

Detailed of Course Structure

Name of the Department: Chemistry

Name of the Programme (U.G./P.G./Ph.D.): Under Graduate

Semester: VI-Semester

Name of the paper/course (unit or title if there are multiple files of the same paper): Basics of Drug Design & Medicinal Chemistry

Name of the teacher: Dr. Biswajit Maji

Sl No	Unit No	Topic	Status
1	Unit I	<ul style="list-style-type: none">➤ Introduction to Medicinal Chemistry (Overall steps to discover a drug from a lead molecule)➤ Various Intermolecular Binding Forces & Drug Targets➤ Enzymes as Drug Target➤ Enzyme Kinetics➤ Receptors: It's Structure and Function➤ Receptors as Drug Target➤ Nucleic Acids as Drug Target	Completed [Handout/Study materials distributed]
2	Unit II	<ul style="list-style-type: none">➤ Pharmacokinetics➤ SAR and QSAR :Hydrophobicity, Electronic and Steric Factors (P, π, σ, E_s) [Physiochemical Properties]	Completed
3	Unit IV	<ul style="list-style-type: none">➤ Antibiotic and Antibacterial Agents	Ongoing

Lecture Note enclosed herewith for Unit II and IV

Disclaimer: There is no claim of the originality of the material and it is given only for the students to study

References:

1. An Introduction to Medicinal Chemistry (Sixth Edition) by Graham Patrick
2. NPTEL Course: Drug Discovery and Medicinal Chemistry by Prof. Harinath Chakrapani, IISER-Pune.
3. The Organic Chemistry of Drug Design and Drug Action by R. B. Silverman and M. W. Holladay

Pharmacokinetics & Pharmacodynamics

• Pharmacodynamics : is the study of how drugs interacts with a molecular target to produce a pharmacological effect,

Whereas pharmacokinetics is the study of how a drug reaches its target in the body and how it is affected on that journey.

• The four main issues in pharmacokinetics, they are — ADME.

- Absorption (A)
- Distribution (D)
- Metabolism (M)
- Excretion (E)

▣ Journey of a Drug

- The preferred route of administration of a drug is by mouth (oral). This is the most cost effective in terms of patient care.
- When a drug is swallowed, it enters Gastrointestinal tract (GIT), which comprises the mouth, throat, stomach and the upper & lower intestines.

• A certain amount of the drug may be absorbed through the mucosal membranes of the stomach, but most passes down into the stomach where it encounters gastric juice and hydrochloric acid.

Thus acid-labile drugs including the local anaesthetics and insulin administered by injection.

• Next if the drug does survive in the stomach, it enters GIT where it encounters with several digestive enzymes.

• Assuming the drug survives this attack, it then has to pass through the cells lining the gut wall.

• Once the drug has passed through the cells of the gut wall, it can enter the blood supply relatively easily. In this stage, the drug passes between cells rather than through them.

(2)

Finally the drug has to be carried by the blood supply around the body to reach its eventual target, which may require crossing further cell membranes - always assuming that it is neither excreted before it gets there nor diverted to parts of the body where it is not needed.

Absorption :

A drug must have the right balance of water & fat solubility. If the drug is too polar (hydrophilic), it does not pass through the fatty cell membranes of the gut wall. If the drug is too hydrophobic, it will be poorly soluble and will instead dissolve in fat globules - resulting in poor absorption.

The right combination of hydrophilic & hydrophobic balance in a drug is very important for effective absorption, so, the MW of the drug should be irrelevant.

Rule of five (Lipinski's Rule of five)

The rule of five was derived from an analysis of compounds from the "World Drugs Index Database" — for making orally active drugs:

- i) a molecular weight less than 500;
- ii) no more than 5 hydrogen bond donor groups.
- iii) no more than 10 hydrogen bond acceptor groups
- iv) a calculated log P value less than +5.

(~~Lipinski's Rule~~ ✓)

In a nutshell, For orally active Drug molecules:

- a) The Drug must be stable enough to chemical and enzymes
- b) It must reach the target in therapeutic concentration $[IC_{50}]$.

Distribution :

- Highly polar drugs can be orally active if they are small to pass between the cells of the gut wall, are recognized by carrier proteins, or taken across the gut wall by pinocytosis.

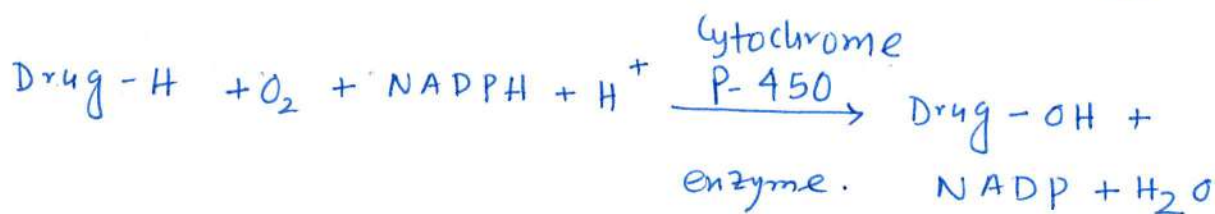
- Once a drug has been absorbed it is rapidly distributed around the blood supply, then distributed more slowly to the various tissues and organs.
- The vessels carrying blood around the body are called arteries, veins and capillaries. Each capillary is very narrow — not much wider than the RBC that pass through it. Its walls are made up a thin, single layer of cell packed tightly together.
- However, there are pores between the cells which are 90-150 Å in diameter — large enough to allow most drug-sized molecules to pass through, but not large enough to allow the plasma proteins present in blood to escape. ~~so~~
- Therefore, drugs do not have to cross cell membranes in order to leave the blood system, and can freely & rapidly distributed into the aq. fluid surrounding the various tissues & organs of the body.

Metabolism :

Most drugs undergo some form of metabolic reaction, resulting in structures known as metabolites. These metabolites do not have any activity. In exceptional cases, the metabolite may even be more active than the parent drug. Prodrug strategy discovered based on drug metabolism concept.

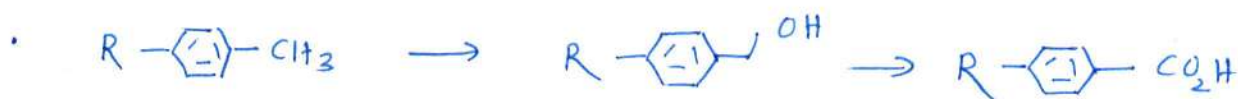
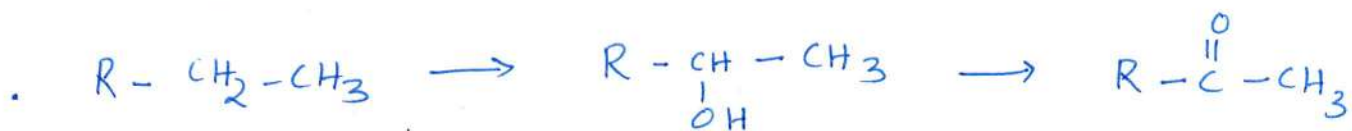
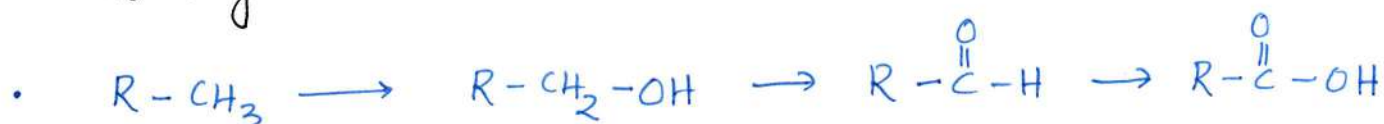
- phase I and phase II metabolism
↓ (metabolism occur in liver)
- if the drug is polar, it will be quickly excreted by kidney. However, non-polar drugs are not easily excreted so, the purpose of drug metabolism is to convert more polar molecules that can be easily excreted.
- Non-specific enzymes (cytochrome P450 enzymes in the liver) are able to add polar functional group to a wide variety of drugs.

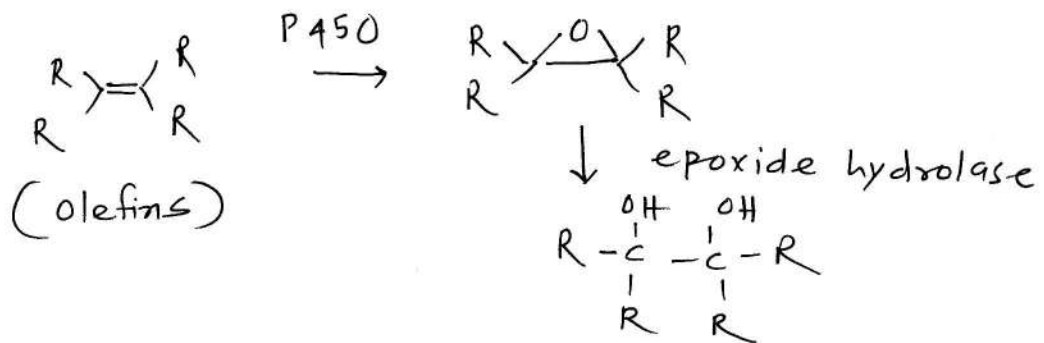
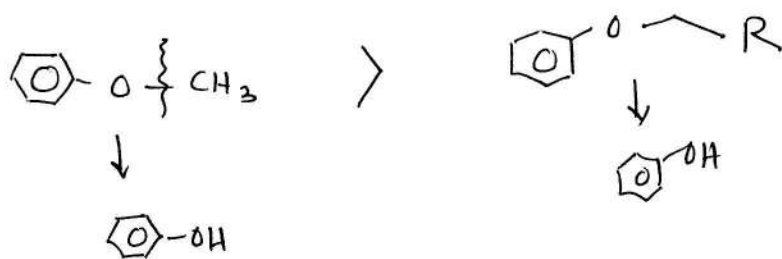
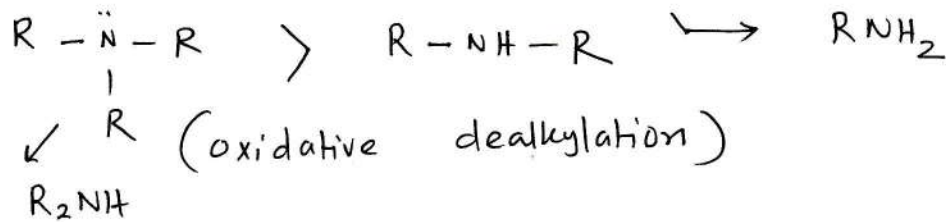
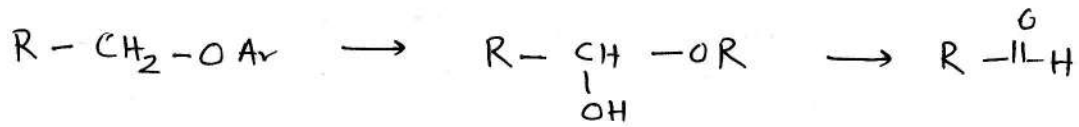
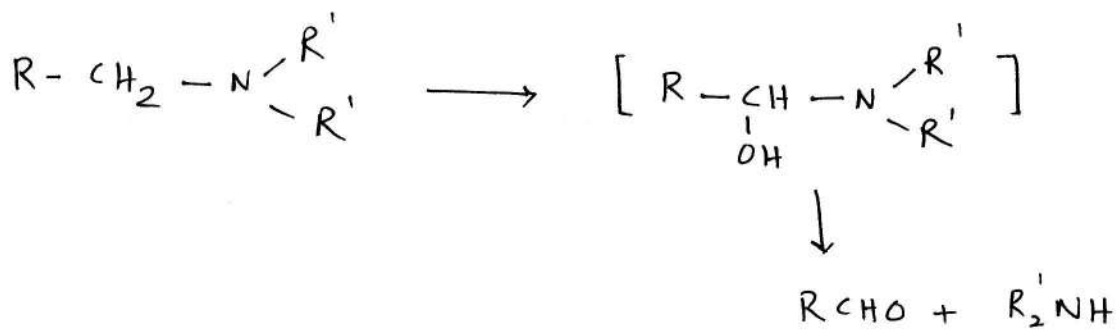
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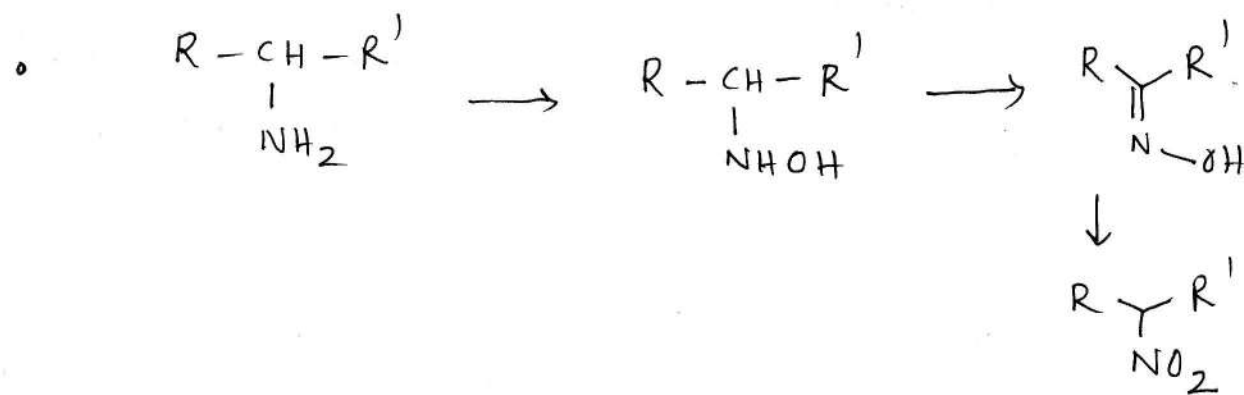
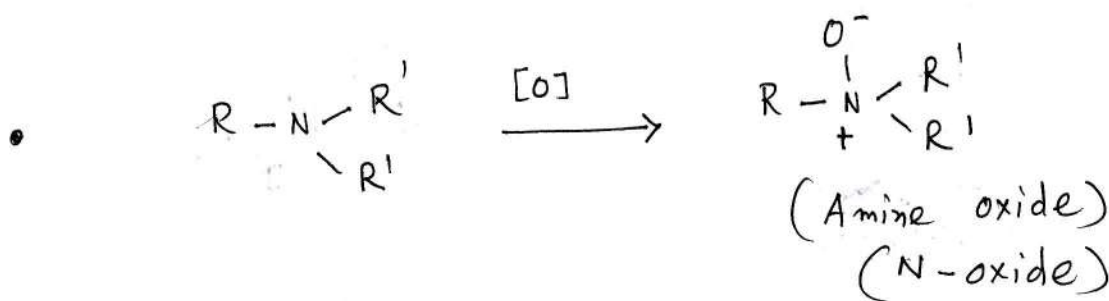
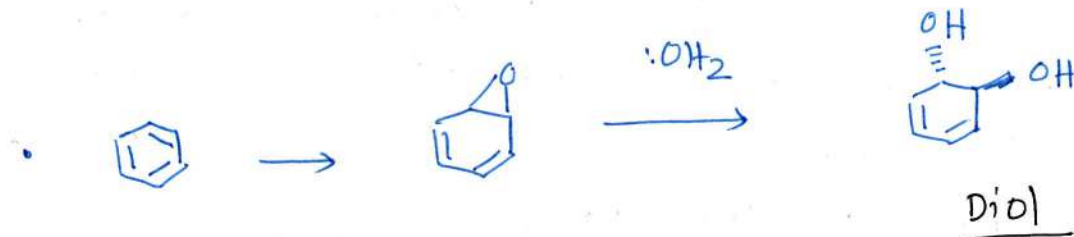
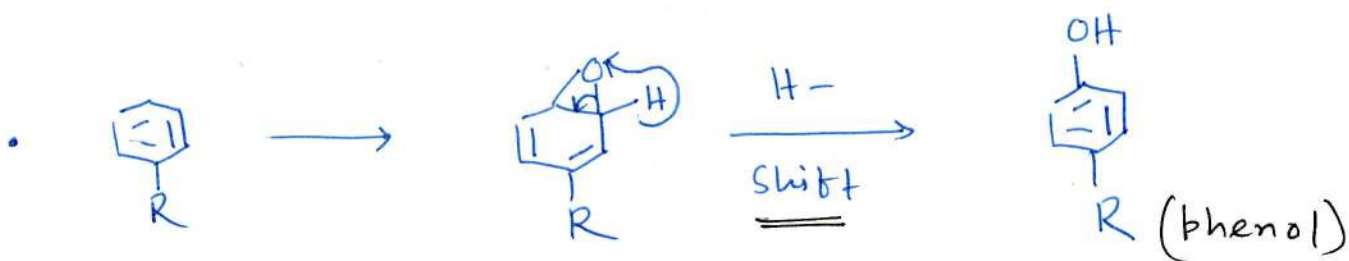
P450 enzymes are haemoproteins (containing haem and iron) and they catalyze a reaction that splits molecular O_2 , such that one of the oxygen atoms is introduced into the drug molecule [drug-H \rightarrow drug-OH] and other part ends up in H_2O . — Monooxygenases.

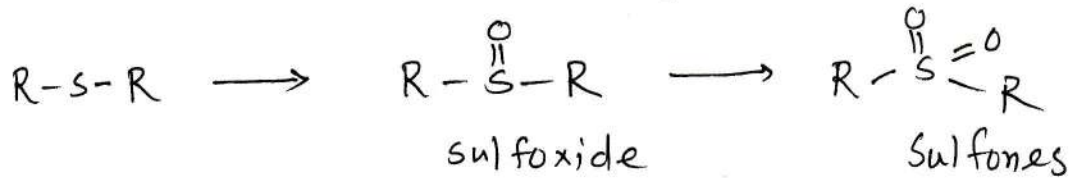
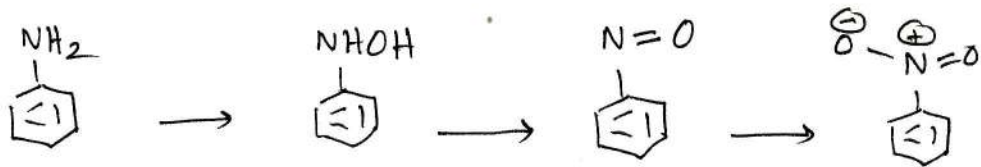
Following reactions are considered : —





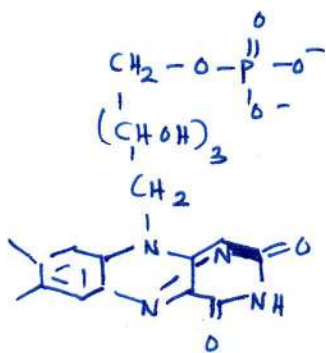
The oxidation of an aromatic ring can lead to the formation of an epoxide as well. This epoxide can undergo a hydride shift to produce a phenol or the ring can be opened with H₂O to give a diol.



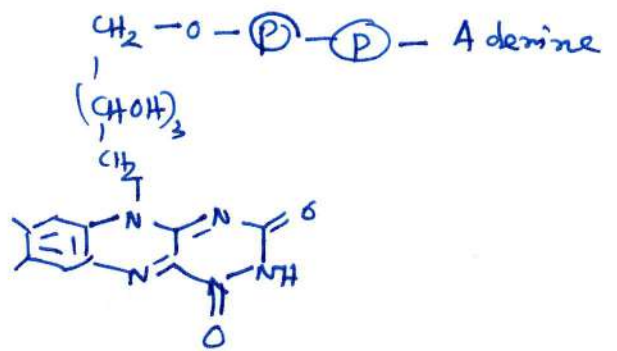


Therefore, Cytochromes P450 are among the chief enzymes that carry out metabolic reactions.

Another group of metabolic enzyme present in the endoplasmic reticulum of liver cells consists of the flavin-containing monooxygenases.



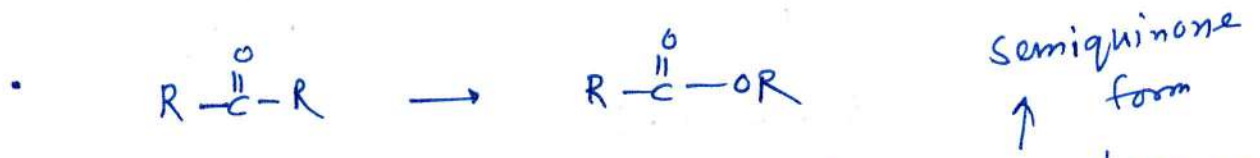
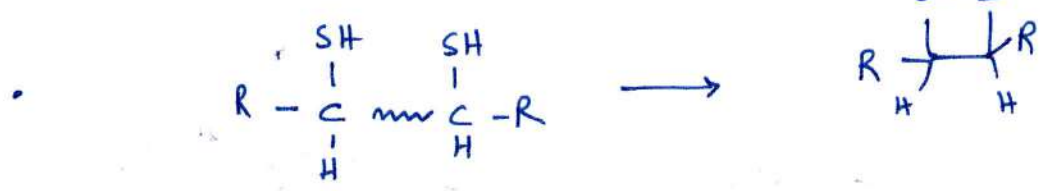
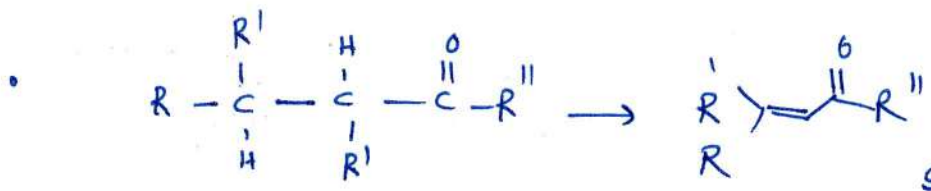
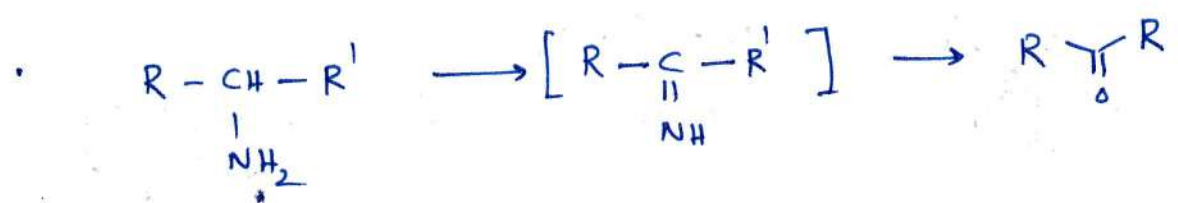
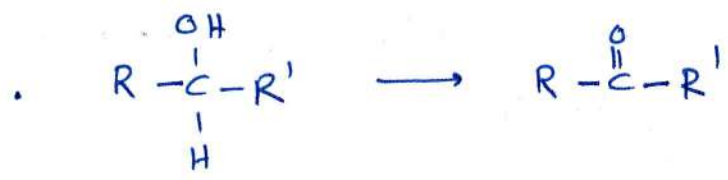
(Flavin mononucleotide)



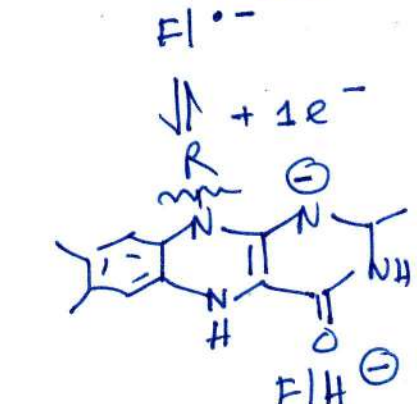
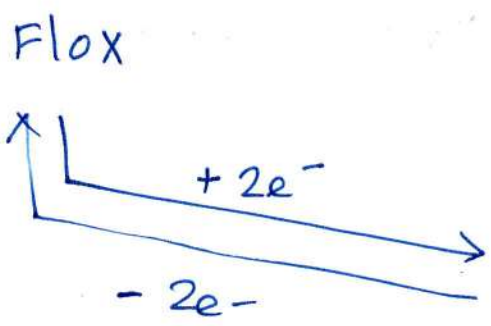
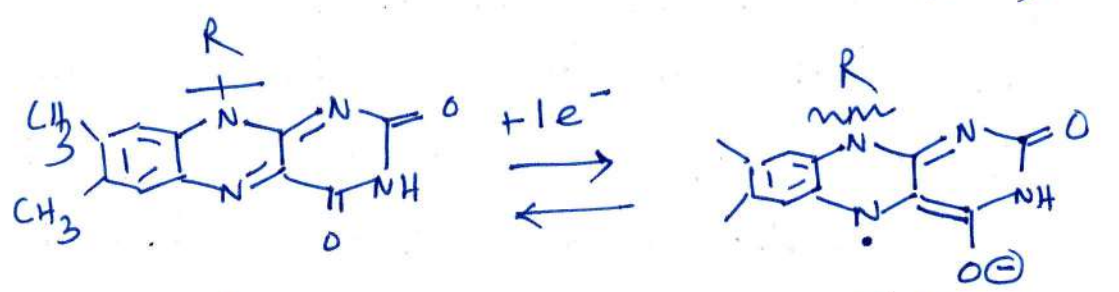
FAD

Flavin adenine dinucleotide.

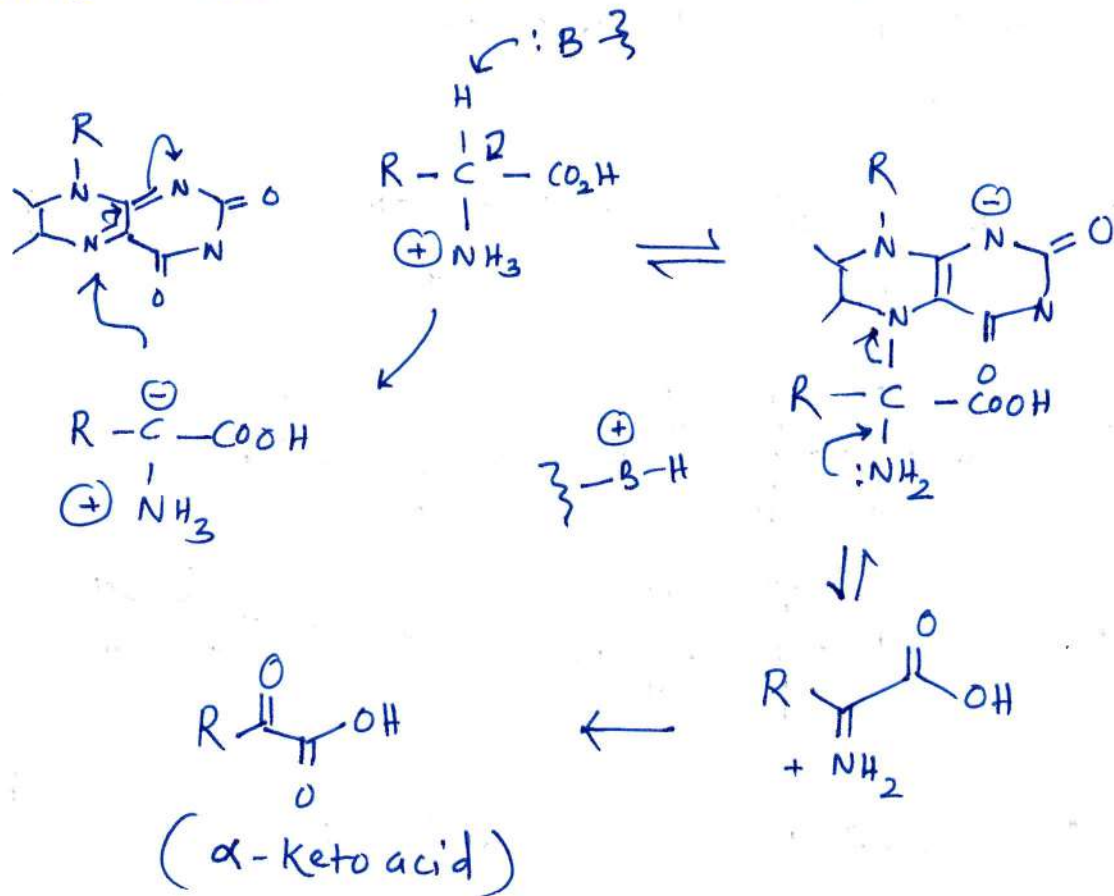
Reactions Catalysed by Flavin - Dependent enzymes.



oxidation/reduction occurs through Fl_{ox}, Fl^{•-} / Fl/H⁻



The flavoenzyme D-amino acid oxidase which catalyzes the oxidation of D-amino acids to α -keto acids & ammonia.



MAO (monoamine oxidase), a flavo-enzyme important in medicinal chemistry. This is one of the enzymes responsible for the catabolism of various biogenic amine neurotransmitters, such as dopamine.

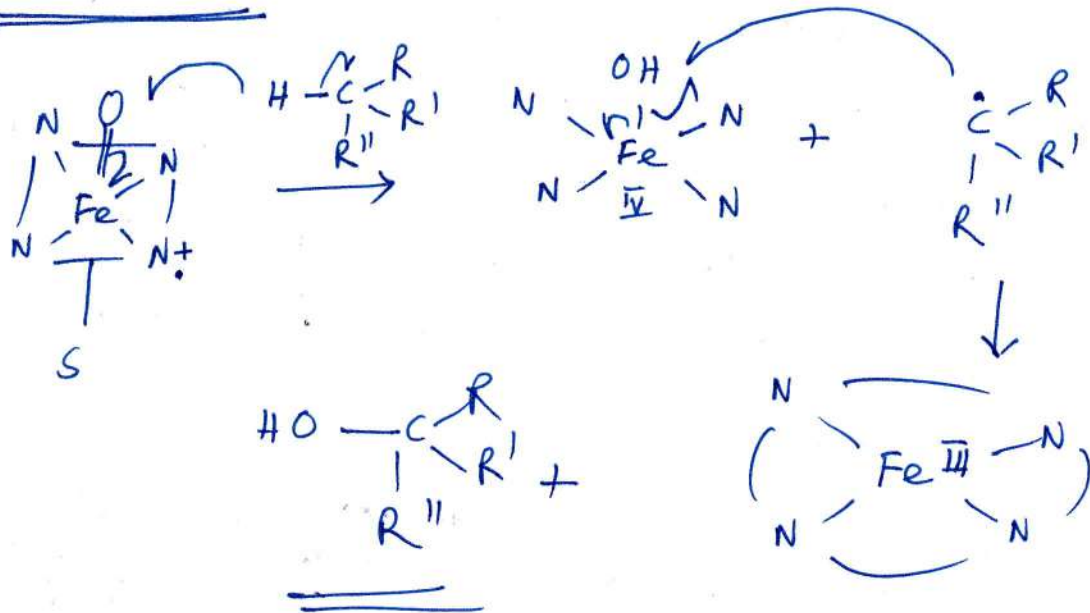


Dopamine

Mechanism of H~~ex~~em-dependent oxidation reaction - "Heme-dependent oxidation"

The reaction is mediated by a "Fe=O" species, which is formed from heme.

Oxidation



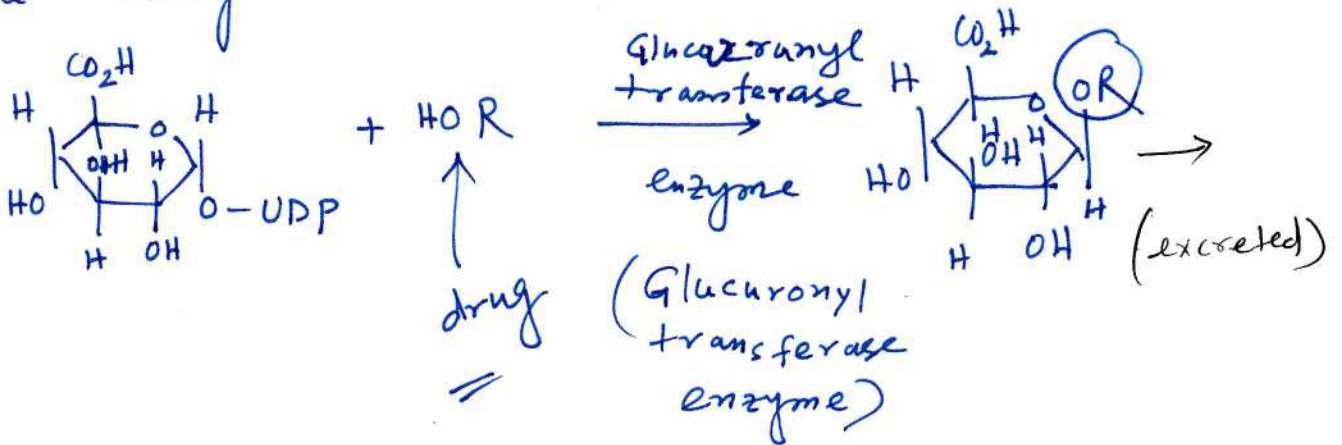
• Esterases and Peptidases

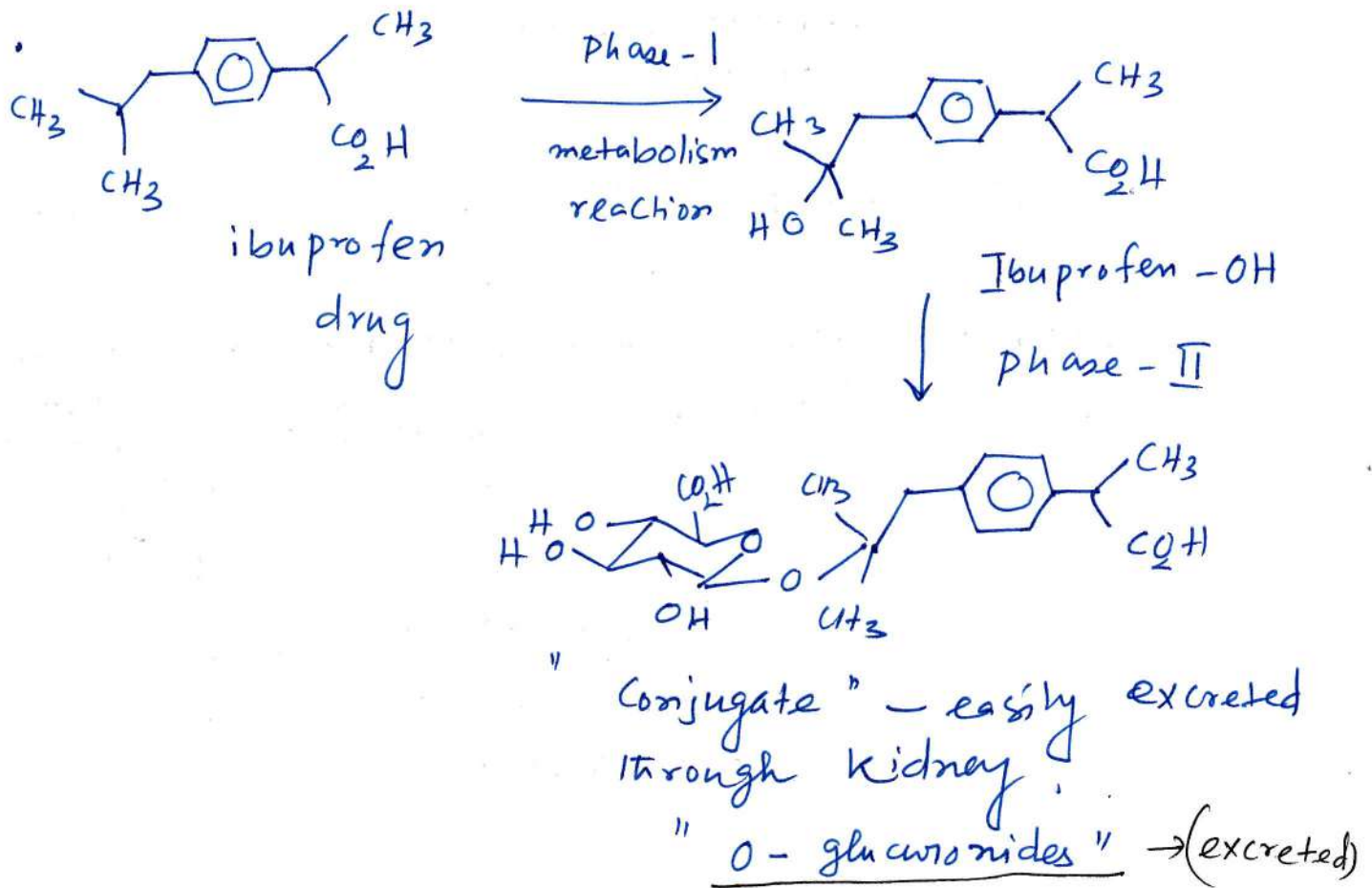


Phase - II Transformations

• Most Phase II reactions are conjugation reactions catalysed by transferase enzymes.

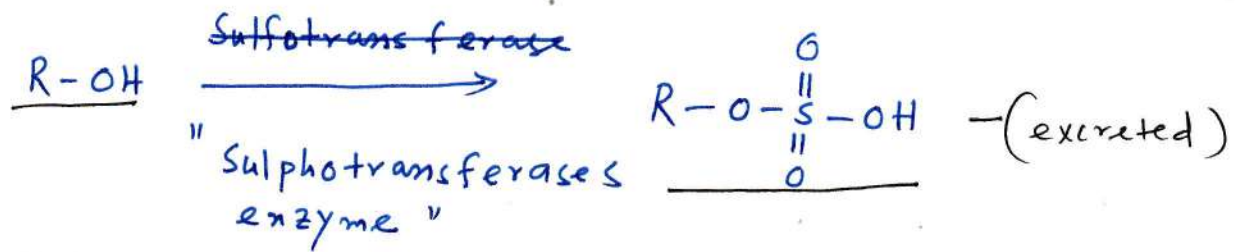
• Glucuronic acid conjugation is the most common of these reactions. Phenol, hydroxylamine, carboxylic acids form O-glucuronides by reaction with UDP-glucuronate such that a highly polar glucononic acid molecule is attached to the drug.



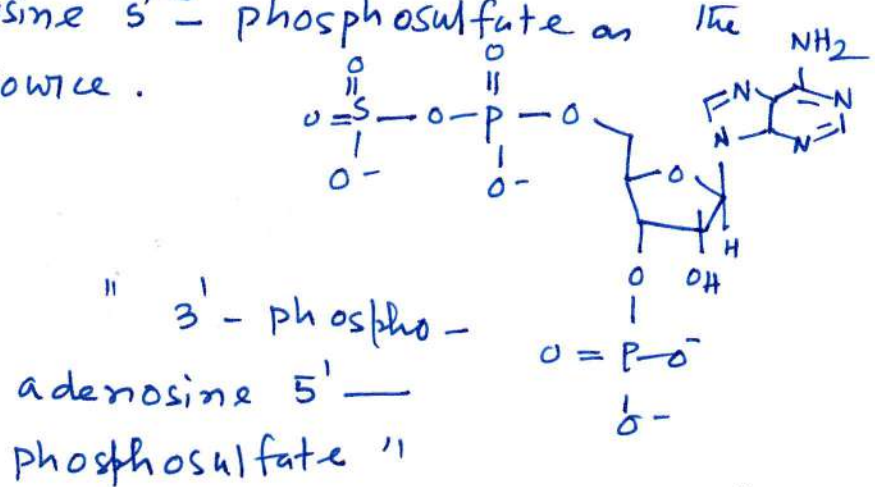


• Phenols, alcohols and amines form O- or N-glucuronides by reaction with UDP-glucose such that the highly polar glucose molecule is attached to the drug.

Another form of conjugation is sulphate conjugation. This is less common than glucuronation and is restricted mainly to phenols, alcohols, arylamines & N-hydroxy compounds.



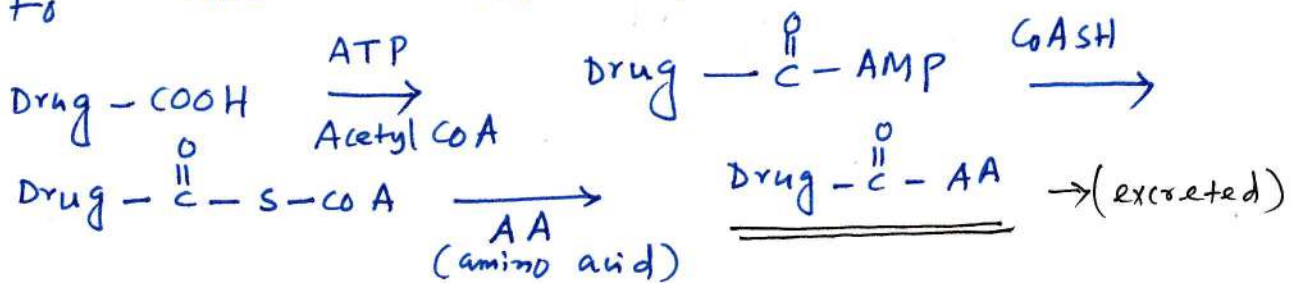
The reaction is catalysed by Sulphotransferases using the cofactor 3'-phosphoadenosine 5'-phosphosulfate as the sulphate source.



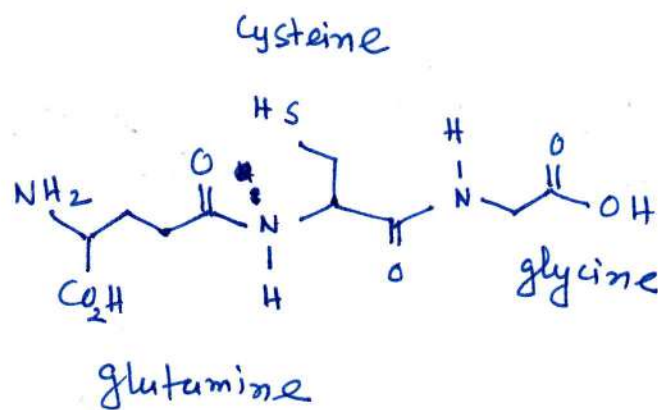
Drugs bearing a carboxylic acid (-COOH) can become conjugated to amino acids by the formation of a peptide link.

In most animals, glycine conjugates are generally formed but L-glutamine is the most common acid used for the conjugation in primates.

The -COOH gr. present in the drug is first activated by formation of a coenzyme A thioester which is then linked to the amino acid.



Electrophilic functional groups such as epoxide [metabolite from Phase I metabolism of olefins], alkyl halides, sulphoxates, disulphides, and radical species — these are reacted with the nucleophilic thiol group of the tripeptide glutathione (GSH)

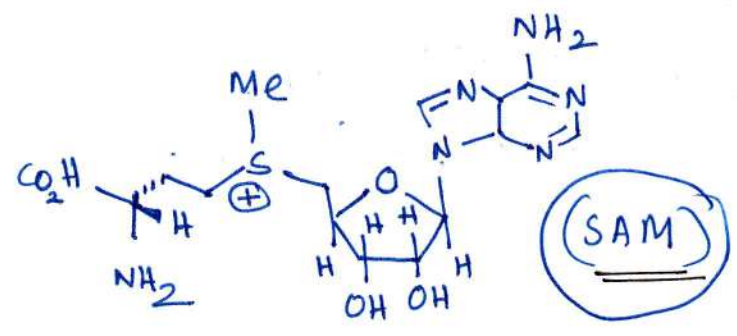


[This glutathione is an antioxidant in plants, animals, fungi and some bacteria. Glutathione also is capable of preventing damage to ~~the~~ important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides and heavy metals etc.]

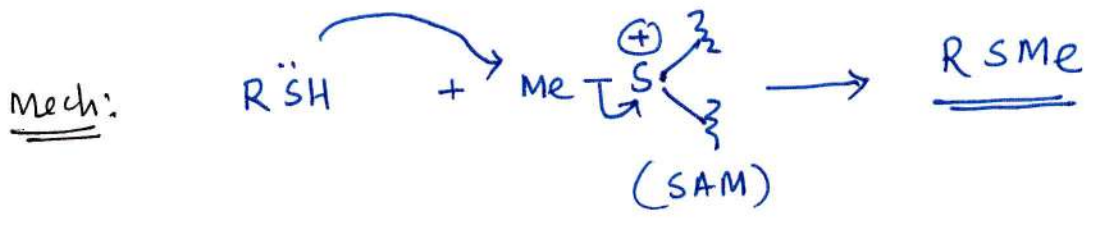
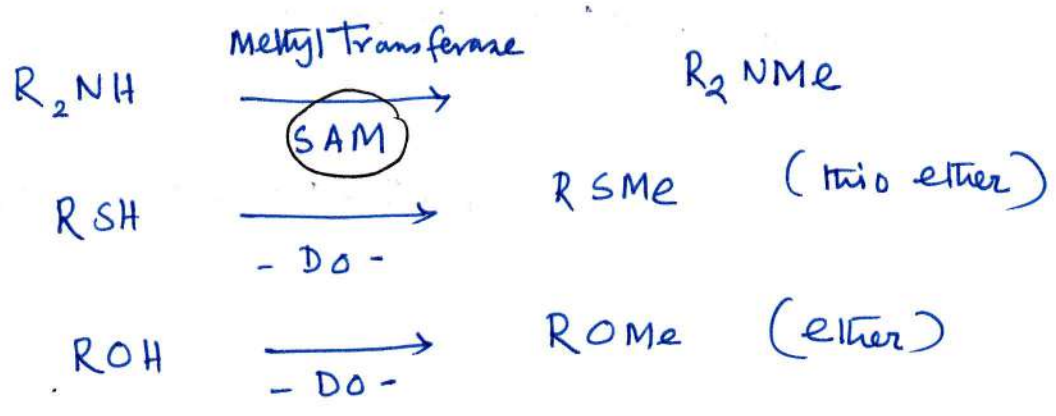
The glutathione conjugation reaction can take place in most cells, especially those in the liver & kidney and is

OK. Not all phase II reactions result in increased polarity.

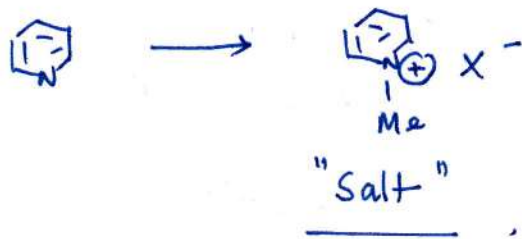
• Methylation and acetylation are important phase II reactions of amine, alcohol & thiol usually decrease the polarity of the drug. The methylation can be done by SAM "S-adenosyl methionine" as a reagent using methyltransferase enzyme.



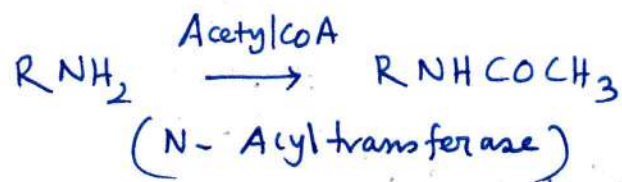
(S-Adenosyl methionine)



An important exception is the methylation of pyridine rings, which leads to polar quaternary salts.



Primary amines are also susceptible to acetylation.



Drugs bearing -COOH also become conjugated with cholesterol.

