

Drug Metabolism

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Introduction

- ❖ Metabolism refers to series of biochemical chemicals reactions occurring in the body to convert drug substance to more easily extractable and nontoxic forms.
- ❖ Metabolism plays an important role in elimination of drugs and foreign substance from the body.
- ❖ Liver is the primary site of metabolism for almost every drug.
- ❖ Several isoforms CYP450 (CYP) enzymes are involved in drug metabolism; they are the most important group of enzymes in phase I metabolism.

Phases of drug metabolism

Metabolism of drugs are divided into two phases

Phase-I

Phase-II

Phase-I

Phase-I converts a parent drug to a more polar metabolites by inserting polar functional groups such as $-\text{OH}$, $-\text{COOH}$, $-\text{SH}$, $-\text{NH}_2$ etc.

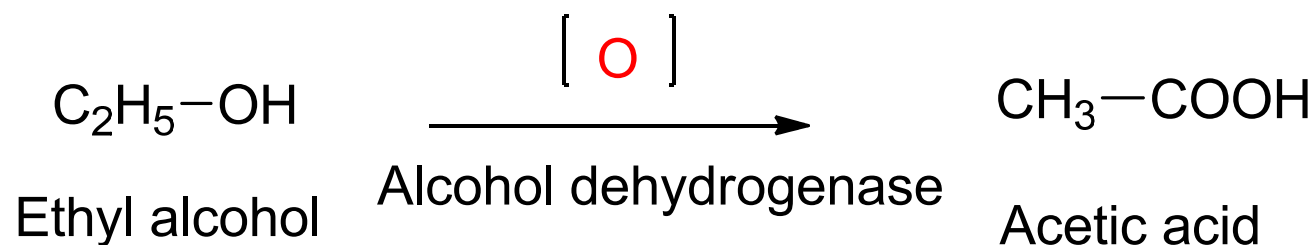
The reactions of phase-I involves oxidation, reduction and hydrolysis.

Oxidation

A large number of drug substances or xenobiotics undergoes metabolism by oxidation. These includes alcohol, aldehydes, olefins, amines, aromatic compound etc.

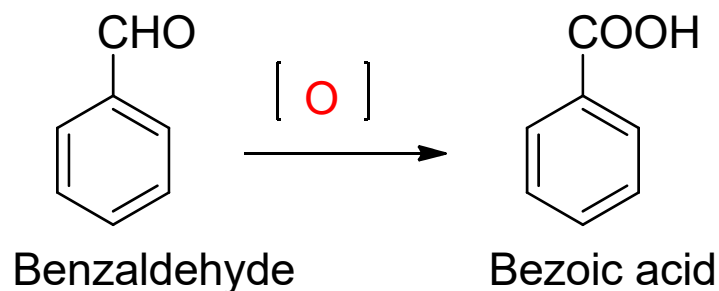
Oxidation of alcohol

Aliphatic and aromatic alcohols undergo oxidation to form the corresponding acids. It is catalysed by alcohol dehydrogenase.



Oxidation of aldehyde

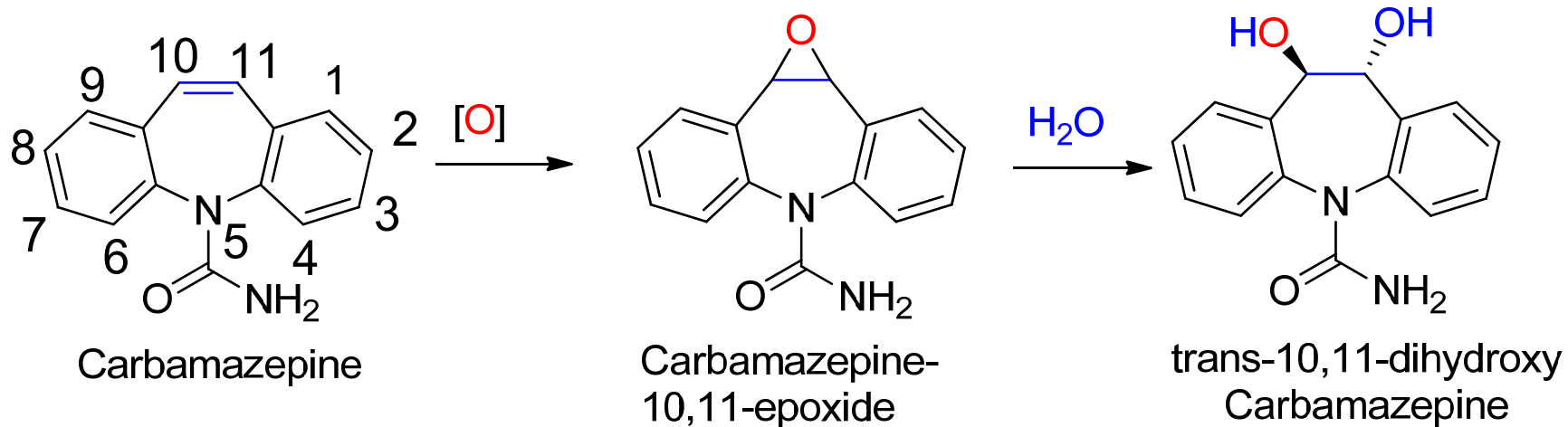
Aldehydes undergo oxidation to form the corresponding acids.



Oxidation of olefins

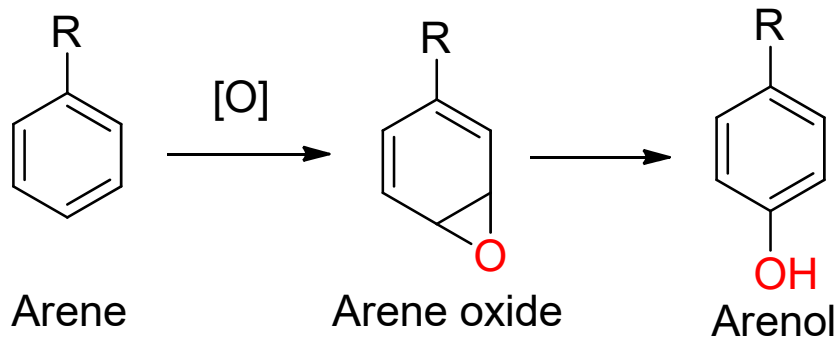
Olefins (compound containing double bond) undergo oxidation to form the corresponding epoxide. The epoxide may further undergo enzymatic hydration to form trans 1,2-dihydroxides.

Example: Carbamazepine undergoes oxidation to form carbamazepine-10,11-epoxide, which on enzymatic hydration forms trans-10,11-dihydroxy carbamazepine.

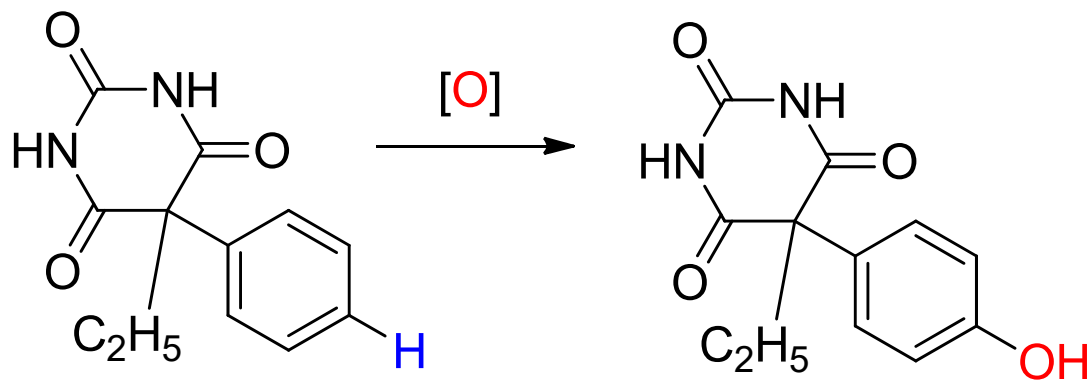


Oxidation of aromatic ring

Aromatic compound undergoes oxidation to form epoxide intermediate, which rearrange to form arenol.



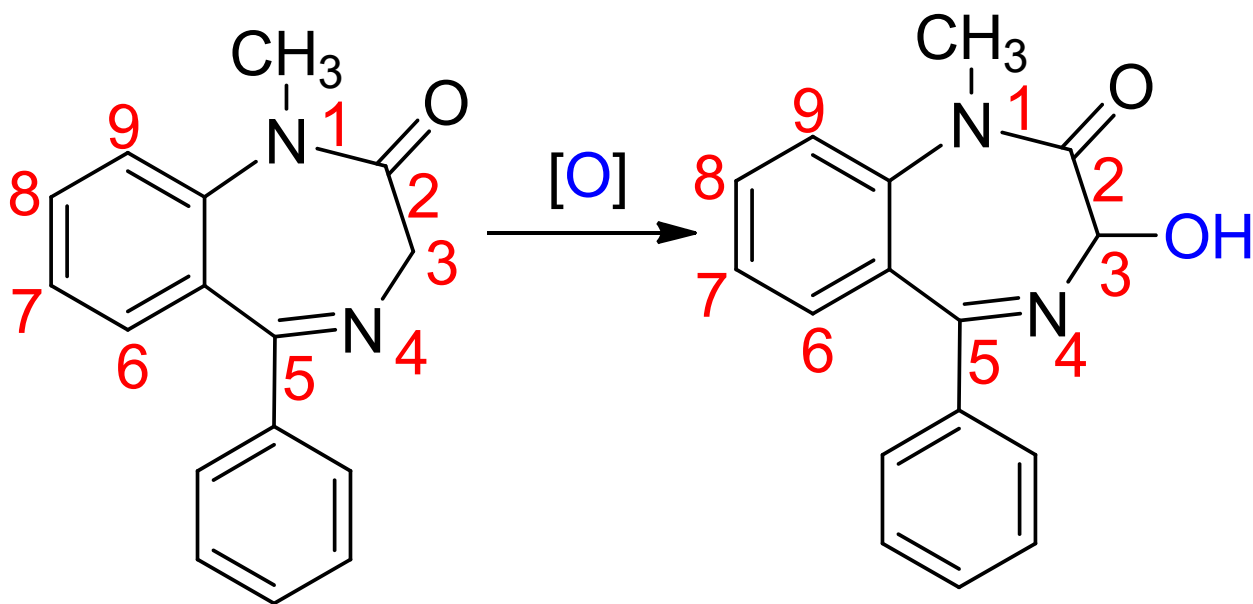
For example phenobarbital undergoes metabolism by oxidation to form hydroxyphenobarbital.



Oxidation of carbon atom α to the carbonyl group

Carbon atom adjacent to carbonyl function undergoes oxidation to form hydroxy derivatives.

e. g. Diazepam undergoes oxidation at 3rd position to form 3-hydroxydiazepam.



Diazepam

3-Hydroxydiazepam

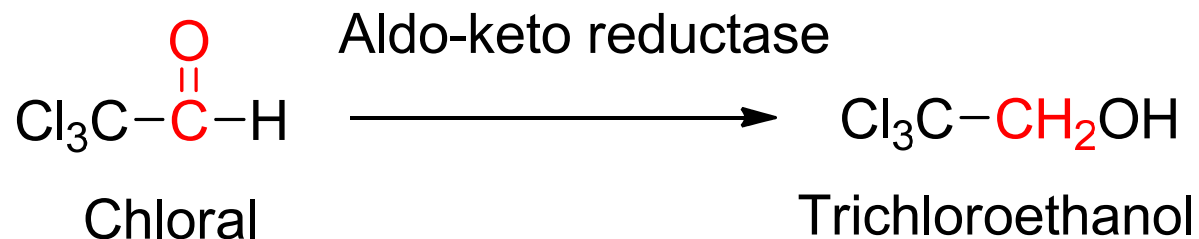
Reduction

Drug substances containing aldehyde, nitro and azo groups undergo metabolism by reduction.

Reduction of aldehyde

Aldehydes and ketones undergoes reduction by enzymes called aldo-keto reductase.

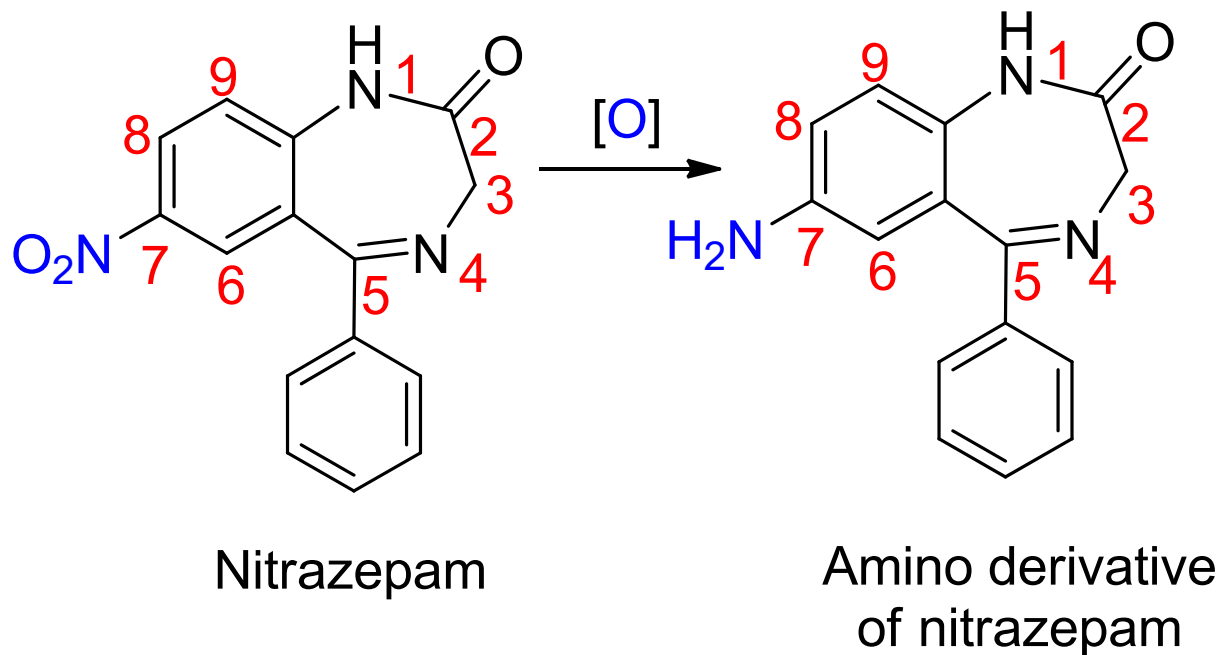
e.g. Bioreduction of chloral a sedative hypnotic drug forms trichloroethanol.



Reduction of nitro compound

Various aromatic nitro drugs undergo enzymatic reduction to the corresponding aromatic amines.

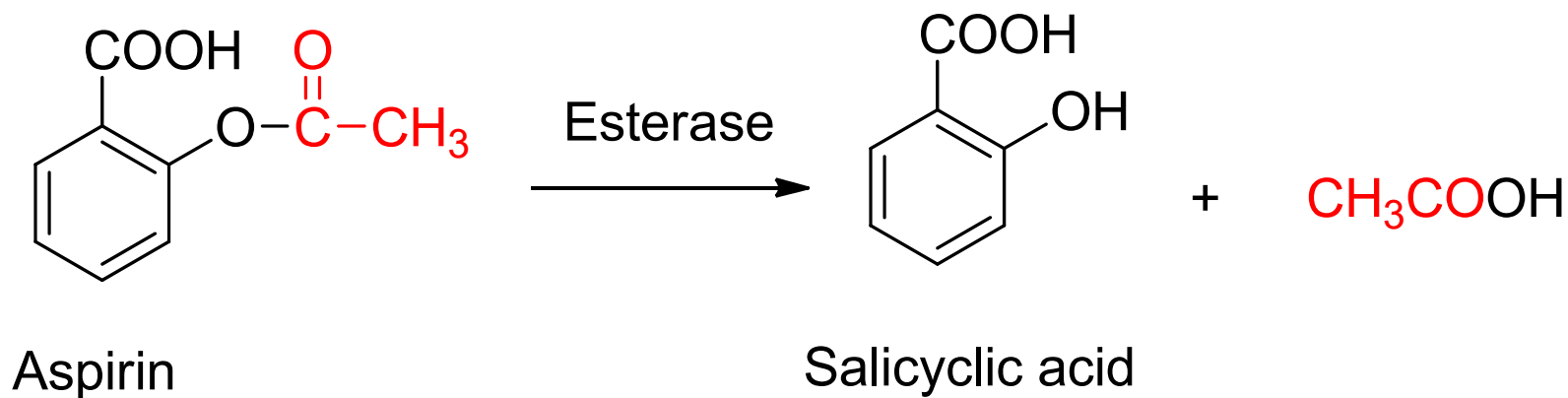
e.g. Nitrazepam extensively metabolises to its 7-amino metabolite.



Hydrolysis

Drugs containing ester and amide functional group undergoes metabolism by hydrolysis.

e.g. Aspirin undergoes metabolism by hydrolysis of the ester functional group to form salicylic acid and acetic acid.



Phase-II

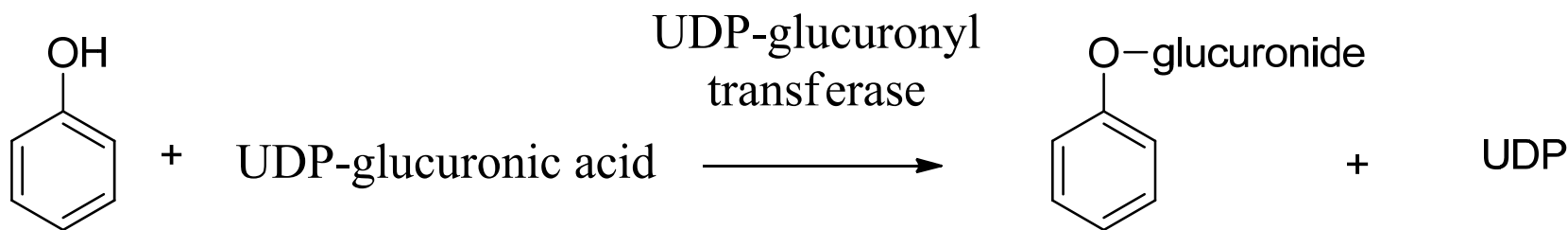
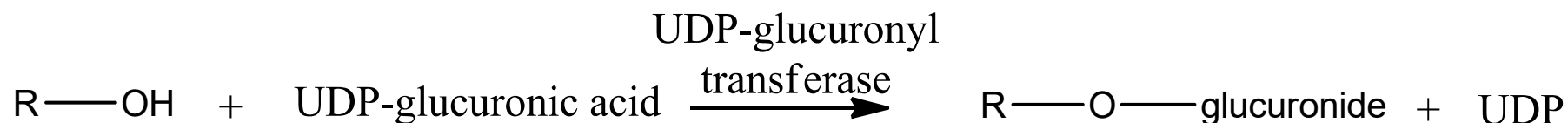
In Phase-II the metabolites formed in Phase-I are converted to more polar and water soluble product by attaching polar and ionisable moiety such as glucuronic acid, sulfate, glycine and glutamic acid.

The resulting conjugated products are relatively water soluble and readily excretable.

Glucuronic acid

Conjugation with glucuronic acid is the most common reaction. The active form of glucuronic acid is UDP-glucuronic acid.

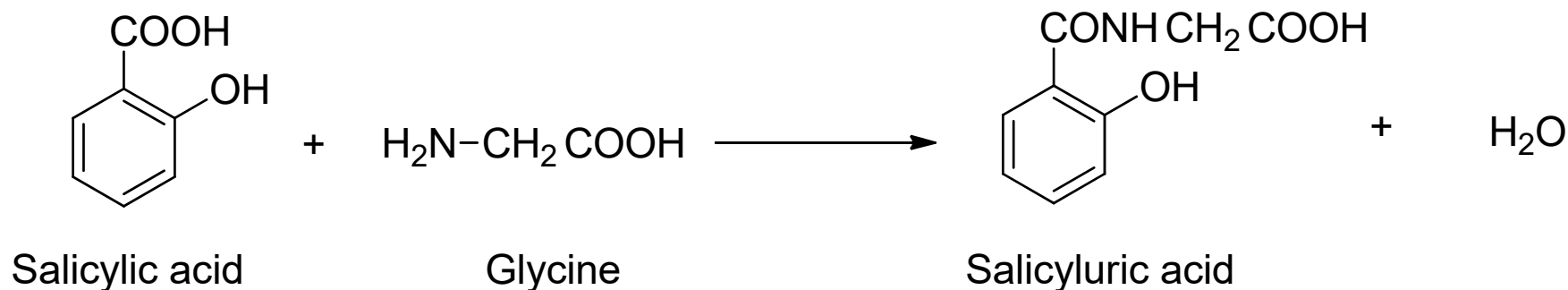
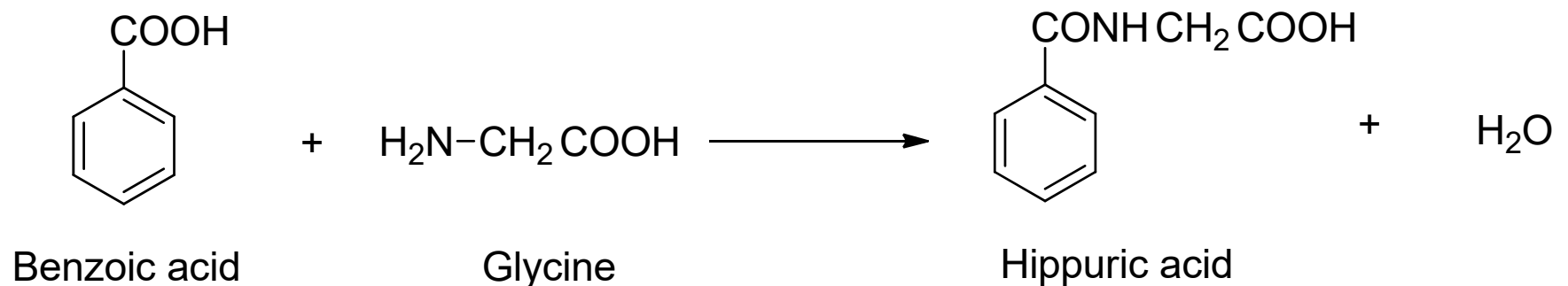
Phenolic and alcoholic hydroxyls are the most common functional group undergoing Glucuronidation in drug metabolism.



Drugs like morphine, acetaminophen, chloramphenicol and propranolol undergo metabolism by glucuronidation.

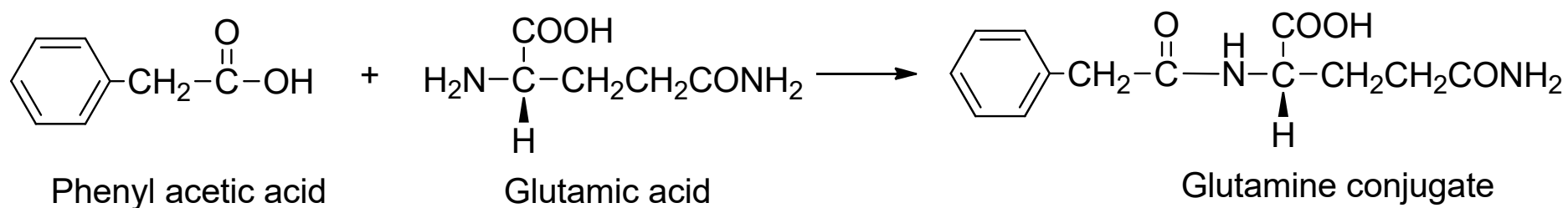
Glycine

Many aromatic carboxylic acids form conjugate with glycine. benzoic acid conjugates with glycine to form hippuric acid, which is a well known metabolic reaction.



Glutamine

Glutamine conjugation occurs mainly with phenylacetic acid to form phenylacetyl glutamine.



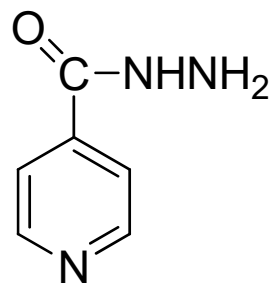
Glutathione

A wide range of organic compounds such as alkyl or aryl halides, nitro compounds, alkanes get conjugated with cysteine of glutathione.

Acetic acid

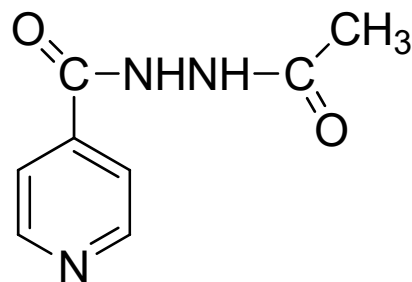
Acetyl-CoA is the active form of acetic acid that takes part in conjugation reaction.

Drugs containing primary amino group such as sulphonamide, hydrazides and hydrazine undergoes metabolism by acylation.

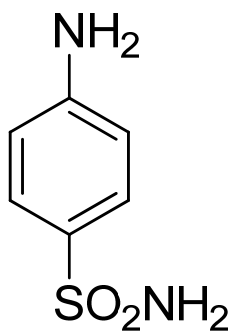


Isoniazid

N-Acetylation



N-Acetylisoniazid



Sulfanilamide

N-Acetylation

