Medicinal Chemistry

Chapter 8

DRUG METABOLISM & PRODRUGS

Section 1: Drug Metabolsim

Contents

DRUG METABOLISM

- When drugs enter the body, they are subject to attack from a range of metabolic enzymes. The role of these enzymes is to **degrade** or **modify** the foreign structure, such that it can be more easily excreted.

- As a result, most drugs undergo some form of **metabolic reaction**, resulting in structures known as **metabolites.**

- Drug metabolites are products formed from drug metabolism

- Drug metabolites are usually less active or inactive (exception – metabolites of prodrugs)

- Some metabolites can possess a different activity from the parent drugs, resulting in side effects or toxicity

- The body treats drugs as foreign substances and has methods of **getting rid** of such chemical invaders.

- If the drug is **polar**, it will be quickly excreted by the kidneys. However, **non-polar** drugs are not easily excreted and the purpose of drug metabolism is to convert such compounds into more polar molecules that can be easily excreted.

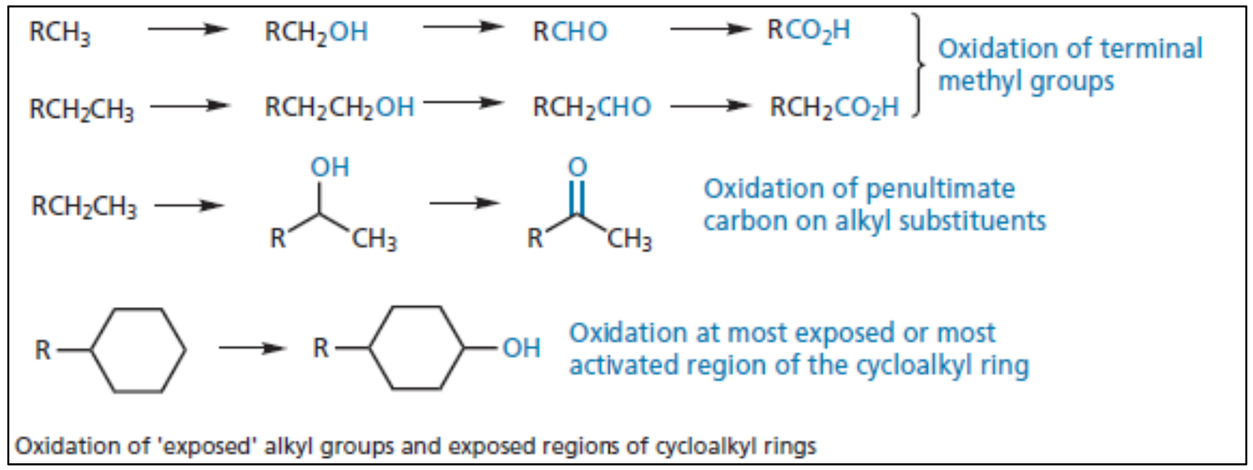
- Non-specific enzymes are able to add polar functional, also some enzymatic reactions can reveal masked polar functional groups which might already be present in a drug. **PHASE I**

- A series of metabolic reactions also occur, mainly in the liver are conjugation reactions, whereby a polar molecule is attached to a suitable polar ‘handle’ that is already present on the drug or has been introduced by a phase I reaction. **PHASE II**

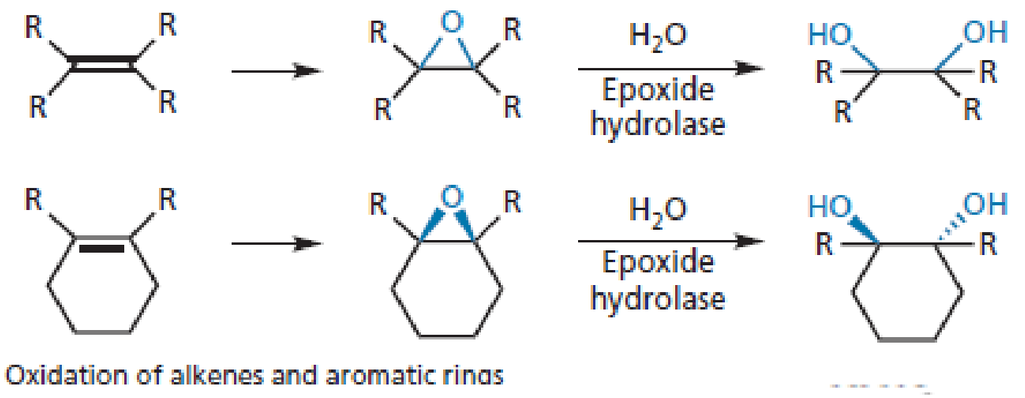
Phase I reactions

- **Cytochromes P450**
- The most important and most extensively studied drug metabolism system in the body is the superfamily of cytochrome P450 monooxygenases (CYP450).
- It's non specific enzymes are able to add polar functional groups to a wide variety of drugs.
- CYP450 acts as a very sophisticated electron transport system responsible for the oxidative metabolism of a large number of drugs and other xenobiotics
- **Reaction of Phase I** involve oxidation, reduction and hydrolysis. Most of these reactions occur in the liver bust some occur in the gut wall, plasma and the lung.

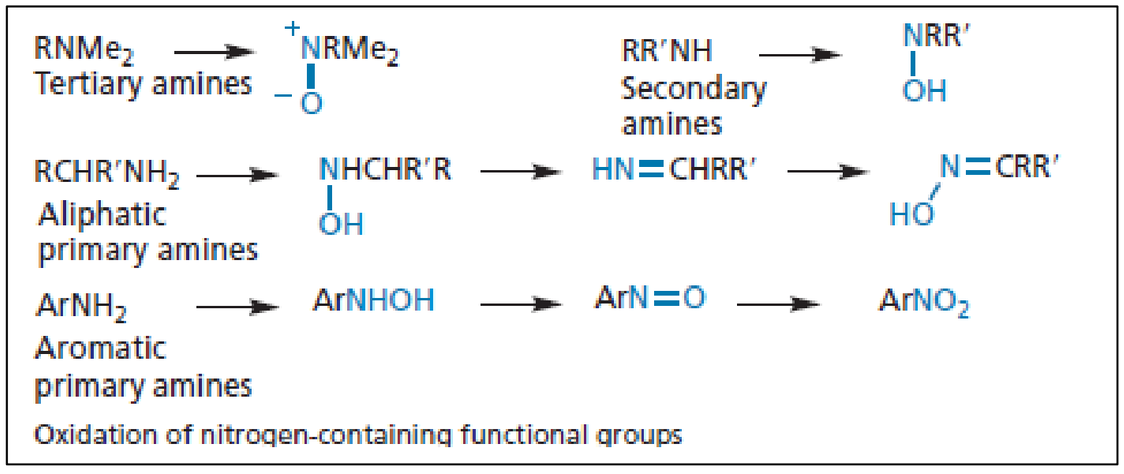
- The structures most prone to **oxidation** are *N*-methyl groups, aromatic rings, the terminal position of alkyl chains and the least hindered positions of alicyclic rings.



Oxidation of 'exposed' alkyl groups and exposed regions of cycloalkyl rings

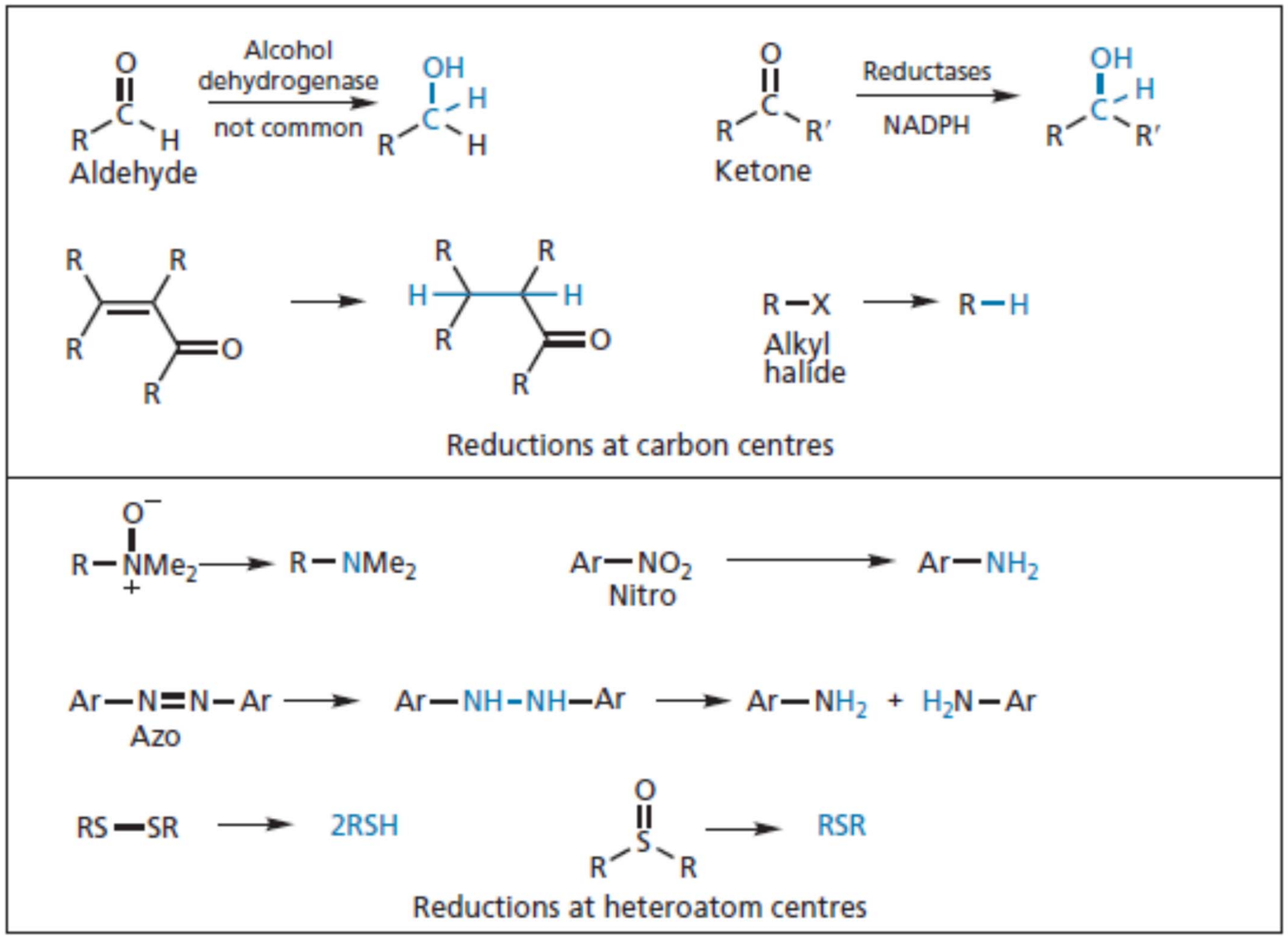


Oxidation of alkenes and aromatic rings

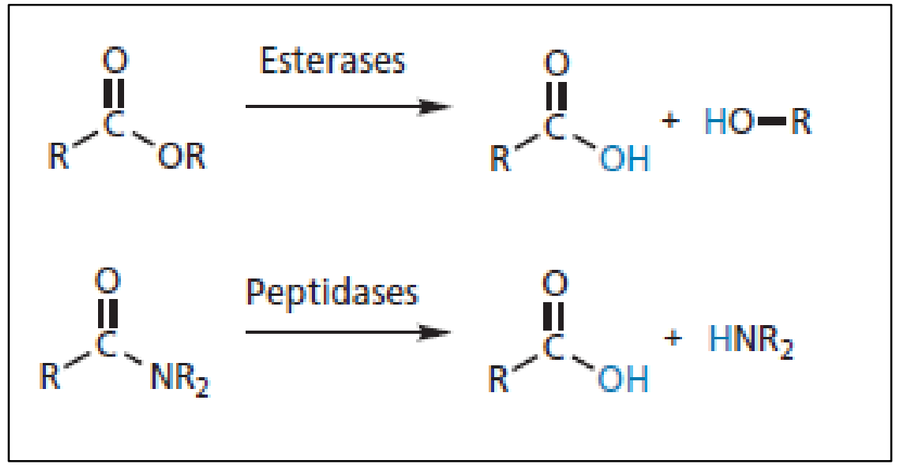


Oxidation of nitrogen-containing functional groups

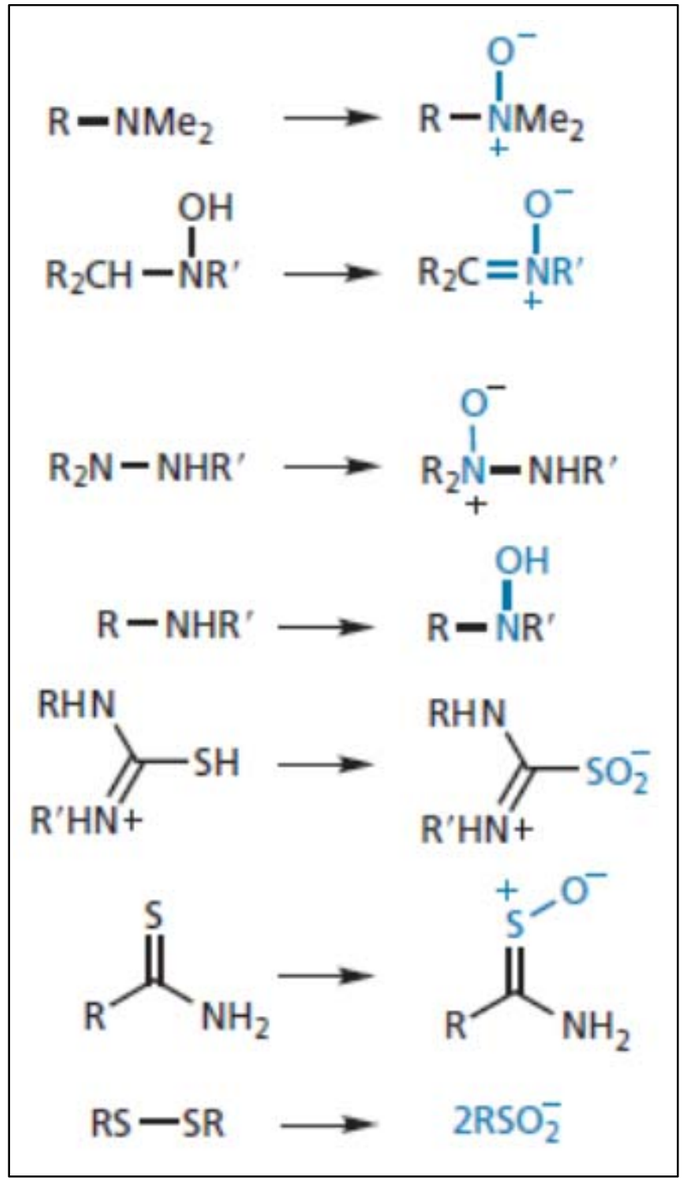
- Reductions of aldehyde, ketone, azo, and nitro functional groups have been observed in specific drugs.
- Many of the oxidation reactions described for heteroatoms are reversible and are catalysed by reductase enzymes. Cytochrome P450 enzymes are involved in catalysing some of these reactions.



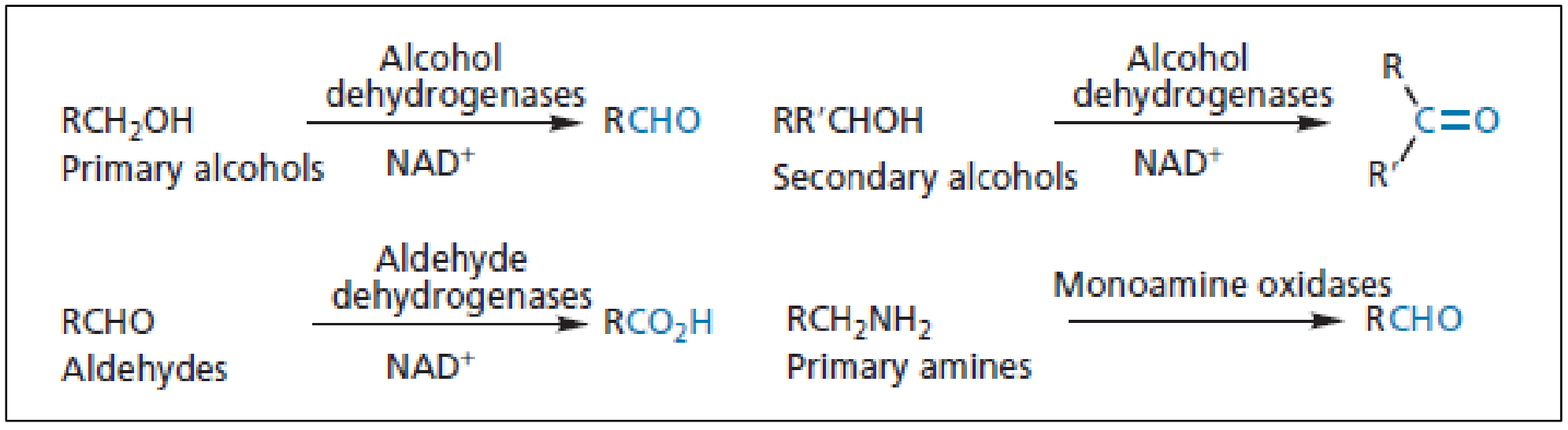
- The hydrolysis of esters and amides is a common metabolic reaction, catalysed by esterases and peptidases respectively. These enzymes are present in various organs of the body, including the liver. Amides tend to be hydrolysed more slowly than esters. The presence of electron-withdrawing groups can increase the susceptibility of both amides and esters to hydrolysis.



Another group of metabolic enzymes present in the endoplasmic reticulum of liver cells consists of the flavin-containing monooxygenases . These enzymes are chiefly responsible for metabolic reactions involving oxidation at nucleophilic nitrogen, sulphur, and phosphorus atoms, rather than at carbon atoms.



Other important oxidative enzymes include alcohol dehydrogenases and aldehyde dehydrogenases. The aldehydes formed by the action of alcohol dehydrogenases on primary alcohols are usually not observed as they are converted to carboxylic acids by aldehyde dehydrogenases.



Phase II

- **Drug conjucation reactions:**
- Conjugation reactions are very important in the biotransformation of drugs and foreign chemicals within the body.
- Conjugation reactions involve the attachment of very hydrophilic species such as glucuronic acid or glycine to xenobiotics and are usually considered to terminate pharmacological action.

- The drug conjugate is much less lipophilic and much more water soluble and is excreted easily by the kidneys.
- The situation is complicated, however, because drugs can be a substrate for more than one metabolising enzyme and there is no ‘pecking order’ or priority for enzyme action.
- This sequential conjugation can give rise to a bewildering array of metabolites and conjugates appearing in the urine or faeces when a drug is administered.

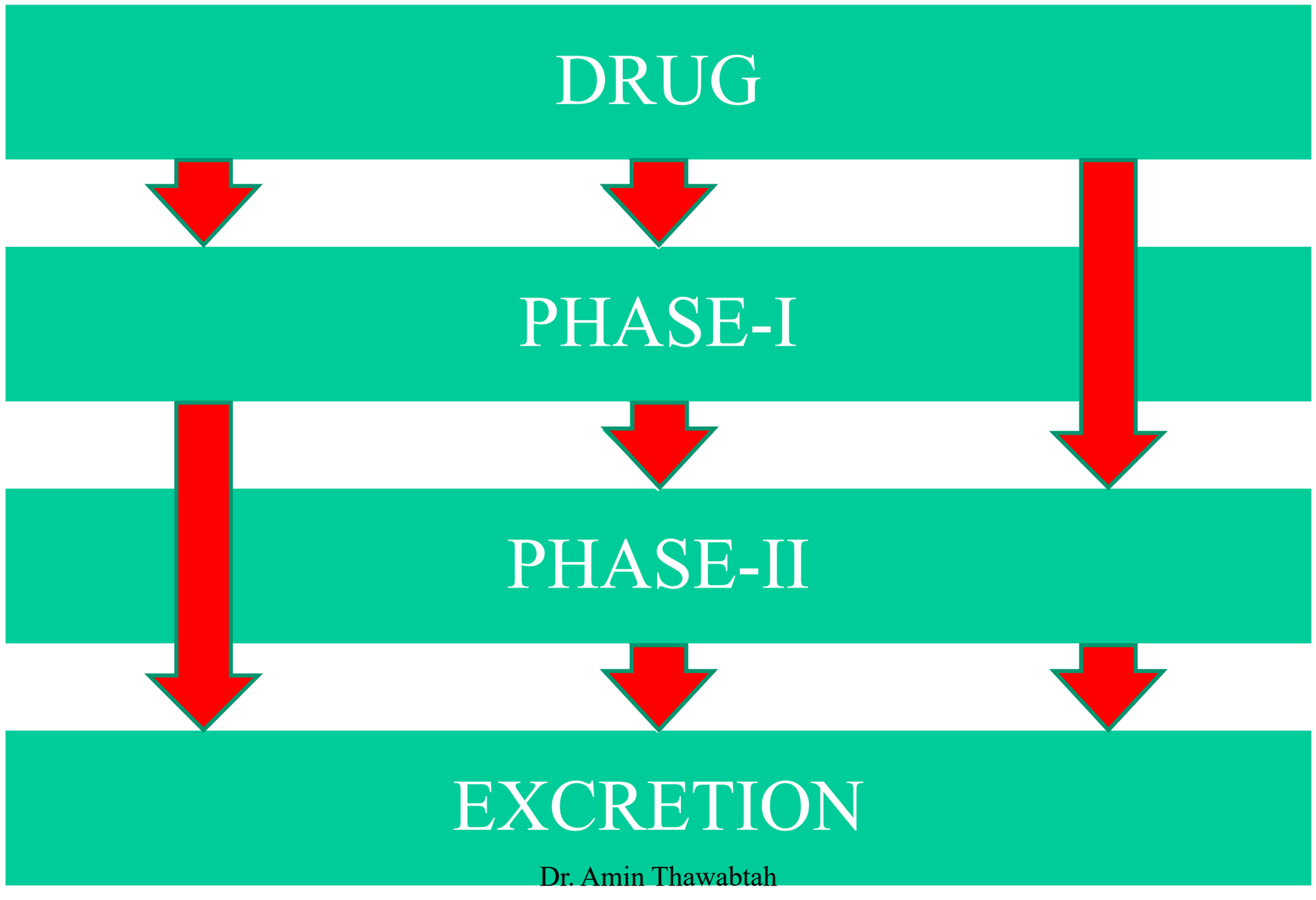
- **Phase I** or functionalization reactions ***do not*** always produce hydrophilic or pharmacologically inactive metabolites.
- Various **phase II** or conjugation reactions, however, can convert these metabolites to ***more polar and water soluble products***. Many conjugative enzymes accomplish this 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.**

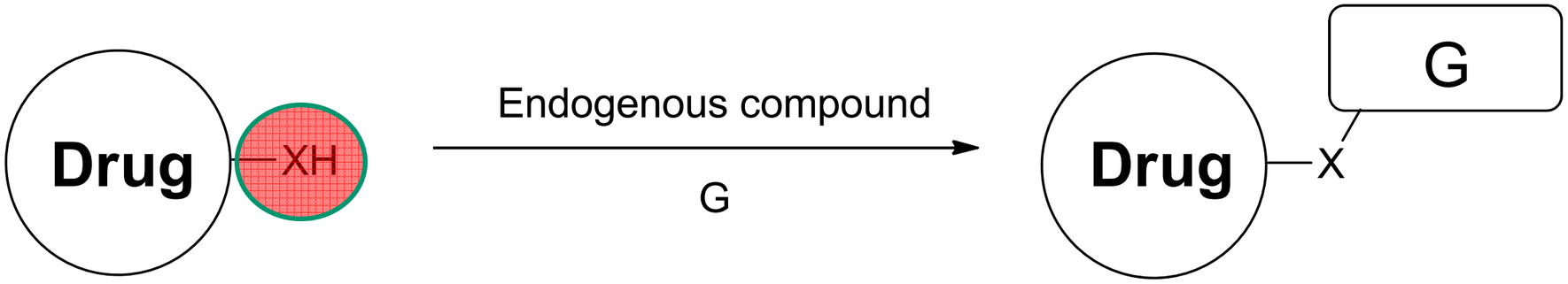
- The resulting conjugated products are relatively water soluble and readily excretable. In addition, they generally are biologically inactive and nontoxic. Other phase II reactions, such as ***methylation*** and ***acetylation***, ***do not*** generally ***increase*** water solubility but mainly serve ***to terminate or attenuate pharmacological activity.***

Phase-II Drug Metabolism Involves the following conjugation reactions that are catalyzed by transferase enzymes:

- ***Glucuronidation.***
- ***Sulfation.***
- ***Amino acid conjugation.***
- ***Methylation.***
- ***Acetylation.***

If the drug does not have such group, it will undergo phase-I metabolism, then **phase-I** metabolite will be conjugated during **phase-II** reactions.


DRUG
PHASE-I
PHASE-II
EXCRETION



Active drug

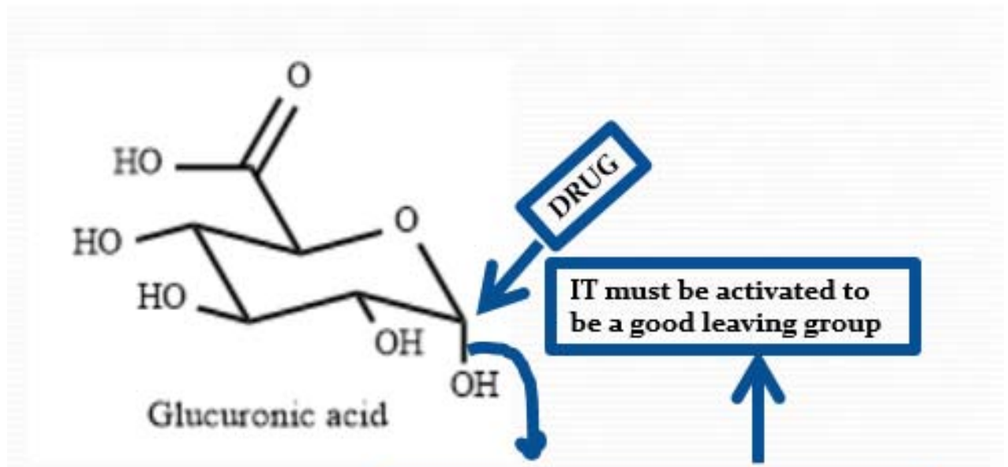
Phase-II drug conjugate

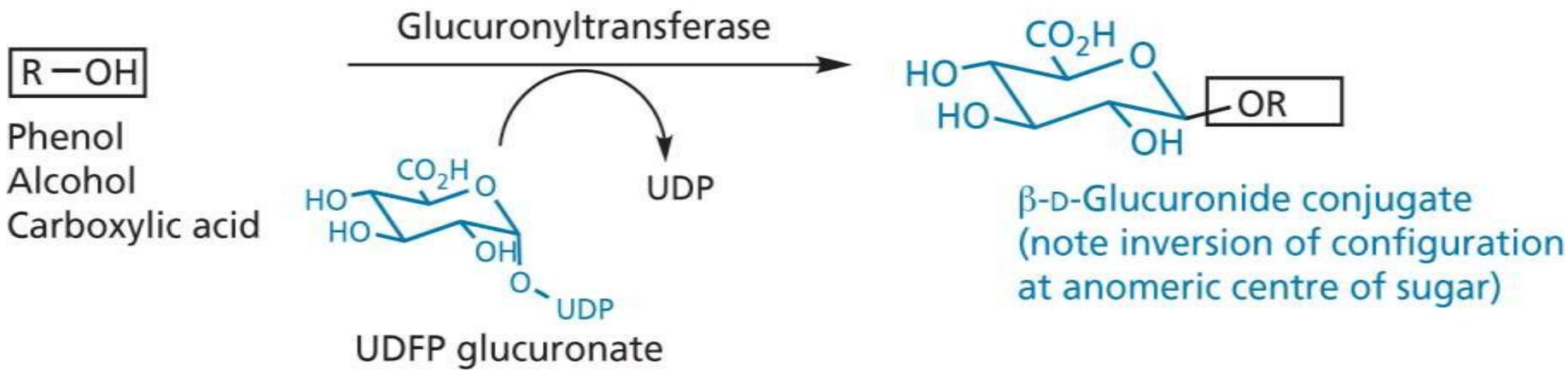
X = O, N, S

Phenol, alcohol and carboxylic acid
Amine (aliphatic and aromatic)
Thiol

Excreted in urine

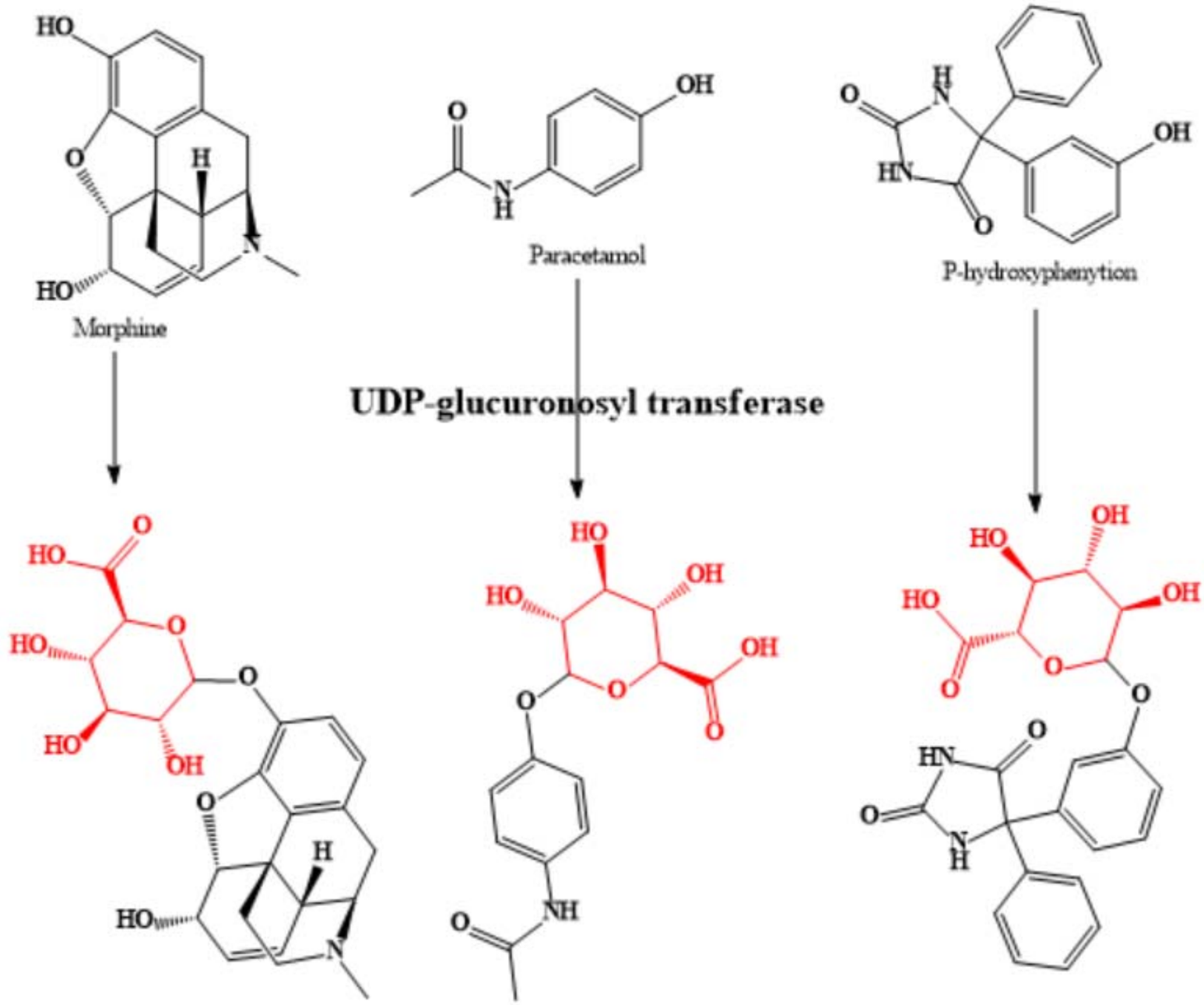
1. *O*-Glucuronide conjugates: by reaction with UDP-glucoronate such that highly polar glucuronic acid molecule is attached to the drug.





I. Hydroxyl Glucuronides:

A- phenols:

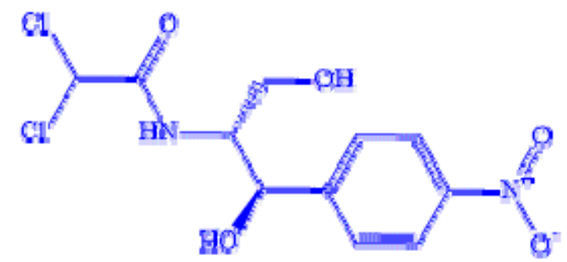


B- Alcohols

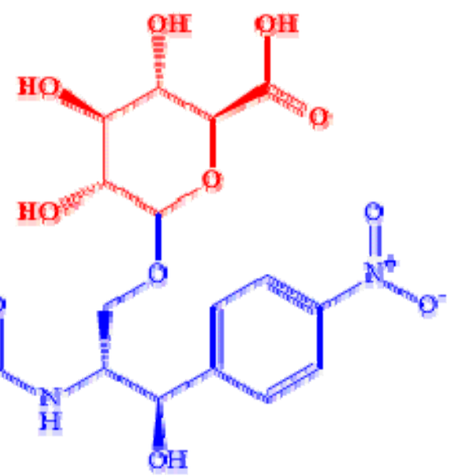
C- Enols

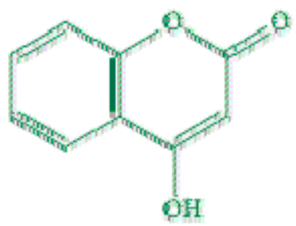
D- N-Hydoxyamines

E- Carboxyl compounds (Arylalkyl acids):

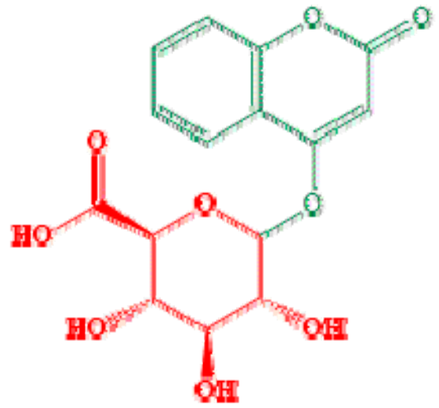


Chloramphenicol

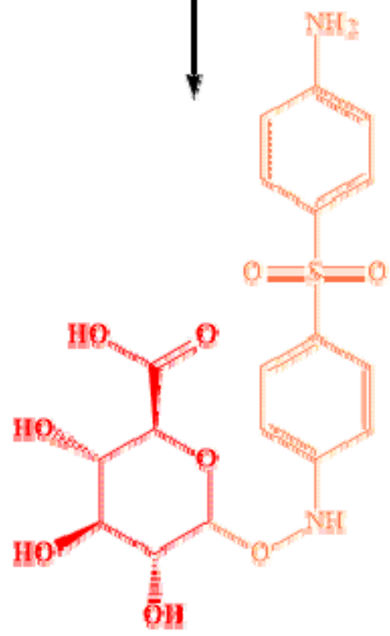




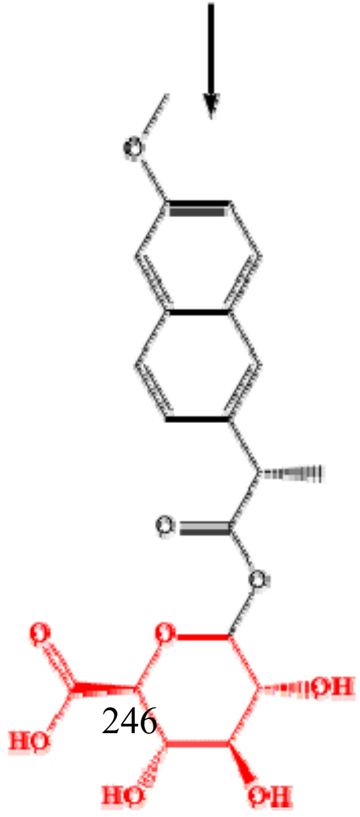
4-hydroxycoumarin



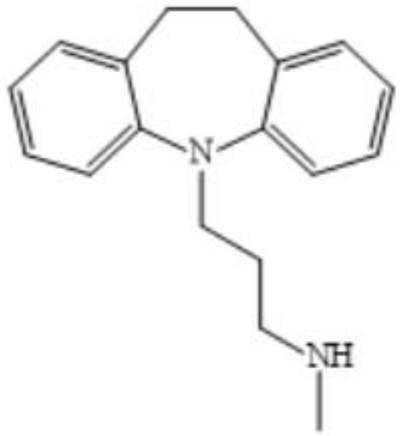
Dapsone hydroxylamine



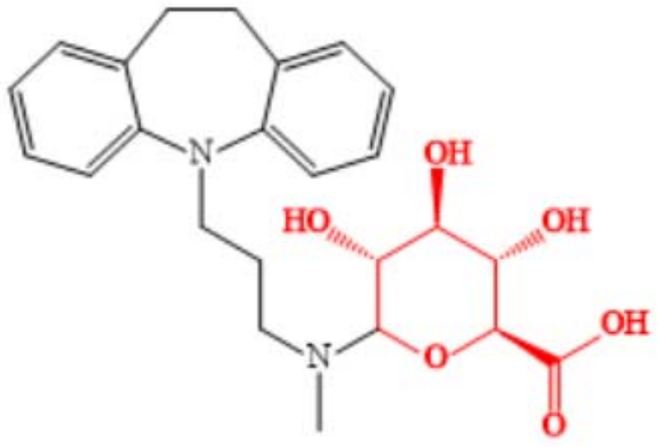
Naproxen

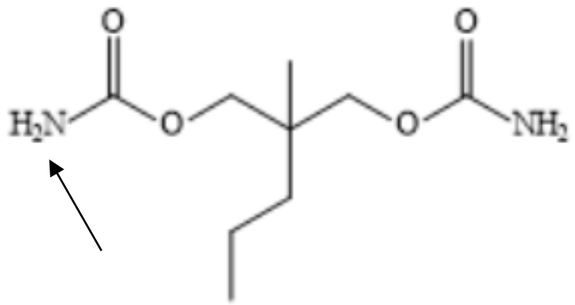


II. Nitrogen Glucuronides:



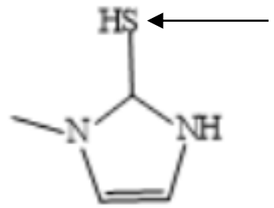
Desipramine





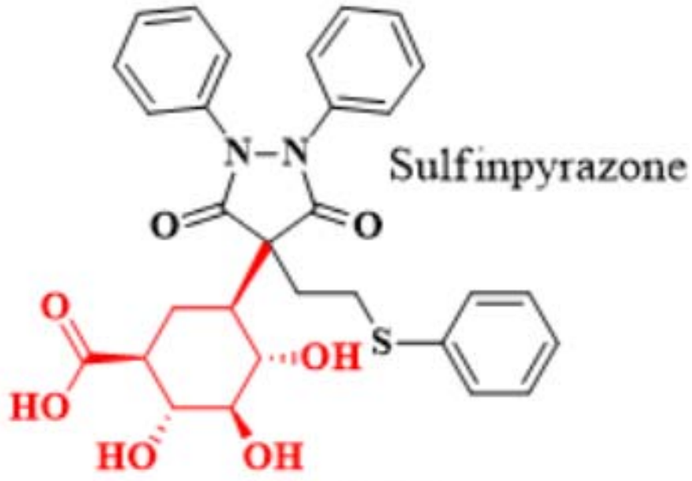
Meprobamate

III. Sulphur Glucuronides:



Methimazole

IV. Carbon Glucuronides



Sulfinpyrazone

Sulfinpyrazone-glucuronidation

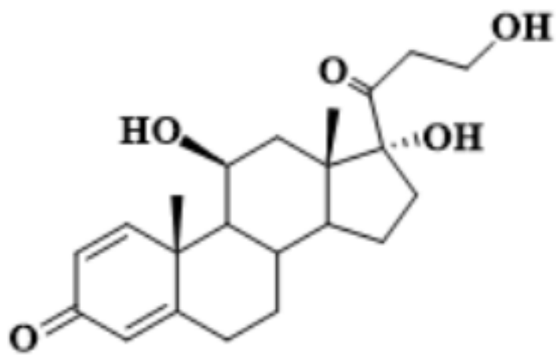
2. Sulfation (sulfate conjugation):

•Occurs primarily for phenols and occasionally for alcohols, arylamines, and *N*-hydroxy compounds

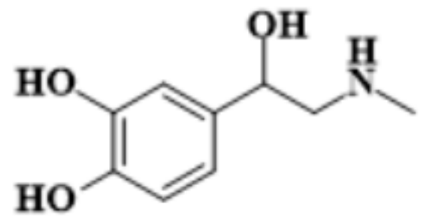
•Catalyzed by sulfotransferase enzyme.

•Sulfotransferase is available mainly in liver, but can be found in kidney, intestine and other tissues

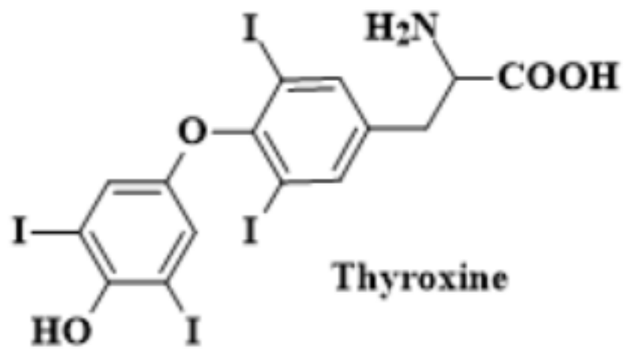
•Also occur for endogenous compounds, such as steroids, thyroxin, catecholamine and heparin.



Prednisolone

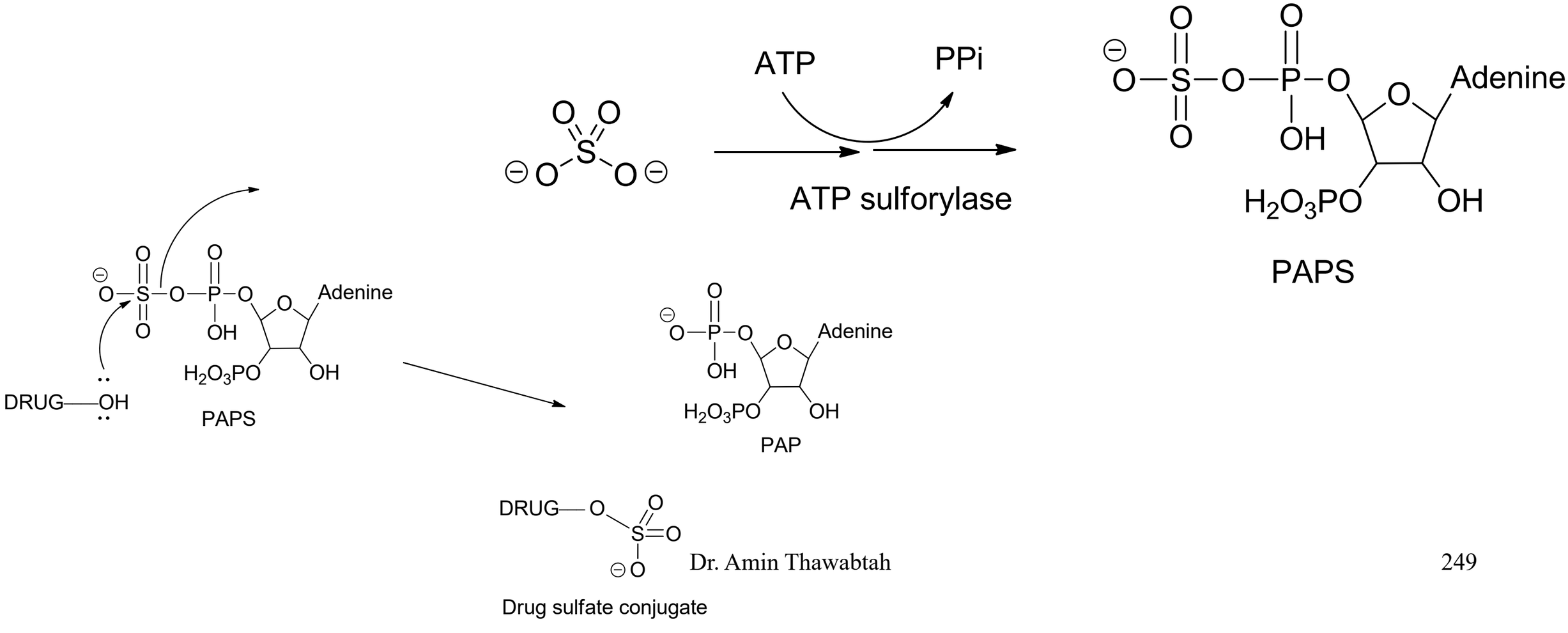


Adrenaline



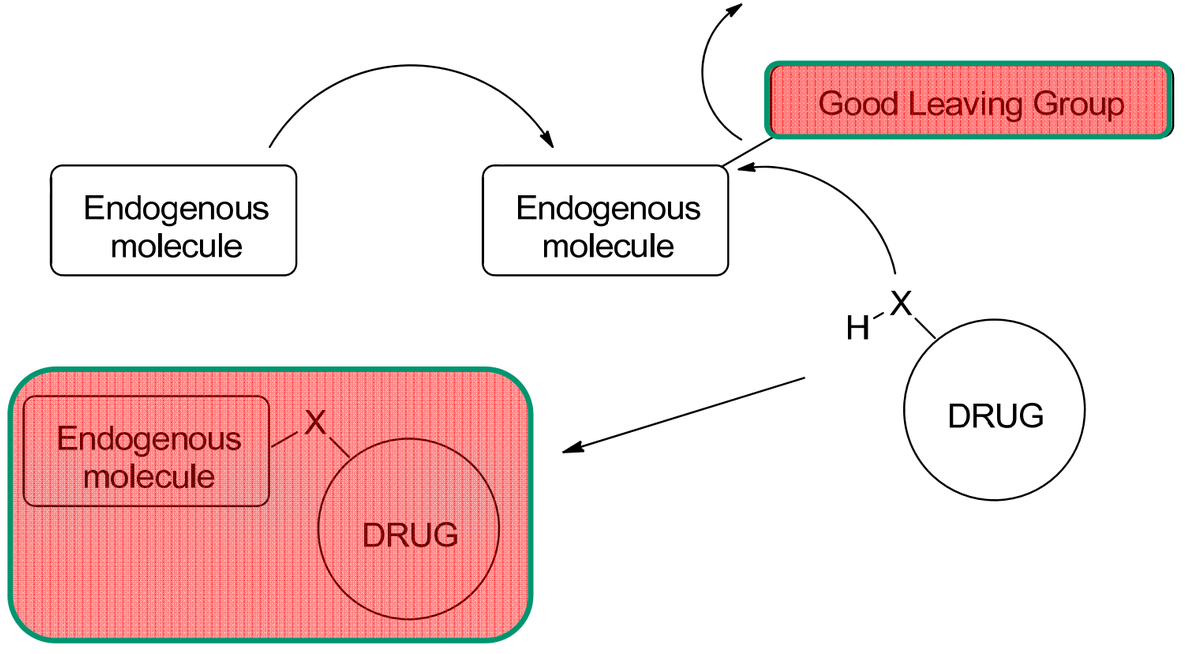
Thyroxine

- The first step is the bioactivation of inorganic sulfate by enzyme **called ATP sulforylase** to give the coenzyme **3'-phosphoadosine-5'-phosphosulfate** (PAPS)
- The second step here is the **transfer** of **sulfate group from the coenzyme PAPS to the acceptor drug by nucleophilic attack**:

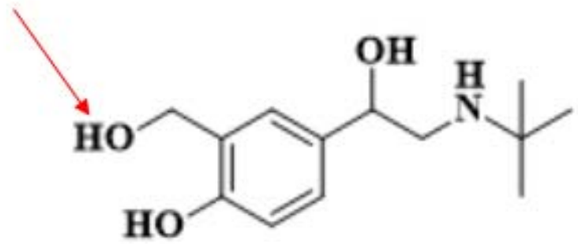


As in all conjugation reactions:

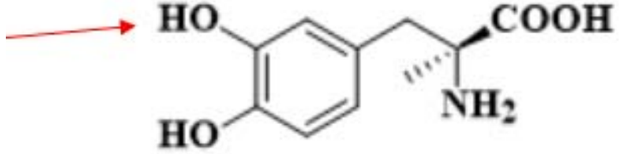
- The endogenous polar group must be activated and converted into electrophilic derivative.
- Then the drug nucleophilic group will attack the reactive form get the polar, ionizable endogenous molecule.



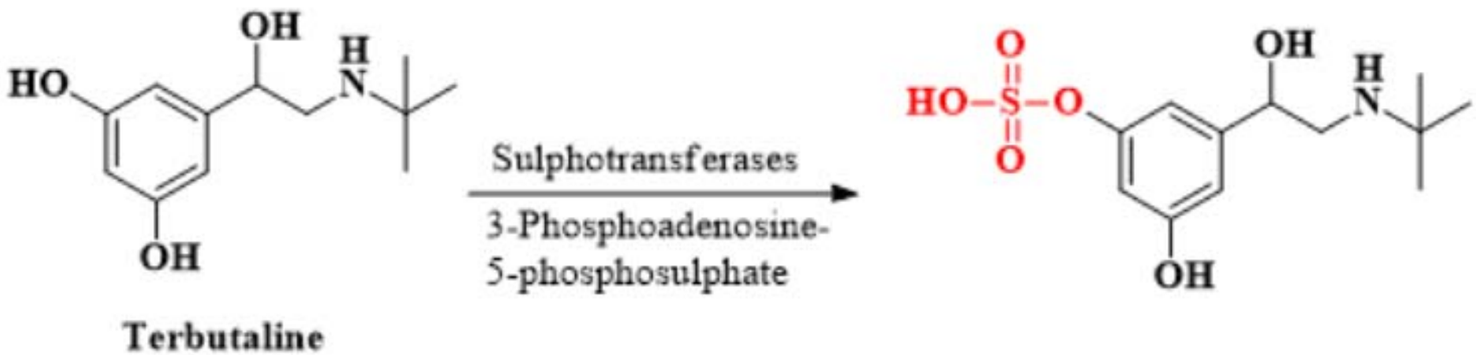
- Phenols are the main group of substrates undergoing sulphate conjugation.
- Drugs containing phenolic moieties are often susceptible to sulphate formation
  - For example the antihypertensive agent:
    - α-Methyldopa is metabolised extensively to its 3-O-sulfate ester in humans.
  - The β-adrenergic bronchodilators:
    - salbutamol and terbutaline also undergo sulphate conjugation as a principal route of metabolism in humans.



Salbutamol



α-methyldopa



Terbutaline

- For many phenols sulpho-conjugation is a minor pathway.

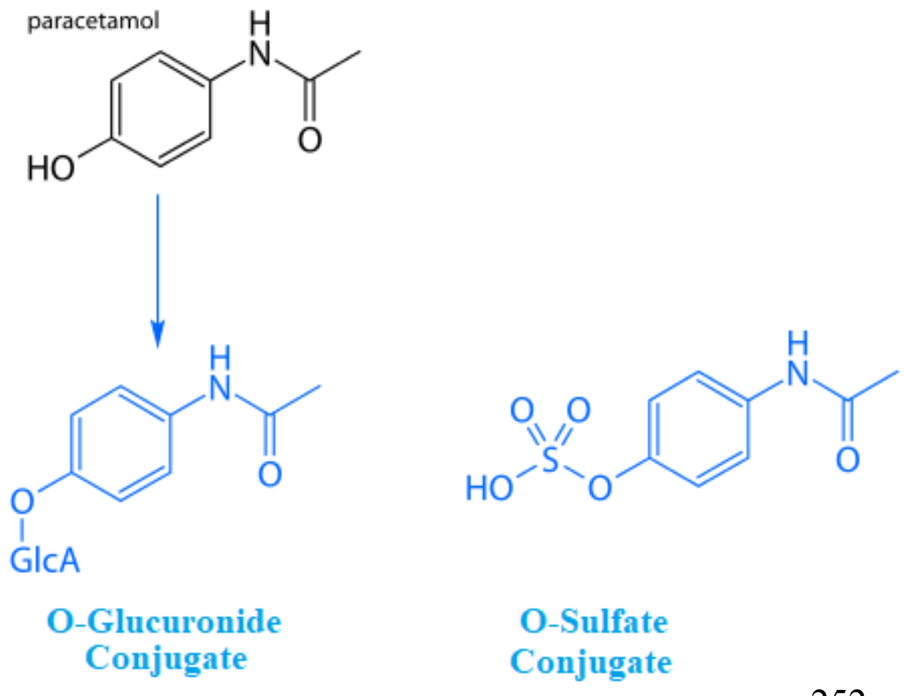
➢ Glucuronidation of phenols is more frequent and predominant in **phenolic** drugs.

➢ In adults, the major urinary metabolite of the analgesic **acetaminophen** is the **O-glucuronide conjugate** with small amount of **O-sulphate conjugate**

- In infants and young children (ages 3 to 9 years) exhibit a different urinary excretion pattern, the **O-sulphate conjugate** is the main urinary product.

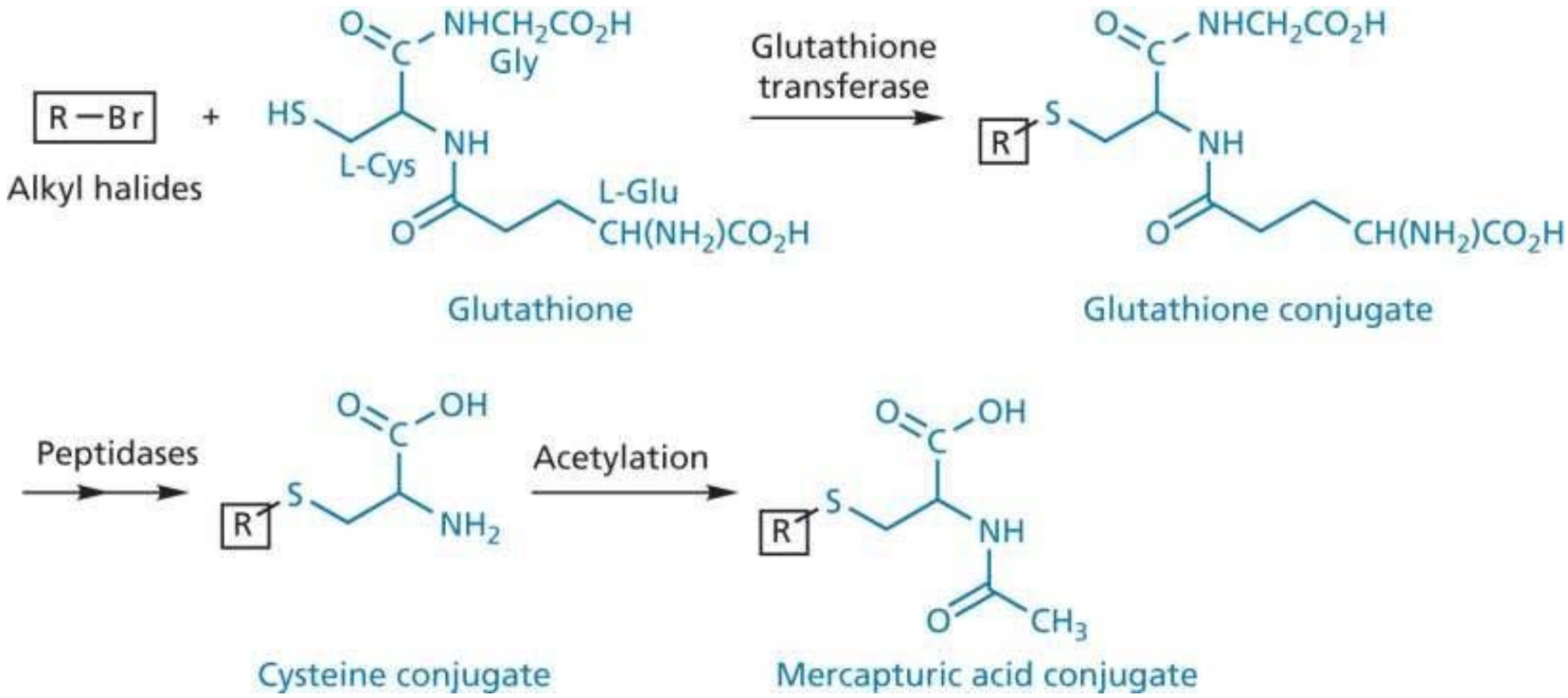
  – ***Because*** neonates and young children have a decreased glucuronidating capacity due to undeveloped glucuronyl transferases.

  – Sulphate conjugation is well developed and becomes the main route of acetaminophen conjugation in this paediatric group.



O-Glucuronide Conjugate **O-Sulfate Conjugate**

3. Electrophilic functional groups, such as epoxides, alkyl halides, sulphonates, disulphides, and radical species, can react with the nucleophilic thiol group of the tripeptide glutathione to give glutathione conjugates which can be subsequently transformed to mercapturic acids. The glutathione conjugation reaction can take place in most cells, especially those in the liver and kidney, and is catalysed by glutathione transferase .

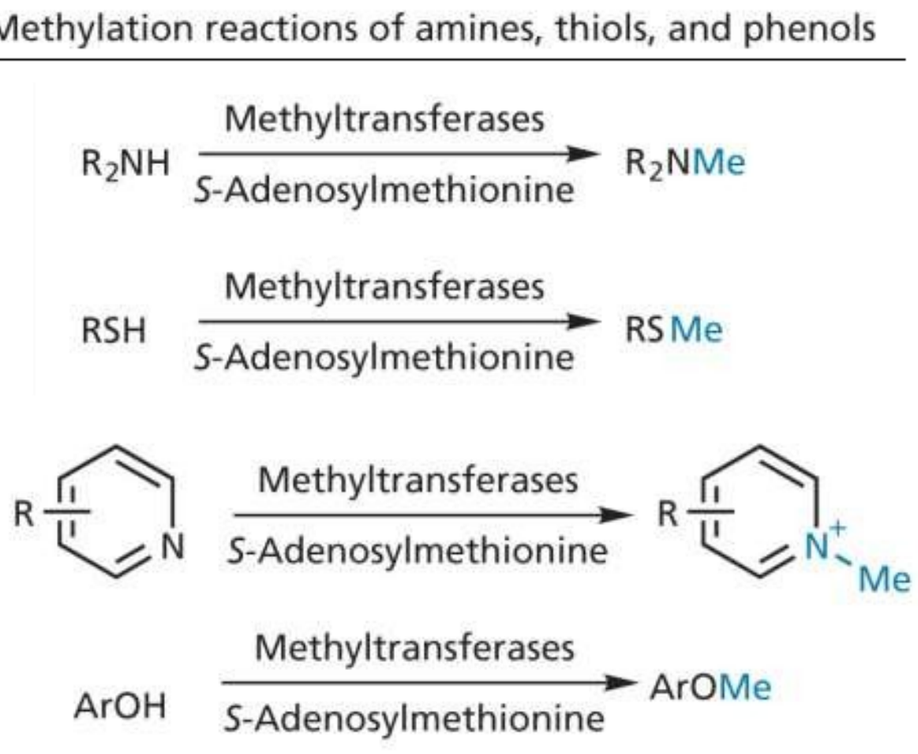


4. Methylation & acetylation:

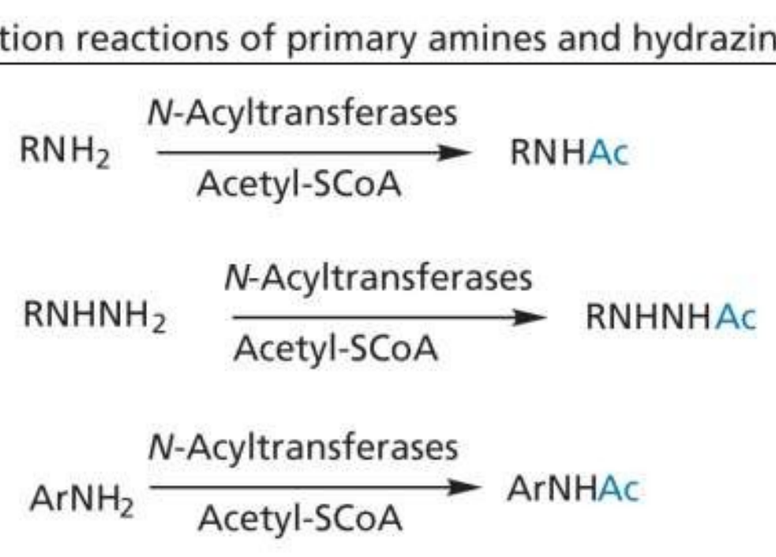
- The functional groups that are susceptible to methylation are **phenols, amines, and thiols.** **Primary amines** are also susceptible to acetylation.

- The enzyme cofactors involved in contributing the methyl group or acetyl group are S-adenosyl methionine and acetyl SCoA respectively.

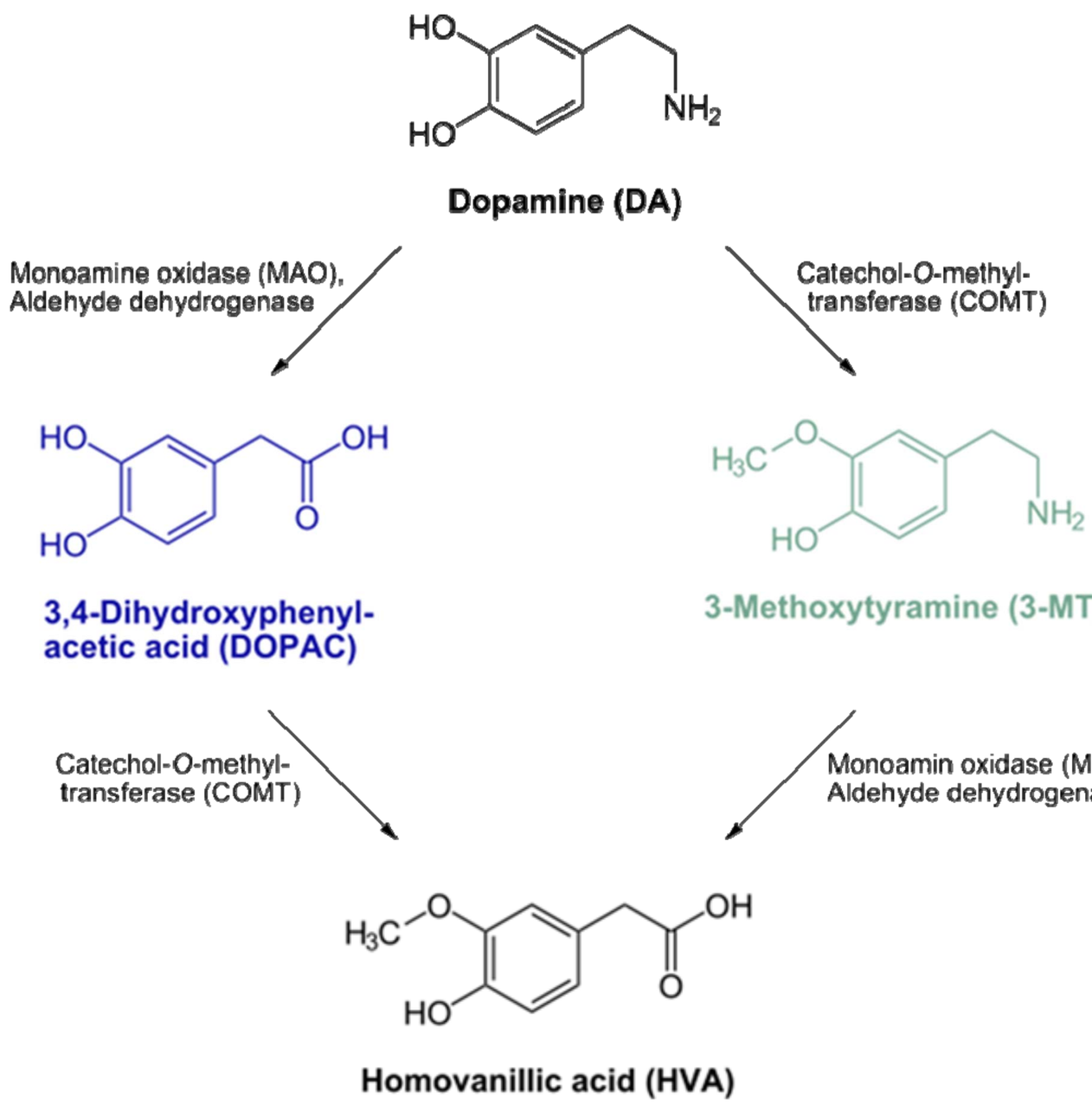
Methylation reactions of amines, thiols, and phenols



Acetylation reactions of primary amines and hydrazines

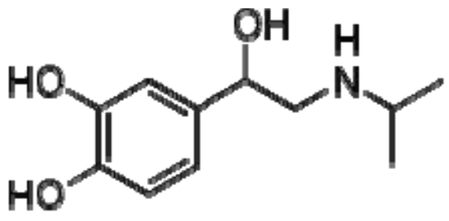


- The most important enzyme for O-methylations is catechol O-methyltransferase, which preferentially methylates the meta position of catechols

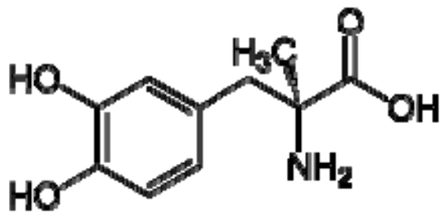


Examples of drugs that undergo significant O- methylation by COMT in humans include:

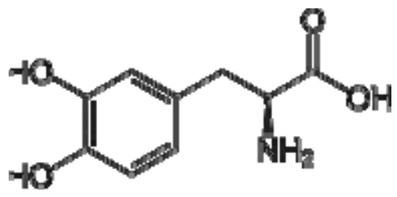
- The antihypernensive methyldopa
- The antiparkinsonism agent levodopa
- Dobutamine
- Selectively O-methylates only one the phenolic OH.
    - Bismethylation does not occur.
- Substrates undergoing O-methylation by COMT must contain an aromatic 1,2-dihydroxy group (catechol group).



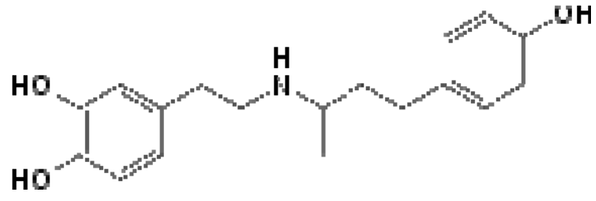
Isoproterenol (Isoprenaline)



Methyldopa



Levodeopa



Dobutamine

Section 2: Prodrugs

Contents

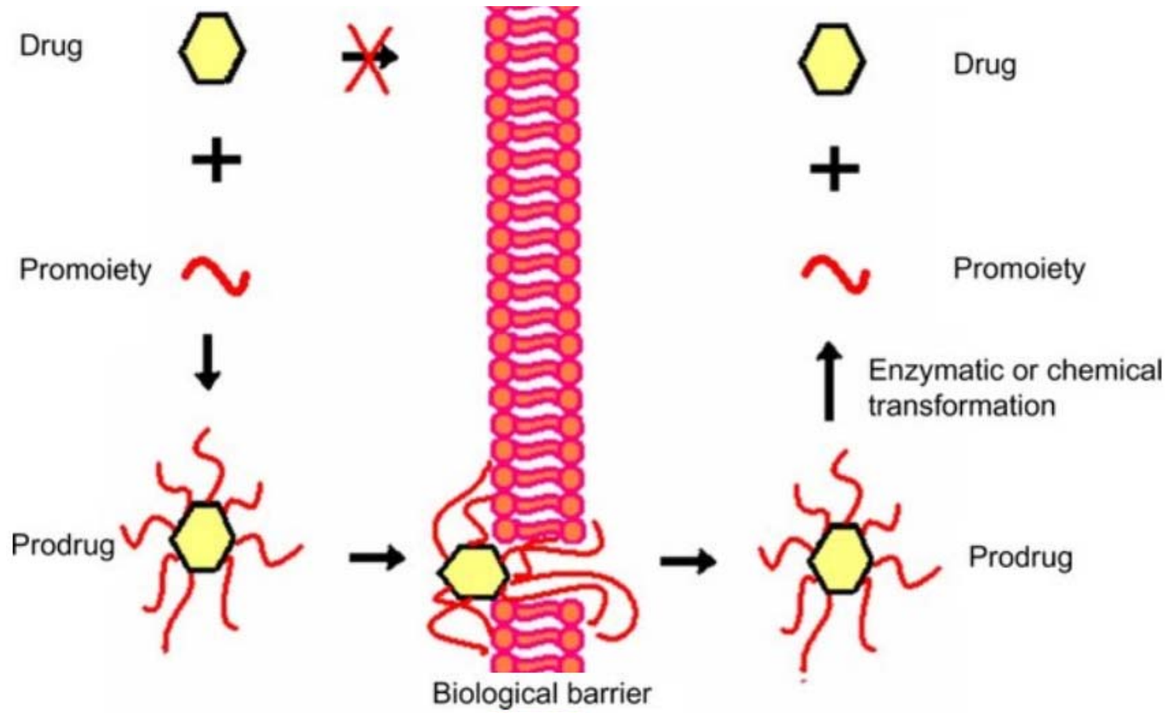
8.2 Prodrugs

Definition

Prodrugs are compounds which are inactive in themselves, but which are converted in the body to the active drug.

They have been useful in tackling problems such as:

- Improving membrane permeability
- Prolonging activity
- Masking toxicity and side effects
- Varying water solubility
- Drug targeting
- Improving chemical stability
- 'Sleeping agents'



Prodrugs activation mechanisms

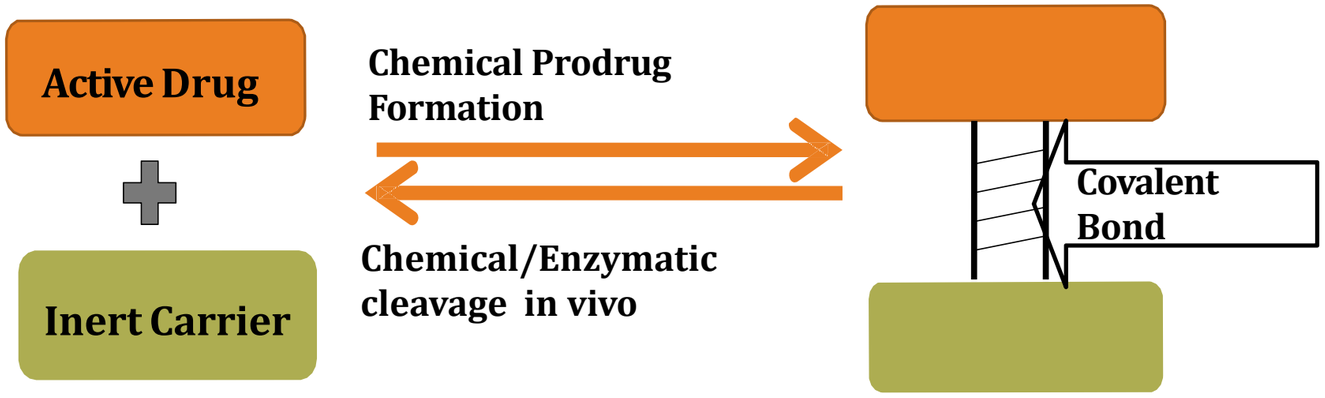
- Variety of mechanisms by which prodrug can be converted into active drug:
    1. Metabolizing enzymes (phosphotase, esterases, peptidase)
    - Interpatient variable
    2. Chemical activation (Hydrolysis, decarboxylation, light activation)
    - Stability issues
    3. Mixture of both
- Two important points: “ Ideal Prodrug ”
    1. The prodrug should be effectively converted to the active form once absorbed in the blood.
    2. Cleavable groups are non toxic.

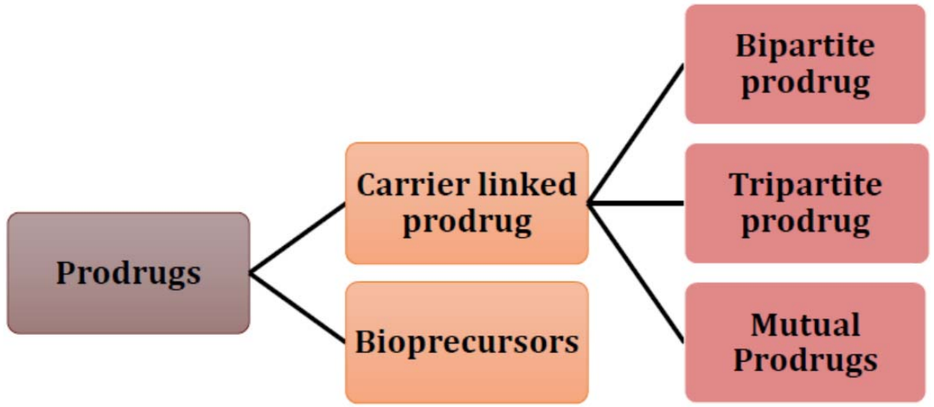
Prodrugs classification

A. Carrier-linked prodrugs

- Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties.

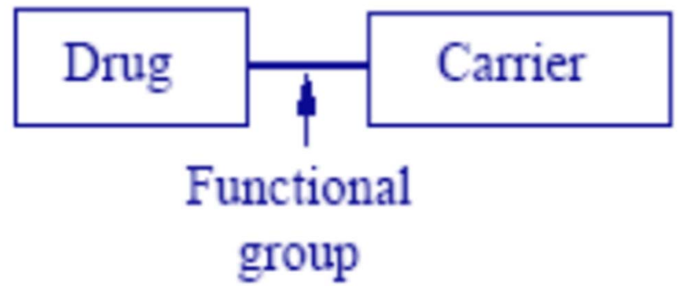
- The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety.



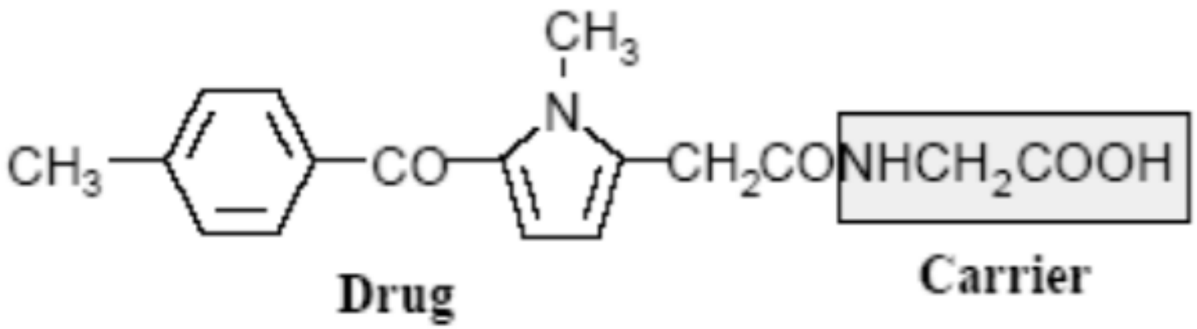


1. Bipartite prodrug

- It is composed of one carrier (group) attached to the drugs.
- Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically.

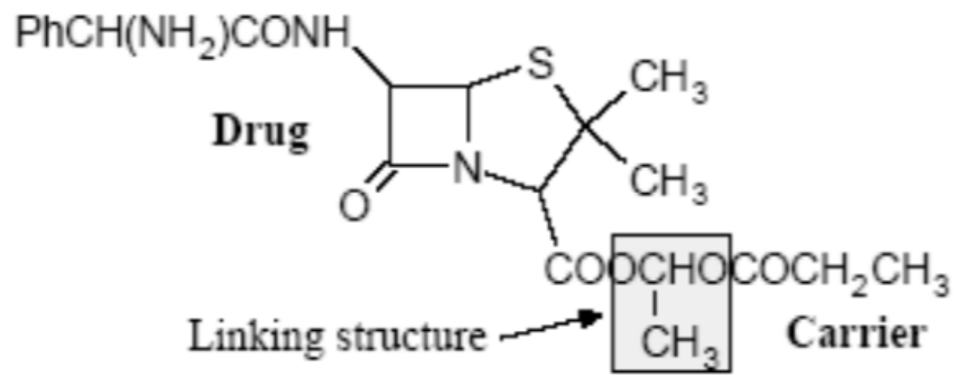


- E.g. Tolmetin-glycine prodrug.



2. Tripartite prodrug

- Structure of most prodrug is bipartite (having two parts) in nature in which parent drug is attached directly to promoiety bond.
- In some cases bipartite prodrug may be unstable, the problem can be overcome by designing a tripartite prodrug (having three parts).
- E.g. Bacampicillin prodrug.



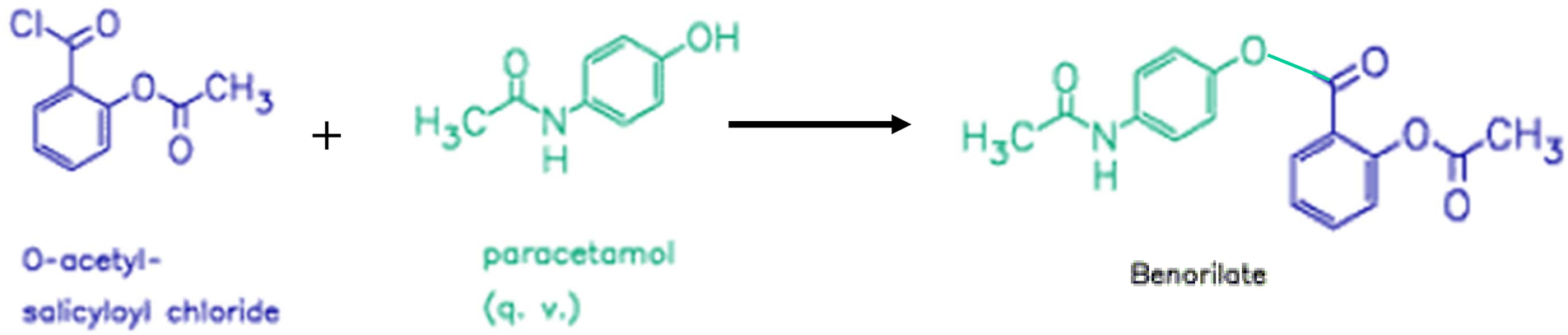
3. Mutual Prodrugs

- A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa.

- A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked.

- Benorylate is a mutual prodrug aspirin and paracetamol.

- Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum.

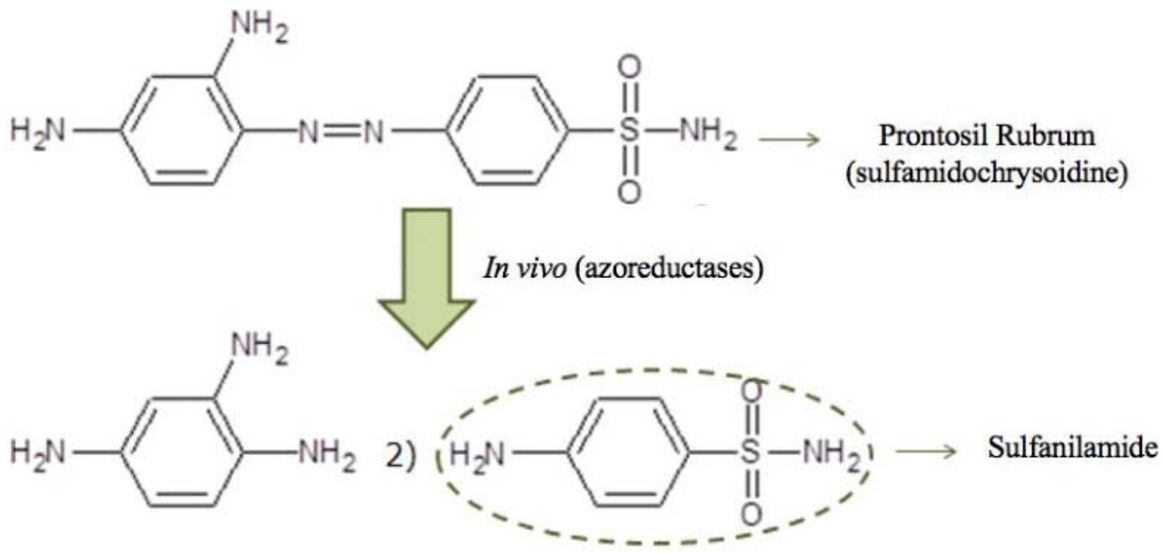


B. Bio-precursors

- Bio- precursor prodrugs produce their effects after in vivo chemical modification of their inactive form.

- Bio-precursor prodrugs rely on oxidative or reductive activation reactions unlike the hydrolytic activation of carrier-linked prodrugs.

- They metabolized into a new compound that may itself be active or further metabolized to an active metabolite



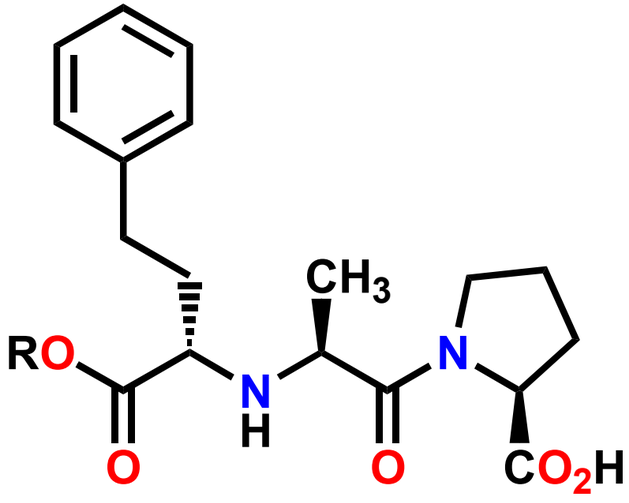
➢ Prodrugs to improve membrane permeability

A. Esters

- Used to mask polar carboxylic acids, alcohols or phenols
- Hydrolysed in blood by esterases
- Used when a carboxylic acid, alcohol or phenol is required for target binding
- Leaving group (alcohol or carboxylic acid) should ideally be non toxic

Examples

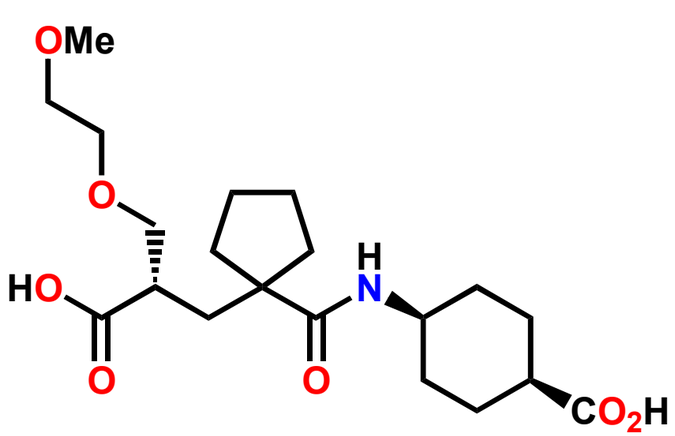
Enalapril for enalaprilate (antihypertensive)



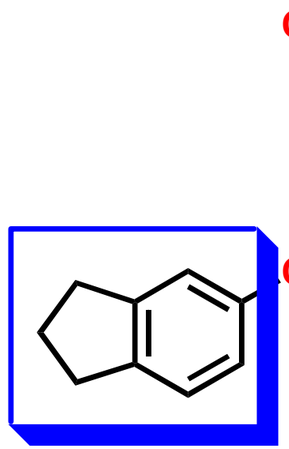
R=Et Enalapril
R=H Enalaprilit

Examples

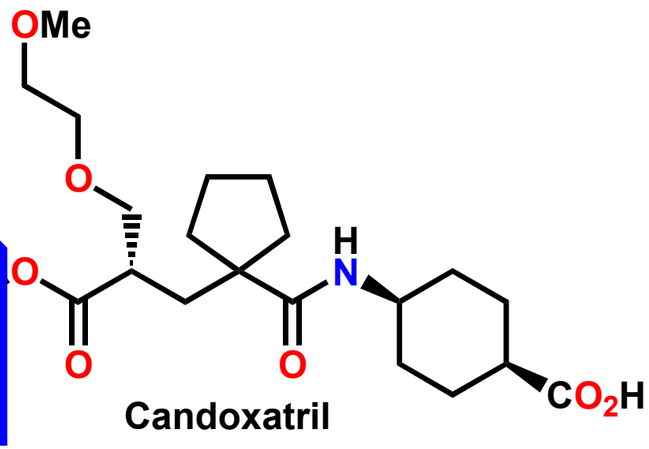
Candoxatril for candoxatrilat (protease inhibitor)



Candoxatrilat



5-indanyl group



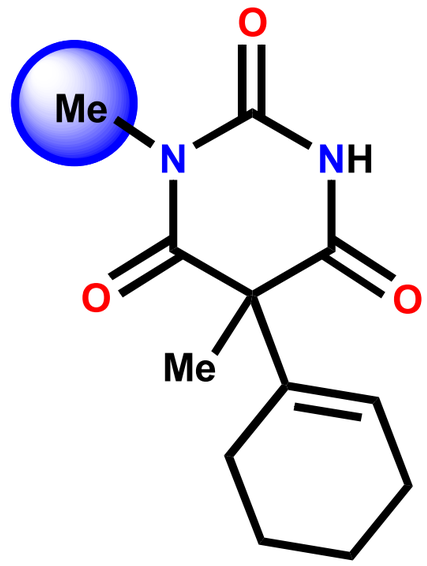
Candoxatril

Notes

- Varying the ester varies the rate of hydrolysis
- Electron-withdrawing groups increase rate of hydrolysis (e.g. 5-indanyl)
- Leaving group (5-indanol) is non toxic

B. *N*-Methylation of amines

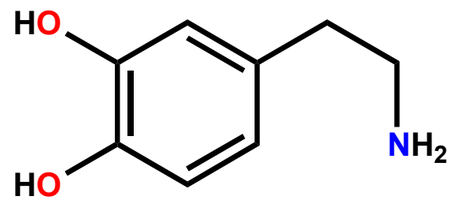
N-Demethylation is a common metabolic reaction in the liver, so polar amines can be *N*-methylated to **reduce polarity** and **improve membrane permeability**. Several hypnotics and anti-epileptics take advantage of this reaction, for example **hexobarbitone**

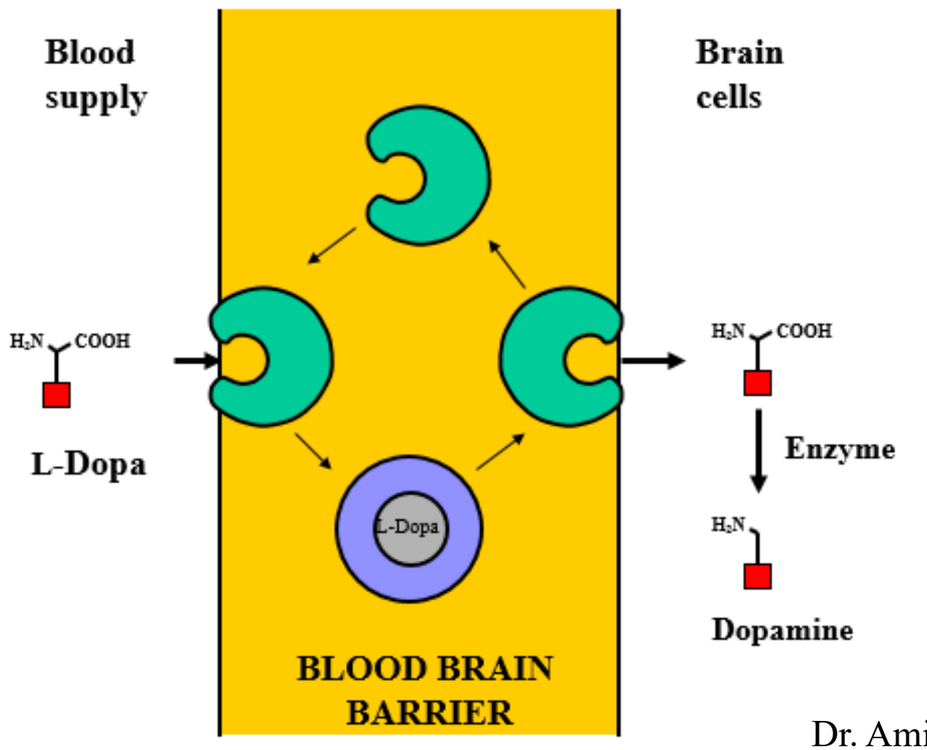


C. Trojan Horse Strategy

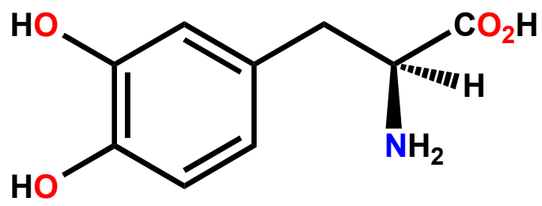
Design a prodrug which can take advantage of transport proteins in the cell membrane, such as the ones responsible **for carrying amino acids into a cell.**

Example - Levodopa for dopamine





Dopamine
- Useful in treating Parkinson's Disease
- Too polar to cross cell membranes and BBB

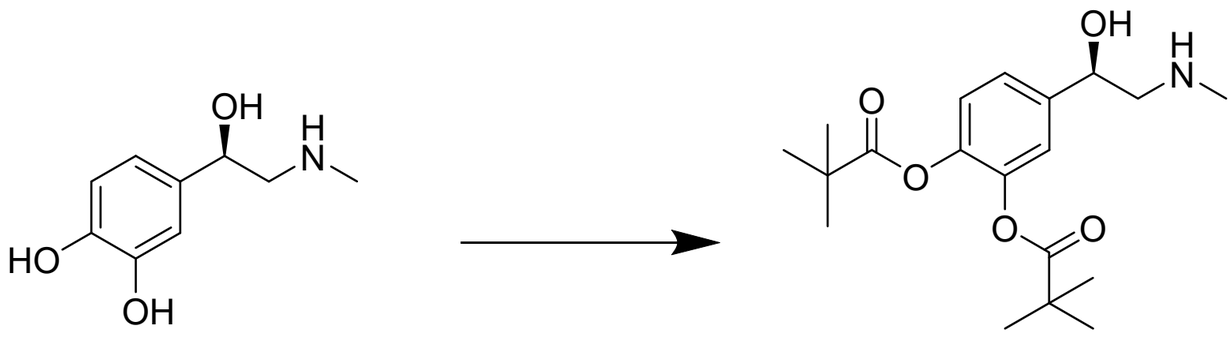


Levodopa
- More polar amino acid
- Carried across cell membranes by carrier proteins for amino acids
- Decarboxylated in cell to dopamine

- **Problem**: - Epinephrine is poorly absorbed through eye tissues

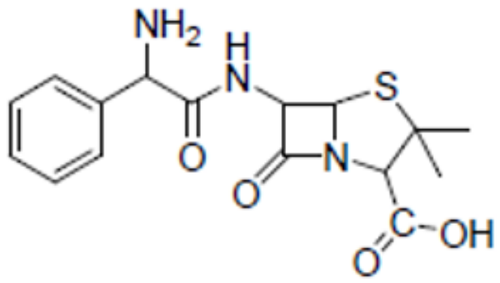
  Solution: The increased lipophilicity relative to epinephnine allows the drug to move across the membrane of the eye easily and achieve higher intraocular concentrations

- The steric bulk of pivalic acid slows down the hydrolysis

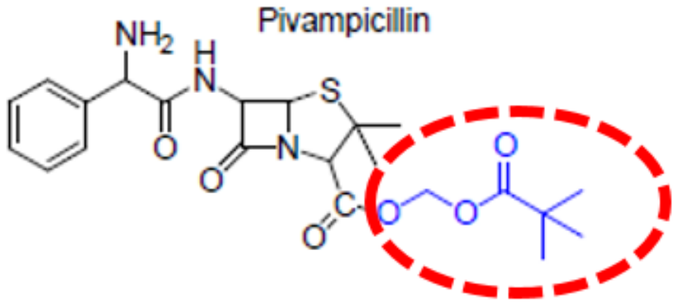


Epinephrine
poor corneal membrane penetration

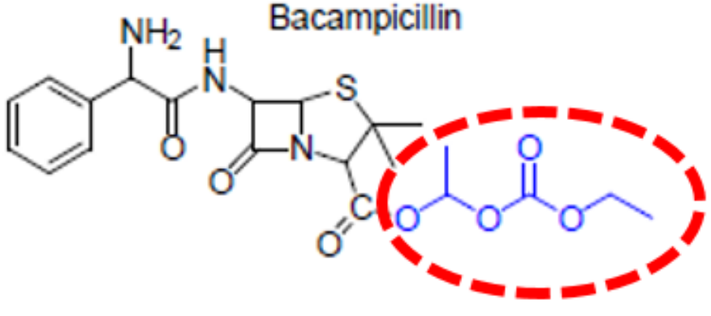
Dipivefrin
better corneal penetration
Used in Glaucoma



Ampicillin



Pivampicillin



Bacampicillin

- Ampicillin is poorly absorbed from the GI tract (~30% absorbed)

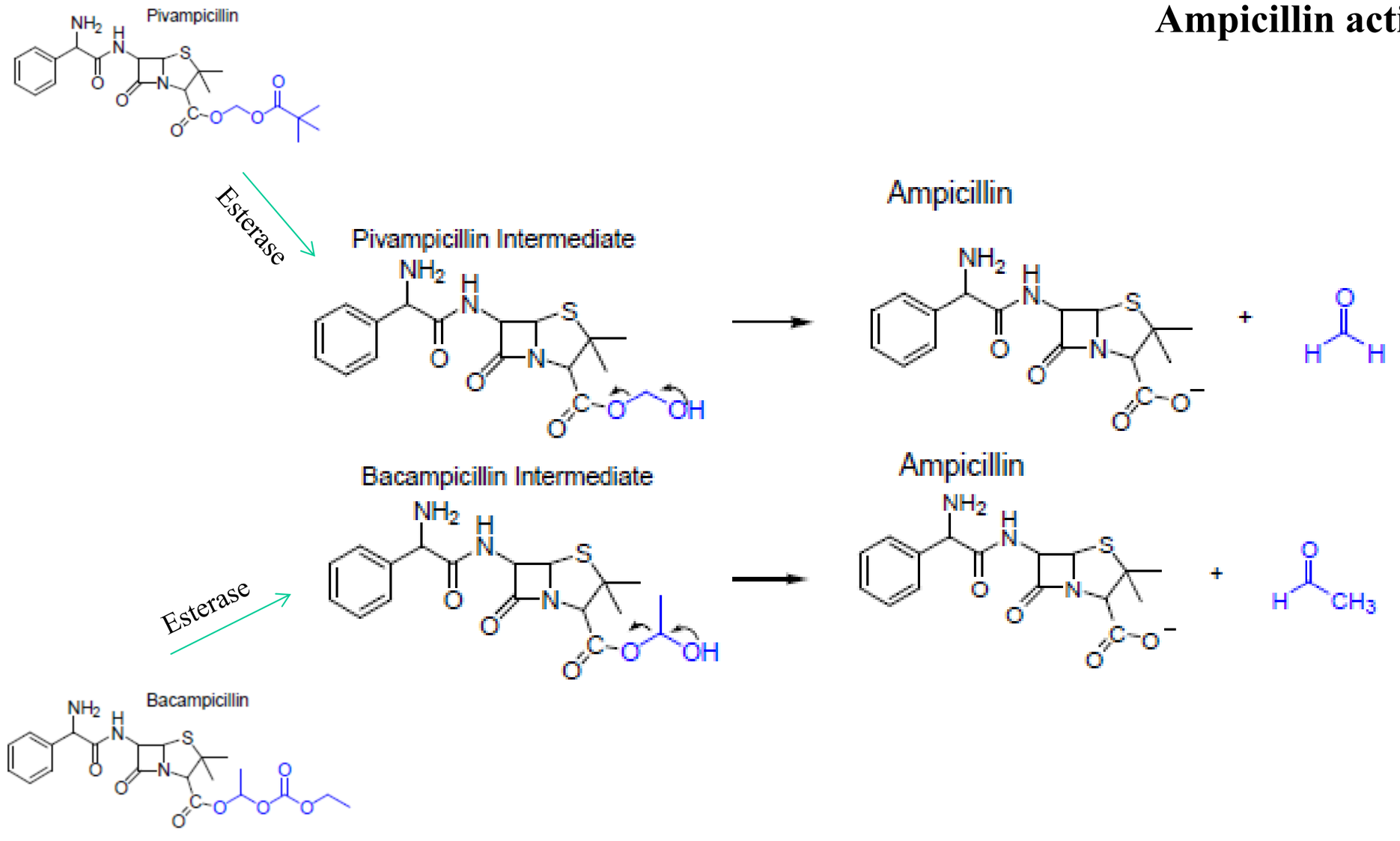
WHY???

- The carboxylic acid functional group (COOH):
  - ✓ Binds the drug to a receptor via ionic or hydrogen bonding.
  - ✓ An ionizable group may prevent drug from crossing a fatty cell membrane.

Solution:

- ✓ Convert the acid function to an ester moiety.
- ✓ The less polar ester can cross fatty cell membranes.
- ✓ The ester group will be hydrolyzed back to the free acid by the esterase in the blood.

Ampicillin activation *In Vivo*



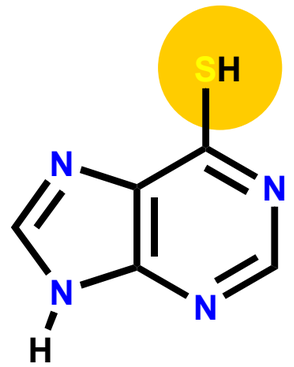
➢ Prodrugs to prolong activity

Sometimes prodrugs are designed to be converted slowly to the active drug, thus prolonging a drug's activity.

A. Mask polar groups

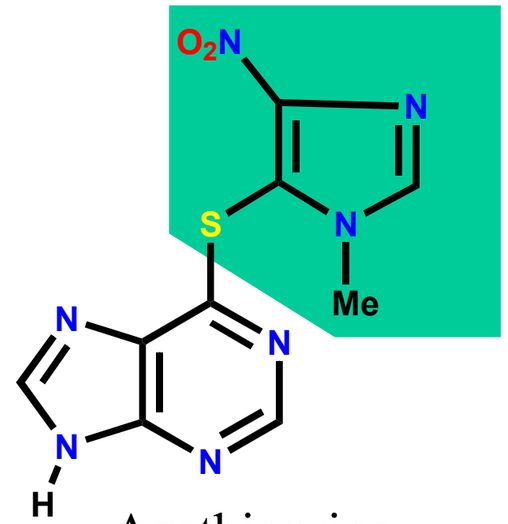
Reduces rate of excretion

Example: Azathioprine for 6-mercaptopurine



6-Mercaptopurine

Suppresses immune response
Short lifetime
Eliminated too quickly



Azathioprine

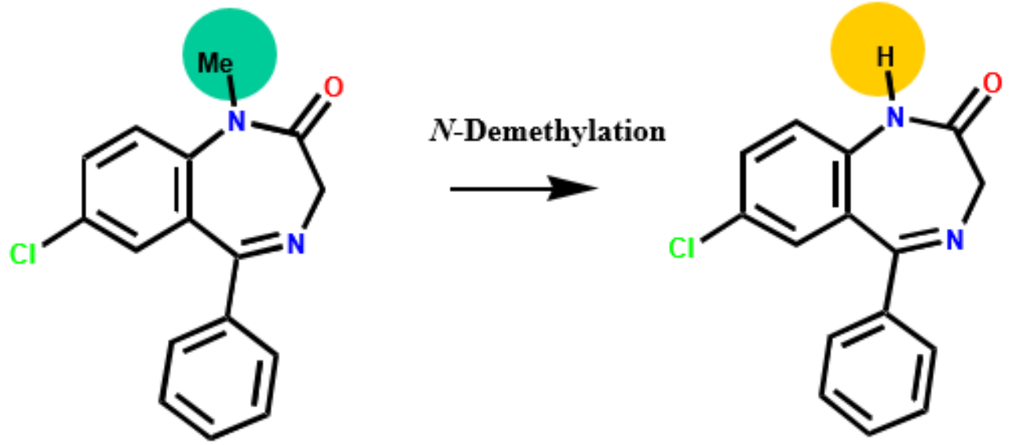
Slow conversion to 6-mercaptopurine
Longer lifetime

Example: Valium for nordazepam

- Valium might be prodrug, and is active because they it's metabolized by *N*-demethylation to nordazepams

- Nordazepam itself has been used as a sedative, but loses activity quite quickly as a result of metabolism and excretion

- Valium, if it is a prodrug for nordazepam, demonstrates again how a prodrug can be used to lead to a more sustained action.



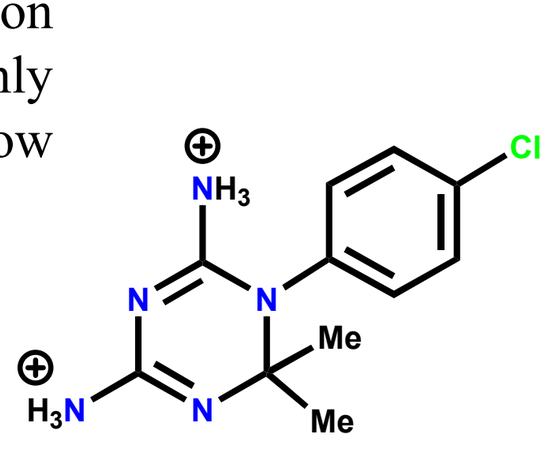
Valium Nordazepam

B. Add hydrophobic groups

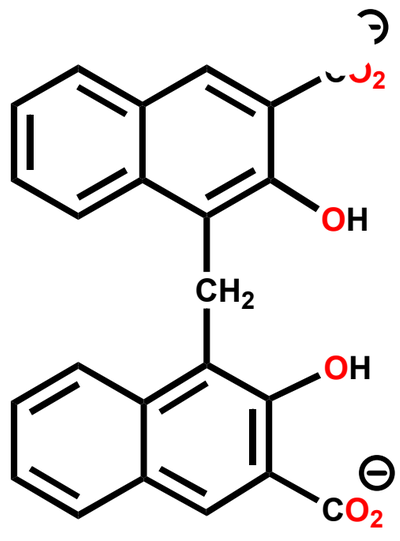
- Most of the drug is stored in fat tissue from where it is steadily and slowly released into the bloodstream.

- The active drug is bound ionically to an anion containing a large lipophilic group and is only released into the blood supply following slow dissociation of the ion complex

Example: Cycloguanil pamoate (antimalarial)



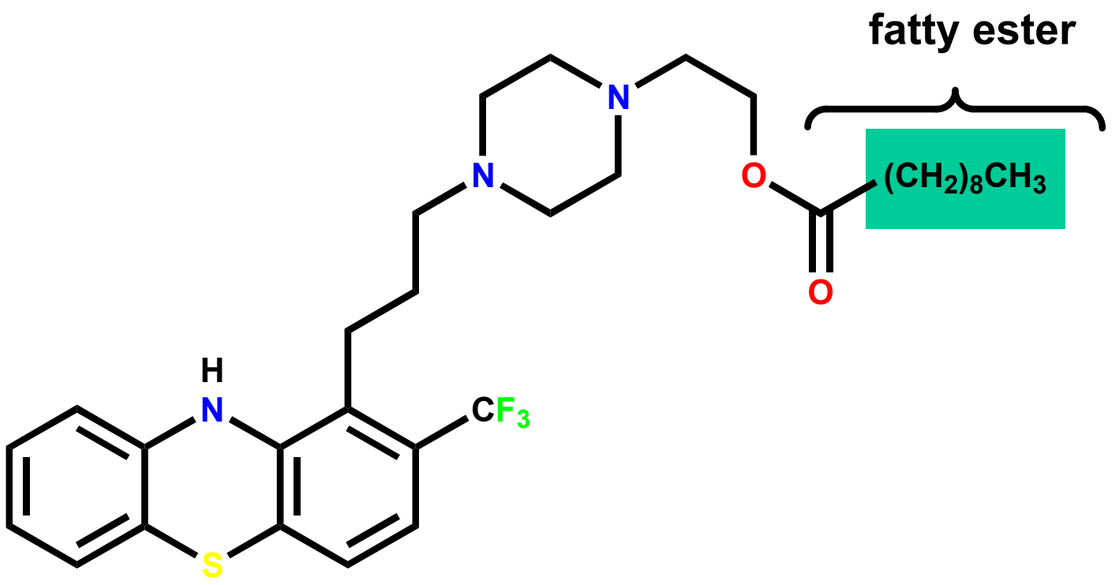
Cycloguanil



Pamoate

Lipophilic

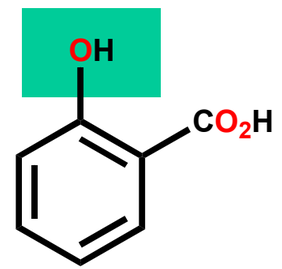
Example: Hydrophobic esters of fluphenazine (antipsychotic)



- lipophilic esters of the antipsychotic drug fluphenazine are used to prolong its action.
- The prodrug is given by intramuscular injection and slowly diffuses from fat tissue into the blood supply, where it is rapidly hydrolysed.

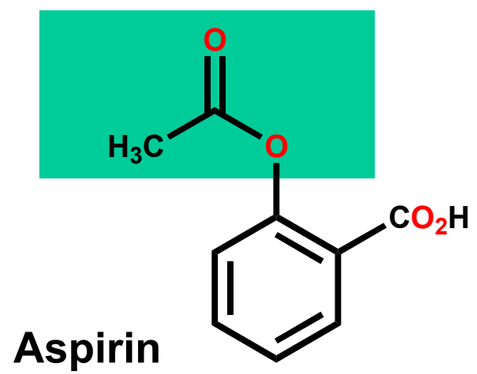
➢ Prodrugs to mask toxicity and side effects

- Prodrugs can be used to mask the side effects and toxicity of drugs
- Salicylic acid is a good painkiller, but causes gastric bleeding because of the free phenolic group. This is overcome by masking the phenol as an ester (aspirin). The ester is later hydrolysed to free the active drug



Salicylic acid

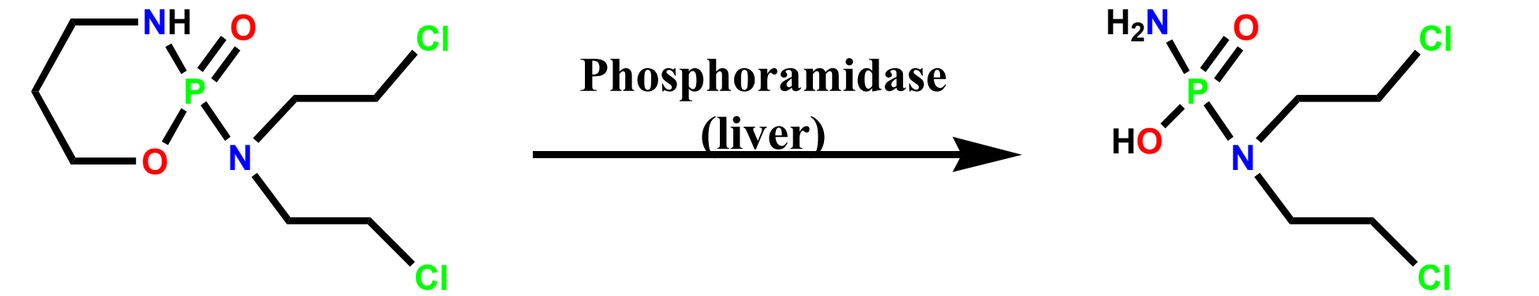
Example: Aspirin for salicylic acid



Aspirin

Cyclophosphamide is a successful, non-toxic prodrug which can be safely taken orally. Once absorbed, it is metabolized in the liver to a toxic alkylating agent which is useful in the treatment of cancer

Example: Cyclophosphoramide for phosphoramide mustard (anticancer agent)



Cyclophosphoramide

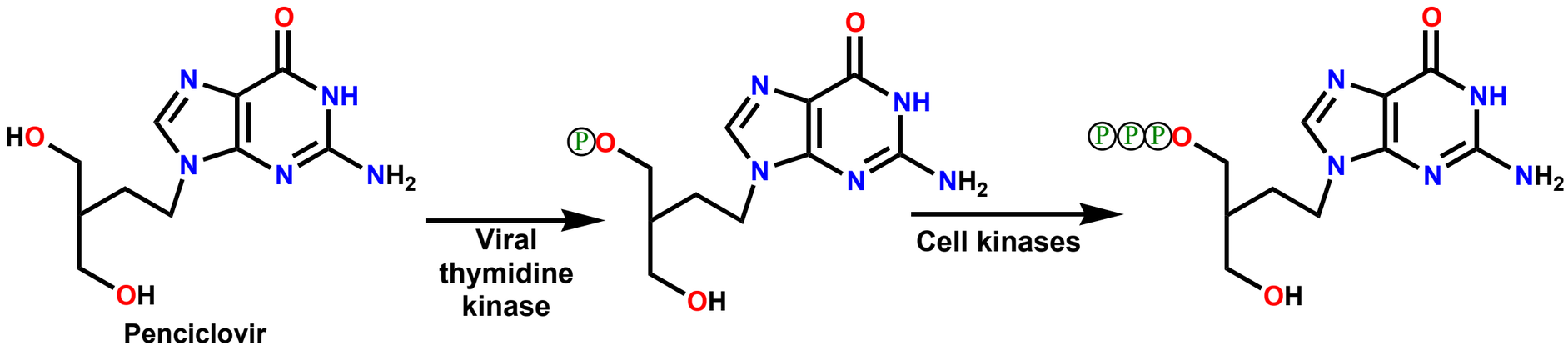
Phosphoramide mustard

Non toxic
Orally active

Alkylating agent

Example: Antiviral drugs

Many important antiviral drugs such as **aciclovir** and **penciclovir** are non-toxic prodrugs which show selective toxicity towards virally infected cells. This is because they are activated by a viral enzyme which is only present in infected cells.



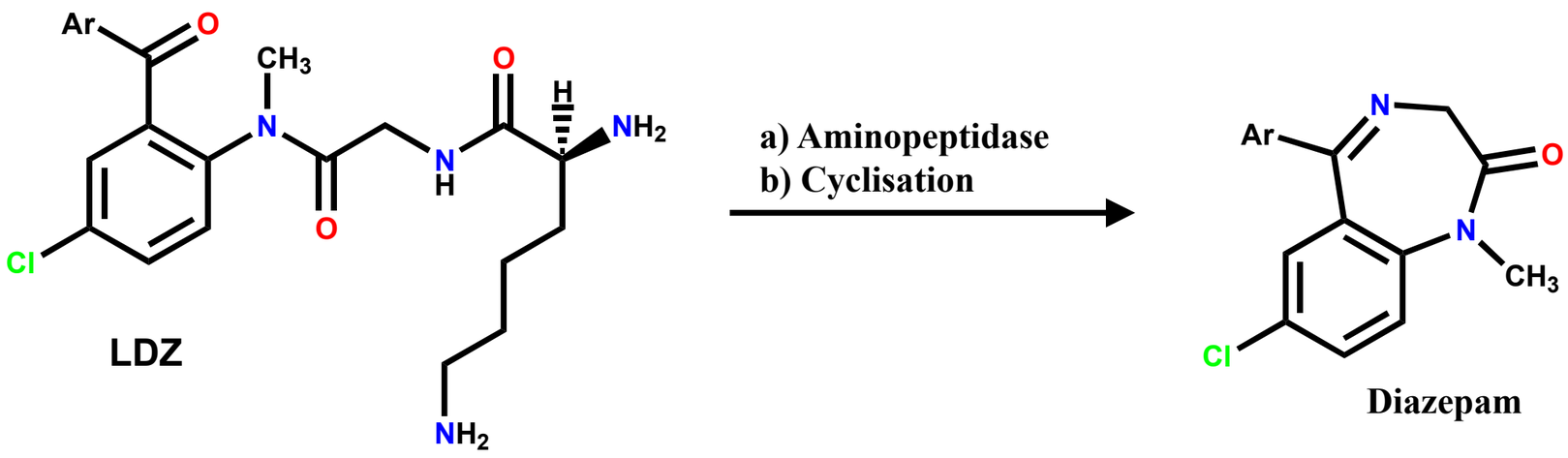
Notes

- **First phosphorylation requires viral thymidine kinase**

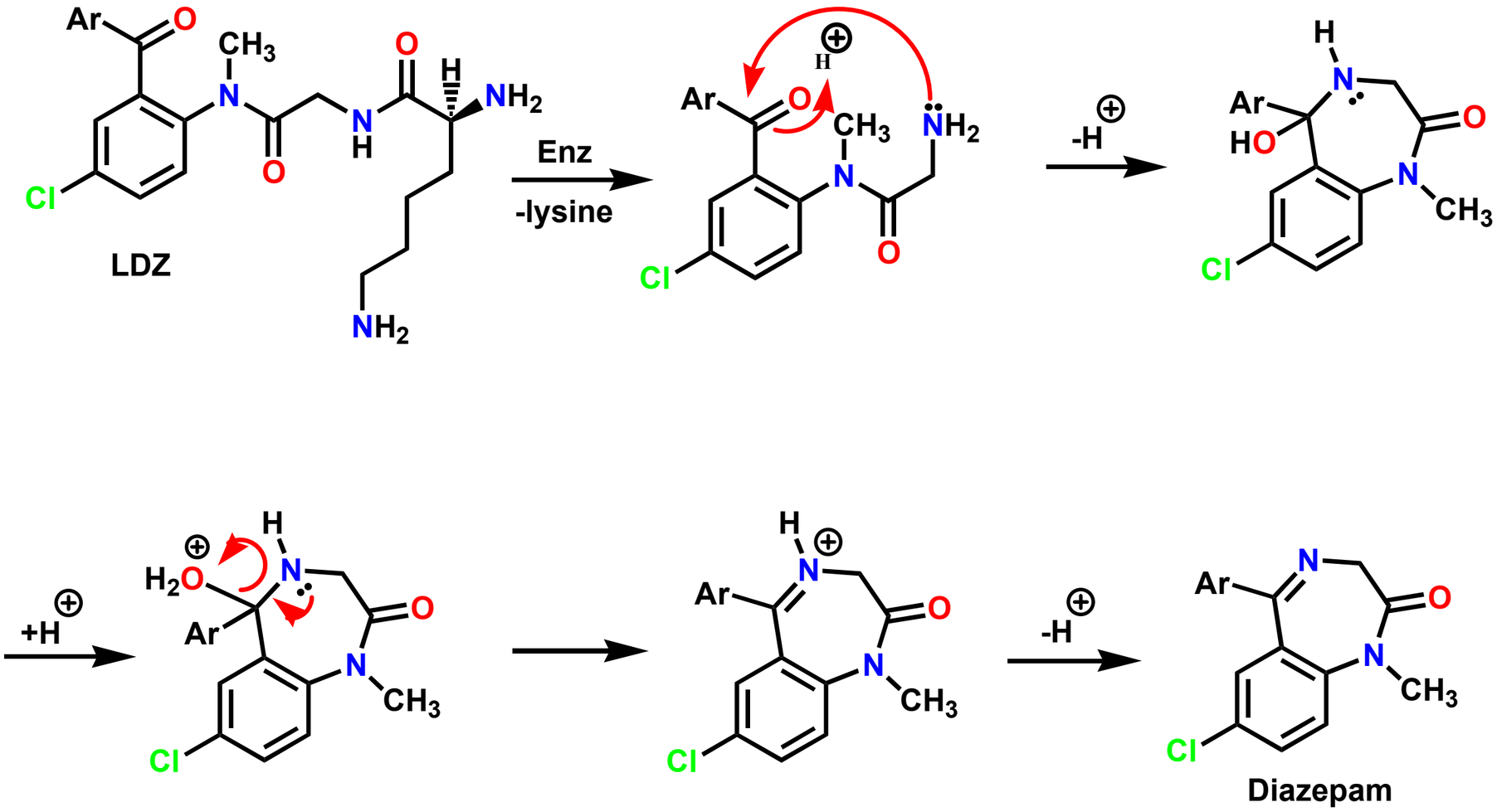
Example: LDZ for diazepam

- LDZ is an example of a diazepam prodrug which avoids the drowsiness side effects associated with diazepam.

- The use of a prodrug avoids this problem. An aminopeptidase enzyme hydrolyses the prodrug to release a non-toxic lysine moiety, and the resulting amine spontaneously cyclizes to the diazepam.



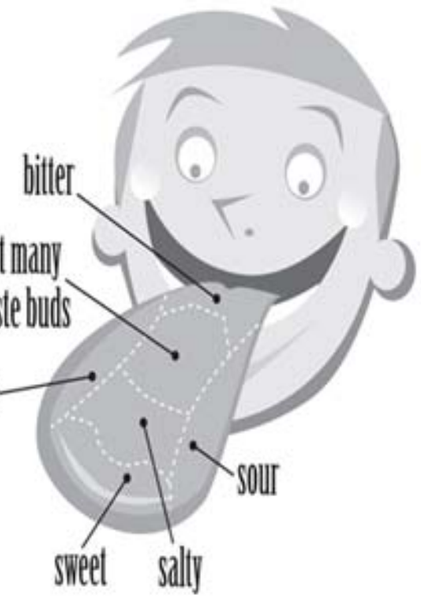
Cycle closing mechanism of activation

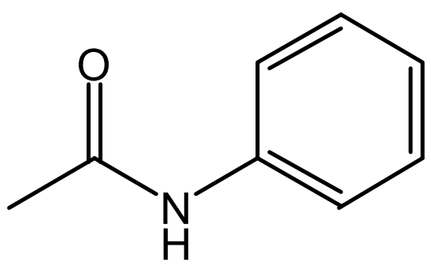


- **Prodrugs to lower water solubility\ and bad taste**

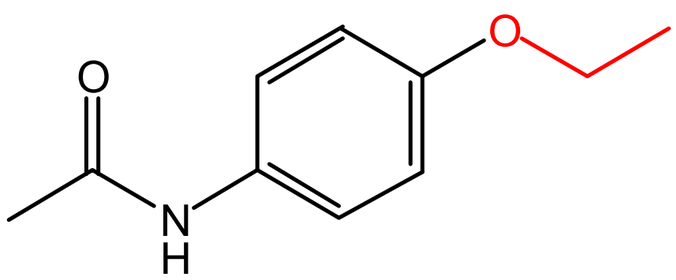
Molecules dissolve in saliva and bind to taste receptors on the posterior part of the tongue.

The taste buds contain very sensitive nerve endings, which are responsible for the production and transmission of electrical impulses to certain areas in the brain that are devoted to the perception of taste.

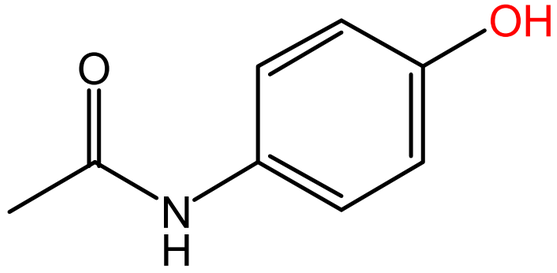




Acetanilide
Bitterless taste

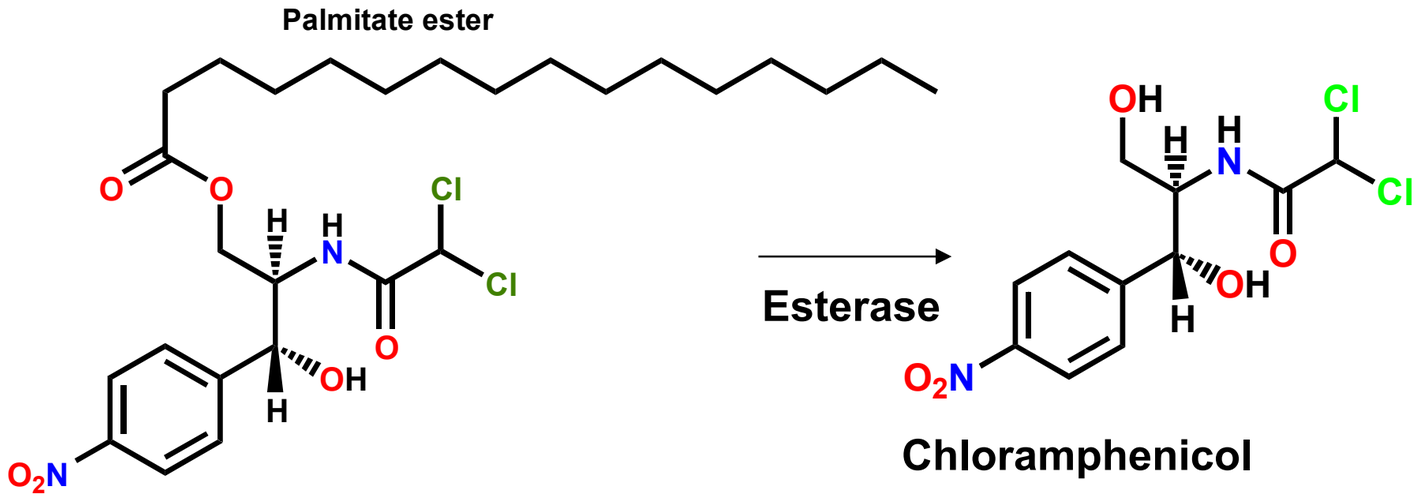


Phenacetin
Slightly bitter taste



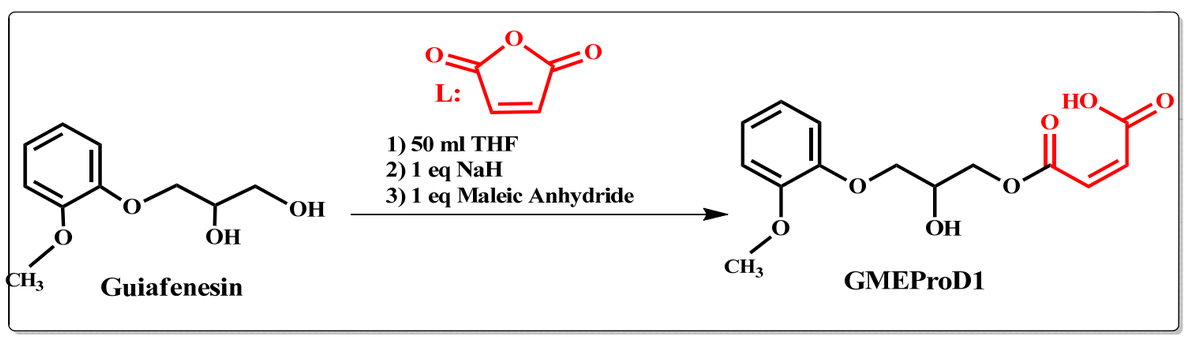
Paracetamol
Bitter taste

Some drugs have a revolting taste! One way to avoid this problem is to reduce their water solubility to prevent them dissolving on the tongue as the bitter taste of the antibiotic **chloramphenicol** can be avoided by using the palmitate ester, This is more hydrophobic because of the masked alcohol and the long chain fatty group that is present. It does not dissolve easily on the tongue and is quickly hydrolysed once swallowed.

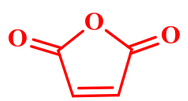


Example: Palmitate ester of chloramphenicol (antibiotic)

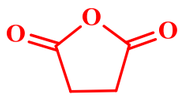
Case Study: Guaifenesin Prodrugs approached, P26-32



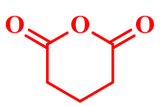
L:



Maleic Anhydride

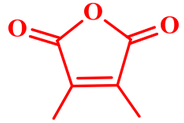


Succinic Anhydride

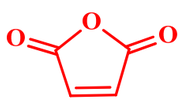


Glutaric Anhydride

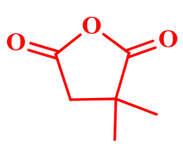
P:



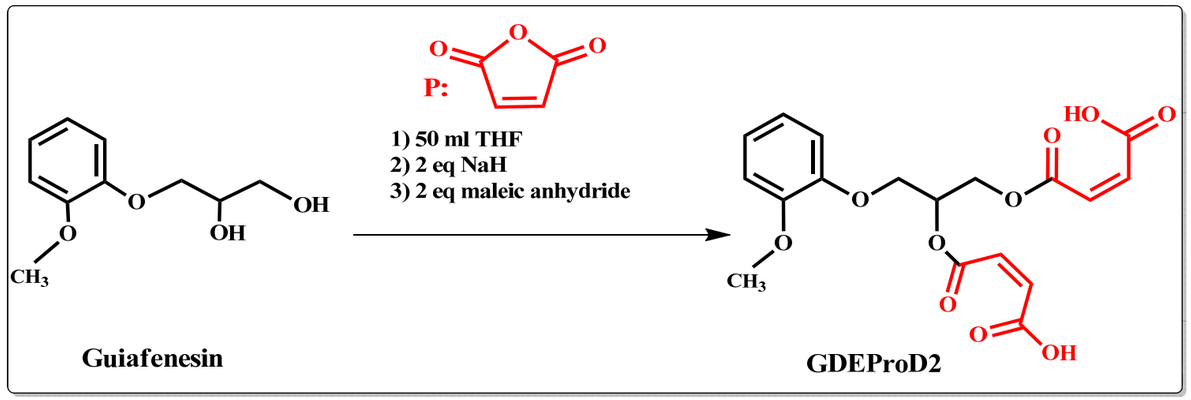
2,3-Dimethyl maleic Anhydride



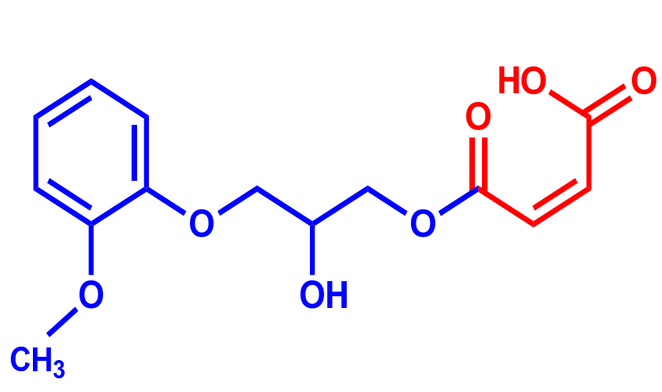
Maleic Anhydride

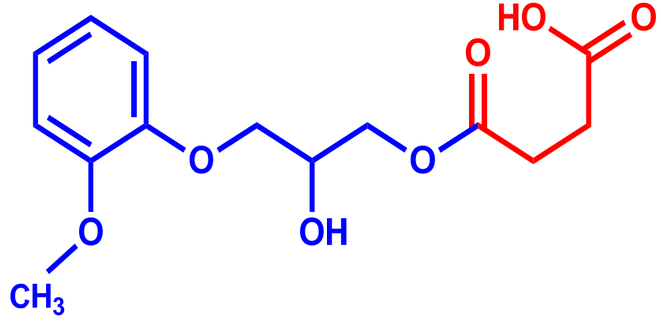


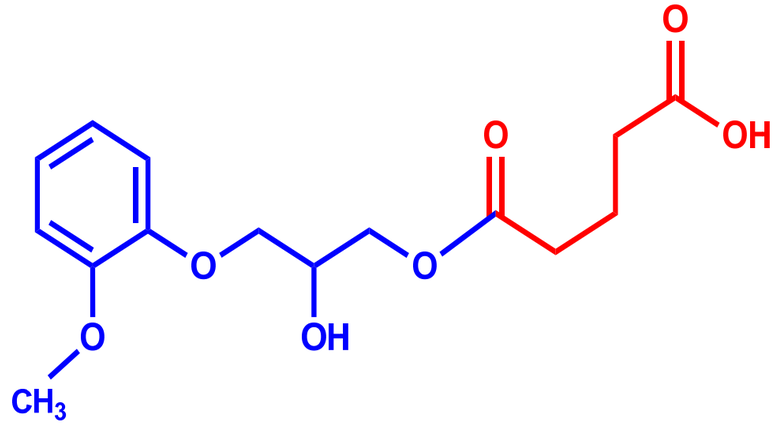
2,2-Dimethyl succinic anhydride

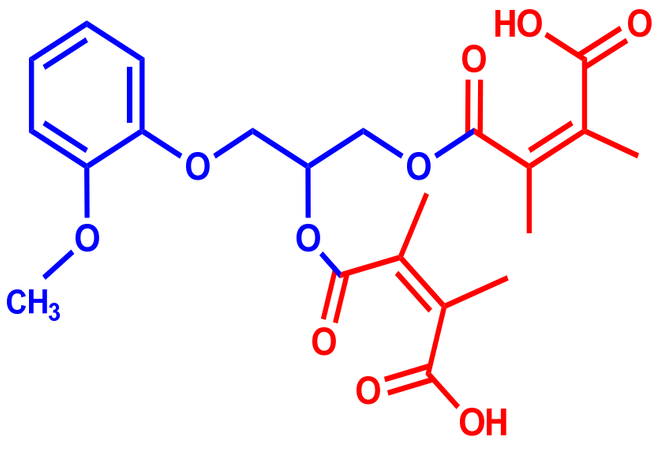


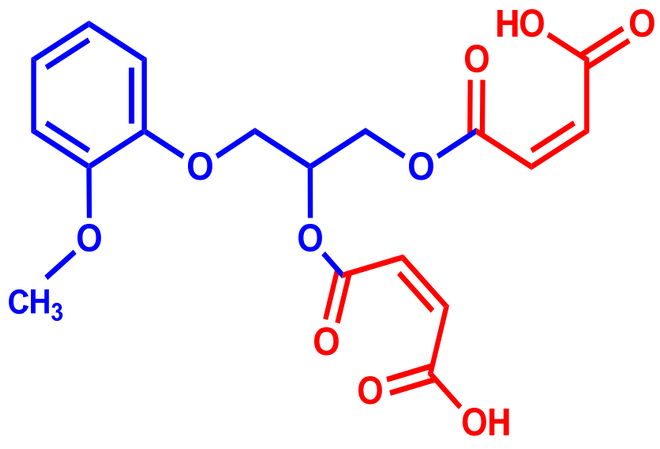
- Mono & Di-ester Prodrugs of guaifenesin

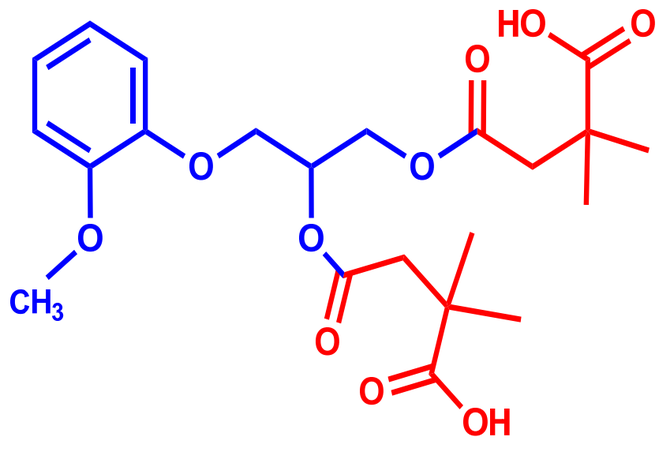




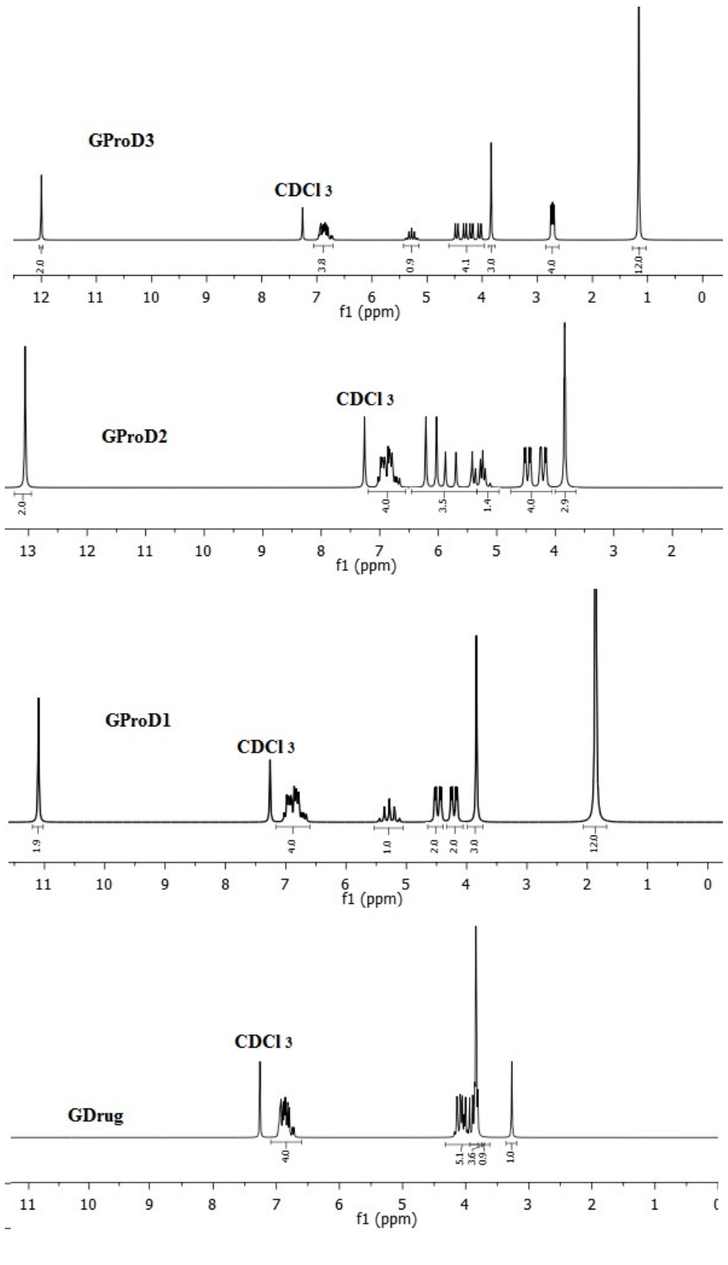


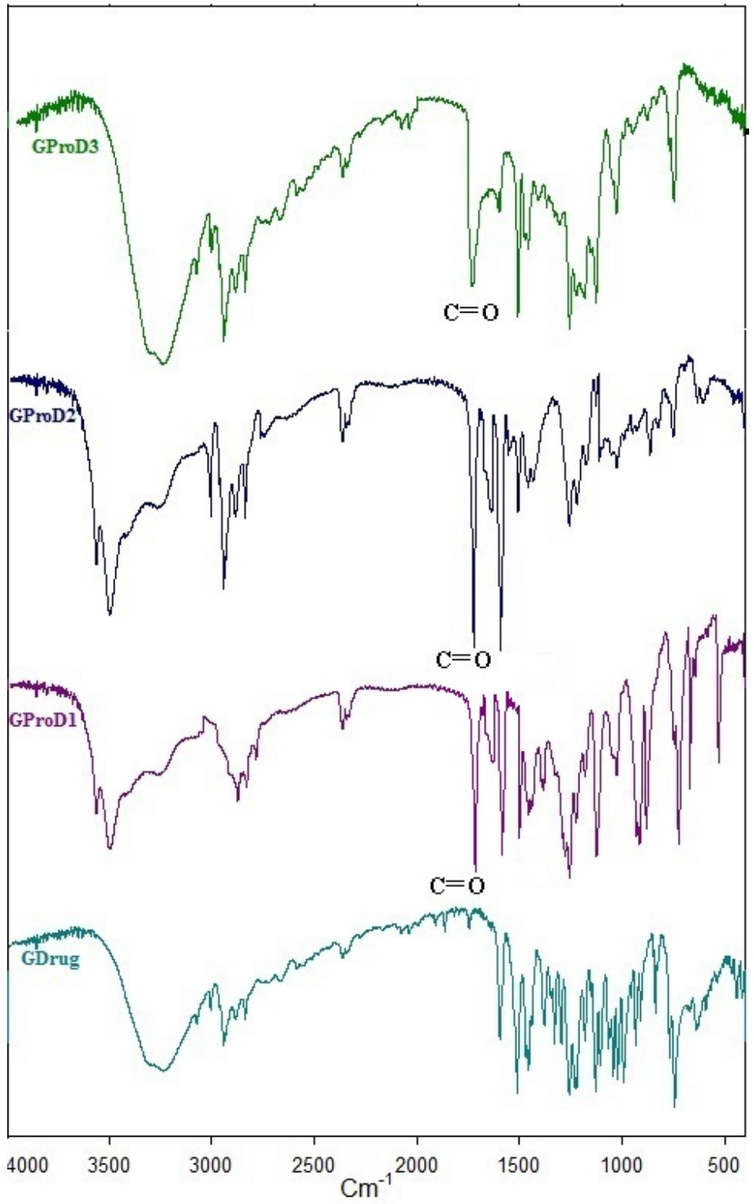


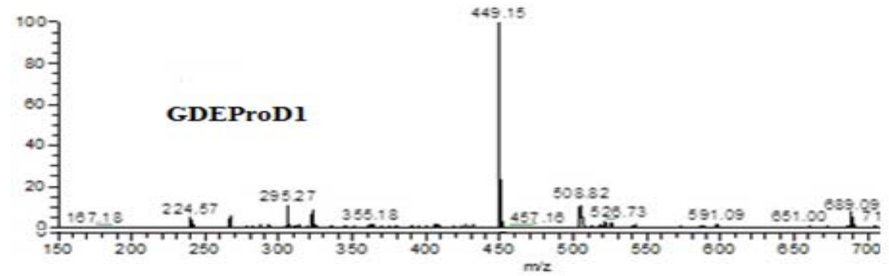


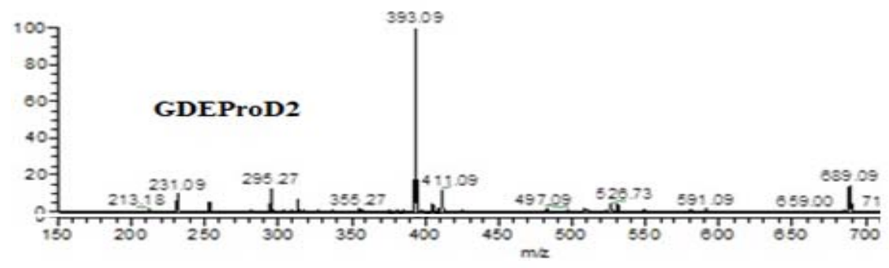


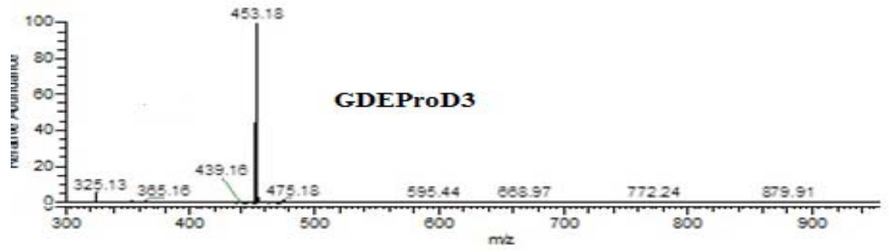
- Characterization

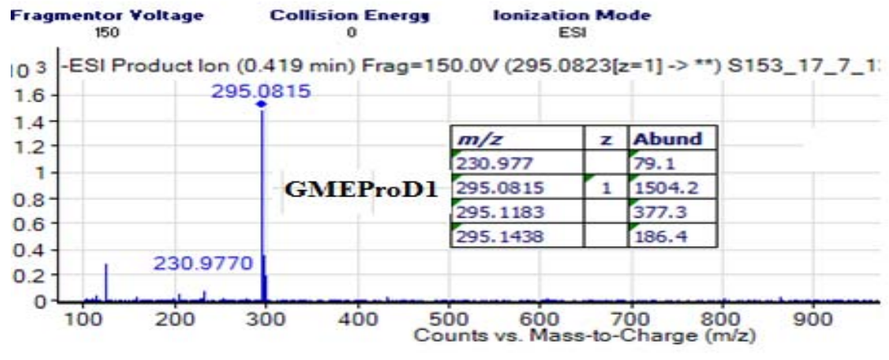




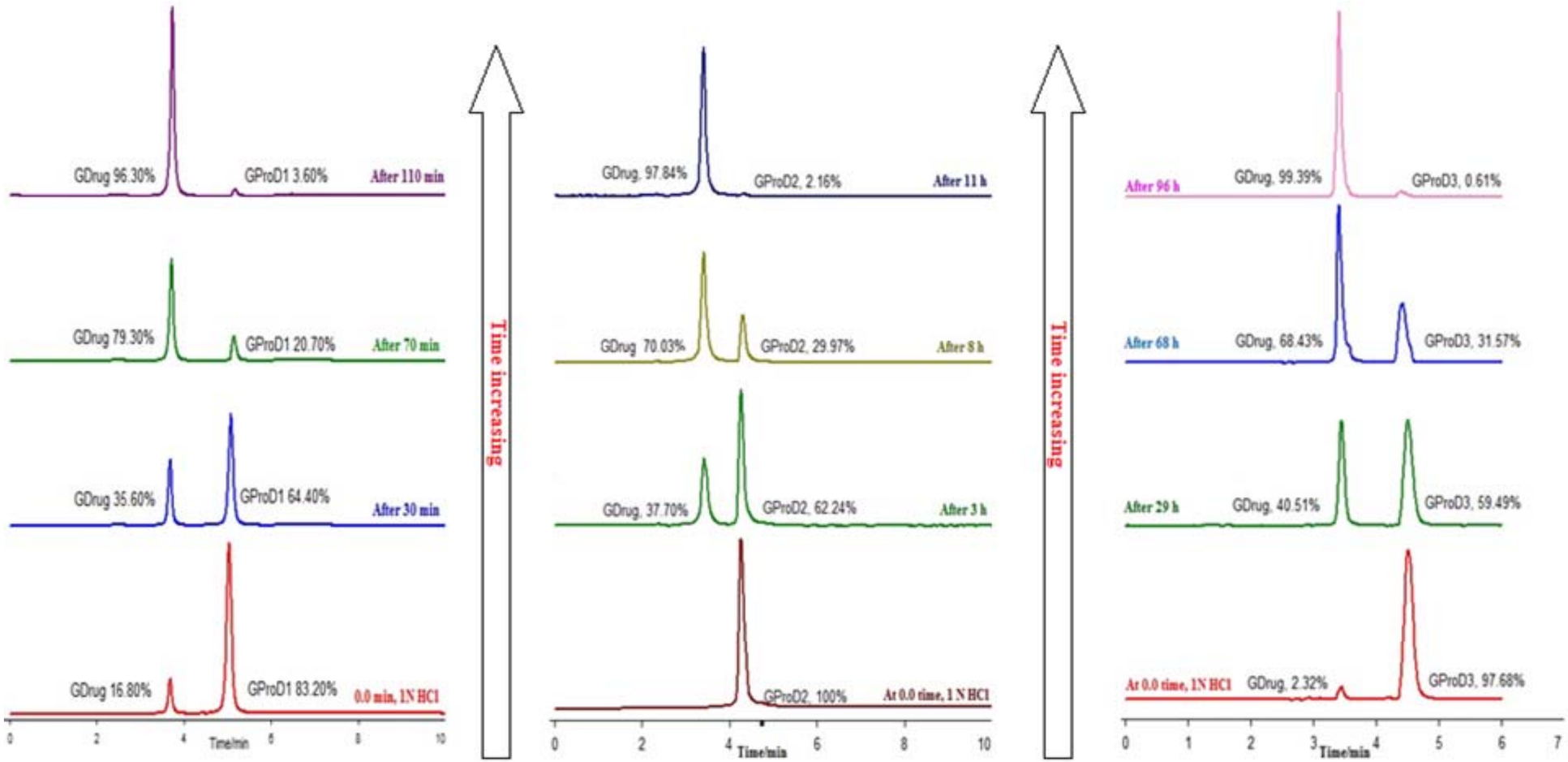








- Hydrolysis study, In-vitro Studies

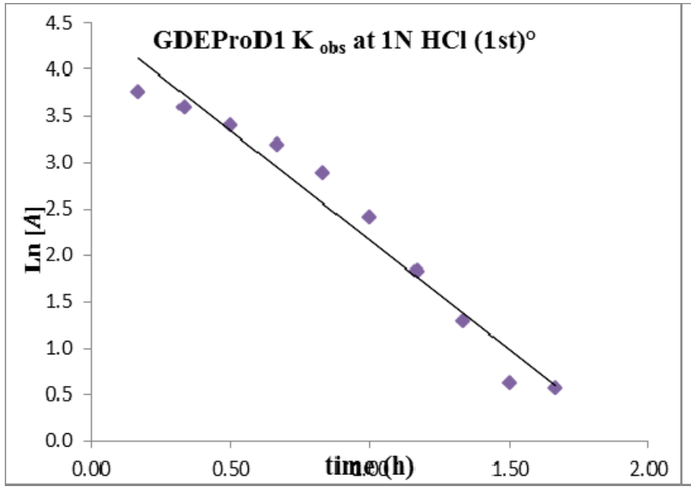


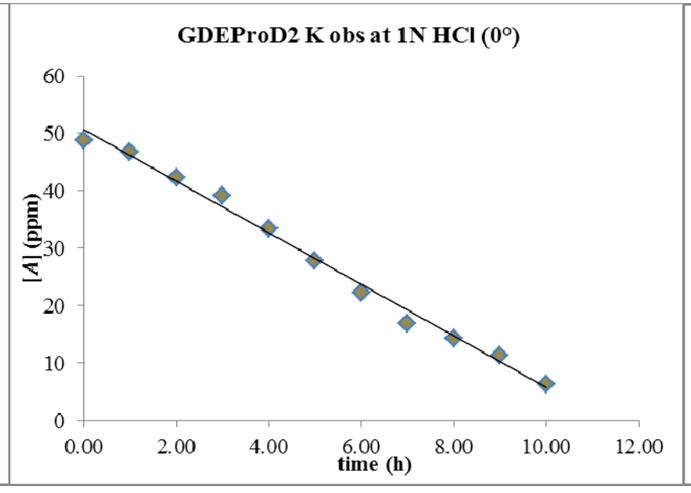
GDEProD1 kinetic study in1N HCl.

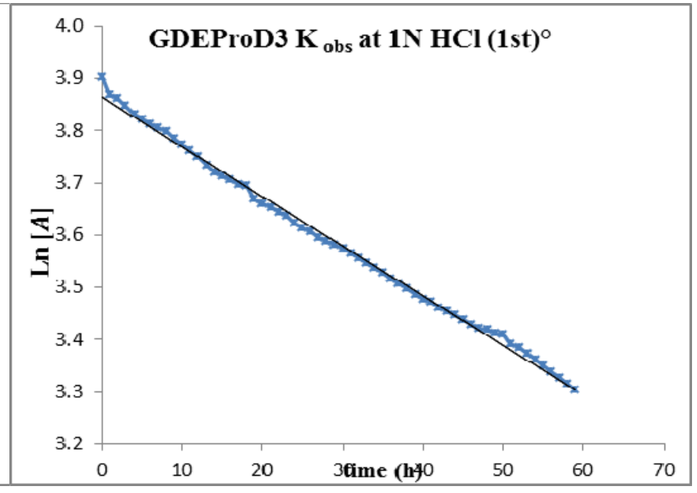
GDEProD2 kinetic study in 1N HCl.

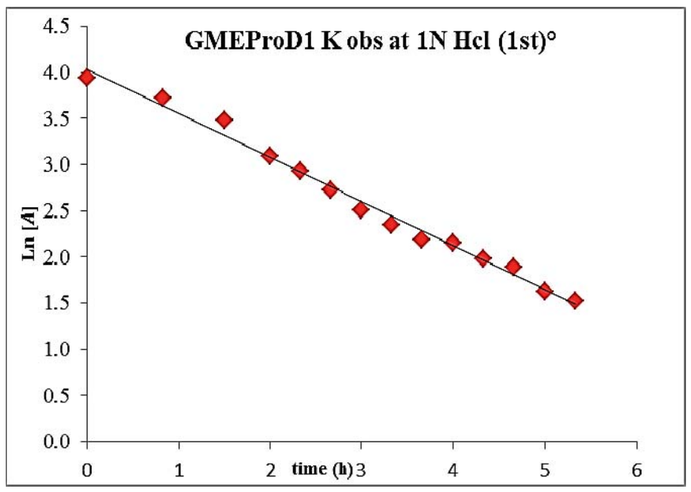
GDEProD3 kinetic study in 1N HCl.

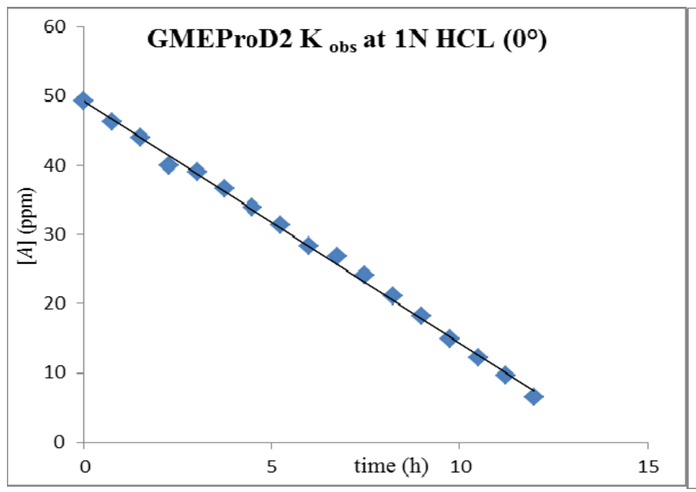
- First and zero order hydrolysis plot of guaifenesin prodrugs in 1N HCl.

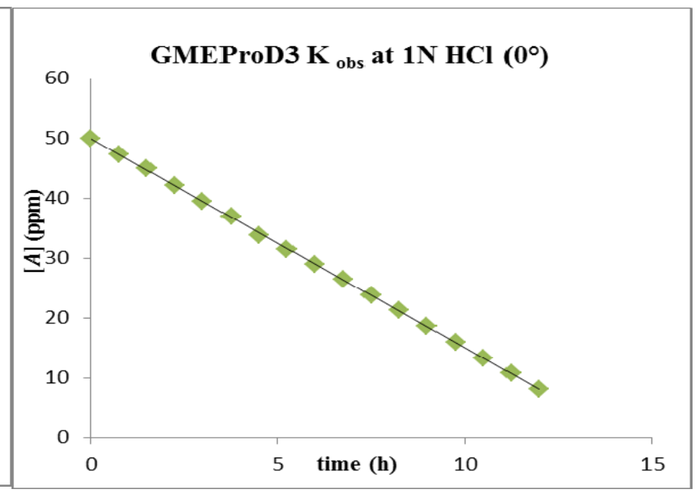












- Calculations

$$[A] = [A°] - k * t \ldots ..$$

$$ln[A] = ln[A°] - kt \ldots ..$$

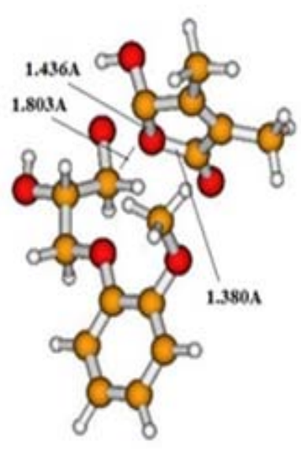
$$t\,(half) = [A°]/2k] \ldots$$

$$t(half) = ln2/k \ldots ..$$

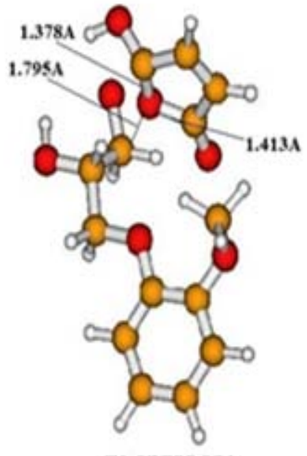
where [A]=[A ^{0}] / 2

	Zero order			First order		
	$t_{1/2}$/h	$K_{obs}X10^{-3}$ h^{-1}	R^2	$t_{1/2}$/h	$K_{obs}X10^{-3}$ $L.h^{-1}.mol^{-1}$	R^2
GDEProD1	0.84	60.6	0.94	**0.30**	**5.2**	**0.95**
GDEProD2	**4.81**	**12.2**	**0.99**	2.97	0.59	0.93
GDEProD3	52.51	1.03	0.96	**73.1**	**0.02**	**0.99**
GMEProD1	2.98	28.9	0.89	**1.45**	**1.60**	**0.98**
GMEProD2	**7.06**	**11.75**	**0.99**	4.67	0.5	0.91
GMEProD3	**7.16**	**11.14**	**0.99**	4.98	0.45	0.94
GDEProD1 in 0.1 N HCl	**3.81**	**14.01**	**0.99**	2.75	0.56	0.85

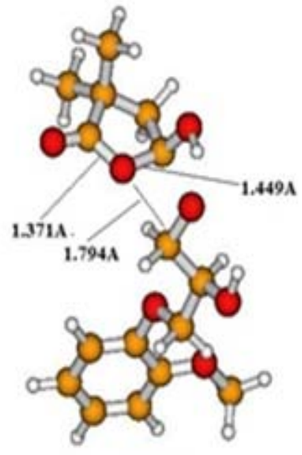
- DFT optimized TS structures for the cyclization reactions of prodrugs indicates that all of them resemble that of the corresponding tetrahedral intermediates. Furthermore, the calculated O-C distances, O1-C6, O8-C6 and O1-C2 are significantly different. The distance range for O1-C6 was 1.378 Å – 1.449 Å, for O8-C6 was 1.792 Å – 1.803 Å and for O1-C2 was 1.371 Å - 1.413 Å.



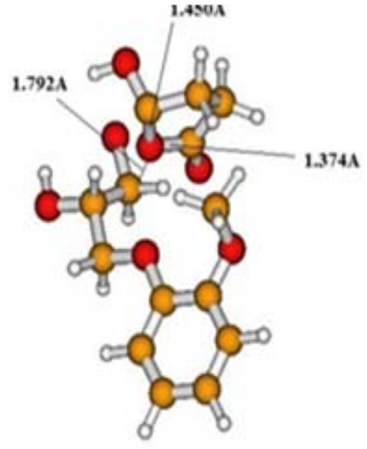
TS GDEPROD1



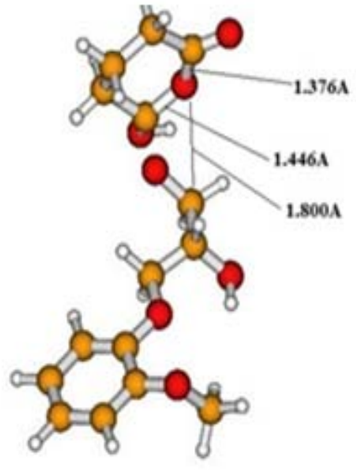
TS GDEPROD2



TS GDEPROD3



TS GMEPROD2



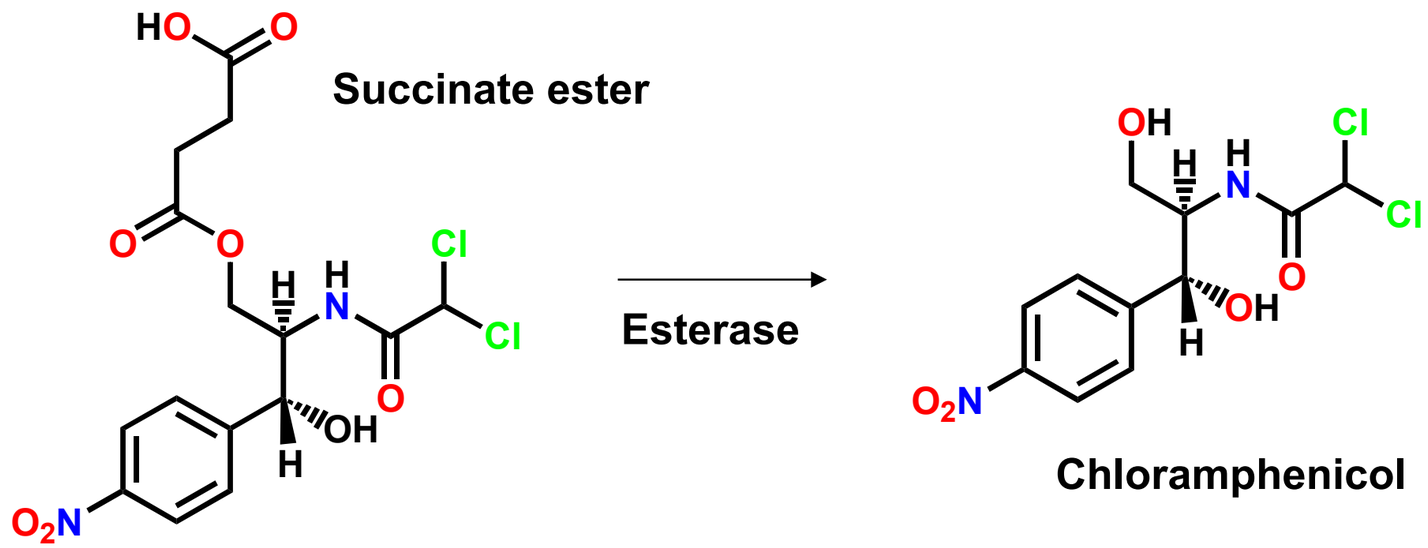
TS GMEPROD3

➢ Prodrugs to increase water solubility

Prodrugs have been used to increase the water solubility of drugs. This is particularly useful for drugs which are given intravenously, as it means that higher concentrations and smaller volumes can be used.

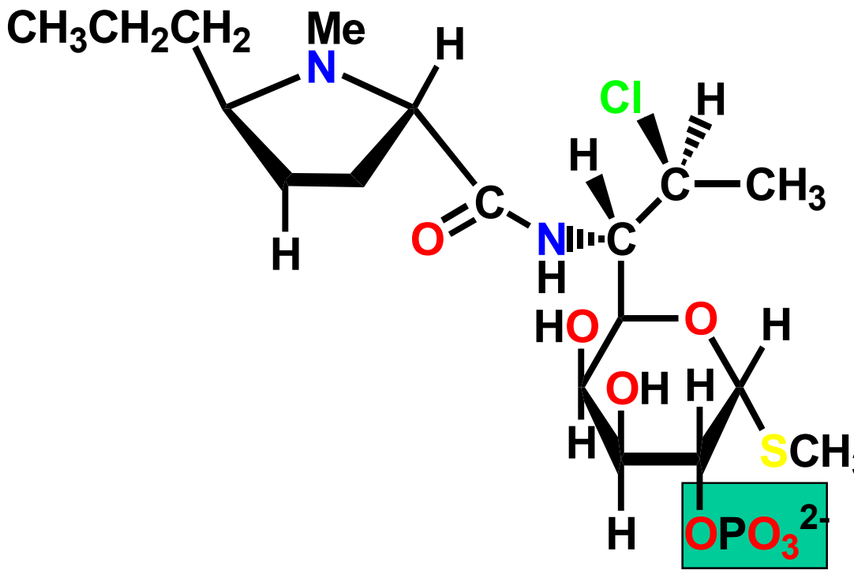
Example: Succinate ester of chloramphenicol (antibiotic)

Increases the latter's water solubility because of the extra carboxylic acid that is present



- Prodrugs designed to increase water solubility have proved useful in **preventing the pain** associated with some injections, which is **caused by the poor solubility** of the drug at the site of injection.

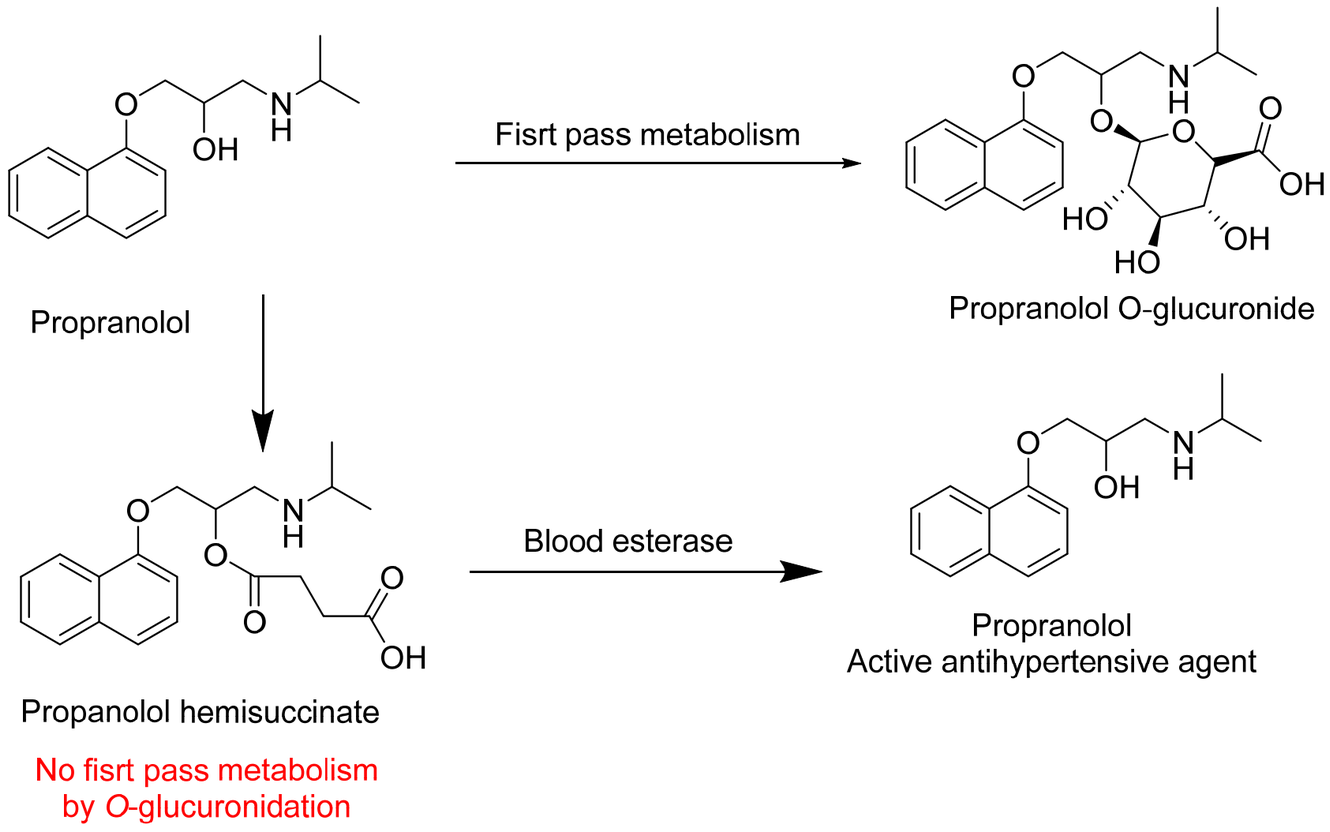
- For example, the antibacterial agent **clindamycin** is **painful** when injected, but this is avoided by using a phosphate ester prodrug which has much better solubility because of the ionic phosphate group



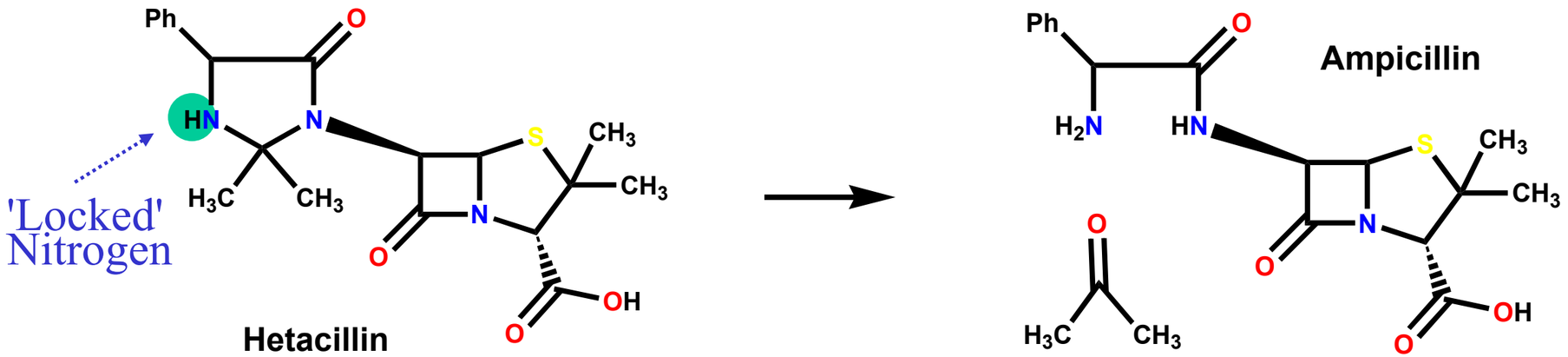
Less painful on injection

➢ Prodrugs for stability

- Problem: propanolol undergo extensive first pass metabolism (glucuronidation)
- Solution: adding ester group on the alcohol will protect it from metabolism



Example: Hetacillin for ampicillin



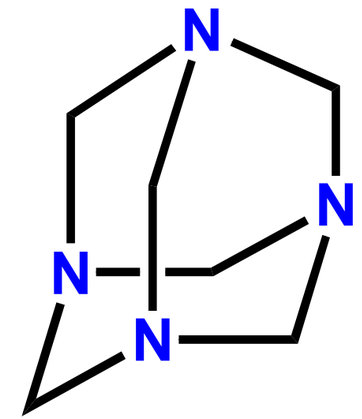
Notes:

•Ampicillin is chemically unstable in solution due to the a-NH_2 group attacking the b-lactam ring

•Nitrogen atom in heteracillin is locked up within a heterocyclic ring

➢ Prodrugs used to target drugs

Methenamine is a stable, inactive compound when the pH is more than 5. At a more acidic pH, the compound degrades spontaneously to generate formaldehyde, which has antibacterial properties.



This is useful in the treatment of urinary tract infections. The normal pH of blood is slightly alkaline (7.4) and so methenamine passes round the body unchanged.

However, once it is excreted into the infected urinary tract, it encounters urine which is acidic as a result of certain bacterial infections. Consequently, methenamine degrades to generate formaldehyde just where it is needed.