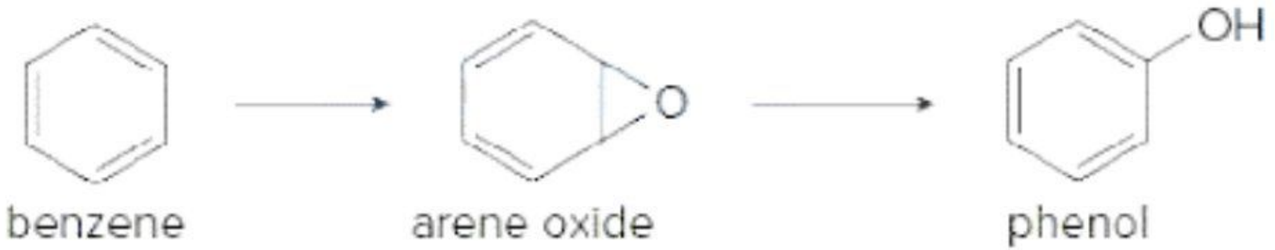
These intermediate spontaneously cleave to form alcohol and carbonyl compound



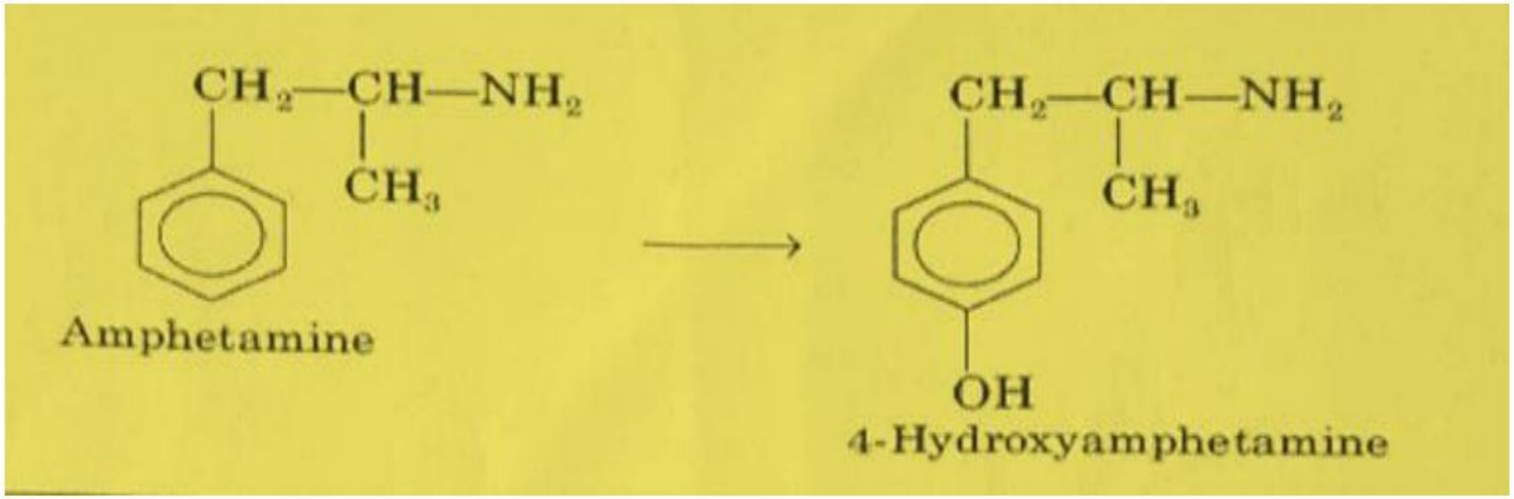
Phenacetin Acetaminophen

4. AROMATIC HYDROXYLATION

Oxidation of aromatic compound into phenol through the formation of highly reactive intermediate

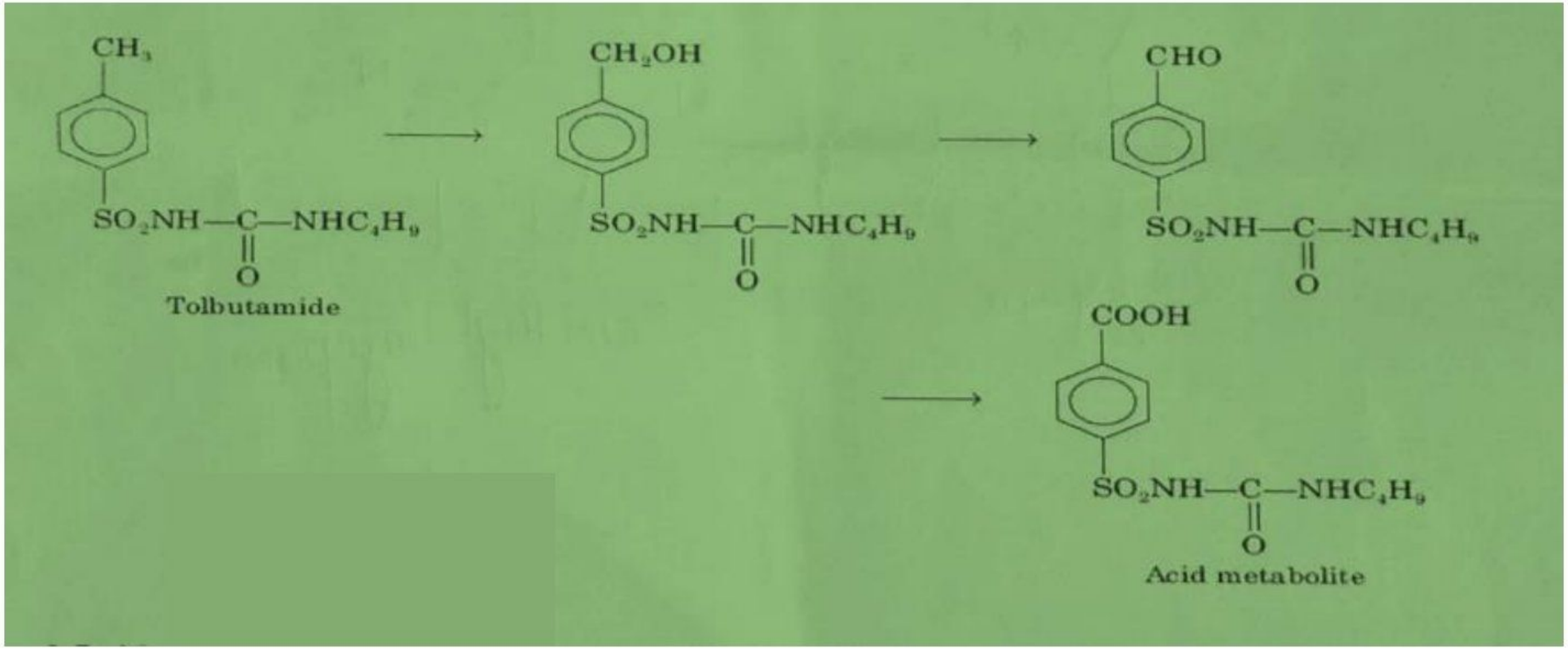


Many phenyl group containing drugs like phenylbutazone, phenytoin, amphetamine, phenformin etc are metabolized by aromatic hydroxylation



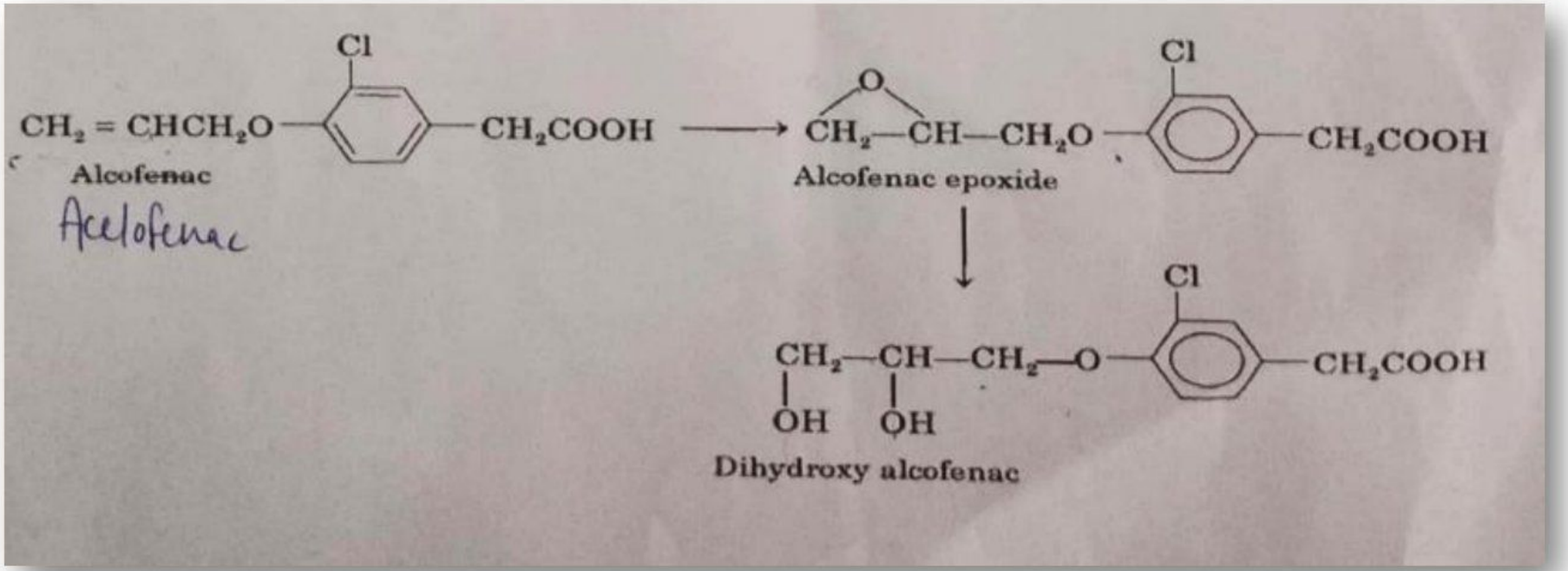
5. OXIDATION OF BENZYLIC CARBONS

Carbon directly attached to aromatic rings are oxidized to aldehydes and carboxylic acid via alcohols



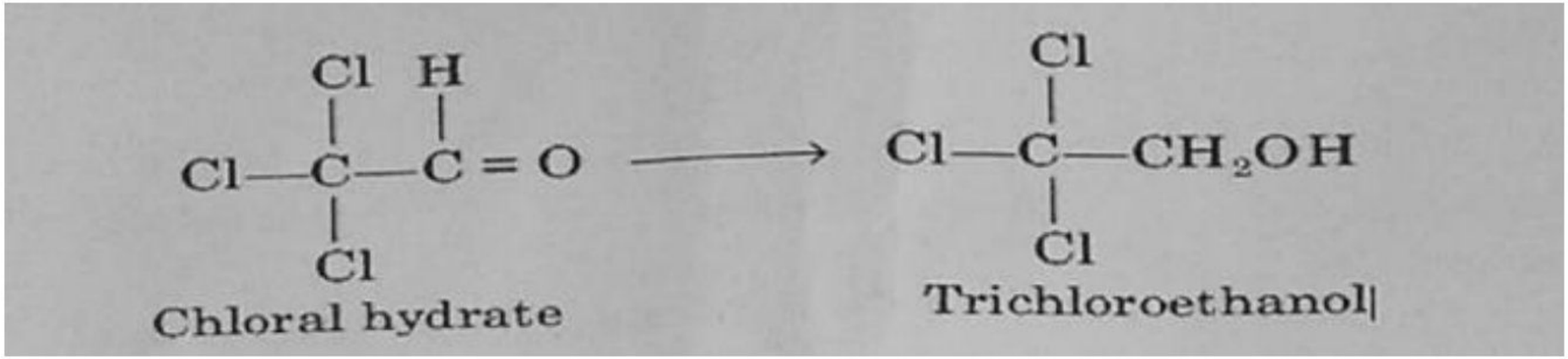
6. OXIDATION OF OLEFINS

Alcofenac is oxidized to dihydroxyalcofenac



REDUCTIVE REACTIONS

- Drugs containing carbonyl, nitro and azo groups are metabolized by reduction to alcohols and amines respectively
- The reduced compounds are conjugated and eliminated from the body. Example-

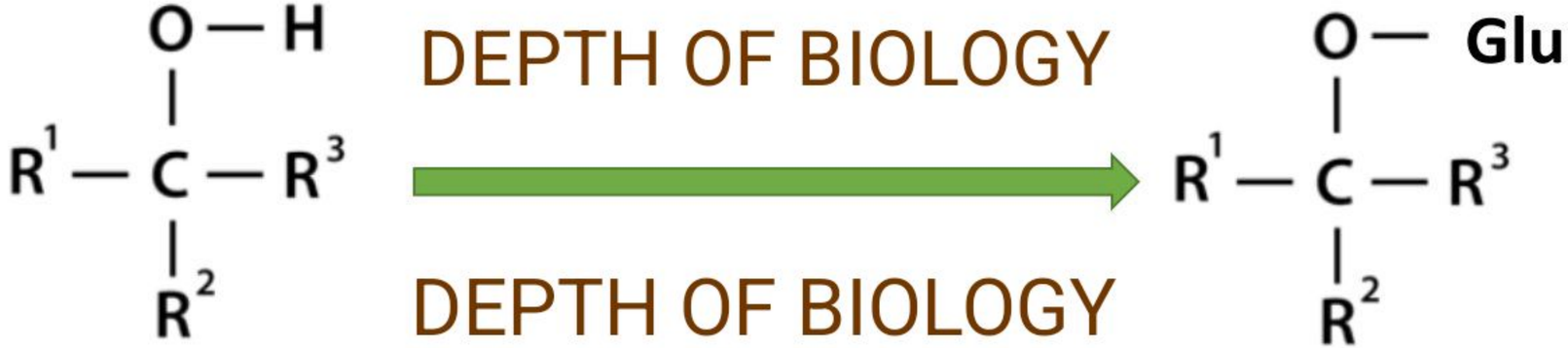


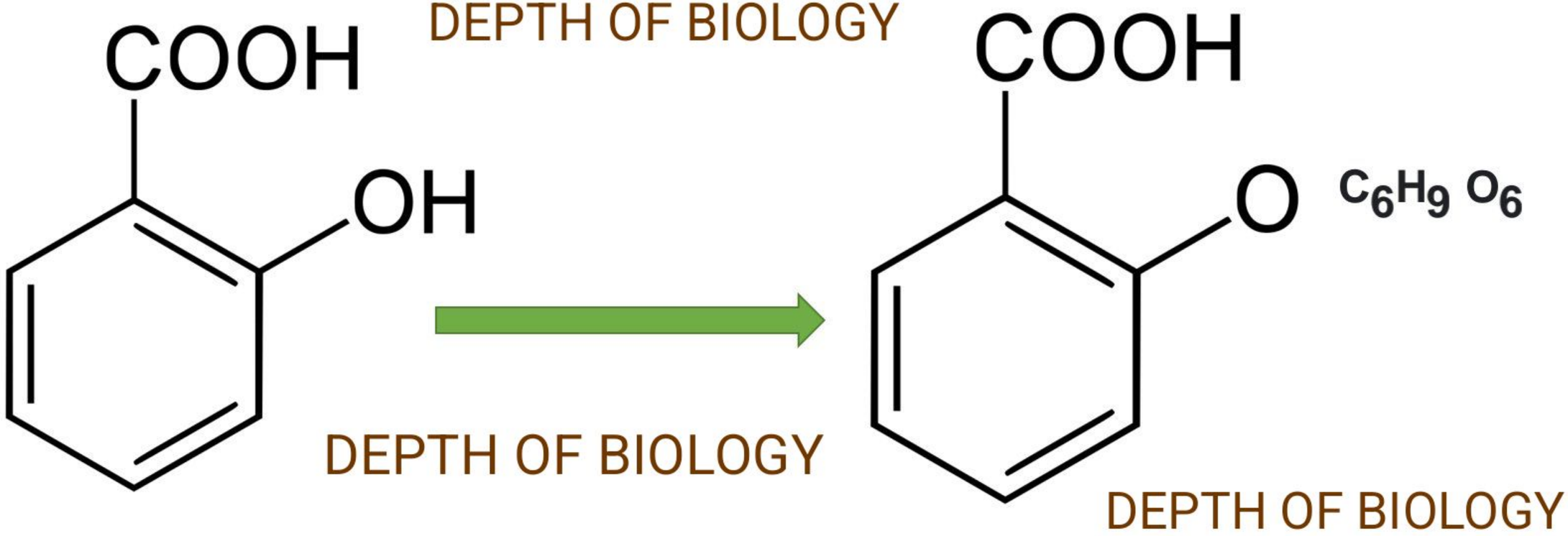
PHASE II REACTION

- Conjugation reaction are also known as phase 2 reactions.
- Phase 2 pathways are synthetic reactions where the product or metabolite from phase 1 gets conjugated
- This produces a large polar metabolite that is readily excreted from the body.
- Phase 2 occurs by glucuronidation, sulfation, amino acid conjugation, acetylation, methylation glutathione conjugation to facilitate elimination
- It introduces hydrophilic functionalities such as glucuronic acid , sulfate, glycine or acetyl group onto the drug or drug metabolite molecules.
- Transferases catalyze these reactions
- Most transferases are located in cytosol except the one that is responsible for glucuronidation which is microsomal enzyme.
- This enzyme is called uridine diphosphate glucuronosyltransferase [UGTs] catalyse the most important phase 2 reaction, glucuronidation

GLUCURONIDATION

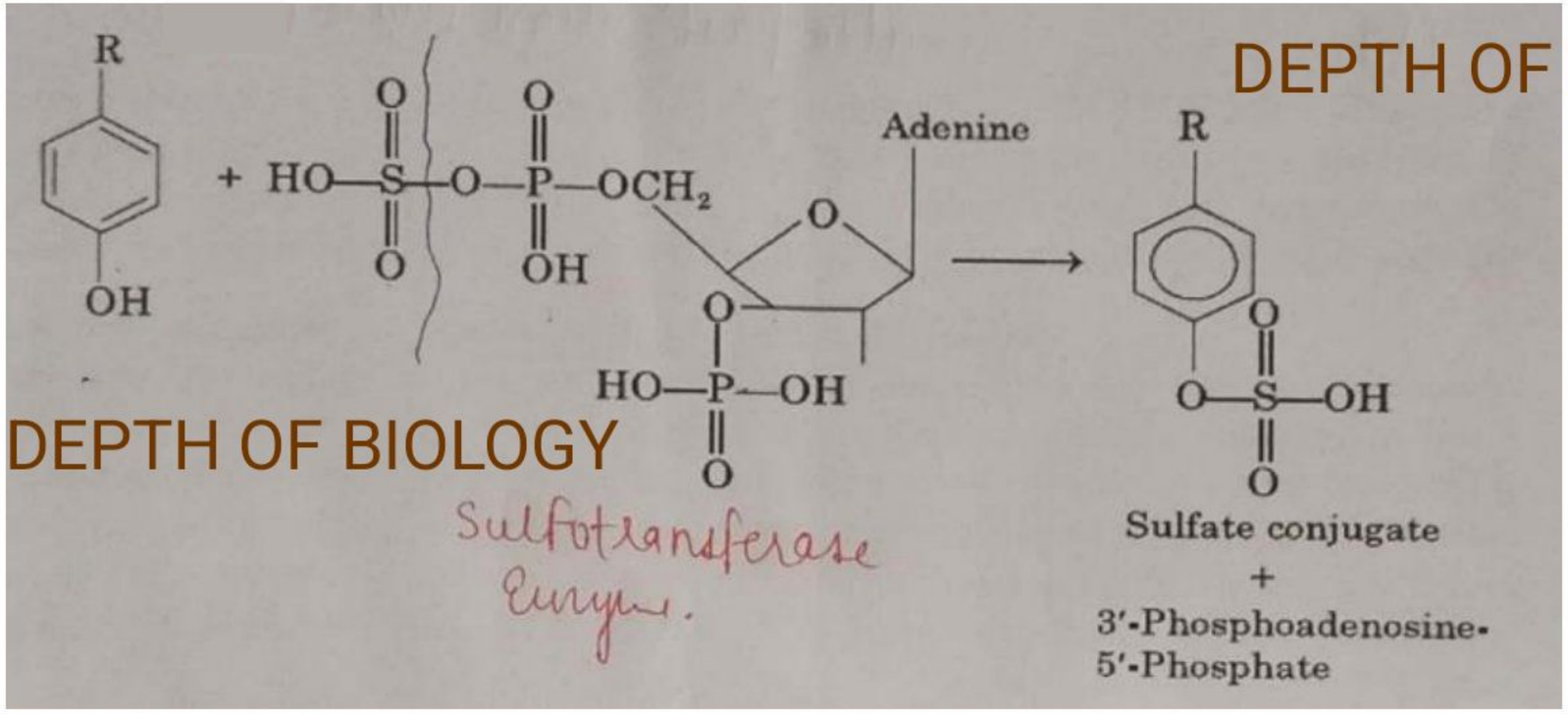
- It involves the conjugation of metabolite with glucuronic acid
- Glucuronic acid molecule is transferred to substrate from a cofactor (uridine-diphosphate-D-glucuronic acid) DEPTH OF BIOLOGY
- Catalyzed by microsomal glucuronyl transferases
- Glucuronides are inactive and rapidly excreted via urine and bile
- Molecules associated with carboxylic acid, alcoholic hydroxyl, phenolic hydroxyl groups undergo glucuronidation reaction





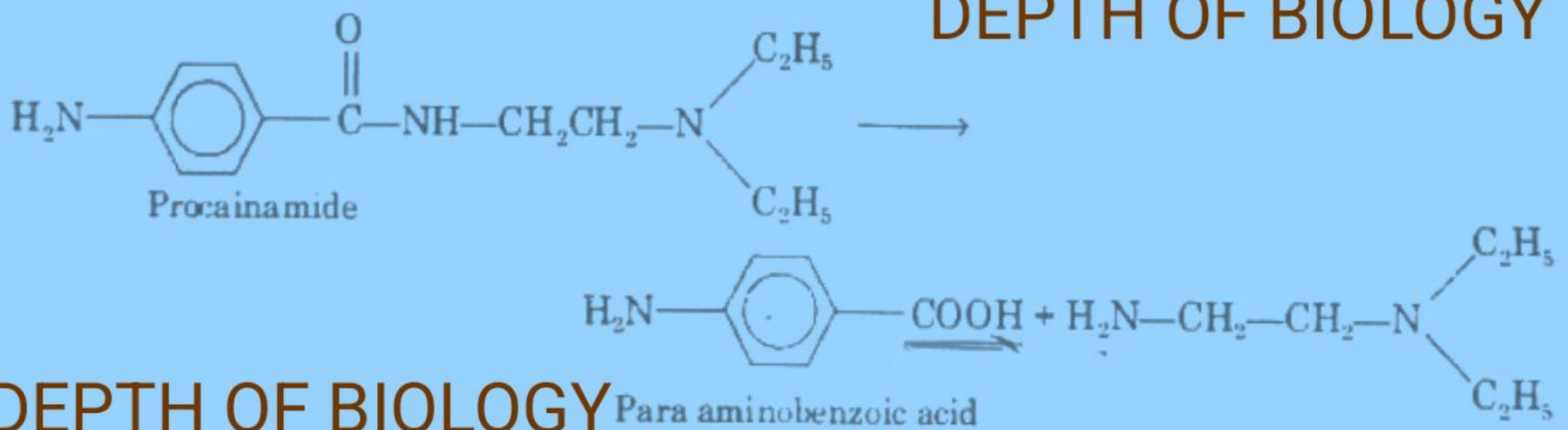
SULFATE CONJUGATION

- Involves transfer of sulphate molecule from co factor to substrate by enzymes – sulfotransferases
- Sulphate conjugation is common conjugation reaction of substrate molecule possessing of alcoholic hydroxyl, phenolic hydroxyl and aromatic amine groups
- example-



HYDROLYSIS

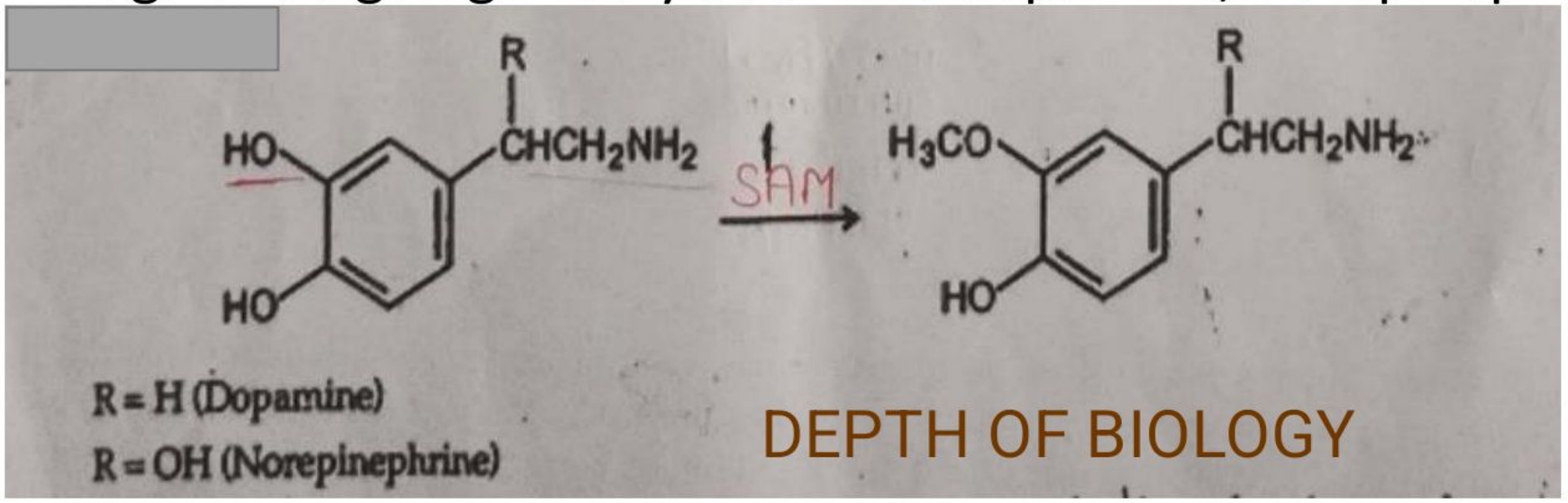
- It is observed for a wide variety of drugs.
- Enzymes involved are – esterases, amidases and proteases
- These reaction generate hydroxyl or amine groups which are suitable for phase 2 conjugation.



METHYLATION

- Most of the endogenous amines undergo methylation and get metabolized.
- Coenzyme SAM [S-adenosyl methionine] provides most of the methyl groups required for methylation
- Enzymes involved in methyl transferase for example COMT [catechol O methyl transferase.

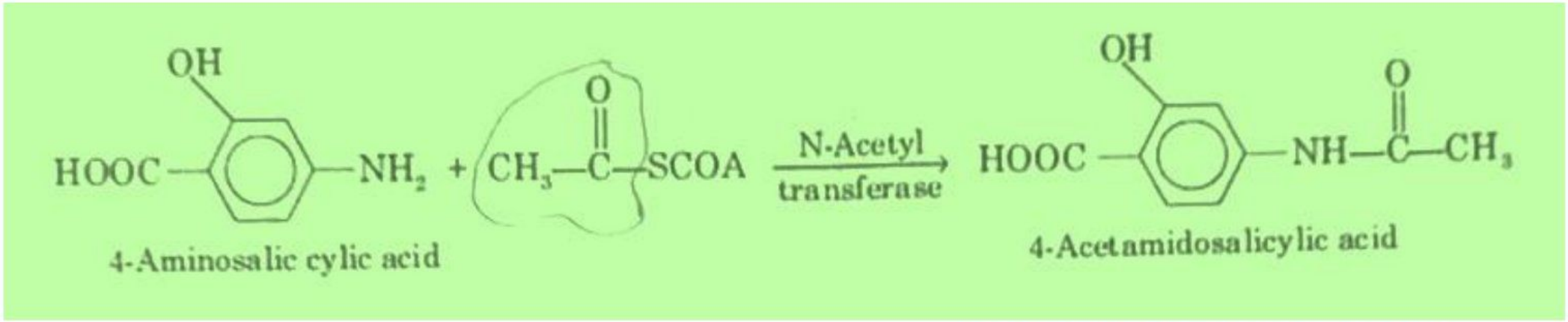
- Drugs undergoing methylation are dopamine, norepinephrine , morphine etc



This is the major reaction which causes the termination of action of various endogenous amines and neurotransmitters present in the body.

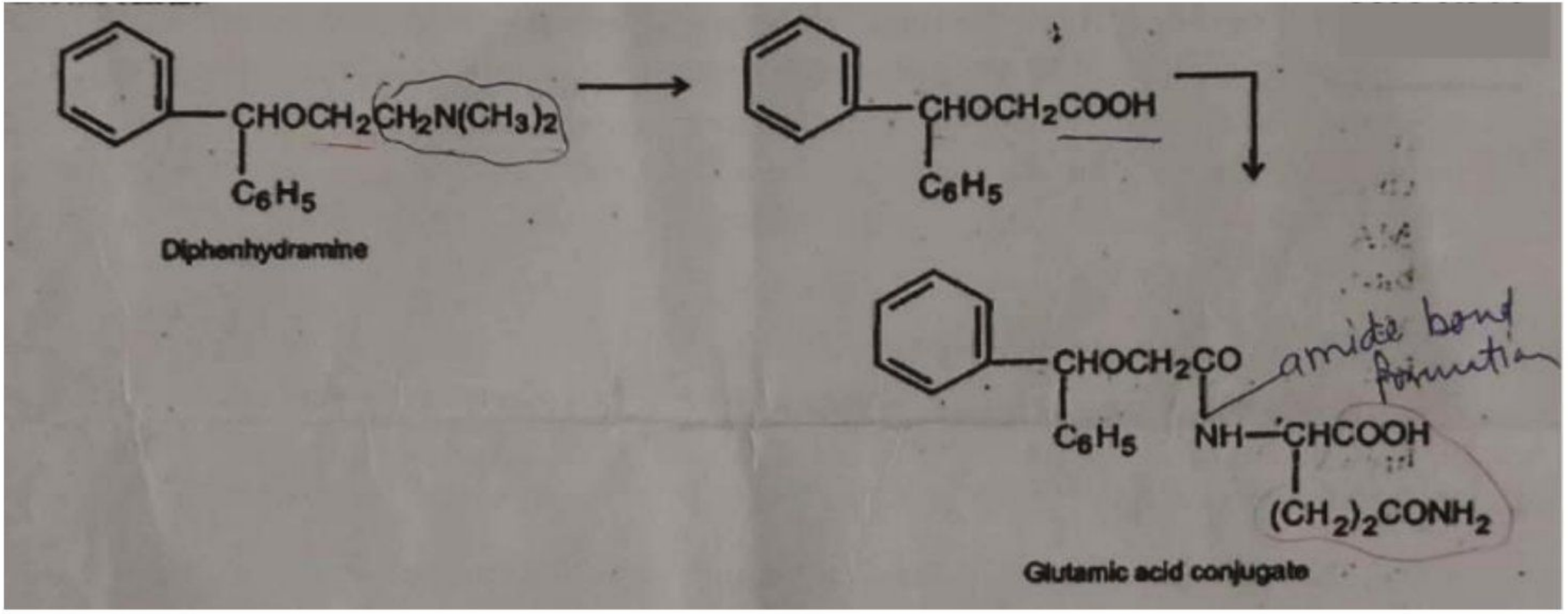
ACETYLATION

- Acetylation is an important metabolic pathway for drugs containing primary amino groups.
- The acetylated conjugates are generally non-toxic and inactive.
- Ex: histamine, procainamide, para amino salicylic acid (PAS), hydralazine, isoniazid.

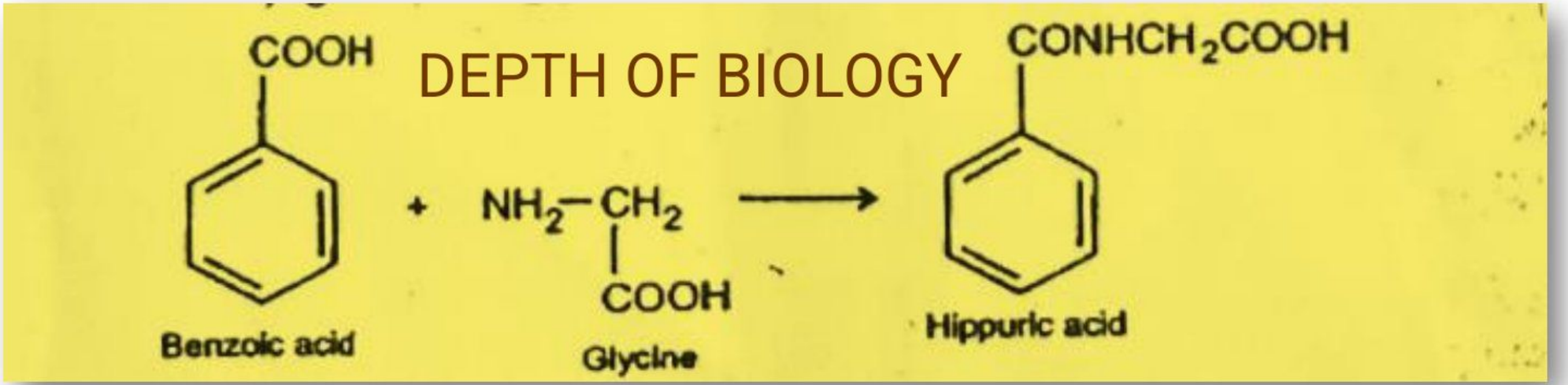


- Drugs having aromatic acids and arylalkyl acids as functional groups undergo conjugation with amino acids like glycine and glutamic acid easily.
- Metabolites of Phase-I biotransformation having carboxyl group also conjugates with glycine.

- For example, Diphenhydramine metabolism.



- Benzoic acid conjugates with glycine to form hippuric acid.



- For this conjugation process, ATP and coenzyme A are required for the activation of the drug substrate and forms an acyl-coenzyme A as an intermdiate which then transfers the acyl group to glycine and hence metabolites the drug.

Cytochrome p450

- The cytochromes P450s [CYPs] are membrane bound proteins with an approximate molecular weight of 50 kD, and contain a heme moiety.
- There are about 30 human cytochrome P450 enzymes out of which only six, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 are the metabolising enzymes.

FACTORS AFFECTING DRUG METABOLISM

1. Physicochemical properties of drugs- Molecular size, shape, acidity or basicity, lipophilicity, pKa, and steric and electronic characteristics of drugs influence its interaction with the active sites of enzymes

2. Chemical factors- A large number of chemical substances such as drugs, insecticides etc. can increase the rate of drug metabolism due to increased rate of formation of newer enzymes or decreased rate of degradation of drug metabolizing enzymes. Ex. Alcohol enhances metabolism of phenobarbitone, phenytoin etc.

3. Diet- The enzyme content and activity is altered by a number of dietary compounds. Fat free diet depresses cytochrome P450 levels since phospholipids, which are important components of microsomes become deficient.

4. Genetic or hereditary factors. Genetic and hereditary factors are the most significant factors in drug metabolism. Genetic differences among individuals or ethnic groups can lead to an excessive or prolonged therapeutic effect or toxic overdose. Ex: The enzyme CYP2D6 metabolises a large number of drugs. The activity of this enzyme varies widely among ethnic groups. About 1% of Arabies, 30% Chinese and 7-10% caucasions are poor metabolizers of CYP2D6 drugs

5. Environmental factors: Environmental factors such as smoking, alcohol consumption and concomitant drug therapy also influence the outcome of drug metabolism. Ex: Cigarette smoke produces polynuclear aromatic hydrocarbons. CYP1A2 metabolises the polynuclear aromatic hydrocarbons to carcinogens responsible for lung and colon cancer

6.Stereochemical aspects of the drug molecule : Stereochemistry of the drug also affects its metabolism by different enzymes. Stereoselective metabolism of drugs is a common example in this case. Metabolizing enzymes have different preference for one enantiomers than the other and hence results in enantioselectivity. For example (-) quinine treats the malaria fever but (-) quinine does not. ii) D (+) glucose gets easily metabolized in the body to give C02 and H20 but L(-) glucose is not metabolised and is excreted as such.

7. Biological factors: Various biological factors which affect metabolism of drug are Age o the patient, Sex of the patient, Diet, Altered physiological state like- pregnancy, disease state and hormonal imbalance etc.