Metabolic Changes of Drugs and Related Organic Compounds

Organic Pharmaceutical Chemistry I

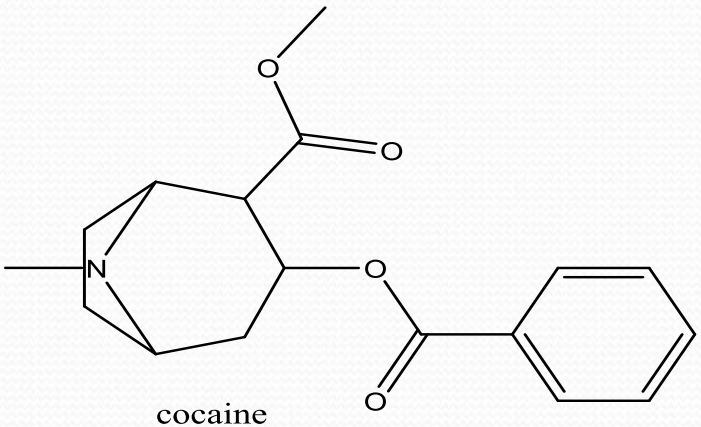
3rd Year Pharmacy

2018-2019

Hydrolytic Reactions

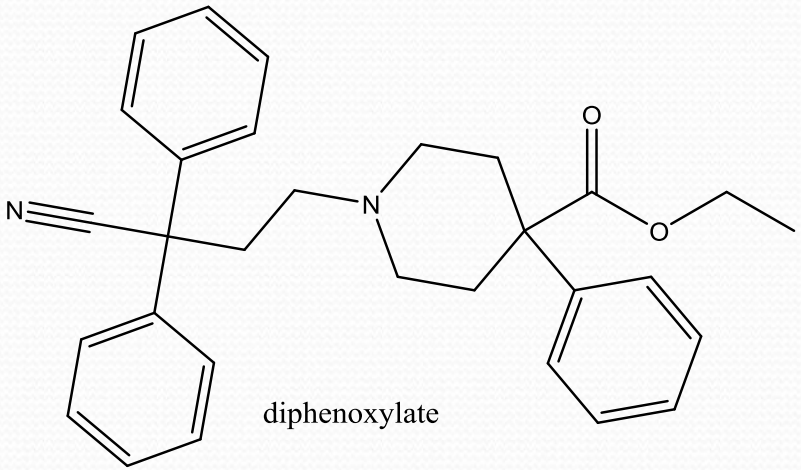
Because of he relative ease of hydrolysing the ester linkage, hydrolyis, is the main pathway for drugs containing ester or amide linkages. Examples are; the hydrolysis of aspirin to……and cocaine to benzoylecogonine and …… . The smaller, methyl group is hydrolysed preferentially.

Exc: Draw the major and minor metabolites of hydrolysis of cocaine.

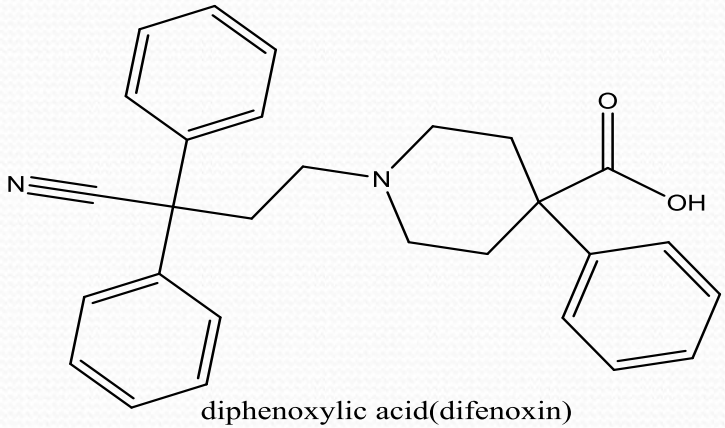


cocaine

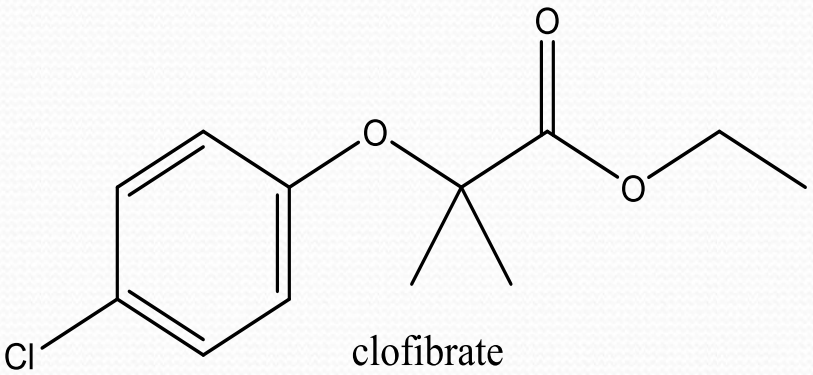
Other examples include retalin, diphenoxylate, clofibrate.



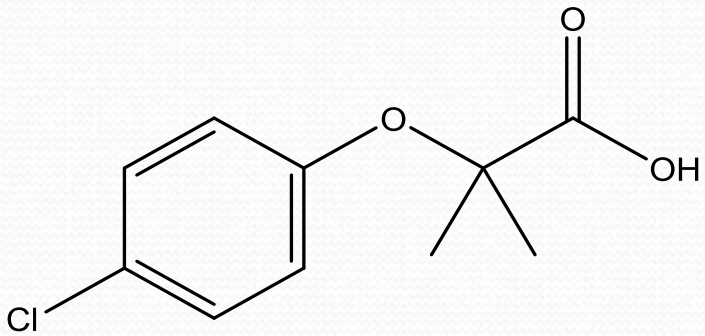
diphenoxylate



diphenoxylic acid(difenoxin)



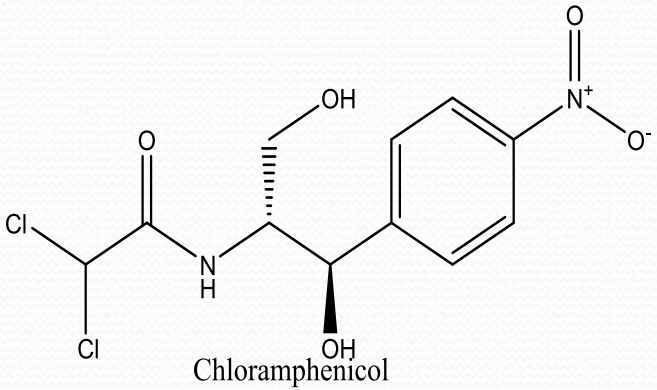
clofibrate



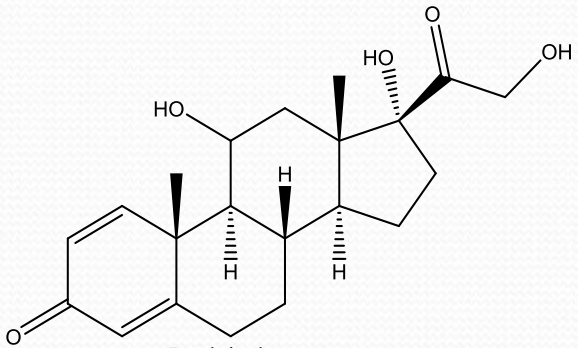
p-chlorophenoxyisobutyric acid, clofibric acid

Hydolysis and Prodrugs

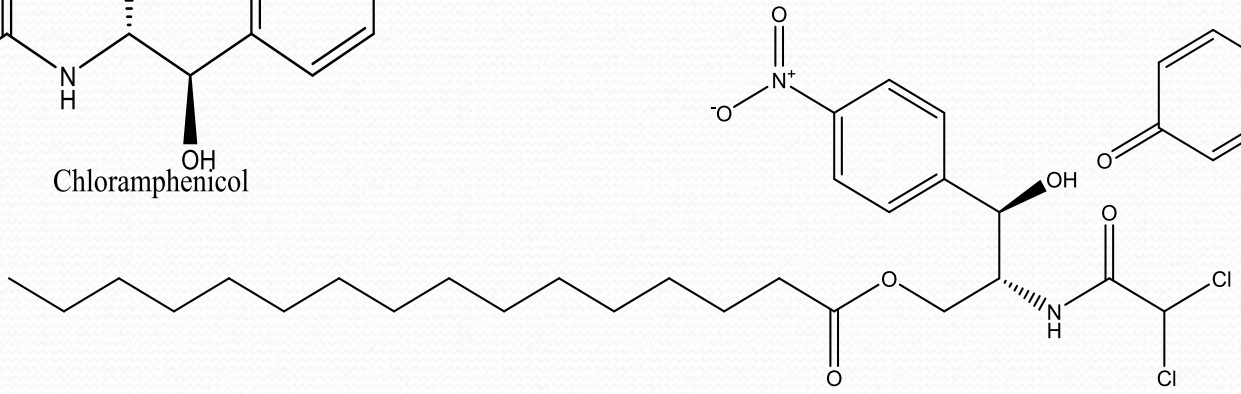
Drug	Effect	Prodrug (derivative)
Chloramphenicol	Taste bitterness	Palmitate ester
Clindamycin	Taste bitterness	Palmitate ester
Carbencillin	Poor oral absorption	Indyl ester
Prednisolone	For parenteral administration	C-21 hemisuccinate sodium



Chloramphenicol



Prednisolone

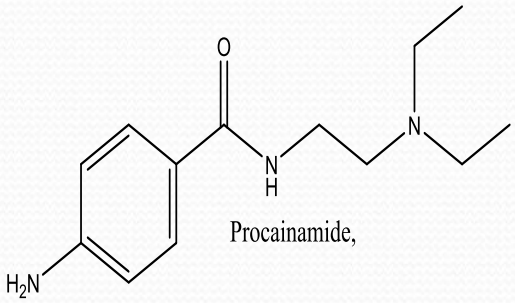


Chloramphenicol palmitate

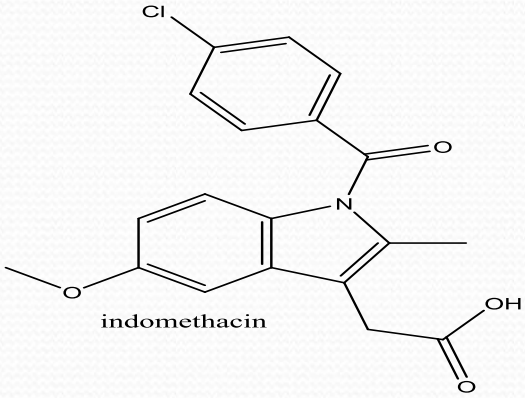
Amides Hydrolysis

As compared to esters, amides are hydrolysed slowly. Exmaples of amides hydrolysis include;

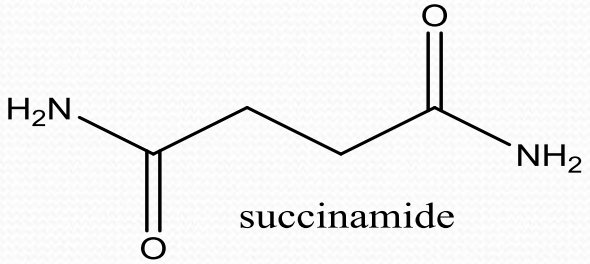
Procainamide, lidocaine, carbamazepine, succinamide and indomethacin.



Procainamide,



indomethacin



succinamide

More Hydrolytic Metabolism

Hydrolysis of recombinant human pepptidedrugs and hormones at the N-or C-terminal amino acids by carboxypeptidase and aminopeptidases in blood and other tissues is well- recognized hydrolytic reaction.

Examples of peptides or protein hormones undergoing hydrolysis include human insulin, growth hormone (GH) prolactin, parathyroid hormone (PTH), and atrial naturitic factor (ANF).

Hydrolysis of phosphate esters e.g. diethylstilbestrol diphosphate, sulphonylurears, cardiac glycosides, carbamate esters, and organophosphate compounds.

Glucuronide and sulphate conjugates are also hydrolysed by glucurnidase and sulphatase enzymes respectively.

PHASE II OR CONJUGATION REATIONS

Phase I reactions do not always produce hydrophilic or pharmacologically inactive metabolites.

However, the products of phase I reactions can be converted to more polar and soluble products.

Many conjugative enzymes accomplish this objective by attaching a small, polar, and ionizable endogenous molecules, such as glucuronic acid, sulfate, glycine and glutamine, to the phase I metabolites or the parent xenobiotic.

As compared to phase I metabolites, phase II conjugated products are relatively more water soluble, readily excretable and biologically inactive and nontoxic

More Conjugation Reactions

Other phase II reactions, such as methylation and acetylation, do not generally increase water solubility but inactivate xenobiotics.

GSH combine with chemically reactive compounds to prevent damage to DNA, RNA and proteins.

Thus while, Phase I reactions are functionalization reactions, Phase II are detoxifying reactions.

Many endogenous compounds such as bilirubin, steroids, catecolamines, and histamine also undergo conjugation reactions and use the same coenzymes, although they appear to be mediated by more specific transferase enzymes.

Other conjugative pathways are of minor importance including; conjugation with glycosides, phosphates and other amino acids and the conversion of cyanide to thiocyanate.

Glucuronic Acid Conjugation

The reasons below demonstrate why glucuronic acid conjugation is the most common conjugative pathway in drug metabolism;

1. Readily available supply of D-glucuronic acid (derived from D-glucose).
2. Numerous functional groups can combine enzymetically with glucuronic acid.
3. Polar group of glucuranic acid (-COOH and 3 –OH) can be attached to xenobiotecs hence increasing thw water solubiloity of the product.

Numerous groups can undergo conjugative glucuronidation incuding; hydroxyl, carboxyl, amines, amides, sulphonamides, sulfhydryl and other carbon glucuronides.

Attachment is normally to carbon atom 1 of the glucuronyl group.

Phenolic and alcoholic groups are the most common groups undergoing glucurindation in drug meabolism.

Morphine, acetaminophen, p-hydroxyphenytoin, tricloroethanol, chloramphenicol and propranolol.

Examples for carboxyl groups include; naproxen and fenoprofen.

Several endogenous substrates are eliminated as glucoronide conjugates which are excreted primarily in the urine.

However, as the molecular mass of the conjugate exceeds 300 Da, biliary excretion may become an important route of elimination through the bile and become subject to hydrolysis and reabsorption in the intestine.

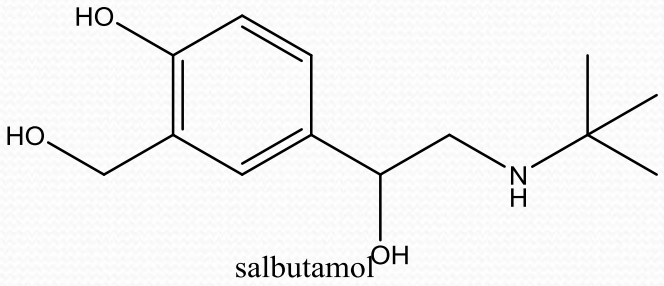
Sulphate Conjugation

- Sulphate conjugation occur mainly with phenols and occasionally with alcohols, aromatic amines and N-hydroxy compounds.
- The body uses a significant portion of the sulphate ions to conjugate with numerous endogenous compounds such as steroids, heparin, chondroitin, catecolamines thyroxine.
- Suphate conjugation generally leads to water-soluble and inactive metabolites.
- However, some O-sulphate conjugates of some hydroxy compounds produce toxic reactive intermediates.

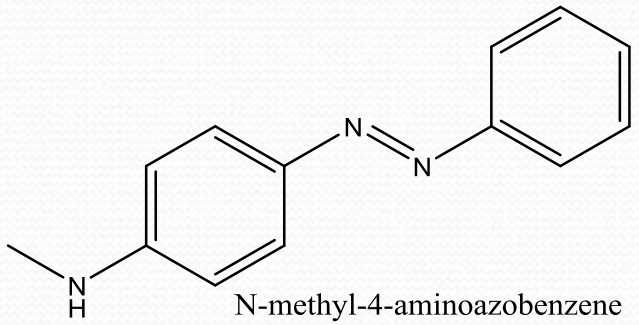
Phenols undergoing sulphate conjugation include;

α-methyldopa, salbutamol and terbutaline.

The sulphate conjugation of N-hydroxyl compounds are of considerable toxocological concern because they can to reactive intermediates that are responsible for cellular toxicity. Examples are N-methyl-4-aminoazobenzene and 2-AAF O-sulphate conjugates are carcinogenic.



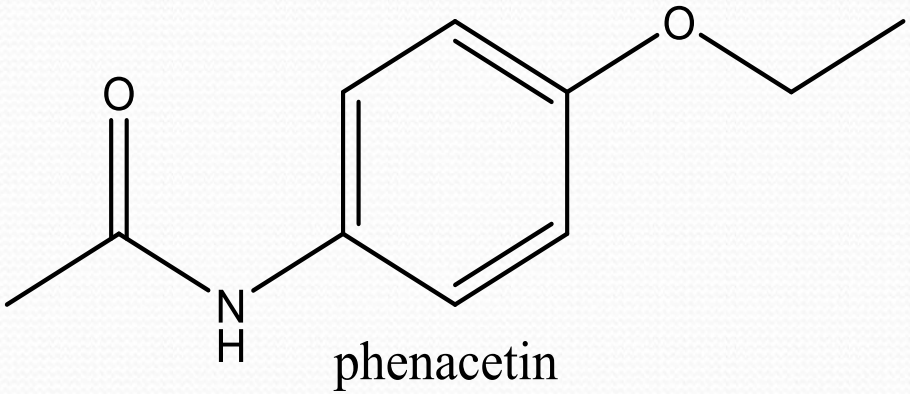
salbutamol



N-methyl-4-aminoazobenzene

The Phenacetin Problem

The same argument applies to the discontinued analgesic phenacetin for its hepatotoxicity and nephrotoxicity.



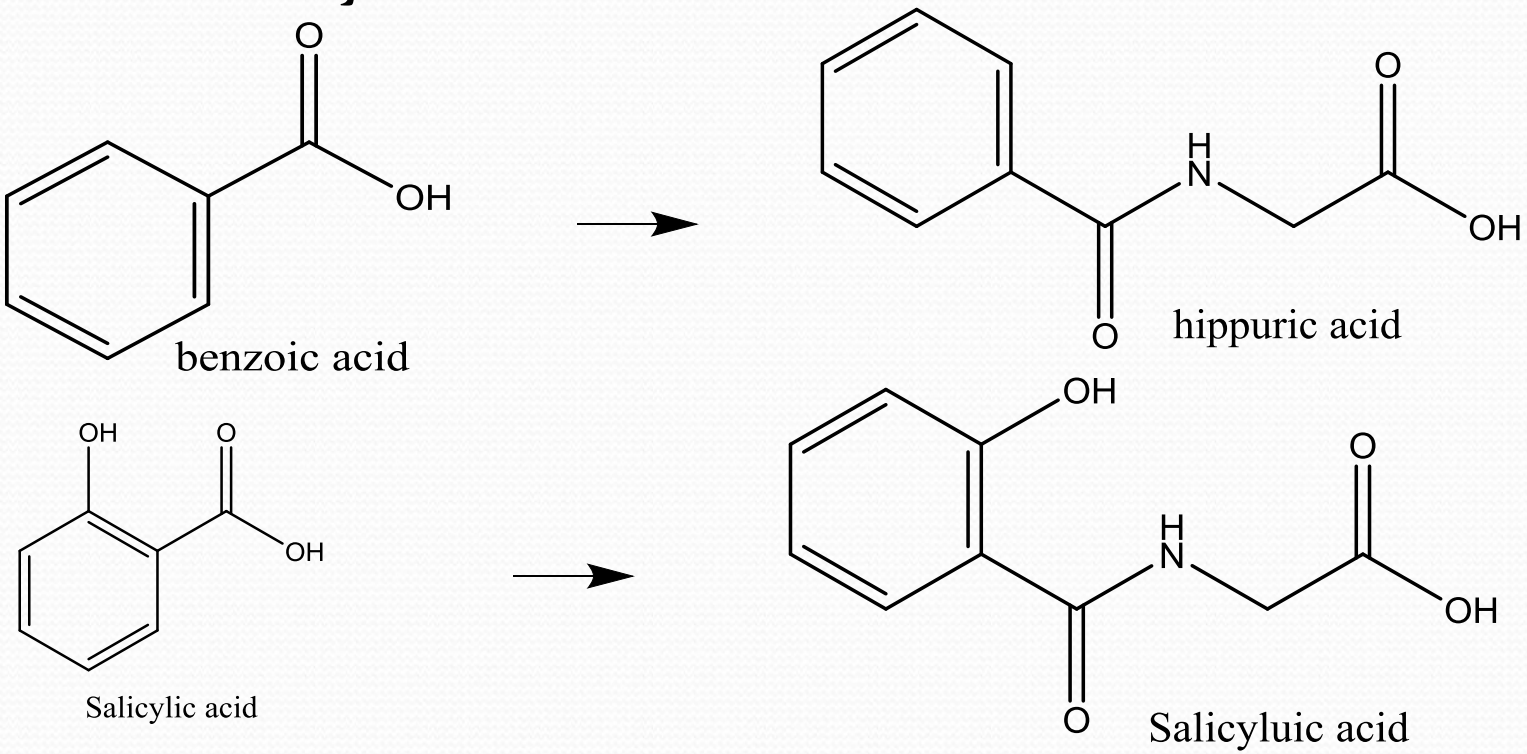
phenacetin

Exc: Demonstrate the role of O-sulphate conjugation in the hepatotoxicity of phenacetin.

Conjugation with Glycine

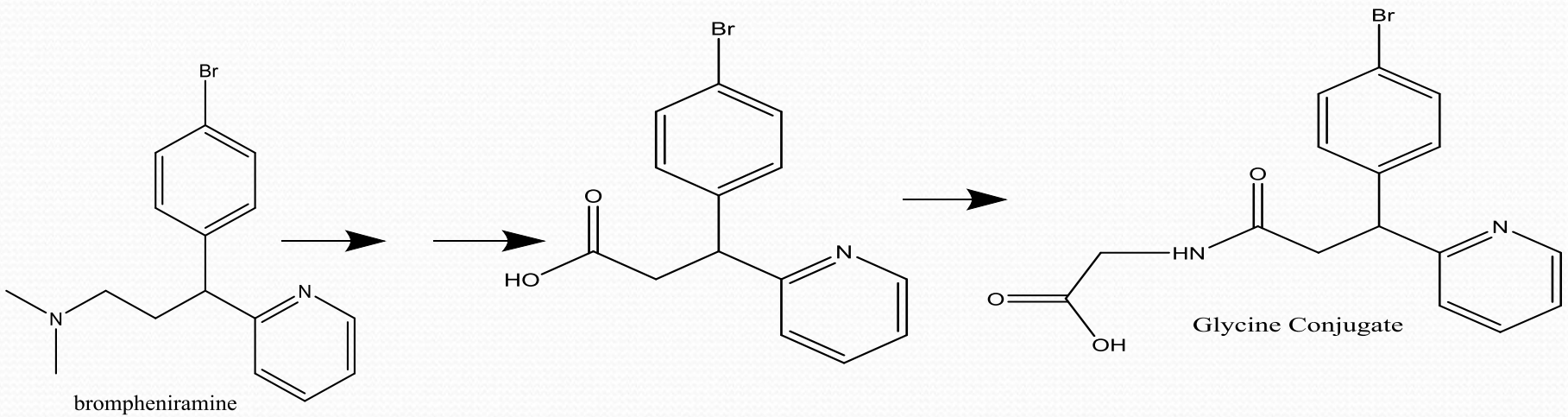
Carboxylic acids, in particular aromatic acids and arylakyl acids are conjugated by glycine and glutamine.

Benzoic acid is converted to its glycine conjugate, hippuric acid and salicyl uric acid in humans.



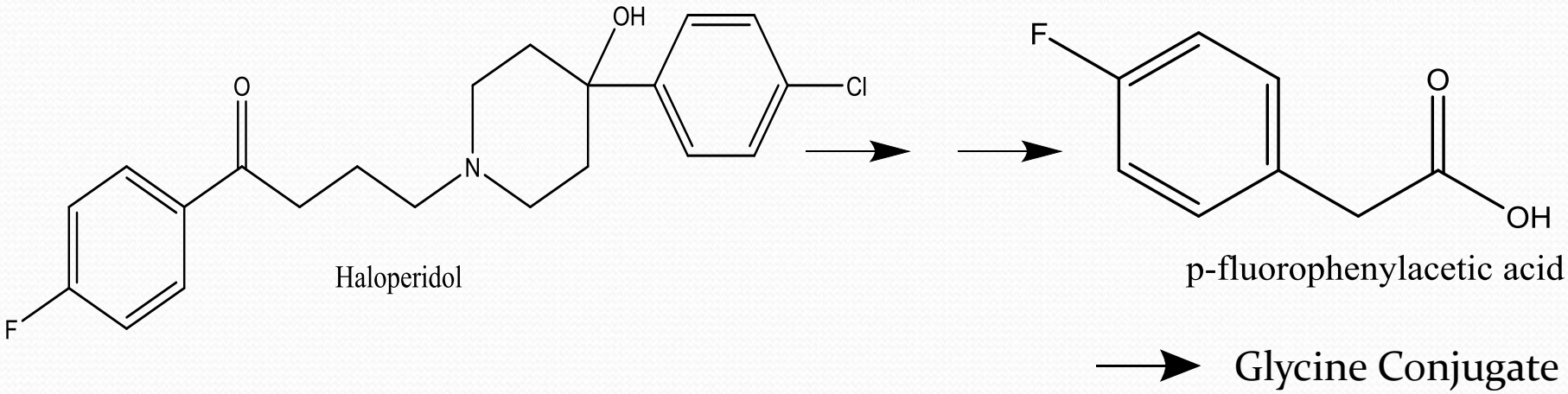
Glycine Conjugation

Carboxylic acid metabolites resulting from oxidation or hydrolysis of many drugs are also susepteable to glucine conjugation, e.g. brompheniramine is oxidized to propionic acid metabolite that is conjugated with glycine in both human and dog.



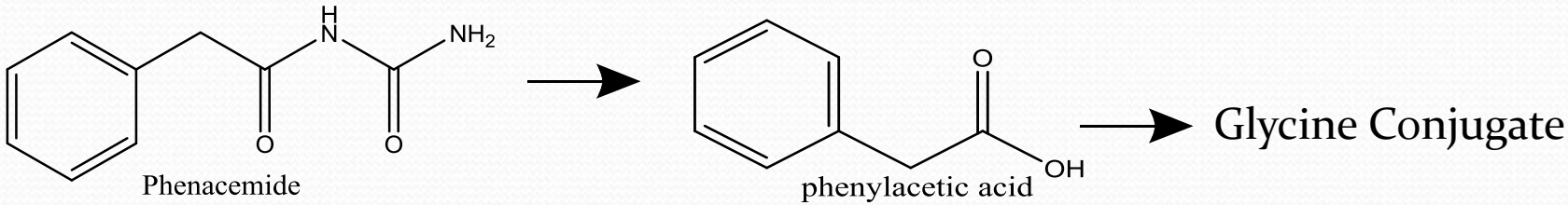
Glycine Conjugation

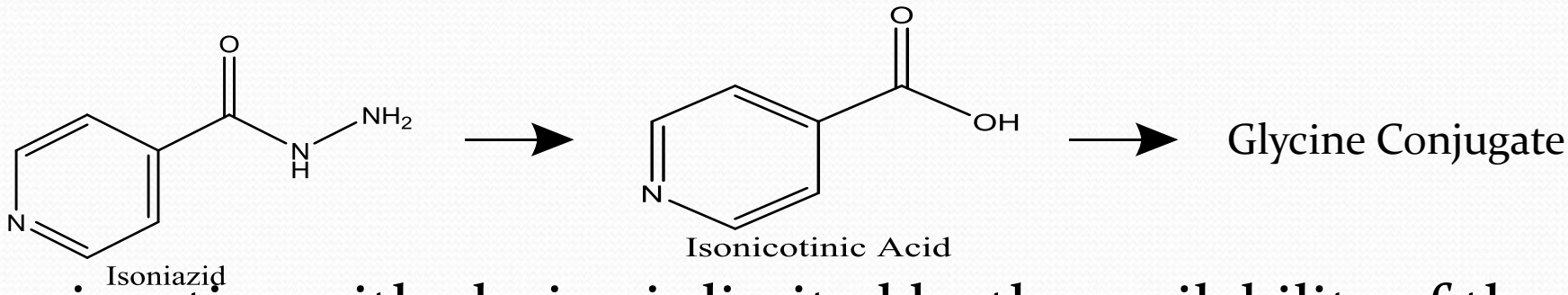
Similarly p-fluorophenylacetic acid derived from the metabolism of the antipsychotic agent Haldol is found as the glycine conjugate in rats.



Glycine Conjugation

Other glucine conjugates include; phenylacetic acid from phenacimide, isonicotinic acid from isoniazid.

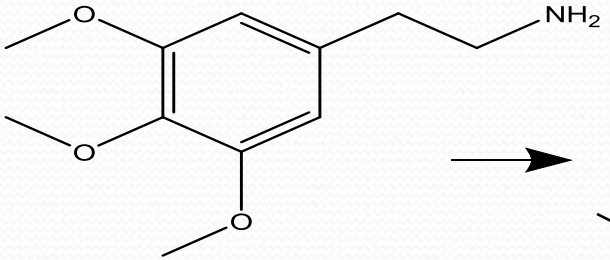




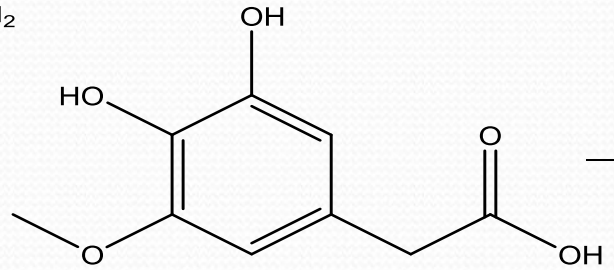
Conjugation with glycine is limited by the availability of the AA and the competition with glucuronidation for the carboxylic acid substrates.

Glutamine Conjugation

Examples of glutamine conjugate include 3,4-dihydroxy-5-methoxyphenylacetic acid metabolite of mescaline.

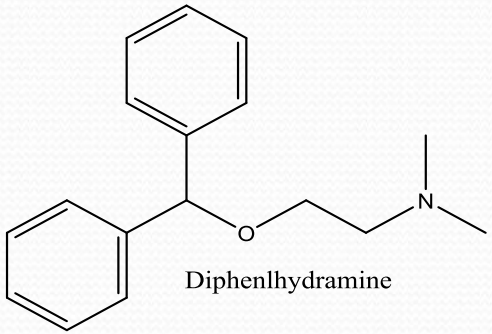


Mescaline

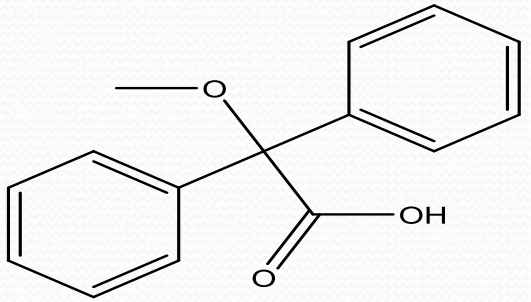


3,4-dihydroxy-5-methoxyphenylacetic acid

Glutamine conjugate



Diphenlhydramine



diphenylmethoxyacetic acid

Glutamine conjugate

Glutamine conjugation occur mainly with arylacetic acids, including endogenous phenylacetic acid and 3-indolylacetic acid.

GSH or Mercapturic Acid Conjugates

GSH conjugation is an important pathway for detoxifying chemically reactive electrophilic compounds.

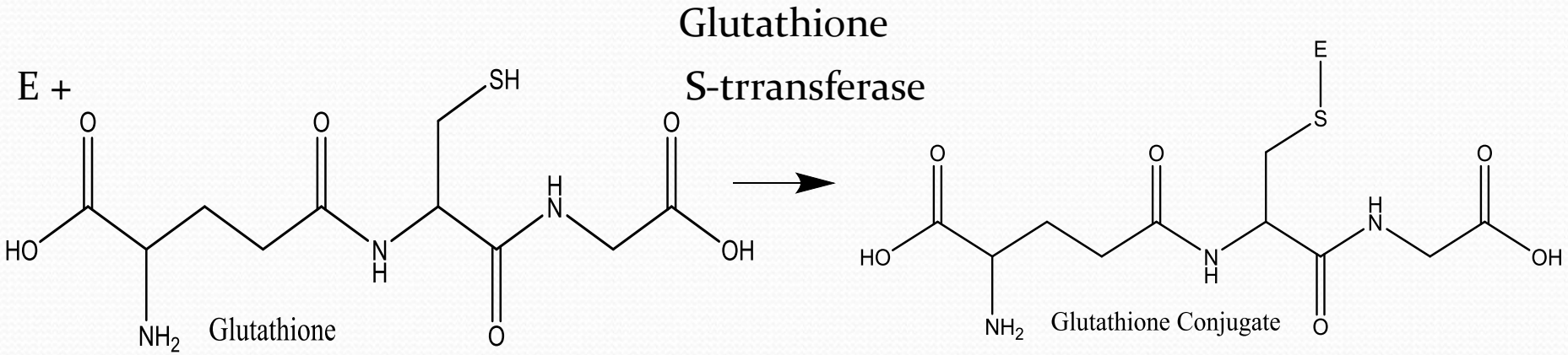
GSH protects vital cellular constituents against chemically reactive species by virtue of its nucleophilic SH group which reacts with electrophiles to form S-substituted GSH adducts.

GSH is a tripeptide (γ-glutamyl-cysteinylglycine) found in most tissues.

GSH or Mercapturic Acid Conjugates

Xenobitoics conjugated with GSH are not excreted but undergo further bioransformation to mercapturic acids.

The process is catalysied by a group of cytoplasmic enzymes called GSH S-transferases found in most tissues especially the liver and kidneys. The second step (transformation to mercapturic acid is catalysed by renal and hepatic microsomal enzymes.



GSH or Mercapturic Acid Conjugates

Exc: Demonstrate the a general GSH conjugation of an elctrophile E and its transformation to mercapturic acid.

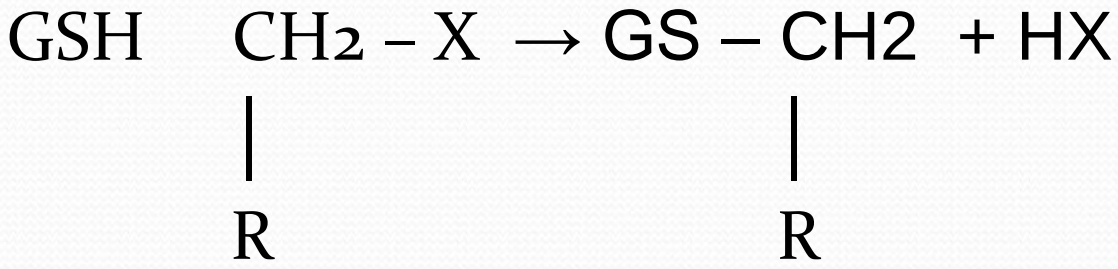
Unlike other phase II reactions, GSH conjugation does not require the inititial formation of an activated coenzyme or substrate. The reactivity of the nuclephilic GSH towards electrophiles provides the driving force for the reaction.

A major prerequisite for GSH substrates are sufficiently

The Mechanisms of GSH Conjugation

1. **Nucleophilic displacement at an electron-deficient carbon or heteroatom**.

Many substrates have eletron –deficient carbon atoms that can react with GSH by aliphatic nucleophilic displacement to form GSH conjugates, as shown below;



R = alkyl, aryl, benzylic, allylic

X = Br, Cl, I, OSO_3, OSO_2 R $OPO(OR)_2$

Nucleophilic displacement often is facilitated when the carbon atom is benzylic or allylic or when X is good leaving group e.g. halide or sulphate.

Many industrial chemicals such as benzyl chloride, allyl chloride and methyl iodide are known to be toxic and carcinogenic.

Organophosphate insectisides are detoxified by two different GSH pathways.

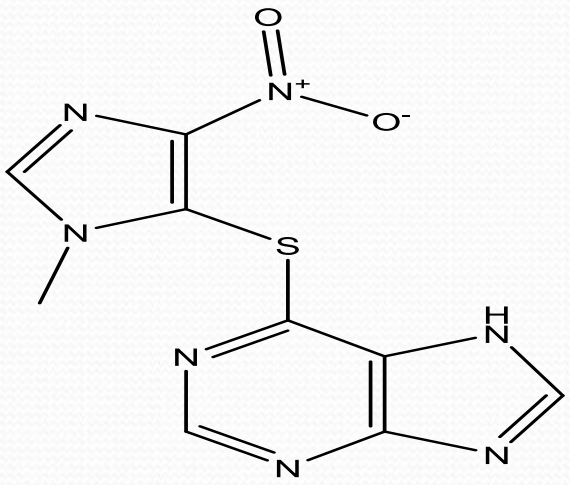
(i) Pathway a aliphatic nuceophilic substitution and yields S-methylglucothione.

(ii) Pathway b involves aromatic nuclophilic substitution and produces S- p-nitrophenylgutathione.

Heteraromatic Nucleoiphilic Substitution with GSH

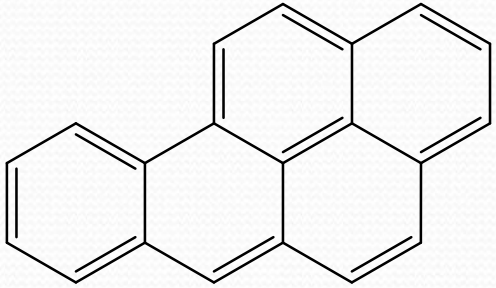
Aromatic or heteroaromatic nucleophilic substitution reactions with GSH can occur only when the ring is rendered sufficiently electron –defiecient by the presence of one or more strongly electron-withdrwing substituents e.g. (NO_2, Cl). Therefore, 2,4-dichloronitrobenzene undergoes GSH conjugation wheras chlorobenzene does not.

Exc; Demonstrate the GSH conjugation of the immunosupressant drug Azathioprine.



Azathioprine

Arene oxides and aliphatic epoxides, examples are benzo[α]pyrene, bromobenzene and styrene are important substrates for GSH. Ring strain increases its activity and facilitates ring opening leading to GSH conjugation.



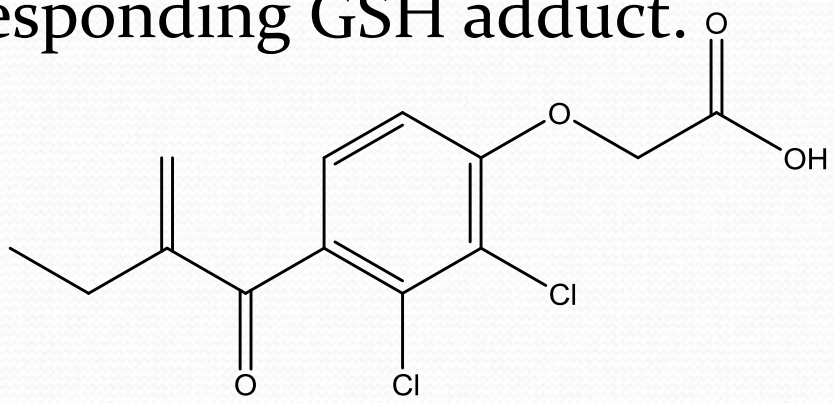
benzo[a]pyrene

GSH Conjugation; Mechanism II

2. Nuceophilic addition of GSH to an electron-deficient double bond occurs mainly in compounds with α,β-unsaturation. These compounds undergo Michael addition reaction with GSH to yield the corresponding GSH adduct.

Exc: Demonstrate a general α,β-unsaturated system with GSH.

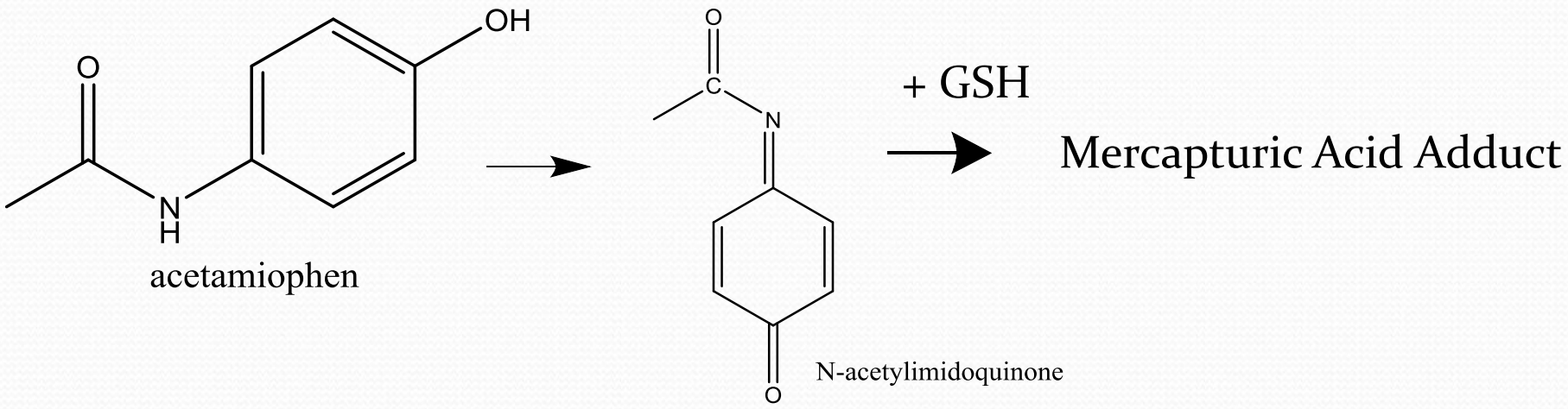
For example, in rats ethacrynic acid, Edecrin (page 98) forms the corresponding GSH adduct.



ethacrynic acid

GSH Conjugation; Mechanism II

Occasionally, metabolic oxidative transformation reactions may generate chemically reactive α,β-unsaturation that reacts with GSH., e.g. acetamiophen gives GSH adduct through Michael addition to N-acetylimidoquinone. (top of page 99)



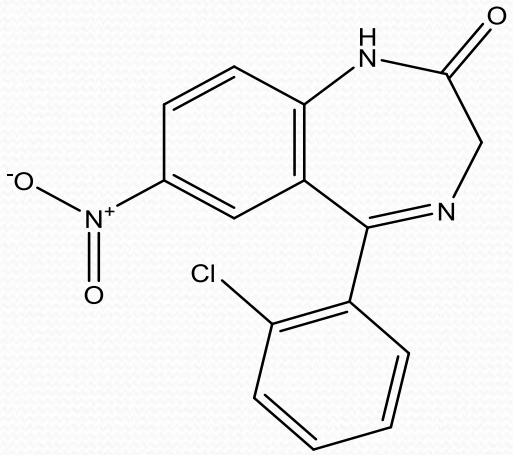
Acetylation

Acetylation is an important metabolic route for drugs containing primary amino groups including;

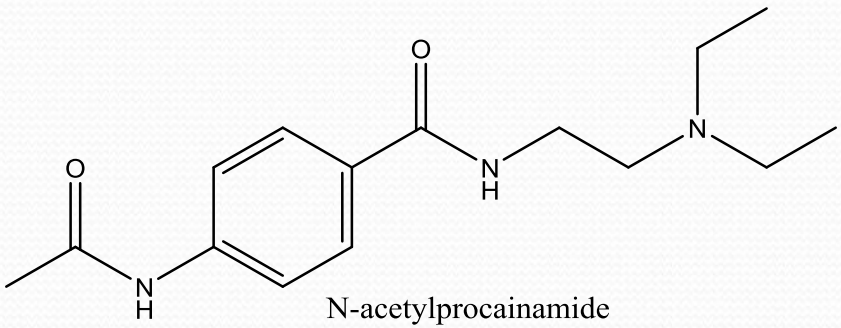
- Primary aromatic amines, $ARNH_2$
- Sulphonamides, $H_2NC_6H_4SO_2NHR$
- Hydrazines,- $NHNH_2$,
- Hydrazides, $-CONHNH_2$
- Primary aliphatic amines, RNH_2

The amide derivatives from these acetylation are generally inactive and nontoxic with little effect on water solubility. However, some products of acetylation may be as active e.g. N-acetylprocainamide or more active e.g. N-acetylisoniaziad as the corresponding parent compound.

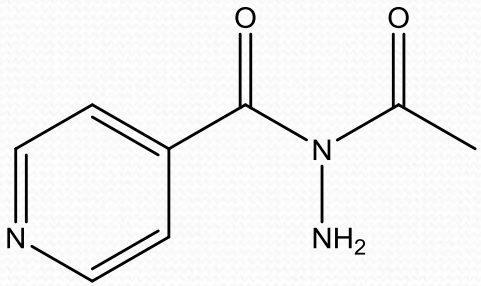
Acetylation



clonazepam



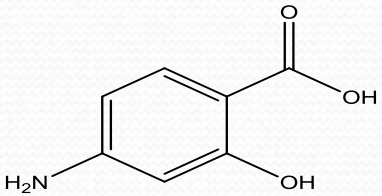
N-acetylprocainamide



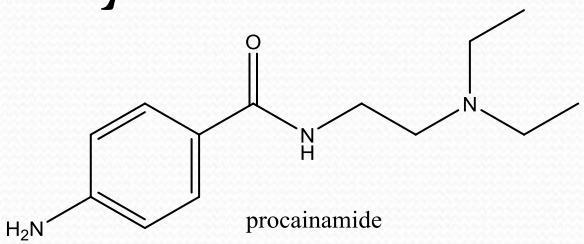
N-acetylisoniaziad

Acetylation

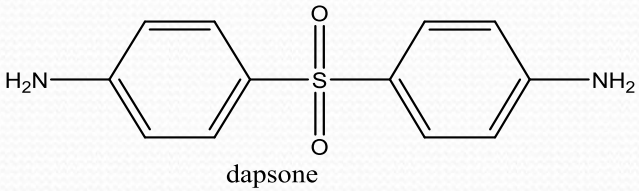
Aromatic compounds with a primary amino group, such as aniline, p-aminobenzoic acid, p-aminosalicylic acid, procainamide and dapsone are especially susceptable to N-acetylation. Acetylation is



p-aminosalicylic acid



procainamide



dapsone

Similar amine metabolites e.g. from the reduction of aryl nitro compounds are also N-acetylated. An example is clonazepam undergoes nitro reduction to 7-amino metabolite which in turn is N-acetylated.

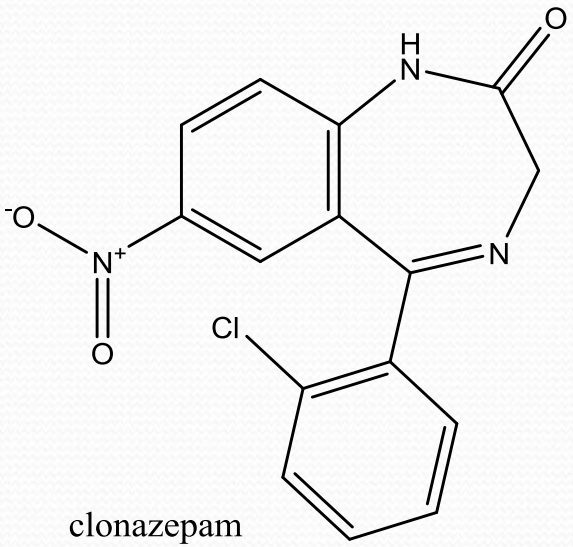
Acetylation

The acetyl group, $CH_3C{=}O$, used in N-acetylation of xenobiotics is supplied by acetyl CoA.

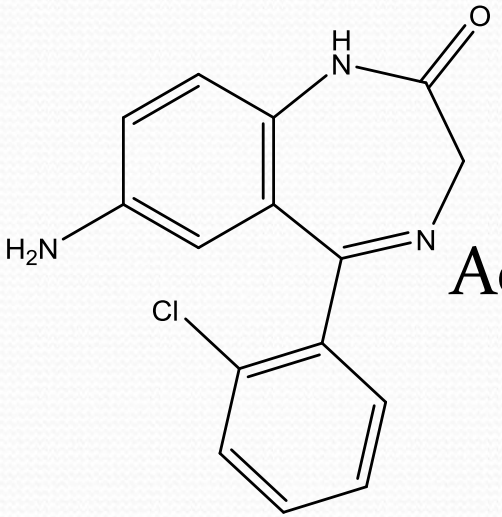
The transfer of this cofactor to the acceptor substrate is carried out by N-acetyl transferases present in hepatic reticular endothelial cells.

Other extrahepatic tissues including the lung, spleen, gastric mucosa, RBCs and lymphocytes are also involved in N-acetylation of xenobiotics.

Another example is benzodiazepam analog, nitrazepam follows similar pathway.



clonazepam



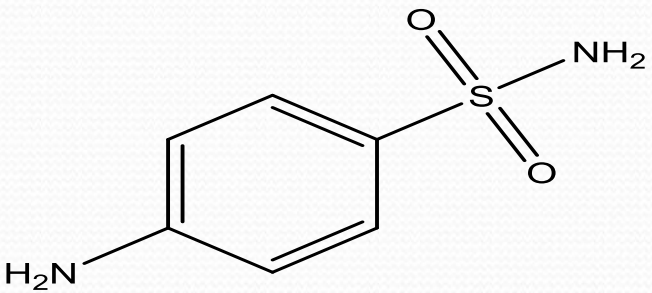
7-amino metabolite

Aceylation

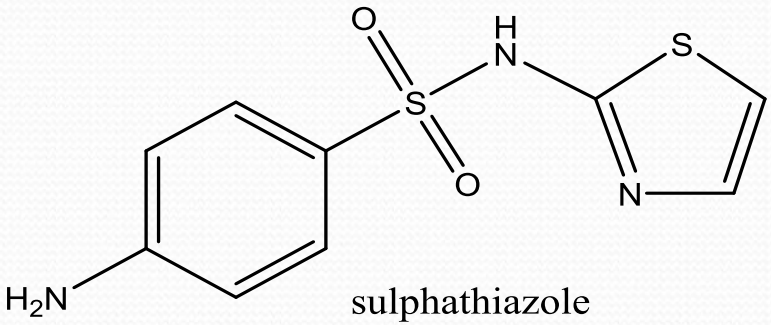
N-Acetylation of Sulphonamides and Crystalluria

The main metabolism of sulphonamides and similar metabolites is N-acetylation, at position N-4 and also at N-1 for sulphanilamide.

Metabolites of N-acetylation of sulphonamides are less water soluble than their parent compounds and have the potential of crystallizing out in renal tubules (crrstalluria) causing kidney damage.



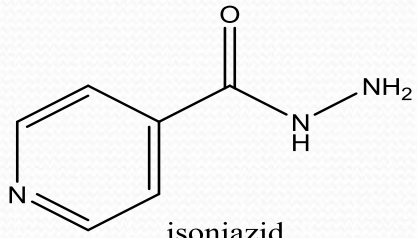
sulphanilamide.



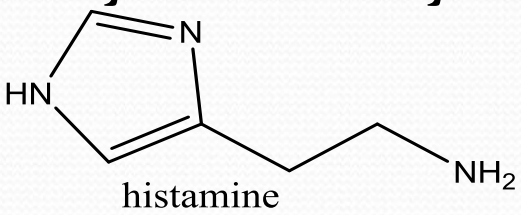
sulphathiazole

Newer sulphonamides have less potential of crstalluria than older sulphonamide derivatives such as sulphathiazole which was replaced by sulphamethazole.

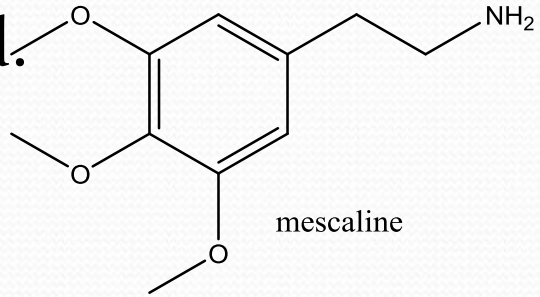
The biotransformation of hydrazine and hydrazide derivatives also proceed by acetylation with hydralazine as an example. Also isoniazid or isonicotinic acid hydrazide is metabolised extensively to N-acetylisoniazid.



isoniazid



histamine



mescaline

Similar acetylation is shown by some primary amines e.g. histamine, mescaline, and the bis-N-demethylated metabolite of α(-) methadol.

In comparison with oxidative deamination, N-acetylation is forms only a minor pathway of the metabolism of this class of compounds.

N-acetylation and the Bimodal Character

- The acetylation of several drugs e.g. isoniazid, hydralazine, procainamide in human population show bimodal character in which the drug is conjugated slowly or rapidly with acetyl CoA. This phenomenon is termed **Acetylation Polymorphism** in which individuals are classified as either slow or rapid acetylator phenotypes.
- These differences are genetics and related to the activity of N-acetyltransferase.

High proportion of Eskimos and Asians are rapid acetylators, whereas Egyptians and Western Europian groups are mainly slow actylators. Other populations are intermediates between these two extremes.

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Implications of Acetylation Polymorphism

The drug acetylation differences have led to significant variation in therapeutic and toxicological responses. Slow acetylators seem more likely to develop adverse reactions, whereas rapid acetylators are more likely to show an inadequate therapeutic response to standard drug doses.

For example the plasma half-lives of the antituberculosis drug (isoniazid) are 45-80 min and 140-200 min for rapid and slow acetyltors respectively. The higher plasma concentrations for the slow acetylators may explain the greater therapeutic response i.e. higher cure rate.

However, slow acetylators may show greater incidance of adverse effects e.g. peripheral neuritis and drug induced systemic lupus erythamtosus syndrome.

Acetylation and Drug interaction;

Phenytoin toxicity associated with concomitant use with isoniazid appear to be more prevalent in slow acetylators as compared to rapid acetylators. This is because isoniazid inhibits the metabolism of phenytoin leading to the accumulation of high levels of phenytoin in plasma.

Furthermore, patients who rapid acetylators appear to be more likely to develop isoniazid-associated hepatitis.

The initial hydrolysis of the N-acetylatedisoniazid to acetylhydrazine leads to oxidation by CYP to chemically reactive acetylation intermediates (acetylhydrazine) that covalently bind to hepatic tissues causing necrosis.

Overcoming Lupus Erythmatosus Syndrome

The tendency of drugs such as hydralazine and procainamide to cause lupus erythmatosus syndrome and to elicit formation of antinuclear antibodies (ANAs) appear to be related to acetylator phenotype, with greater prevalence in slow acetylators.

Rapid acetylators may prevent immunological triggering of ANAs formation and the lupus syndrome. The N-acetylated metabolite of procainamide is an active antiarrhythmic agent as the parent drug and has a half-life twice as long in humans.

Therefore N-acetylated procainamide may be a promising alternative to procainamide as an antiarrhythmic agent with less lupus inducing potential.