Second Semester (2020-2021)

Pharmaceutical Chemistry I

Topic 2

Metabolic Changes of Drugs and Related Organic Compounds

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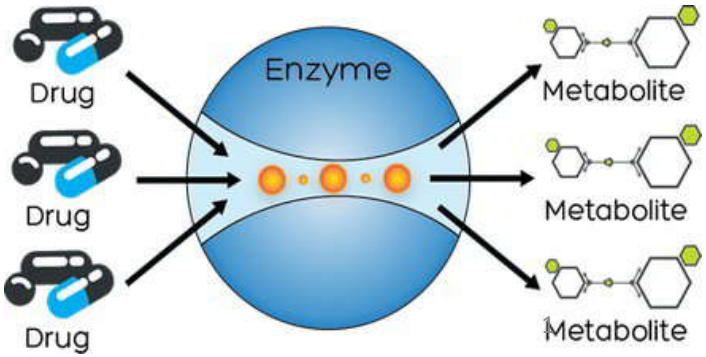
Pharmaceutical Chemistry and Drug Control



Definitions

- ***Metabolic Changes of Drugs and Related Organic Compounds*** describes the human metabolic processes of various functional groups found in therapeutic agents.
- ***Drug Metabolism***: Process of converting a drug into **product** or **inert** substances after or before reaching at the site of action
- Metabolism is an essential pharmacokinetic process, which render lipid soluble and non polar compounds to water soluble and polar compounds so that they are excreted by various process from the body.
- ***Biotransformation***: It is a specific term used for the chemical transformation of xenobiotics in the living organisms.
- ***Xenobiotics***: These are all chemical substances that are not nutrient for the body (foreign body) and which enter the body through ingestion, inhalation or dermal exposure.

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Drug Metabolism

- Most organic compounds entering the body are relatively lipid soluble (lipophilic).
- To be **absorbed**, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract.
- Then, once in the **bloodstream**, these molecules can diffuse passively through other membranes and be **distributed** effectively to reach various target organs *to exert their pharmacological actions*.
- Because of **reabsorption** in the renal tubules, lipophilic compounds are not **excreted** to any substantial extent in the urine.
- Xenobiotics are metabolized through various enzyme systems that change the parent compound to render it more water soluble (hydrophilic).
- Once the metabolite is sufficiently water soluble, it may be excreted from the body.
- If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects.

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Drug Metabolism

- Thus, the formation of water-soluble metabolites:

  I. Enhances drug elimination

  II. Leads to compounds that are generally pharmacologically inactive and relatively nontoxic.

- Drug metabolism reactions have traditionally been regarded as detoxication (or detoxification) processes.

- Unfortunately, it is incorrect to assume that drug metabolism reactions are always detoxifying:

  Many drugs are biotransformed to pharmacologically active metabolites. These metabolites may have significant activity that contributes substantially to the pharmacological or toxicological effects ascribed to the parent drug.

- Occasionally, the parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite) → referred to as **Prodrugs**

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Phases of Metabolism

Phase 1 Reaction (Non Synthetic Phase)	Phase 2 Reaction (Synthetic Phase)
• It is called **Functionalization Reaction** • **Function:** Introduction of functional groups such as -OH, -NH_2, -SH, -COOH into the compound to produce more water soluble compound. • **Reaction type:** Oxidation, Reduction and Hydrolysis.	• It is called **Conjugation Reaction** • **Function:** Conjugation of functional groups of a compound or its metabolites with endogenous substrate to form water soluble conjugated products. • **Reaction type:** Glucuronidation, sulfation, Glutathione conjugation , Acetylation and Methylation.

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Gastrointestinal Mucosa

- If Important site for extra hepatic metabolism of orally administered drugs and contains:

1. CYP 3A4 isozyme ⟶ Drug metabolism.
2. p-glycoprotein ⟶ Drug extrusion to GIT
3. *Esterases* are important for metabolism of ester prodrugs
4. Bacteria micro flora also produce *azo and nitro reductases* for activation of prodrugs E.g. sulfasalazine
5. Intestinal *β−glucuronidase* enzyme is also responsible for hydrolysis of glucuronide conjugates that are circulated in bile e.g. digoxin

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Role of cytochrome P450 monooxygenases in oxidative biotransformations

- The CYP monooxygenases are located in the endoplasmic reticulum of liver cells
- The CYP enzymes are heme proteins:
  - Iron-containing porphyrin called protoporphyrin IX
  - Protein portion is called the apoprotein
- *The name cytochrome P450 is derived from the fact that the reduced (Fe^{2+}) form of this enzyme binds with carbon monoxide (CO) to form a complex that has a distinguishing spectroscopic absorption maximum at 450 nm.*
- They are involved in:

1. The metabolism of many drugs and dietary substances
2. Synthesis of steroid hormones and other extracellular lipid signaling molecules

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Role of cytochrome P450 monooxygenases in oxidative biotransformations

- General stoichiometry that describes the oxidation of many xenobiotics (R-H) to their corresponding oxidized metabolites (R-OH) is given by the following equation:

$$\mathbf{RH + NADPH + O_2 + H^+ \rightarrow ROH + NADP^+ + H2O}$$

- The enzyme systems carrying out this biotransformation are referred to as **mixed-function oxidase** or **monooxygenases**
- The reaction requires both molecular oxygen and the reducing agent NADPH
- During this oxidative process, one atom of molecular oxygen is introduced into the substrate R-H to form R-OH and the other oxygen atom is incorporated into water
- CYP enzymes, are responsible for transferring the oxygen atom to the substrate R-H

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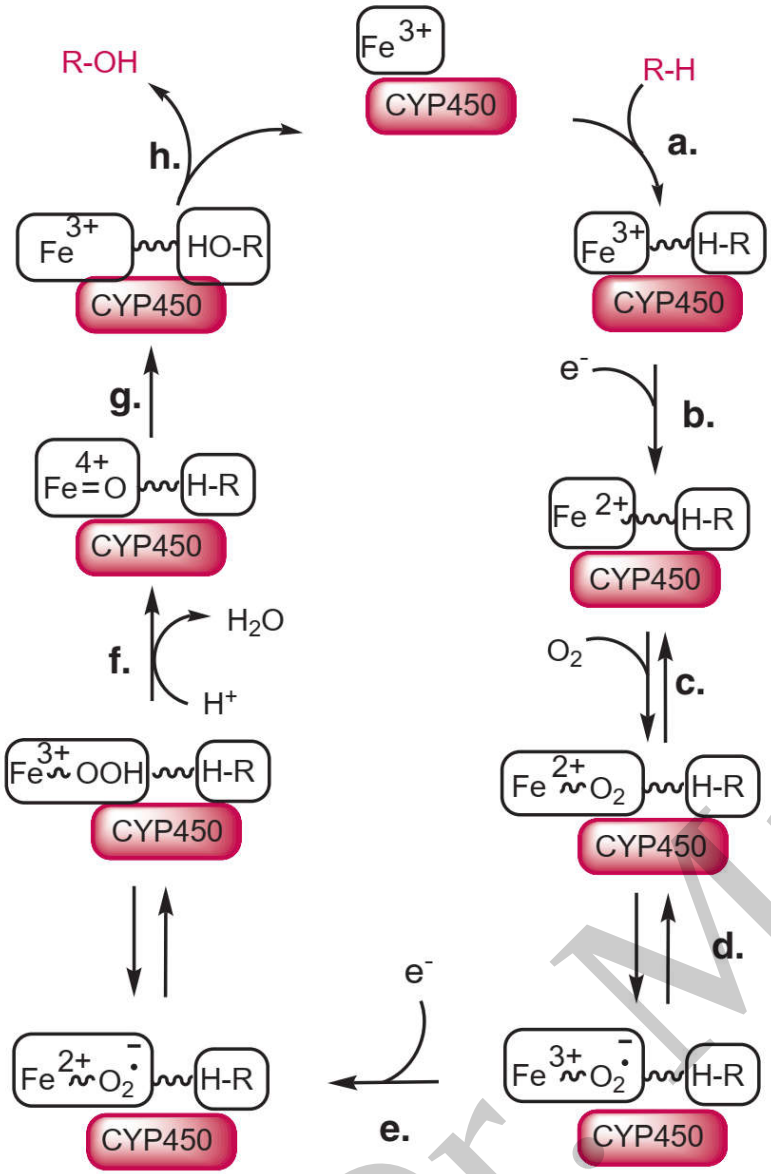

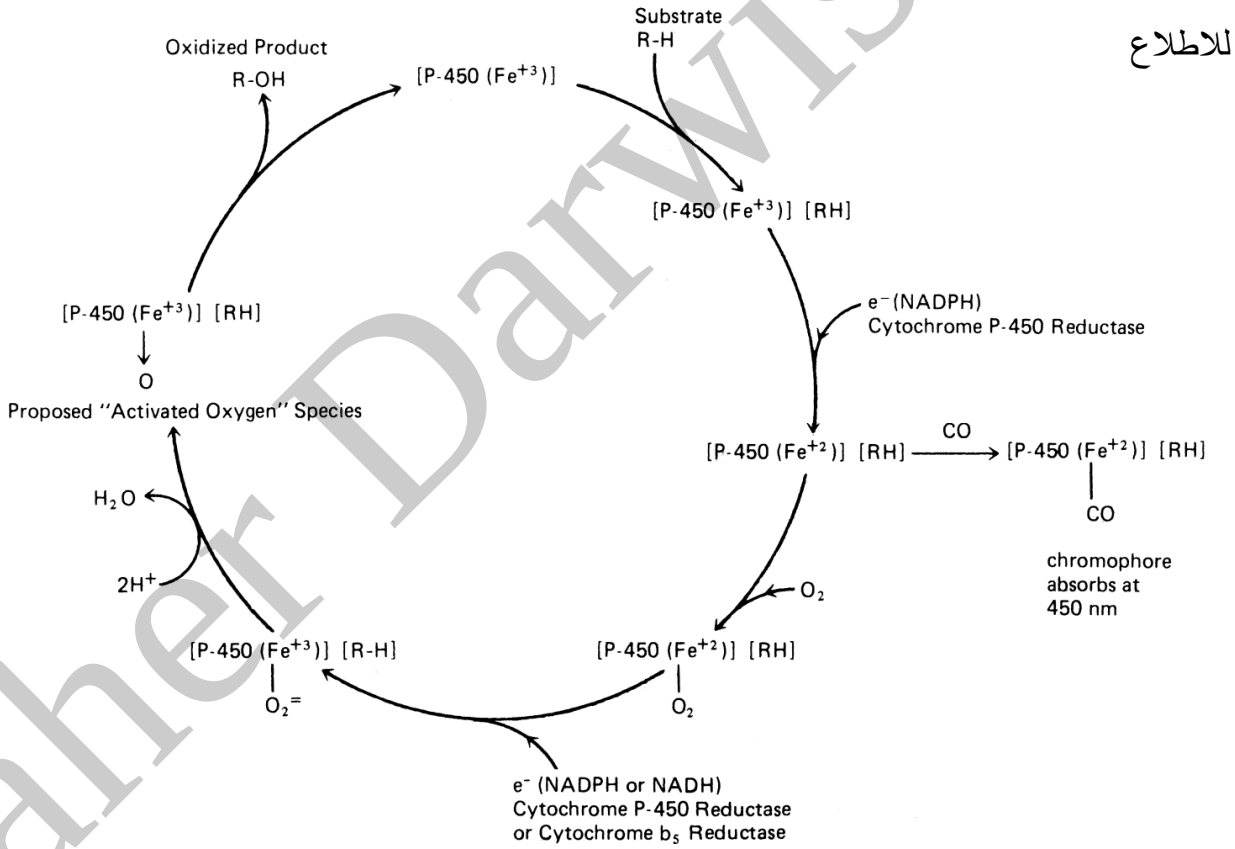

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Proposed catalytic reaction cycle involving cytochrome P450 in the oxidation of xenobiotics

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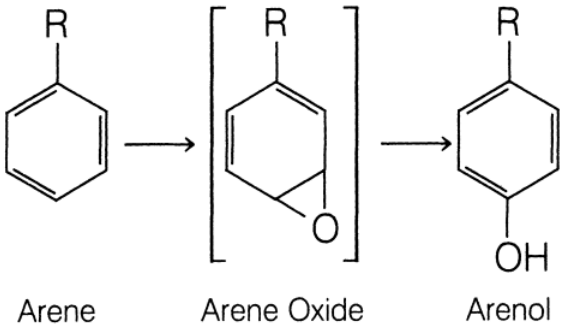
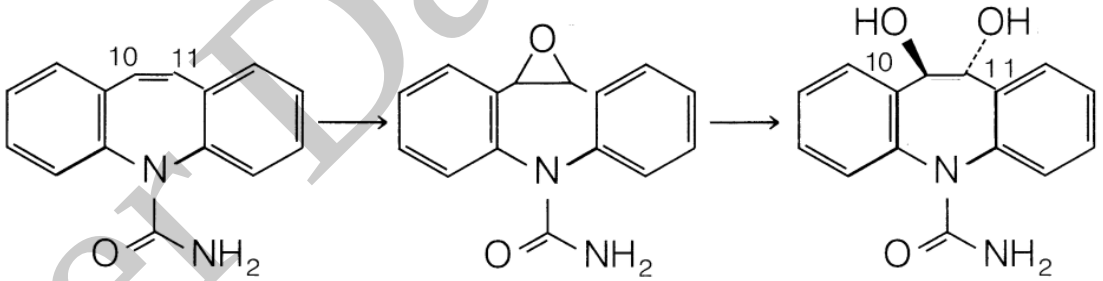
1 Oxidative Reactions

1- Oxidation of Aromatic Moieties

Refers to the mixed-function oxidation of aromatic compounds (arenes) to their corresponding phenolic metabolites (arenols)



Arene Arene Oxide Arenol



Carbamazepine Carbamazepine-10,11-epoxide *trans*-10,11-Dihydroxy-carbamazepine

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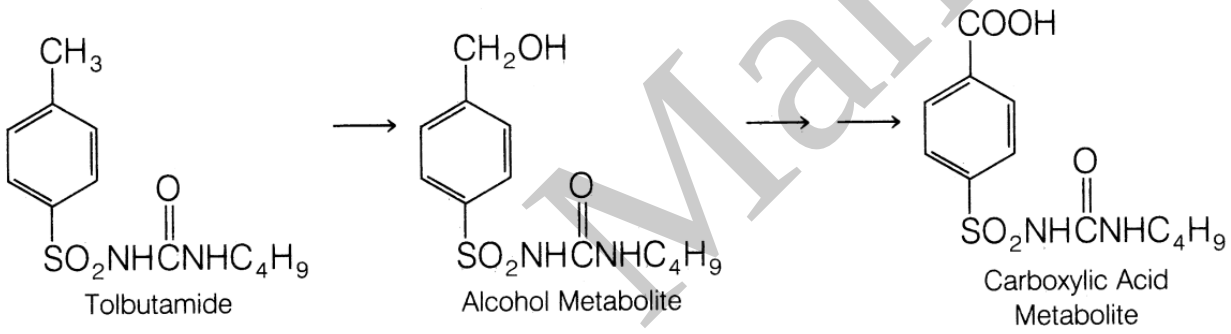
1 Oxidative Reactions

3- Oxidation at Benzylic Carbon Atoms

- Carbon atoms attached to aromatic rings (benzylic position) are susceptible to oxidation, thereby forming the corresponding alcohol (**carbinol**) metabolite
- Primary alcohol metabolites are often oxidized further to aldehydes and then carboxylic acids (CH2OH → CHO → COOH), and secondary alcohols are converted to ketones by **alcohol and aldehyde dehydrogenases**
- Alternatively, the alcohol may be conjugated **directly** with glucuronic acid.



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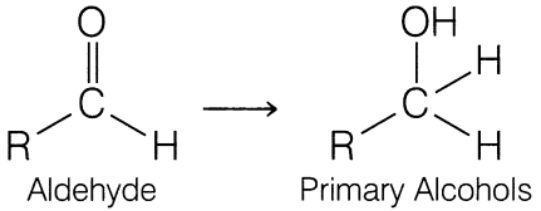
2 Reductive Reactions

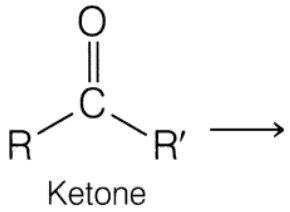
- Reductive processes play an important role in the metabolism of many compounds containing carbonyl, nitro, and azo groups:
  - ✓ Carbonyl compounds generates alcohol derivatives
  - ✓ Nitro and azo reductions lead to amino derivatives
- The hydroxyl and amino moieties of the metabolites are much more susceptible to conjugation than the functional groups of the parent compounds ⟹ reductive processes, facilitate drug elimination

1- Reduction of Aldehydes and Ketones Carbonyls

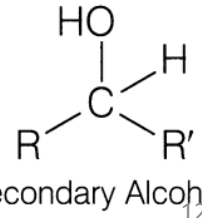
- The carbonyl moiety, particularly the ketone group, is encountered frequently in many drugs
  - ➢ Aldehydes are reduced to primary alcohols
  - ➢ Ketones are generally resistant to oxidation and are reduced mainly to secondary alcohols



Aldehyde → Primary Alcohols



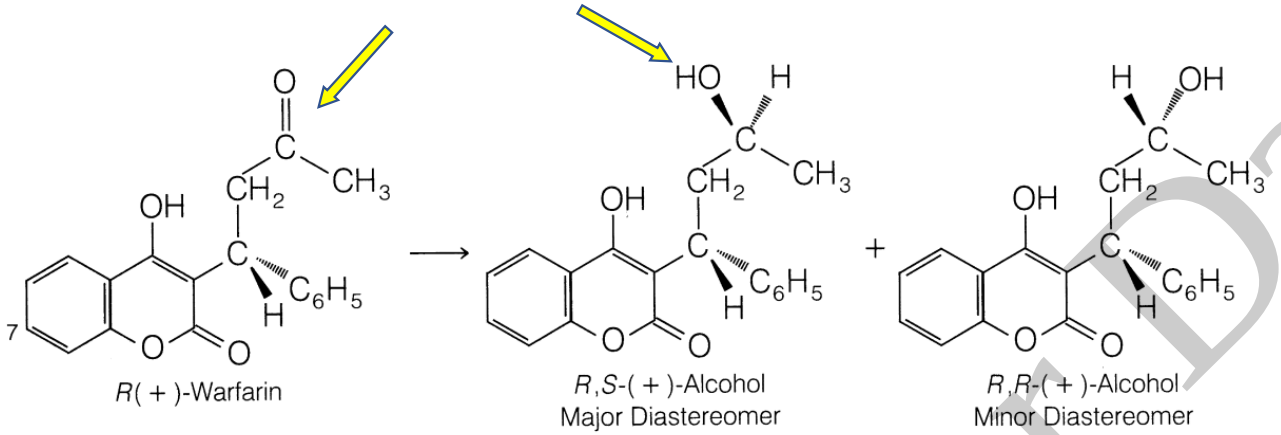
Ketone →

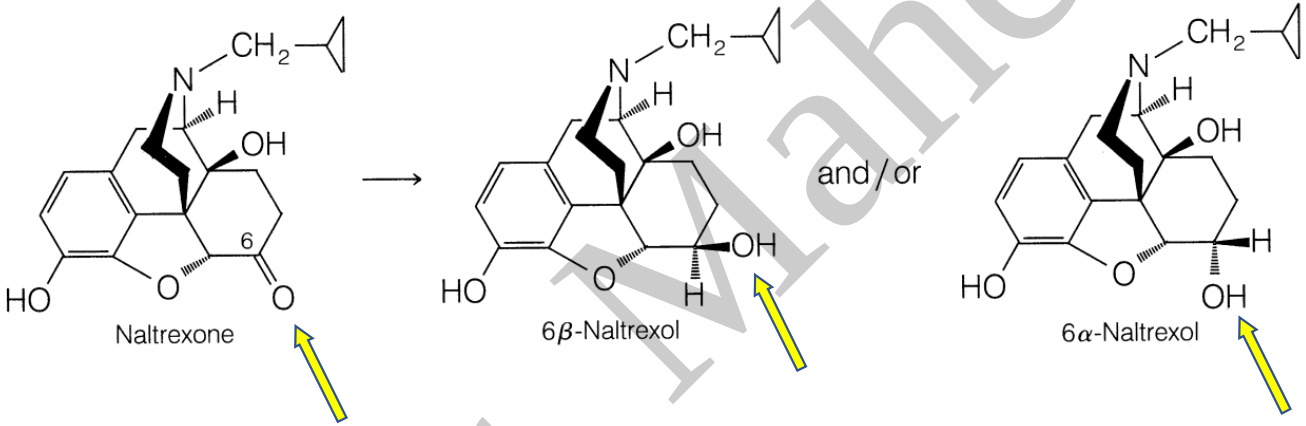


Secondary Alcohols (stereoisomeric products possible)

2 Reductive Reactions

1- Reduction of Aldehydes and Ketones Carbonyls





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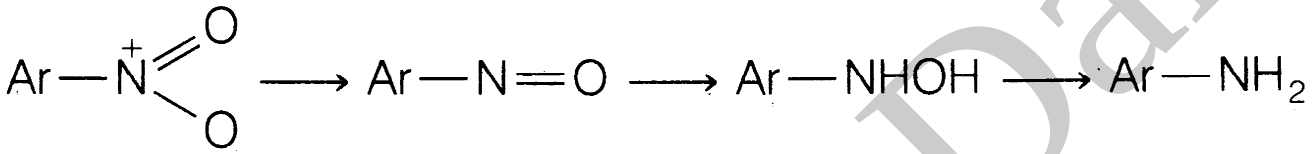
2 Reductive Reactions

2- Reduction of Nitro and Azo Compounds

- The reduction of aromatic nitro and azo xenobiotics leads to aromatic primary amine metabolites
  - Aromatic nitro compounds are reduced initially to the nitroso and hydroxylamine intermediates



Nitro → Nitroso → Hydroxylamine → Amine

  - Azo reduction is believed to proceed via a hydrazo intermediate (-NH-NH-) that subsequently is cleaved reductively to yield the corresponding aromatic amines

Azo → Hydrazo → Amines

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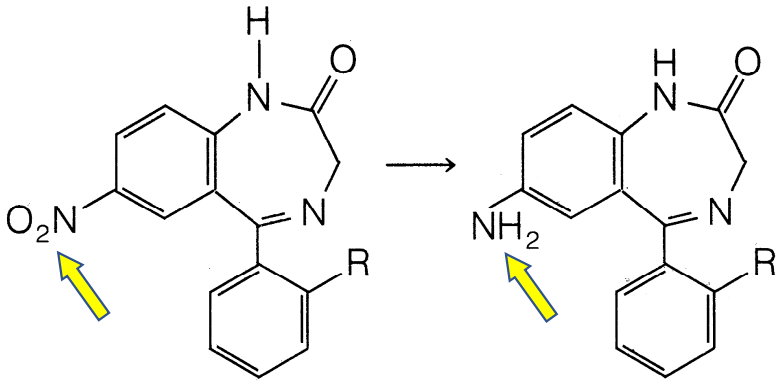
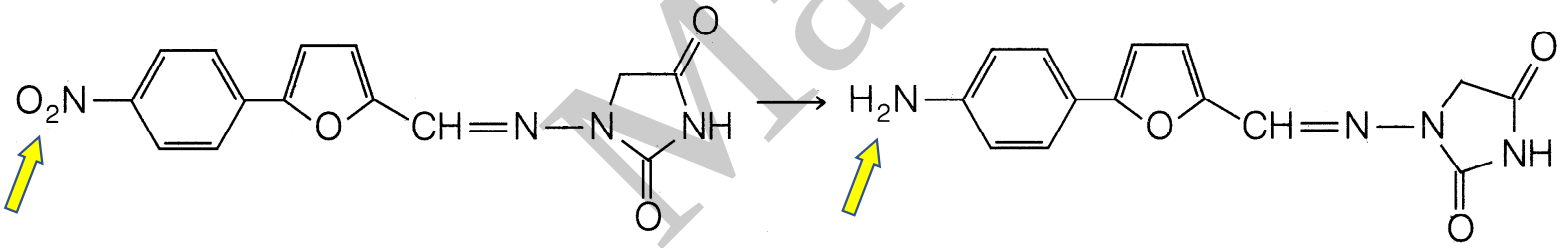
2 Reductive Reactions

2- Reduction of Nitro and Azo Compounds



Clonazepam, R = Cl
Nitrazepam, R = H

7-Amino Metabolite



Dantrolene

Aminodantrolene

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3 Hydrolytic Reactions

1- Hydrolysis of Esters and Amides

- The metabolism of ester and amide linkages in many drugs is catalyzed by hydrolytic enzymes present in various tissues and in plasma.
- The metabolic products formed generally are polar and functionally more susceptible to conjugation and excretion than the parent ester or amide drugs.
- The enzymes carrying out ester hydrolysis include several nonspecific esterases found in the liver, kidney, and intestine as well as the pseudocholinesterases present in plasma.
- Amide hydrolysis appears to be mediated by liver microsomal amidases, esterases, and deacylases.
- Hydrolysis is a major biotransformation pathway for drugs containing an ester functionality.

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Phase II or conjugation reactions

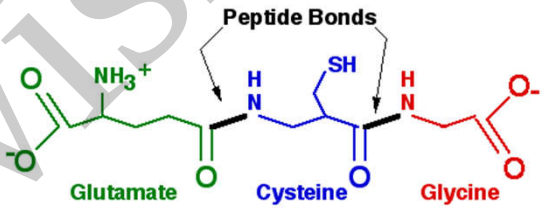
- Phase I or Functionalization reactions **do not always** produce hydrophilic or pharmacologically inactive metabolites.
- Various phase II or conjugation reactions can convert these metabolites to more polar and water soluble products.
- Many conjugative enzymes accomplish this objective by attaching small, polar, and ionizable endogenous molecules, such as glucuronic acid, sulfate, glycine, and glutamine, to the phase I metabolite or parent xenobiotic.
- The resulting conjugated products are relatively water soluble and readily excretable.
- Other phase II reactions, such as methylation and acetylation, do not generally increase water solubility but mainly serve to terminate or attenuate pharmacological activity

1- Glucuronic Acid Conjugation الاقتران الغلوكورونـي

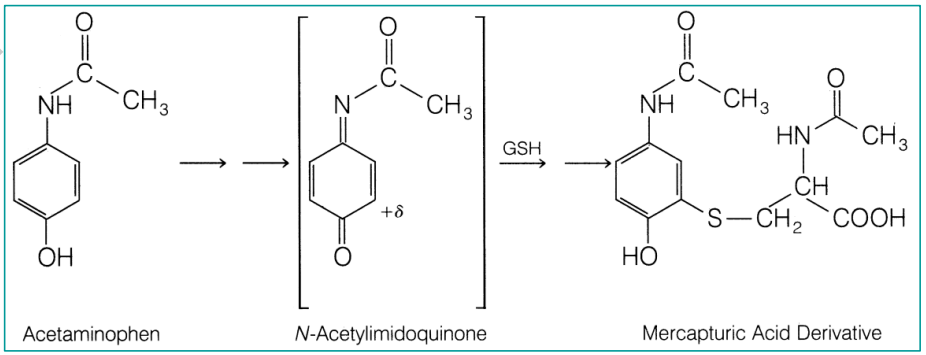
- Glucuronidation is the most common conjugative pathway in drug metabolism for several reasons:

1. A readily available supply of D-glucuronic acid (derived from D-glucose),
2. Numerous functional groups that can combine enzymatically with glucuronic acid
3. The glucuronyl moiety when attached to xenobiotic substrates, greatly increases the water solubility of the conjugated product.

2- Glutathione or Mercapturic Acid Conjugates



- GSH conjugation is an important pathway for detoxifying *chemically reactive electrophilic compounds*.
- GSH protects vital cellular constituents against chemically reactive species by nucleophilic SH (thiol) group.
- Glutathione have thiol group which react with electrophilic substrate, electrophilic reaction is catalyzed by enzyme glutathione transferase.



5- Acetylation الأستلة

- Acetylation constitutes an important metabolic route for drugs containing primary amino groups.
- This encompasses:
  A. primary aromatic amines (Ar—NH_2)
  B. sulfonamides ($H_2NC_6H_4SO_2NHR$)
  C. hydrazines (—$NHNH_2$),
  D. hydrazides (—$CONHNH_2$)
  E. primary aliphatic amines.
- The amide derivatives formed from acetylation of these amino functionalities are generally inactive and nontoxic.
- *Primary function of acetylation is to terminate pharmacological activity and detoxification*

6- Methylation المثيلة

- Methylation generally does not lead to polar or water-soluble metabolites, except when it creates a quaternary ammonium derivative.
- Most methylated products tend to be pharmacologically inactive.
- The coenzyme involved in methylation reactions is S-adenosylmethionine (SAM).

Factors affecting drug metabolism

1. Age Differences
2. Species and Strain Differences
3. Hereditary or Genetic Factors
4. Sex Differences
5. Enzyme Induction
6. Enzyme Inhibition
7. Miscellaneous Factors Affecting Drug Metabolism