Topic 7: Pharmacokinetics

Dr. Mohyeddin Assali
PhD. Medicinal chemistry-Nanomedicine
Department of pharmacy
Faculty of Medicine & Health sciences

1. PHARMACOKINETICS

Notes

- Factors affecting whether a drug will reach its target site
- Active drugs *in vitro* may be inactive *in vivo*
- The most potent drug at its target site may be useless clinically
- Drug design should consider both binding interactions and pharmacokinetics

Factors to consider (ADME)

- Drug Absorption
- Drug Distribution
- Drug Metabolism
- Drug Excretion

2. DRUG ABSORPTION

Notes

- Orally taken drugs must cross the gut wall to reach the blood supply
- Most orally active drugs pass through the cells lining the gut wall
- Thus, drugs are required to cross two fatty cell membranes
- Balance of hydrophilic / hydrophobic character is required
- Orally active drugs usually obey Lipinski's Rule of Five
- Polar drugs can be administered by injection
- Polar drugs can be targeted vs gut infections

2.1. IONISATION OF DRUG MOLECULES

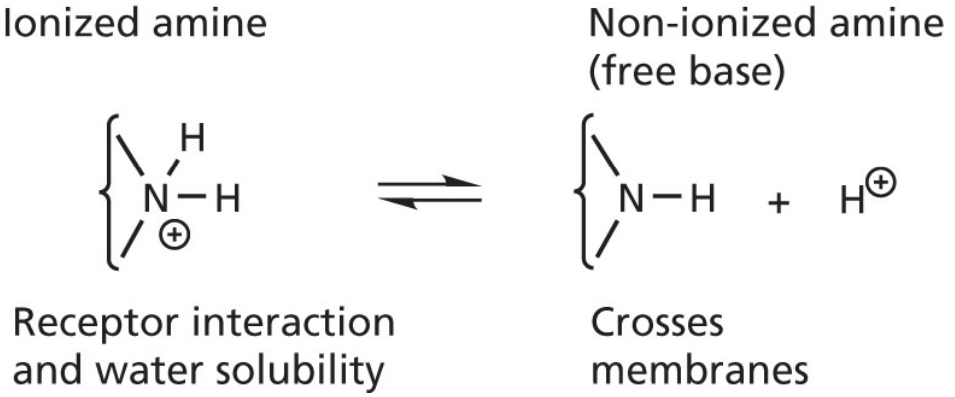
• The drug must be chemically stable to survive the stomach acids, and metabolically stable to survive the digestive enzymes in the GIT as well as that in the liver.

• It must have the correct balance of water versus fat solubility “not too polar nor too fatty”.

• It is noticeable how many drugs contain an amine functional group. It is important in a drug´s binding interactions with its target.

• Amine groups affect the hydrophilic/hydrophobic balance, as they are weak bases and it is found that the most effective drugs are amines having a pKa value range 6-8.

• it means, they are ionized at blood pH and can easily equilibrate between their ionized and non-ionized forms. This allows them to cross cell membranes in non-ionized form, while the ionized form gives the drug water solubility and permits good binding with the target .



• the extent of ionization at a particular pH can be determined by the **Henderson-Hasselbalch equation**.

$$pH = pK_a + \log \frac{[base]}{[acid]}$$

• For example when acetic acid (pKa 4.76) is in solution at pH 4.76. The Henderson-Hasselbalch equation can be written as follows:

$$pH = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

•From this relationship for acetic acid it is possible to determine the degree of ionisation of acetic acid at a given pH.

Thus when the pH = 4.76 then:

$$4.76 = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

$$\log \frac{[CH_3COO^-]}{[CH_3COOH]} = 0 \qquad \text{Then, } \frac{[CH_3COO^-]}{[CH_3COOH]} = 10^0 = 1$$

Acetic acid is 50% ionised at pH 4.76

• When ammonia (pKa 9.25) is in a solution with at pH 9.25. Henderson- Hasselbalch equation can be written as follows:

$$9.25 = 9.25 + \log \frac{[NH_3]}{[NH_4^+]}$$

$$\log \frac{[NH_3]}{[NH_4^+]} = 0 \text{ , then } \quad \frac{[NH_3]}{[NH_4^+]} = 10^0 = 1$$

Ammonia is 50% ionised at pH 9.25.

• An alternative way of writing the expression giving the % ionization for an acid or base of a particular pKa value at a particular pH value is:

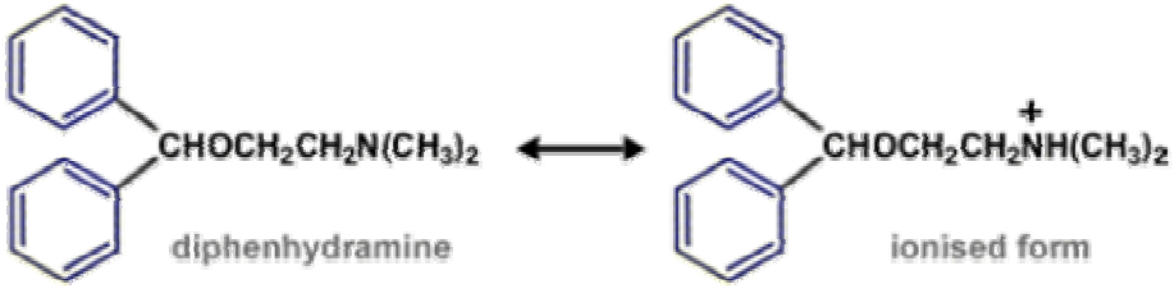
For Acid:

$$\% \text{ Ionisation} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$

For Base:

$$\% \text{ Ionisation} = \frac{10^{pKa - pH}}{1 + 10^{pKa - pH}} \times 100$$

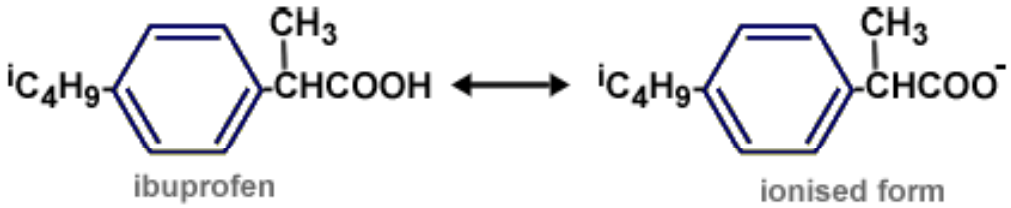
• **Diphenhydramine** This drug contains one basic nitrogen and has a pKa of 9 and at pH 7.0 its % ionisation can be calculated as follows



$$\% \text{ Ionisation diphenhydramine} = \frac{10^{9.0-7.0}}{1+10^{9.0-7.0}} \times 100$$

$$= \frac{10^{2.0}}{1+10^{2.0}} \times 100 = \frac{100}{101} \times 100 = 99.0\%$$

• **Ibuprofen** This drug contains one acidic group and has a pKa of 4.4 and pH 7.0 its % ionization can be calculated as follows

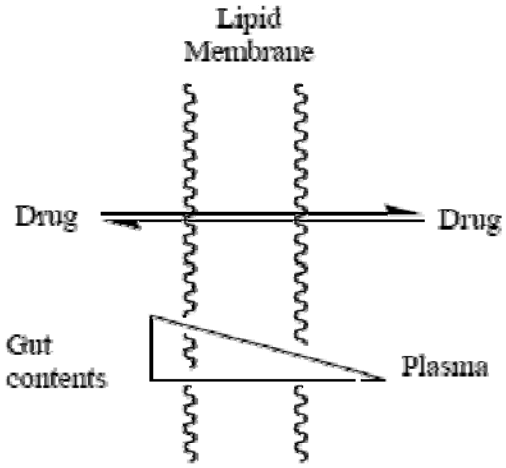


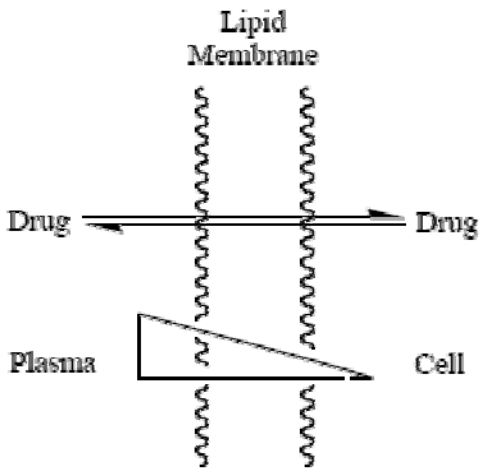
$$\% \text{ Ionisation ibuprofen} = \frac{10^{7.0-4.4}}{1+10^{7.0-4.4}} \times 100$$

$$= \frac{10^{2.6}}{1+10^{2.6}} \times 100 = \frac{398}{399} \times 100 = 99.8\%$$

2. Partition Coefficient

- The drug being a lipophilic or hydrophilic is important:
  - To get into the body (Through dosage form).
  - Move around the body
  - Pass through biological membranes:





2.2. PARTITION COEFFICIENT

• the partition coefficient of the molecule, the **P** refers the concentration of the drug in octanol (lipid part) to that in water .

$$P = \frac{[drug]_{octan-1-ol}}{[drug]_{water}}$$

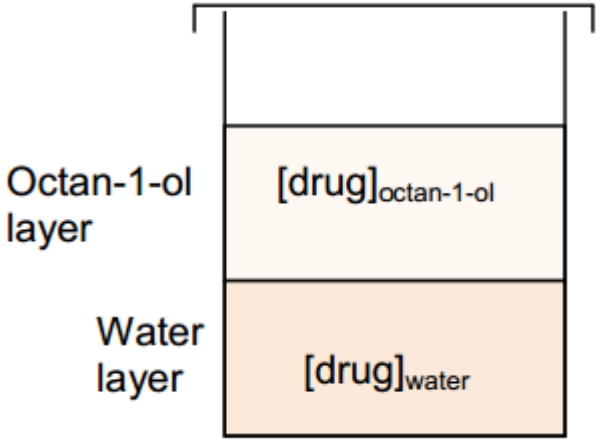
where

$[drug]_{octan-1-ol}$ = concentration of drug in octan-1-ol

$[drug]_{water}$ = concentration of drug in water

• If P > 1 the solute favours the organic solvent.

• Since P varies for common compounds over at least ten orders of magnitude it is normal to use log P.



• Log P is the sum of the hydrophobic and hydrophilic characteristics of the organic functional groups making up the structure of the molecule.

• Each organic functional group contained within the molecule contributes to the overall hydrophobic/hydrophilic nature of the molecule.

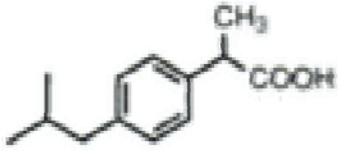
• A hydrophobic/hydrophilic value (the hydrophobic substituent constant, π) can be assigned to each organic functional group. The equation below defines this relationship:

$$\text{LogP} = \Sigma\pi \text{ (fragments)}$$

•when calculating logP from hydrophobic substituent constants, the sum is usually referred as logPcalc or **ClogP** to distinguish it from an experimentally determined value ($\text{logP}_{\text{meas}}$ or MlogP).

Hydrophilic-lipophilic Values (π V) for Organic Fragments (10)

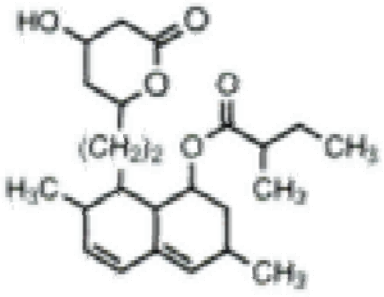
Fragments	π Value
C (aliphatic)	+0.5
Phenyl	+2.0
Cl	+0.5
O_2NO (nitrate ester)	+0.2
IMHB (intramolecular hydrogen bond)	+0.65
S	0.0
O=C–O (carboxyl)	−0.7
O=C–N (amide, imide)	−0.7
O (hydroxyl, phenol, ether)	−1.0
N (amine)	−1.0
O_2N (aliphatic)	−0.85
O_2N (aromatic)	−0.28



Ibuprofen

Fragments	π
6 carbons	+3.0
1 phenyl	+2.0
1 carboxyl	-0.7
logP	+4.3

MlogP +3.5; ClogP +3.68



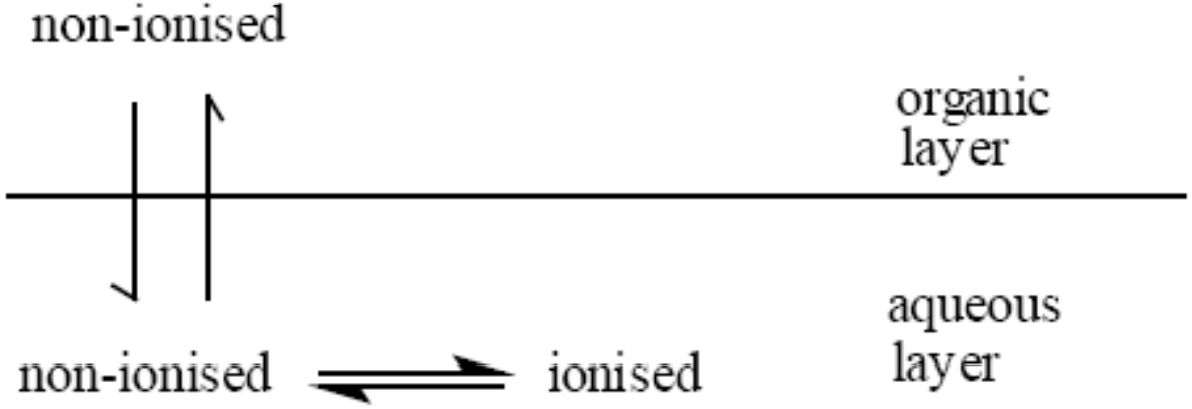
Lovastatin

Fragments	π
22 carbons	+11.0
1 alcohols	-1.0
2 carboxyls	-1.4
logP	+ 8.6

MlogP +4.26; ClogP +4.08

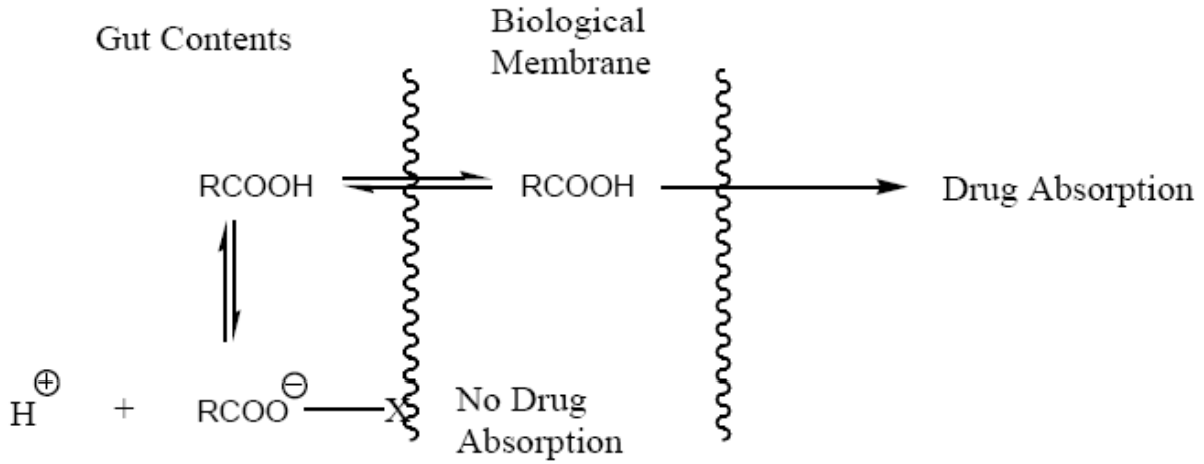
Partitioning of acids and bases:

- In practice the concentration of ionised material in the organic layer is often very small.

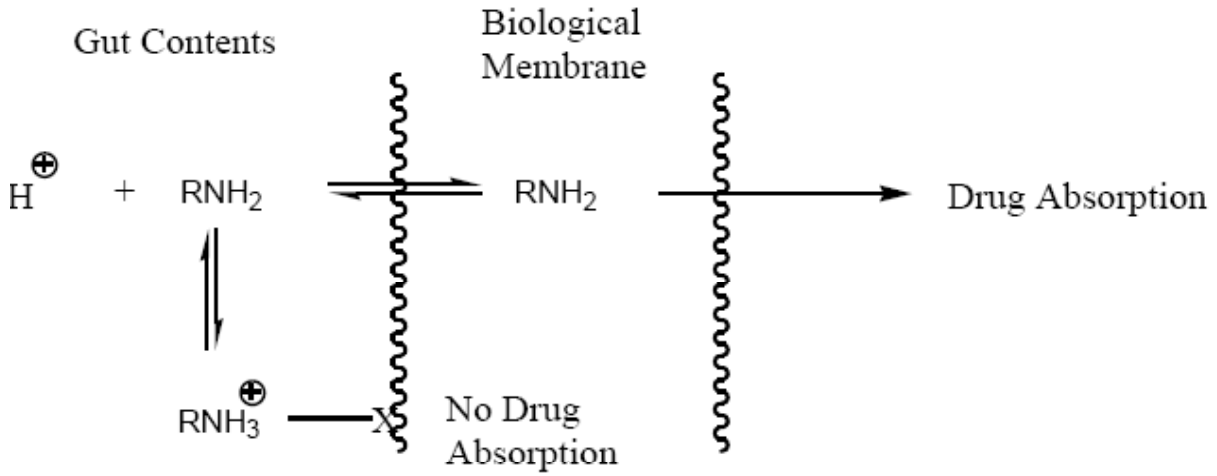


- Only the unionized form of drug can partition across the biological membrane (Providing it is lipophilic).
  - This allows the drug to be absorbed across the membrane
- The ionised form tends to be more soluble
  - This is required for drug administration and distribution

- The pH of solutions will influence the partitioning and solubility properties of acidic or basic drugs.
- The pH of the gastro-intestinal tract varies
  - So the equilibrium between the ionized and unionized varies
  - This has important effect on drug absorption.
- For example: Drugs that are acids (RCOOH) has a pKa of 4.0



Basic drugs (RNH_2) have a Pka of 7.



- It is possible to derive from the Henderson-Hasselbalch equation an expressions for the variation in the partitioning of organic acids and bases into organic solvent with respect to the pH of the solution that they are dissolved in.

$$P_{app} = \frac{P}{1 + 10^{pH - pKa}}$$

  - **P:** is a constant because it refers to the partition coefficient of only the UNIONISED form
  - **P_{app}:** is the apparent partition coefficient, which varies with pH.
  - P_{app} can predict the behaviour of a compound at all pH values as long as we know P and pK_a.

P_{app} of acids:

$$P_{app} = \frac{P}{1+10^{pH-pKa}}$$

- At pH values below the pKa; P_{app} = P,
- Because ionisation is suppressed and we are dealing with only the unionized form of the species.
- At pH values above the pKa the value of P_{app} decreases because the species is ionizing and moving into the aqueous layer.

- This relationship is very simple and allows us to predict the distribution at all pH values, provided that we know pKa and log P, for any given compound.

P_{app} of bases:

$$P_{app} = \frac{P}{1 + 10^{pKa - pH}}$$

- At pH values well above pK_a, the base exists almost completely in the non-ionised form and we find that $P_{app} = P$.
- At pH values below pK_a, increasing acidity tends to protonate the amine in the aqueous layer, reducing the conc.

- When a compound, acid or base, is 50% ionised (i.e. $pH = pK_a$) its partition coefficient is half that of the drug in the unionised state.

$$\mathbf{P_{app} = \frac{P}{1 + 10^{0}} = \frac{P}{2}}$$

2.3. Lipinski's Rule of Five

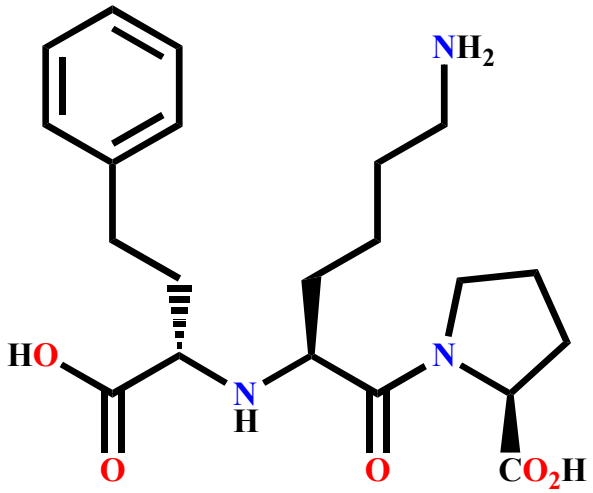
Orally active drugs generally show a balance of hydrophilic/hydrophobic properties and obey at least three of the following rules:

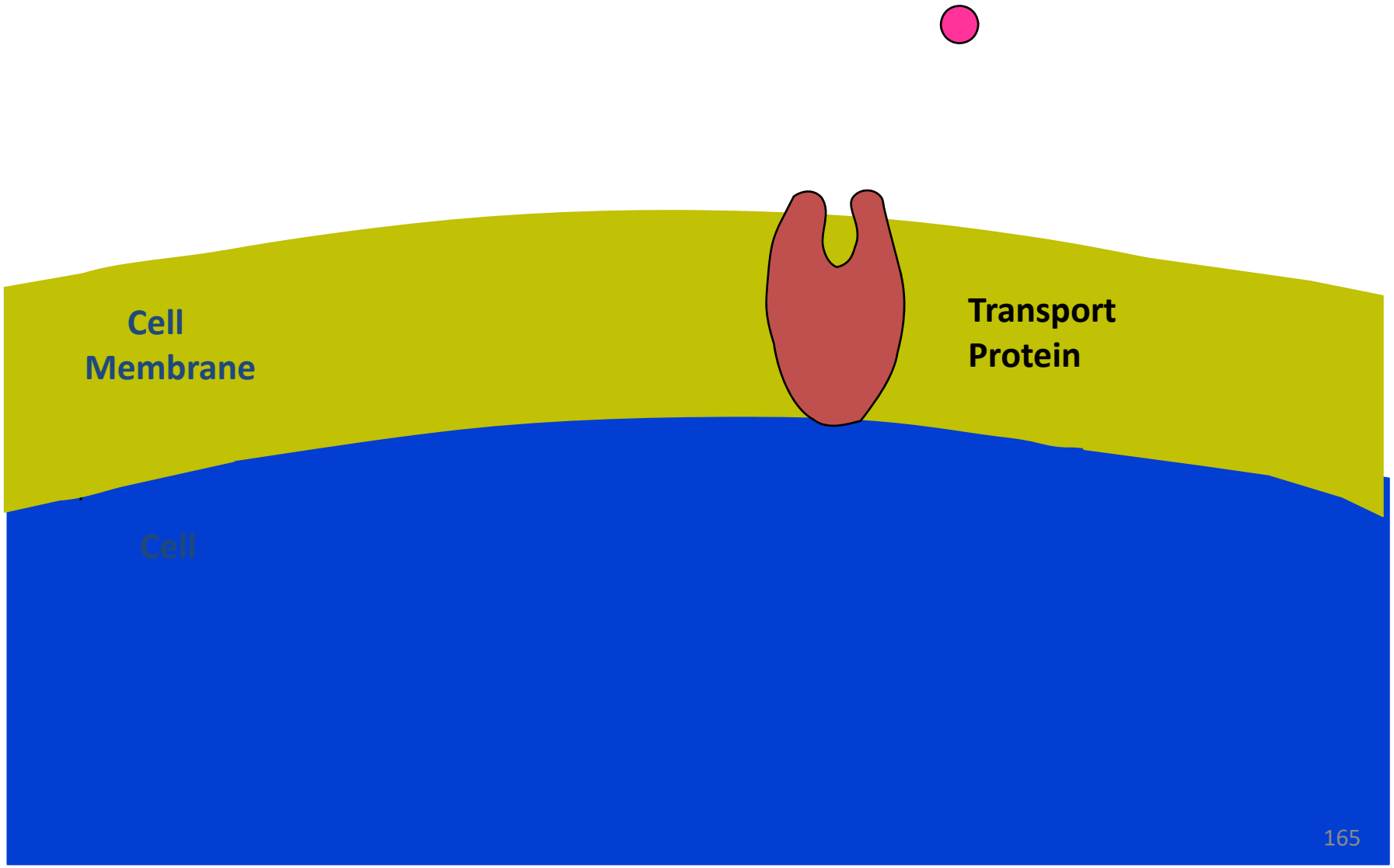
- **MW < 500**
- **No more than 5 HBD groups**
- **No more than 10 HBA groups**
- **log P < +5**

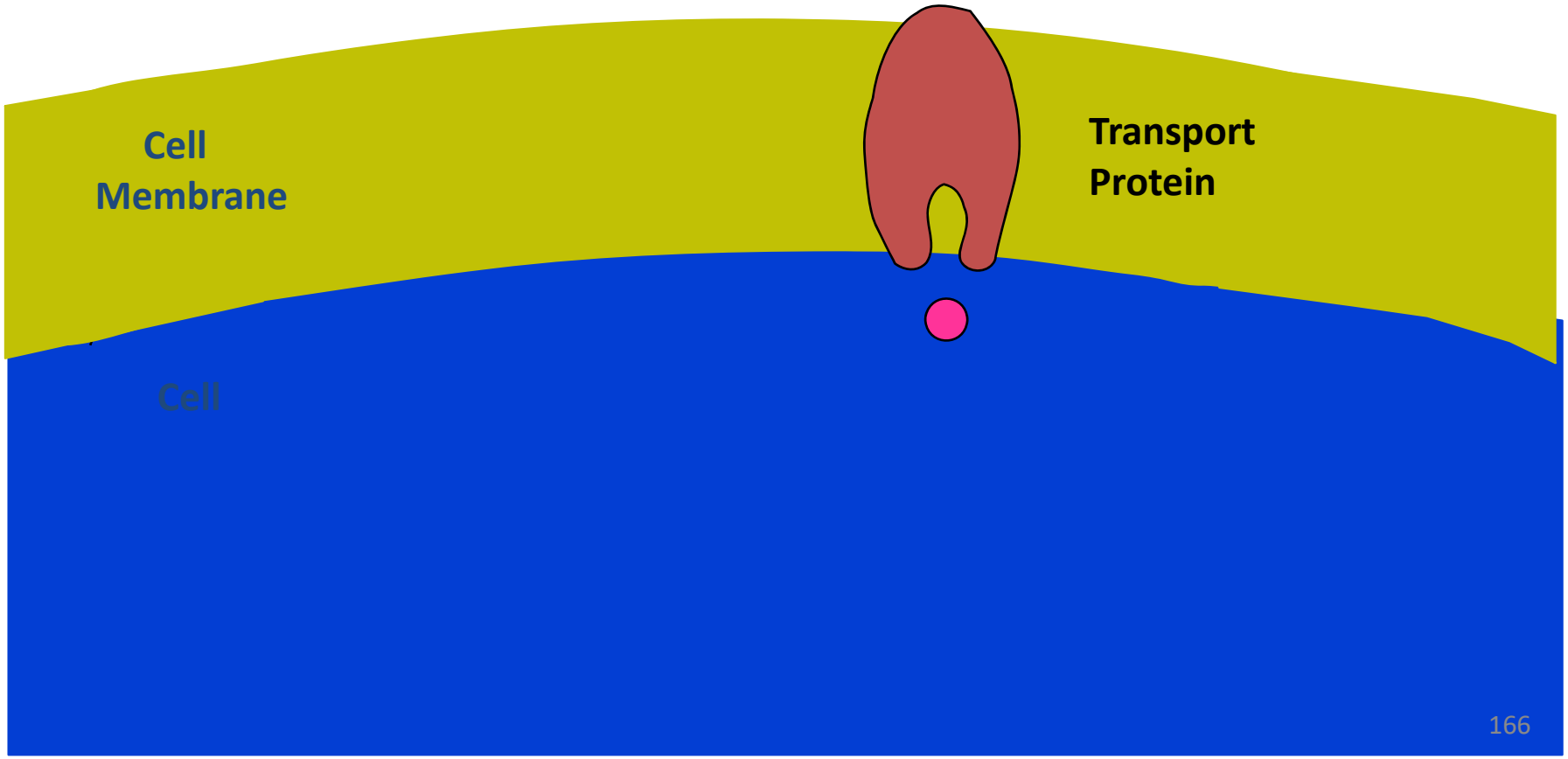
Not foolproof - several exceptions
Lipinski's 'rules' are really guidelines

Exceptions

- Small polar molecules (MW <200) that cross the gut wall through small pores between cells
- Polar molecules carried across the membrane by transport proteins - amino acids, nucleic acid bases and some drugs (e.g. lisinopril)

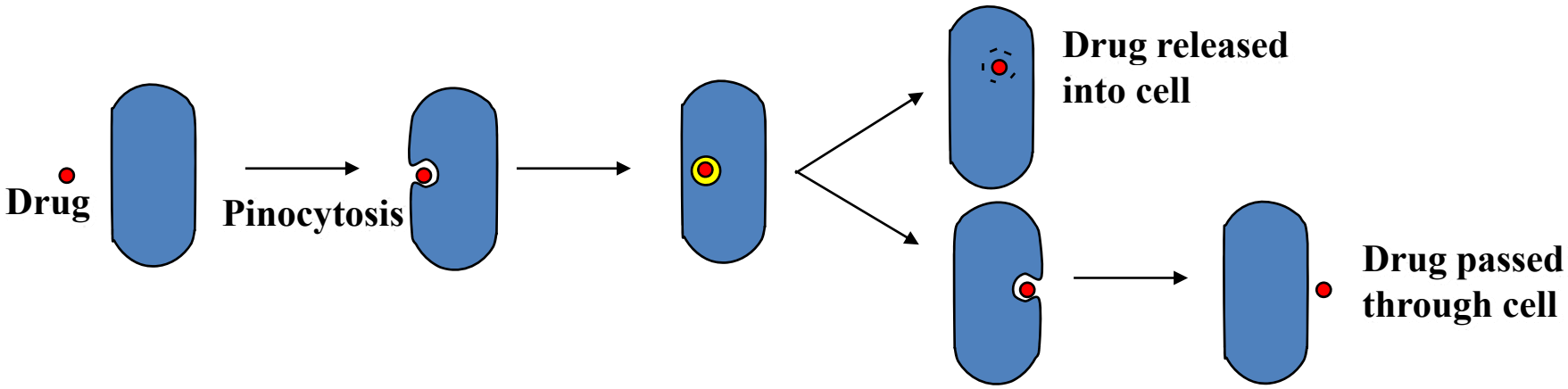



Cell
Membrane
Transport
Protein
Cell


Cell
Membrane
Transport
Protein
Cell

Exceptions

Pinocytosis - a process allowing passage of large polar drugs into a cell without actually crossing the cell membrane



Veber's parameters

- **Molecular flexibity is important to drug absorption**
- **Too many rotatable bonds is bad for absorption**
- **The polar surface of the molecule plays a role**
- **Molecular weight is not a factor**

Total no. of HBDs and HBAs ≤ 12
Number of rotatable bonds ≤ 10

or

Polar surface area < 140 Angstroms
Number of rotatable bonds ≤ 10

2.4. SOLUBILITY AND THE STRUCTURE OF DRUG

• The structure of a compound will influence its solubility in water and lipids.

• Water solubility will depend on:

- The number and nature of the polar groups in its structure.

*Polar groups that ionize in water will usually result in a higher water solubility than those that do not ionize.

- The size and nature of the compound's carbon–hydrogen skeleton.

*Aromatic compounds do tend to be less soluble in water than the corresponding non aromatic compounds.

• The water solubility of a lead compound can be improved by two general methods:

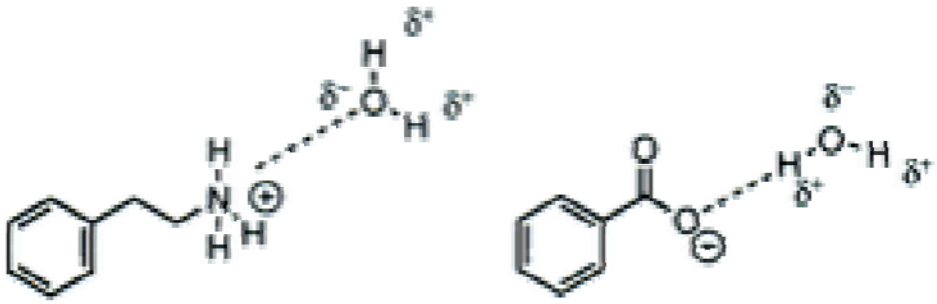
a. Salt formation

b. Incorporating water solubilizing groups into its structure

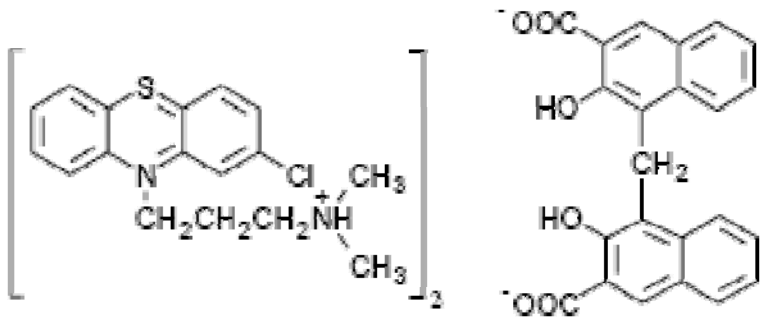
a. Salt formation:

• Salts of drugs dissociate in water to produce hydrated ions.

•The degree of water solubility of a salt will depend on the structure of the acid or base used to form the salt



- Salts of low water solubility can be used as a drug depot.
  - Penicillin G procaine has low solubility in water.
    - When administered as a suspension by intramuscular injection it acts as a depot by slowly releasing penicillin.
  - Low solubility used to change the taste of drugs to make them more palatable to the patient.
    - The antipsychotic chlorpromazine hydrochloride has a very bitter taste
    - The water-insoluble embonate salt is almost tasteless and can be administered orally in the form of a suspension.



Chlorpromazine embonate

b. The incorporation of water solubilizing groups to drug structure

- Incorporation of polar groups into the structure of a compound
  - -This will result in the formation of an analogue with a better water solubility.

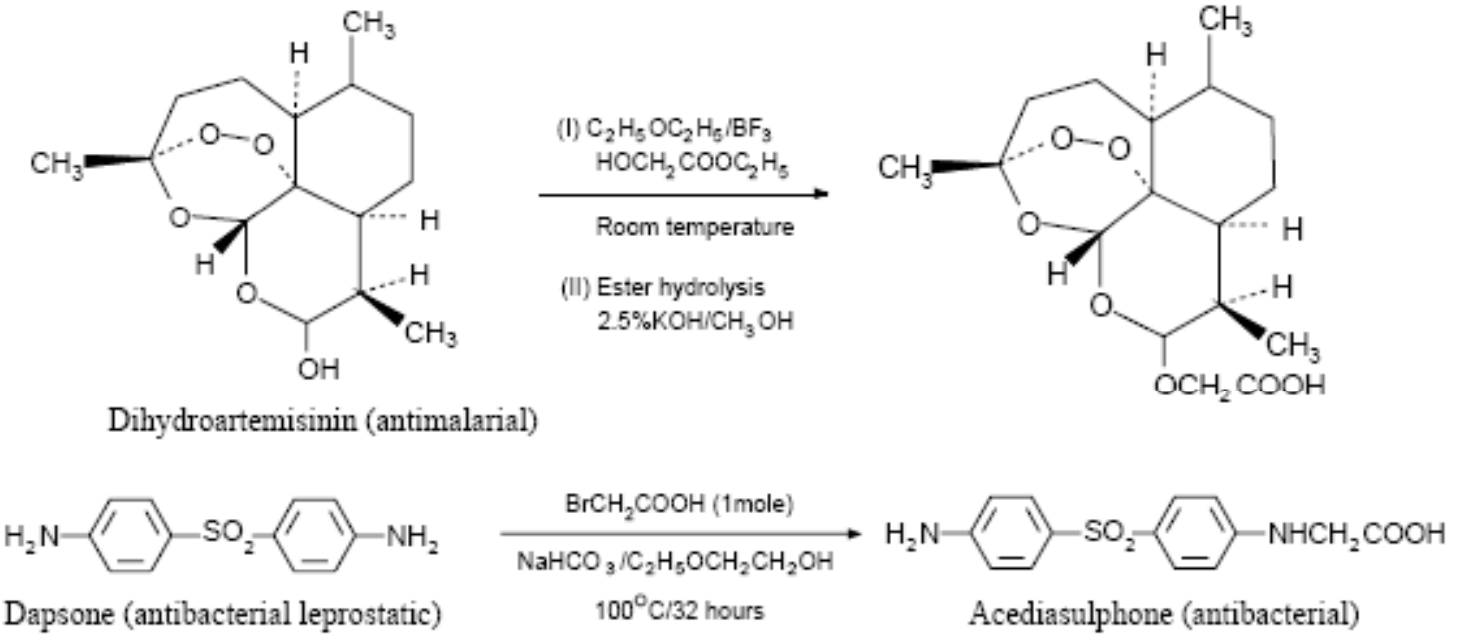
- The incorporation of strongly polar will enhance water solubility:
  - - alcohol, amine, amide, carboxylic acid, sulphonic acid

- Water solubilizing groups are best introduced at the beginning of a drug synthesis
  - -They may be introduced at any stage.
  - -To avoids the problem of changing the type and nature of the drug–receptor interaction.

A. Introducing carboxylic acid groups

– By Alkylation of alcohols, phenols and amines with suitably substituted acid derivatives.

- O-alkylation of alcohols and phenol
- N-alkylation for amines is used to introduce carboxylic acid

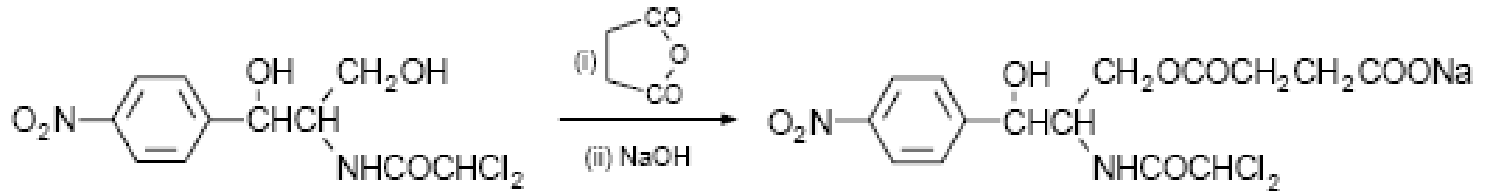


Dihydroartemisinin (antimalarial)

Dapsone (antibacterial leprostatic)

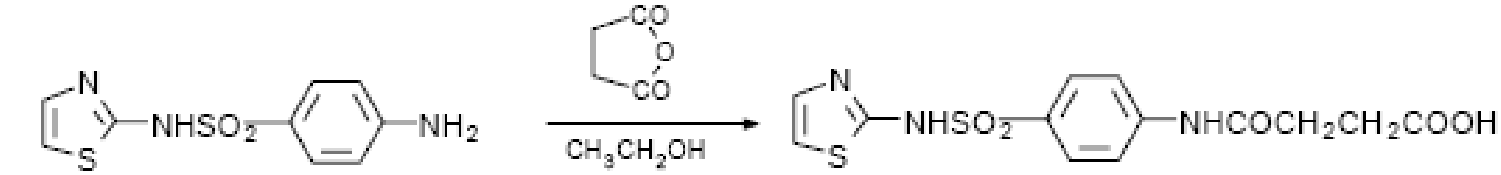
Acediasulphone (antibacterial)

– Acylation of alcohols, phenols and amines with the anhydride of the appropriate dicarboxylic acid.



Chloramphenicol (antibacterial)

Chloramphenicol sodium succinate (antibacterial)

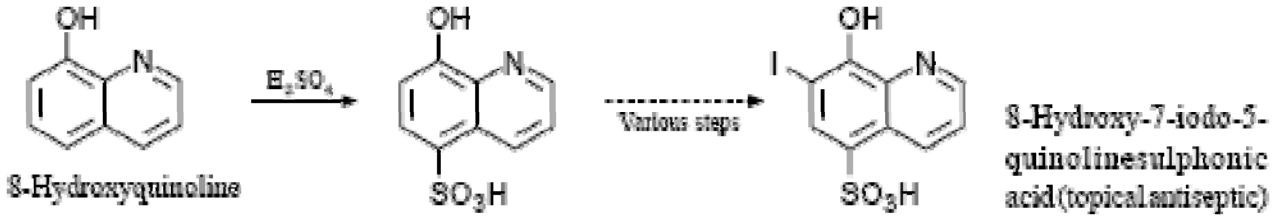


Sulphathiazole (antibacterial)

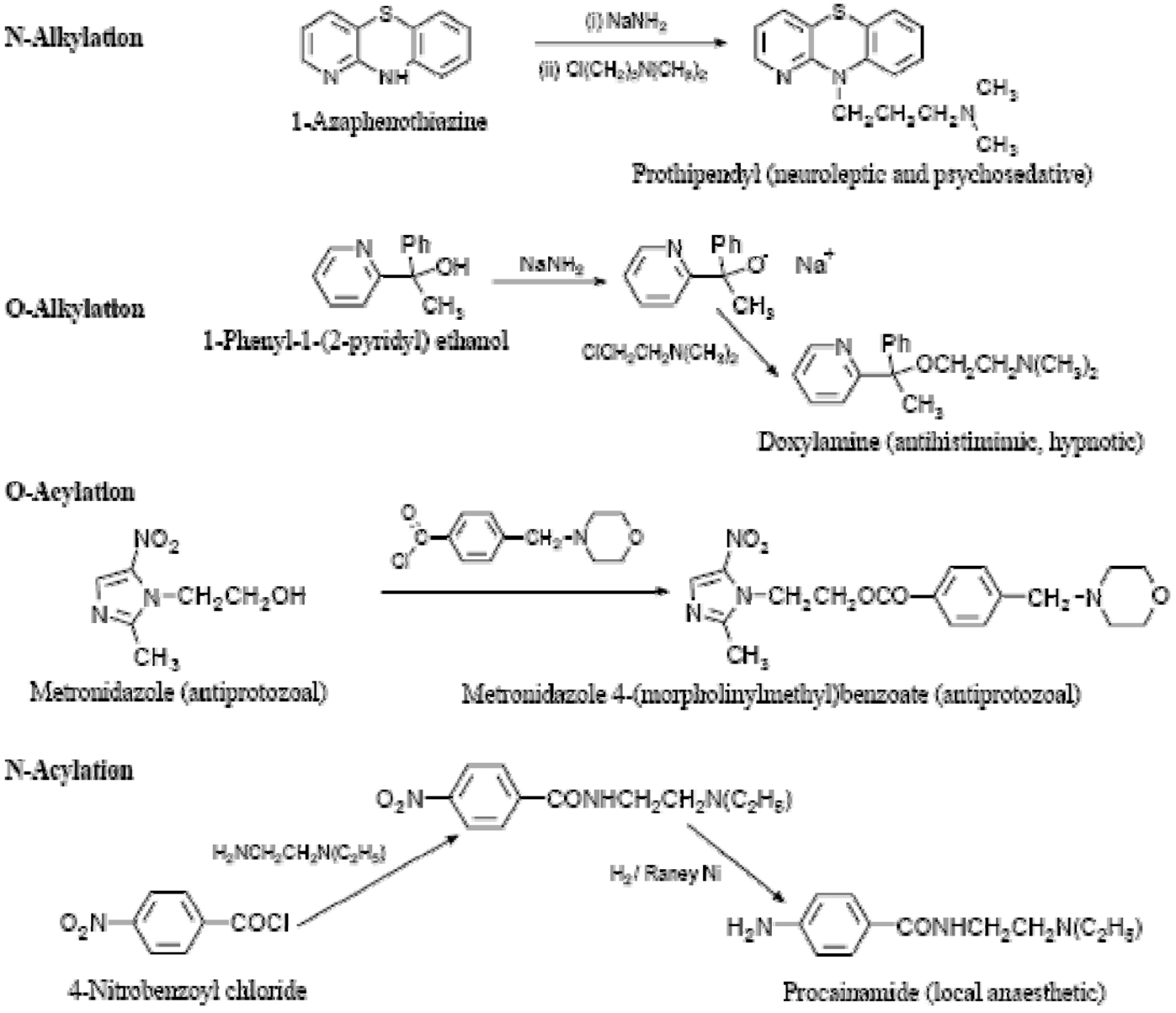
Succinyl sulphathiazole (antibacterial)

B. Introducing Sulphonic acid groups:

– Sulphonic acid groups can be incorporated into the structures by direct sulphonation with concentrated sulphuric acid

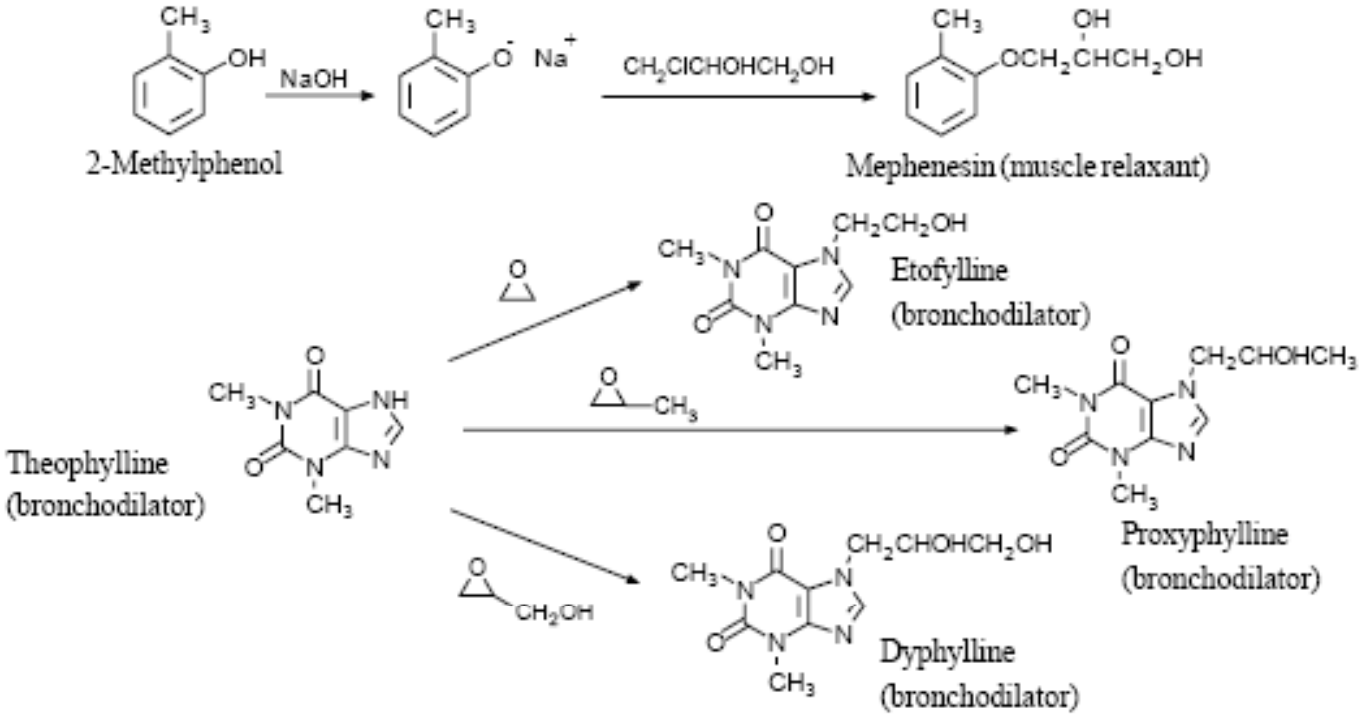


C. Introducing a basic groups



D. Polyhydroxylation:

- The introduction of polyhydroxy chains is used to improve water solubility,
- Hydroxyethoxy and dihydroxy residues have been introduced by:
  - Reaction of the corresponding monochlorinated hydrin
  - Also by using a suitable epoxides



Improving lipid solubility

- The commonest way to improve lipid solubility is:
  - To introduce non-polar groups into the structure
  - Or replace polar groups by less polar groups.
    - Methyl, fluoro and chloro groups are commonly used for this purpose.

3. DRUG DISTRIBUTION

• Once across the gut wall, the drug enters blood vessels, cells lining the blood vessels are loose fitting. No need for the drug to cross cell membranes

• Drug can quickly cross blood vessel walls through pores between the cells

• Drugs absorbed orally are first taken to the liver, modification of the drug is possible by enzymes in the liver - drug metabolism

• A certain percentage of the absorbed drug is often deactivated by drug metabolism in the liver before distribution occurs round the body - **first pass effect**

• Drug is distributed evenly throughout the blood supply within 1 min of absorption.

• Uneven distribution round body due to uneven blood supply

• Rapid distribution from blood vessels to tissues and organs

• Drug be effective if its target site is a receptor situated in a cell membrane or has to enter a cell if target is within the cell

• Blood concentration drops rapidly after absorption due to distribution, macromolecular binding such as albumin so lower the level of free drug, and storage in fat tissue (e.g. barbiturates) so it is difficult to estimate the safe dosage.

• Blood brain barrier hinders polar drugs from entering brain
  -tight fitting cells line the capillaries in the brain
  -capillaries have a coating of fat cells

• Can increase polarity of peripherally acting drugs to reduce CNS side effects

4. DRUG METABOLISM

Notes:

- **Foreign chemicals are modified by enzyme-catalysed reactions, mostly in the liver - detoxification**

- **Metabolic reactions also occur in blood, gut wall and other organs**

- **Drug metabolites are products formed from drug metabolism**

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

- **Modification of a structure may interfere or prevent binding interactions with a target (pharmacodynamics)**

4. DRUG METABOLISM

Notes:

- **Orally absorbed compounds pass through the liver before distribution to the rest of the body**

- **A percentage of orally absorbed drug is metabolised in the liver prior to distribution round the body - the first pass effect**

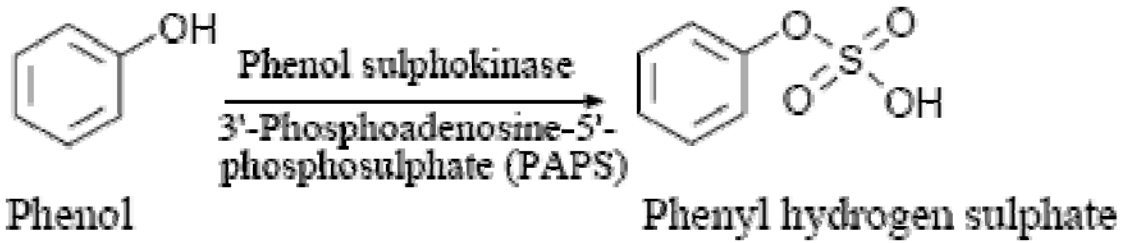
- **Compounds absorbed by other routes avoid the first pass effect and circulate round the body before reaching the liver**

- **A percentage of non-orally absorbed compounds never reaches the liver due to distribution into fat, cells and tissue**

Pharmacological effect of metabolised drugs

1. **Inactive metabolites:**

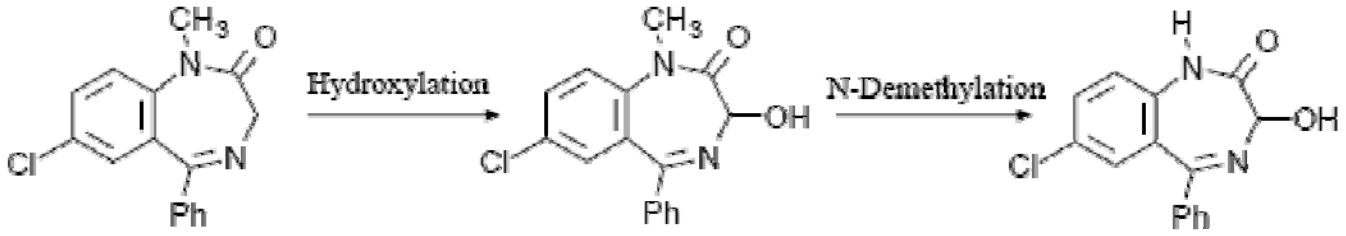
- Due to detoxification processes.
  - For example, the detoxification of phenol to phenyl hydrogen sulphate.
  - This is pharmacologically inactive.
  - This compound is very water soluble and so is readily excreted through the kidney.



Phenol Phenyl hydrogen sulphate

2. Metabolites with a similar activity to the drug

- But these metabolites will have :
  - A different potency
  - A different duration of action
  - Or both (with respect to the original drug).
- The anxiolytic diazepam:
  - Metabolised to the anxiolytic temazepam (short duration)
  - This in turn is further metabolised by demethylation to the anxiolytic oxazepam (short duration of action).



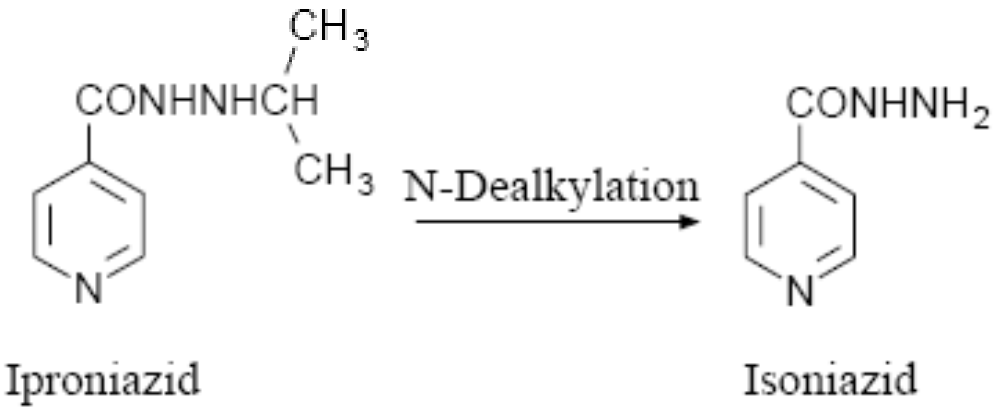
Diazepam
Assival®

Temazepam

Oxazepam
Vaben®

3. Metabolites with a dissimilar activity to the drug

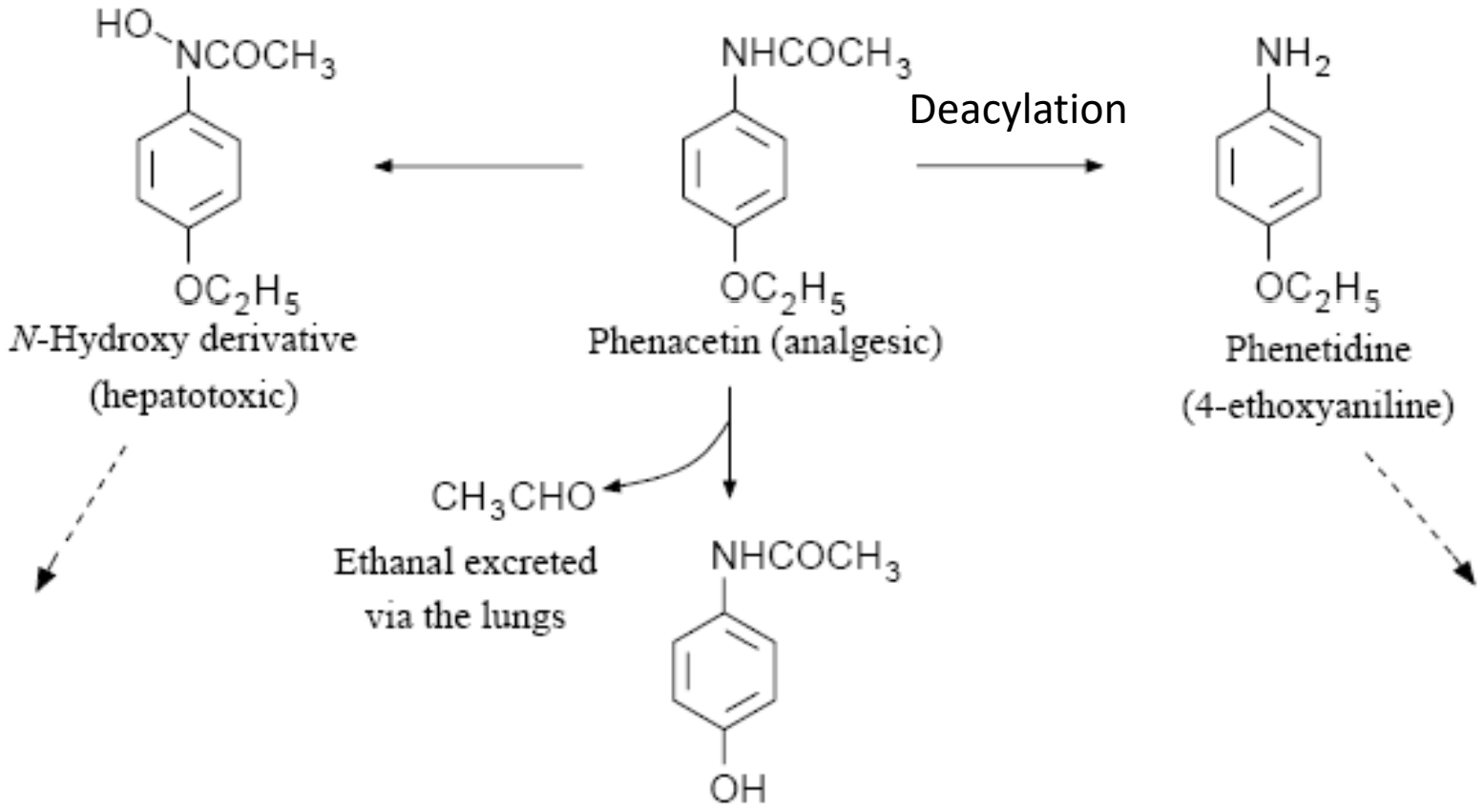
- The activity of these metabolites are different to the parent drug.
  - For example, the antidepressant iproniazid is metabolised by dealkylation to the antituberculous drug isoniazid.



Iproniazid Isoniazid

4. Toxic metabolites

- The toxic action arises because :
  - The metabolite activates an alternative receptor
  - Or acts as a precursor for other toxic compounds.
- Deacylation of the analgesic phenacetin yields *p*-phenetidine:
  - Act as the precursor of substances that cause the methaemoglobinaemia (a modification of haemoglobin) in the blood.
    - This condition causes headaches, shortness of breath, cyanosis, sickness and fatigue.
  - Phenacetin is also metabolised via its N-hydroxy derivative and cause liver damage.


HO
NCOCH3
OC2H5
N-Hydroxy derivative
(hepatotoxic)
NHCOCH3
OC2H5
Phenacetin (analgesic)
Deacylation
NH2
OC2H5
Phenetidine
(4-ethoxyaniline)
CH3CHO
Ethanal excreted
via the lungs
NHCOCH3
OH

4. DRUG METABOLISM

Phase I and Phase II Reactions

Notes:

- **Metabolic reactions are defined as phase I or phase II**

- **Most phase I reactions add a polar 'handle' to the molecule**

- **Phase II reactions are often carried out on functional groups which have been added by Phase I reactions**

- **Increasing the polarity of a compound increases the rate of drug excretion**

- ***Cytochrome P450 enzymes* catalyse phase I oxidations**

Phase I metabolism:
1) Phase I catalyzed by Cytochrome P450 enzymes

• Located in liver, they are haemoproteins "containing haem and iron" and they belong to general class of enzymes called the monooxygenases.

• There are at least 33 different cytochrome P450 enzymes grouped into four main families CYP1-CYP4.

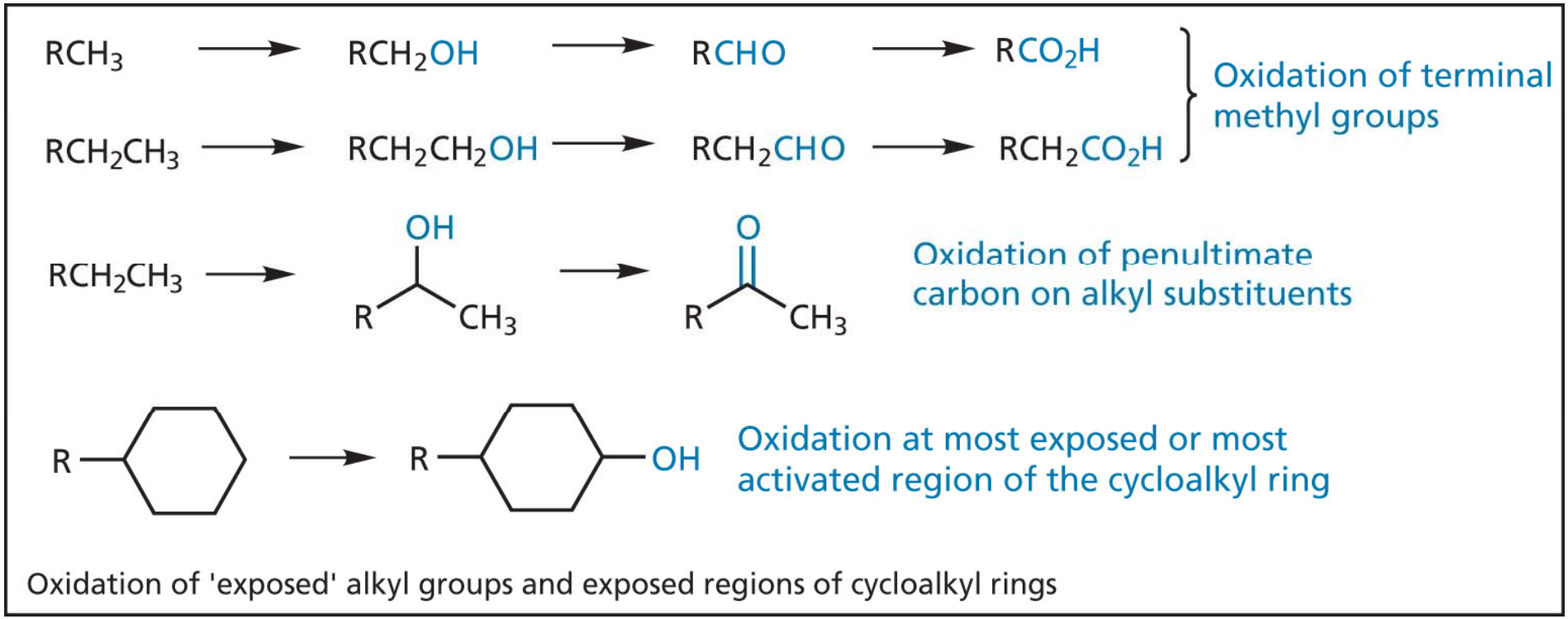
• Within each family there are various subfamilies designated by a letter, and each enzyme within that subfamily is designated by a number.

• E.g. CYP3A4 is enzyme 4 in the subfamily A of the main family 3; and it is responsible for the metabolism of most drugs.

• Most drugs in current use are metabolized by five primary CYP enzymes "**CYP3A4, CYP2D6, CYP2C9, CYP1A2, & CYP2E1**".

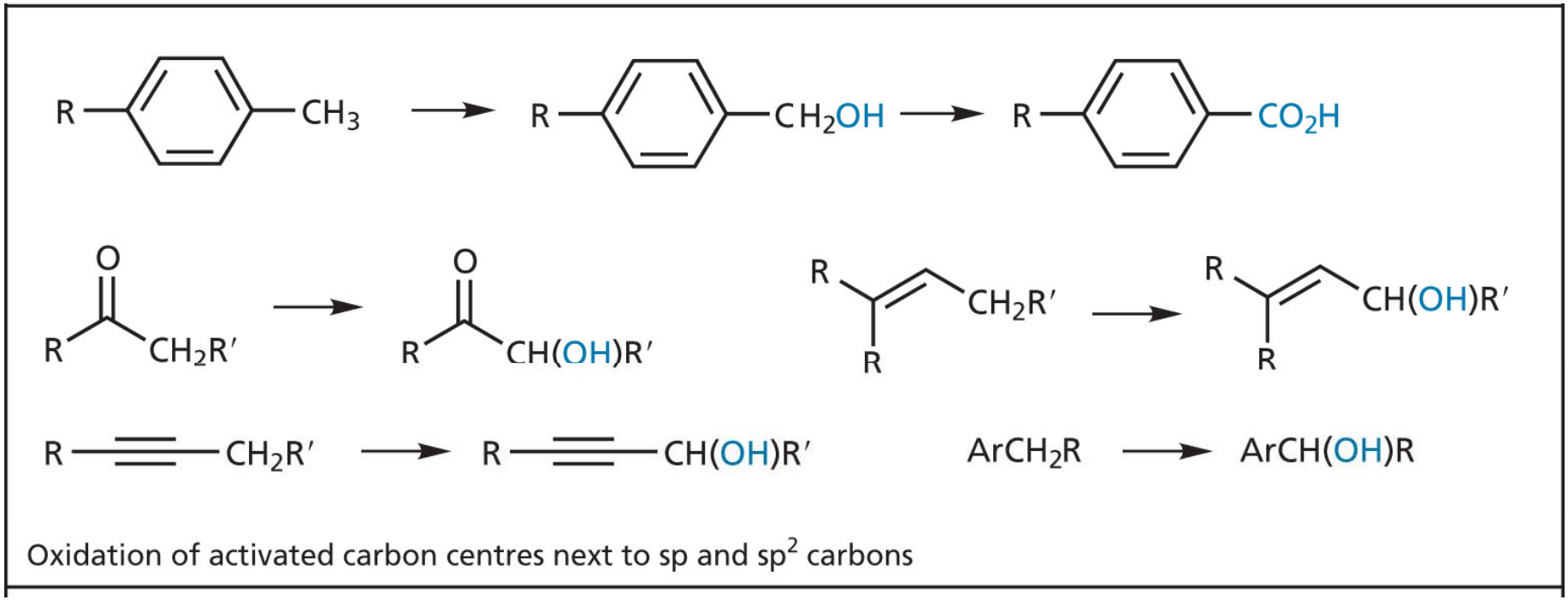
1.1) Oxidation of carbon atoms can occur if the carbon atom is either exposed "easily accessible to the enzyme" or activated.

• the terminal and penultimate carbons are the most exposed carbons in the chain. The carbon is oxidized to form alcohols which may be oxidized further to carboxylic acids.



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

1.2) Activated carbon atoms next to an sp^2 carbon centre "allylic or benzylic positions" or an sp carbon centre "propynylic position" are more likely to be oxidized than exposed carbon atoms.

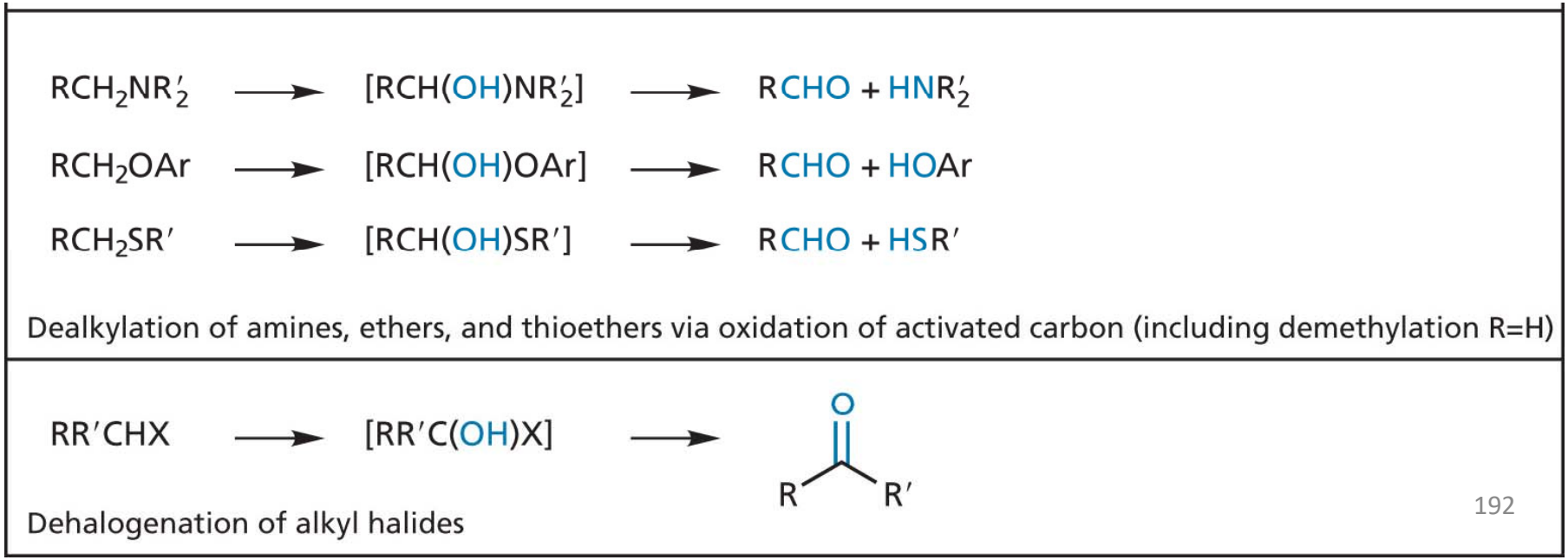


Oxidation of activated carbon centres next to sp and sp^2 carbons

1.3) Carbon atoms which are alpha to a heteroatom are also activated and prone to oxidation.

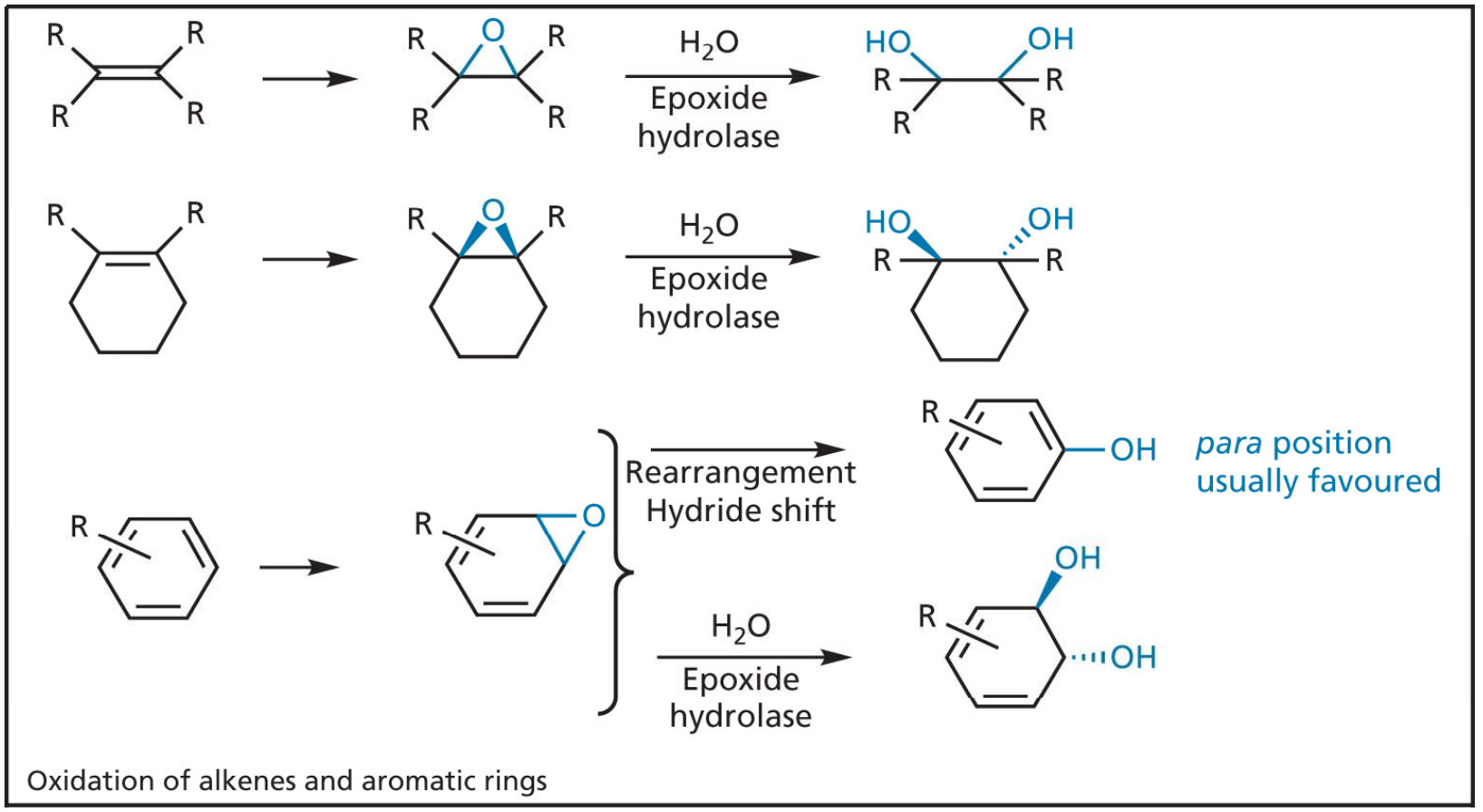
• hydroxylation results in an unstable metabolite that is immediately hydrolysed resulting in the dealkylation of amines, ethers, & thioethers or the dehalogenation of alkyl halides.

• the resulting aldehyde is further oxidized to carboxylic acid by aldehyde dehydrogenases. 3º amines are more reactive to oxidative dealkylation than 2º amines coz their greater basicity.



1.4) CYP450 also catalyse the oxidation of unsaturated sp^2 & sp carbon centres present in alkenes, alkynes & aromatic rings.

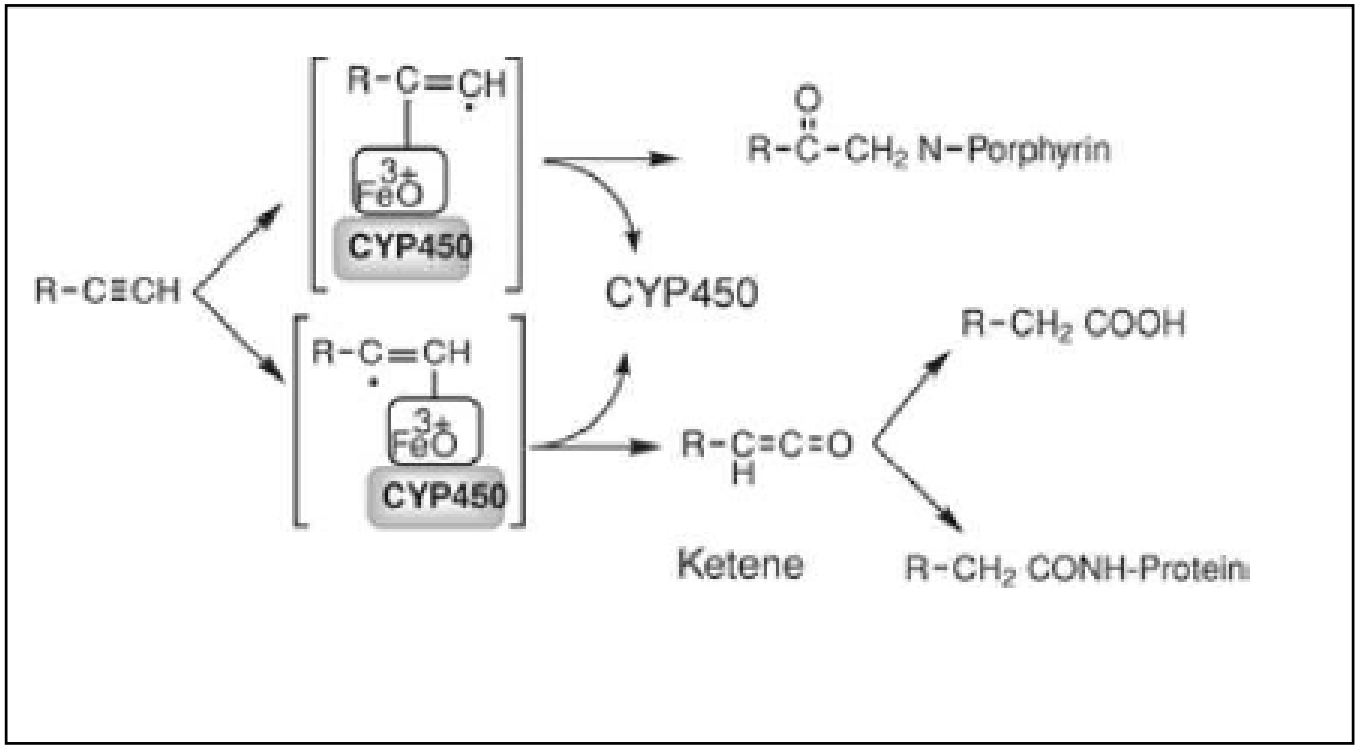
• electron-rich aromatic rings are likely to be epoxidized more quickly than those with electron—withdrawing substituents.



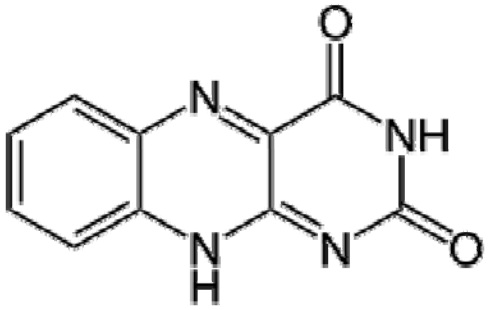
Oxidation of alkenes and aromatic rings

Oxidation of Alkynes (acetylenes):

- Like the alkenes, are readily oxidized but usually faster.
- Depending on which of the two alkyne carbons are attacked, different products are obtained .
  - If attachment of CYP450 occurs on penultimate will give a ketone
  - If attachment of CYP450 occurs on the terminal alkyne carbon
    - Will give ketene intermediate which is readily hydrolyzes with water to form carboxylic acid
    - Or it can alkylate nucleophilic protein side chains.


R-C≡CH
R-C=CH
CYP450
R-C-CH2 N-Porphyrin
CYP450
R-CH2 COOH
R-C=C=O
H
Ketene
R-CH2 CONH-Protein

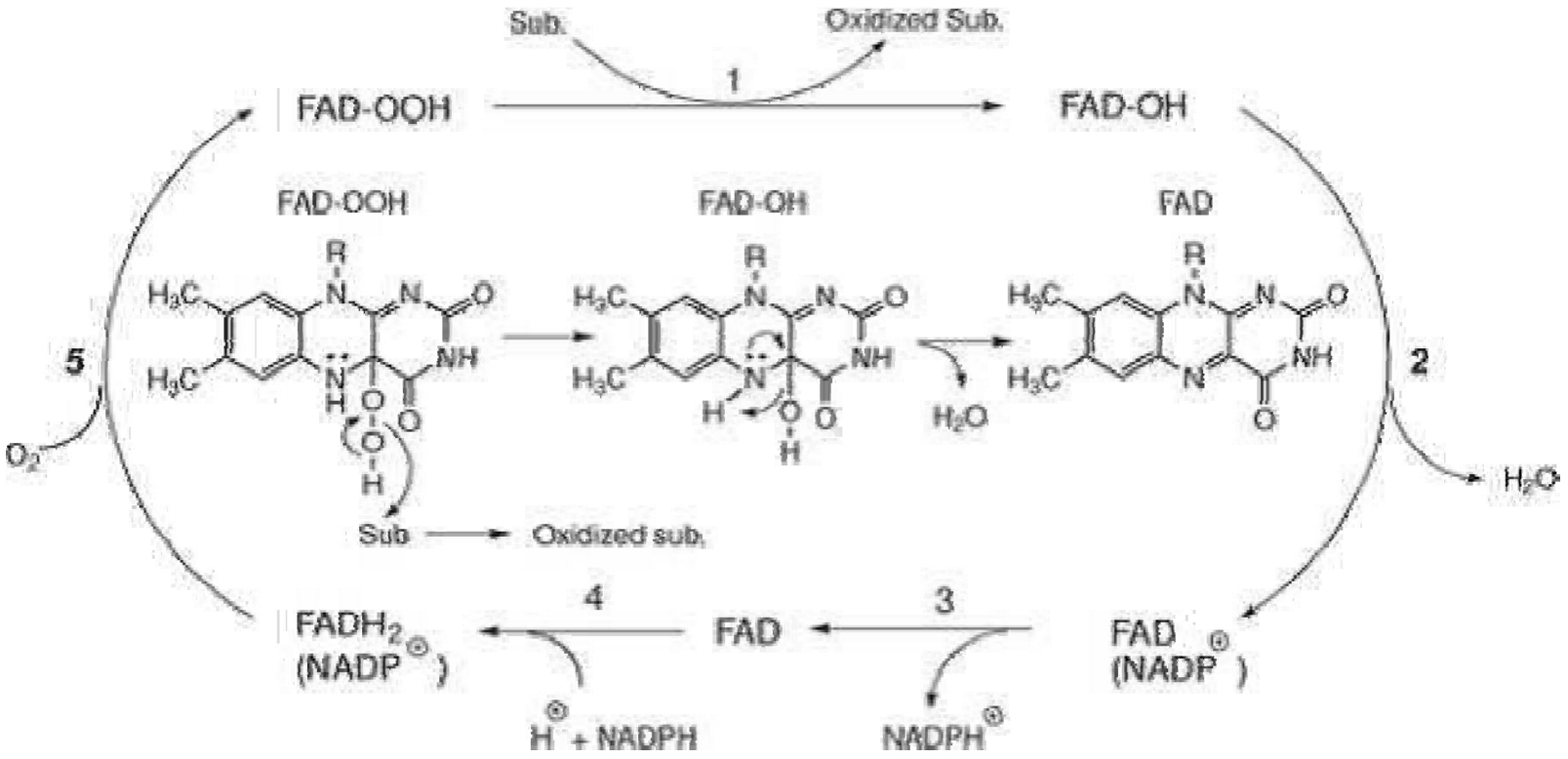
2. Oxidations Catalyzed by Flavin Monooxygenase (FMO):



Flavin

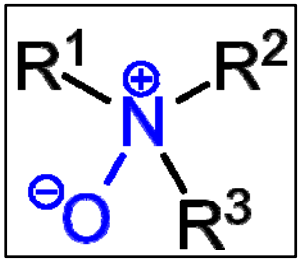
- They are the major hepatic monooxygenase systems
- They are responsible for the oxidation of many drugs containing nitrogen, sulphur, or phosphorus
- The FMO
  - They are non-selective oxidases.
  - These enzymes have:
    - FAD (flavin adenine dinucleotide) group
    - It also require either NADH or NADPH as coenzyme
  - They exhibits broader substrate specificities than CYP450 monooxygenases .

- FMO is present within the cell in its enzyme-bound activated hydroperoxide (Enz-FAD-OOH)
  - In this state it is ready to oxidize the substrate that binds to it.
  - Dioxygen binds with a reduced flavin.
  - This forms hydrogen peroxide intermediate
  - It uses a nucleophilic displacement mechanism
  - The reactive oxygen of Flavin-4α-hydroperoxide attack a lone electron pair on a heteroatom
    - Such as Nitrogen or Sulfur
    - But not reactive enough to attack a typical C-H bond.
- Steps 2 to 5 shown in the graph:
  - Represent regeneration of Enz-FAD-OOH from Enz-FAD-OH

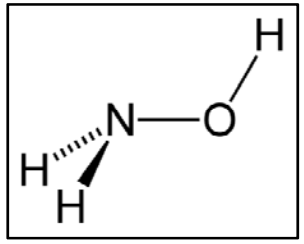

Sub.
Oxidized Sub.
1
FAD-OOH
FAD-OH
FAD-OOH
FAD-OH
FAD
5
2
O_2
H_2O
Sub
Oxidized sub.
4
3
$FADH_2$ ($NADP^{\oplus}$)
FAD
FAD ($NADP^{\oplus}$)
$H^{\oplus}$ + NADPH
$NADPH^{\oplus}$

2.1. Oxidation of Nitorgen:

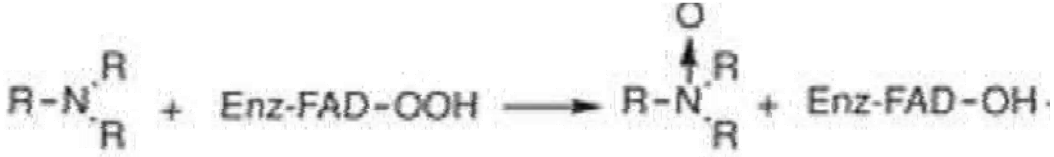
- In general N-oxygenation of amines forms either
  - Stable N-oxides →



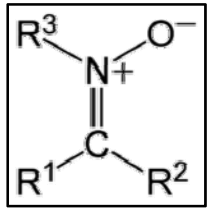
  - Hydroxylamines →

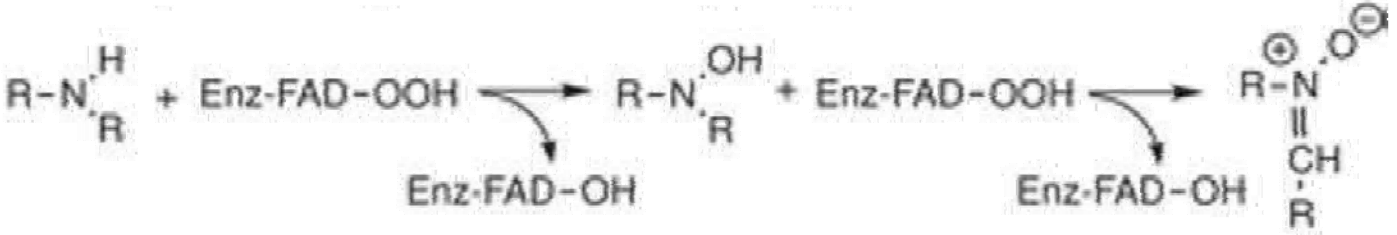


- Nitrogen functional groups that are oxidized by FMO and excreted in the urine include the following:
  - The tertiary acyclic & cyclic amines
    - They form stable amine oxides



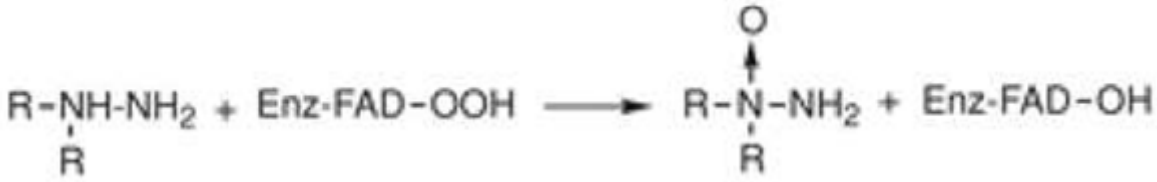
  - Secondary acyclic & cyclic amines are oxidized to
    - Hydroxylamines
    - Nitrones →





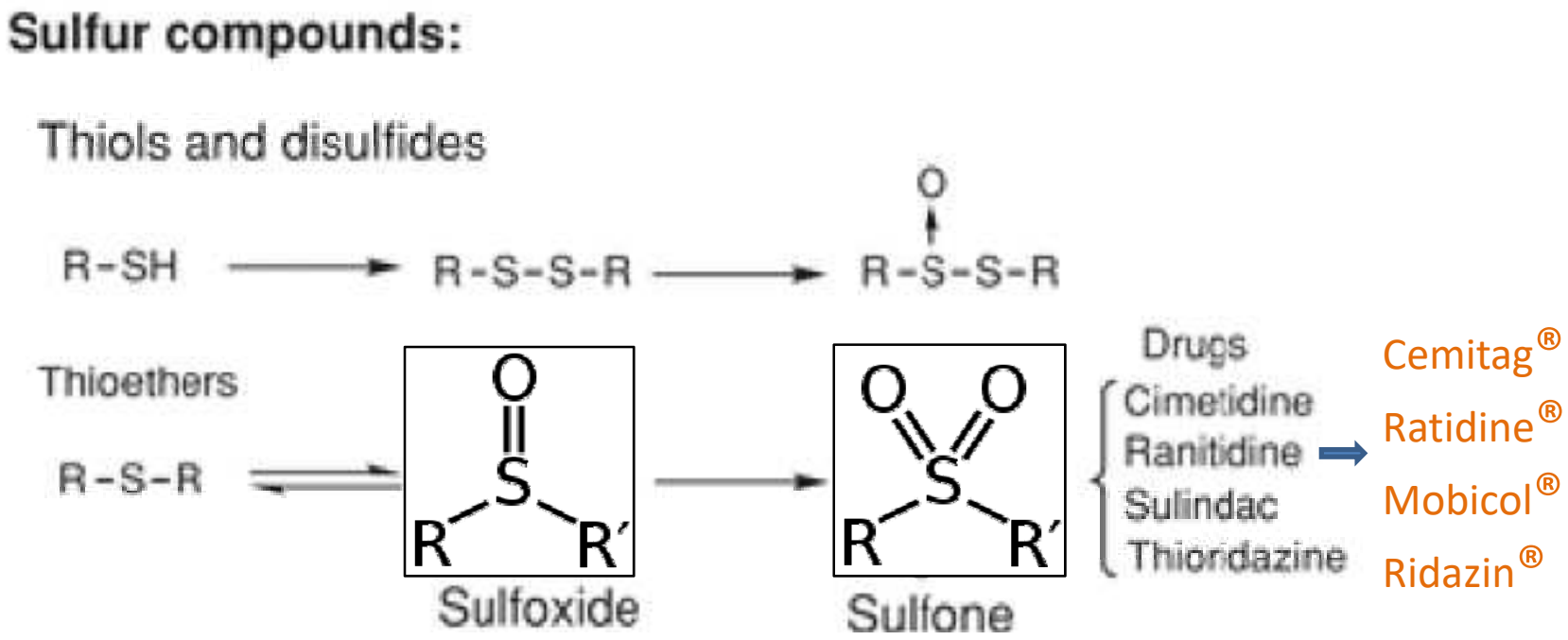
– Aryl amine are oxidised to:
  - Hydroxyl amine

– N,N disubstituted hydrazine (R_2N-NH_2)
  - They form stable amine oxides



2.2. Oxidation of sulphur:

- It occurs almost exclusively by FMO.
- Sulfides are oxidized to sulfoxides and sulfones of which are eliminated in the urine.

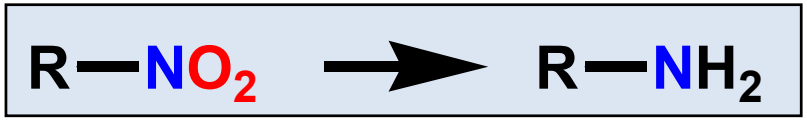


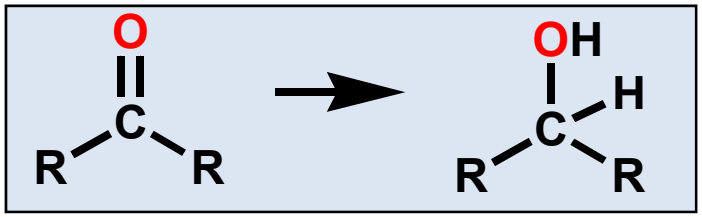
3) Phase I catalyzed by other enzymes

3.1) Monoamine oxidases are involved in the deamination of catecholamines “mainly dopamine, norepinephrine & epinephrine”.

3.2) Alcohol dehydrogenases & aldehyde dehydrogenases, the aldehydes formed by the action of Alcohol dehydrogenases that they are converted to carboxylic acids by aldehyde dehydrogenases.

4) Reductive phase I are less common than oxidation, but reduction of aldehyde, ketone, azo and nitro functional groups have been observed.



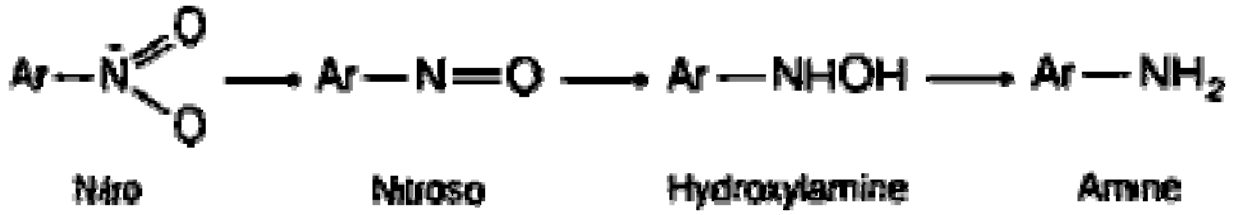


4.1. Reduction of Nitro and Azo Compounds

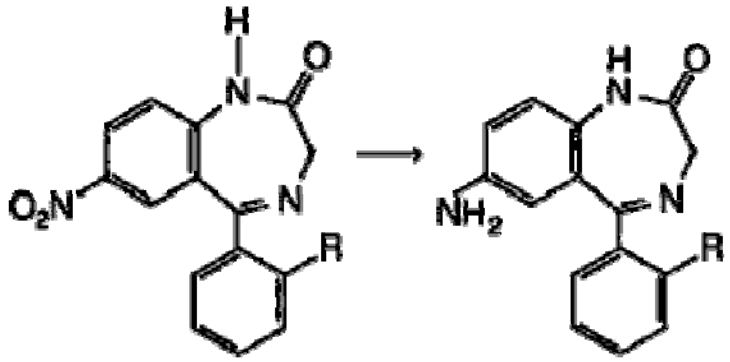
- The reduction of aromatic nitro and azo xenobiotics
  - leads to aromatic primary amine metabolite.

A- Aromatic nitro compounds:

  - They are reduced initially to the nitroso and hydroxylamine intermediates.



- Examples of aromatic nitro drugs undergo enzymatic reduction to the corresponding aromatic amines.
  - For example, the 7-amino benzodiazepine derivatives clonazepam and nitrazepam
  - They are metabolized extensively to their respective 7-amino metabolites in human

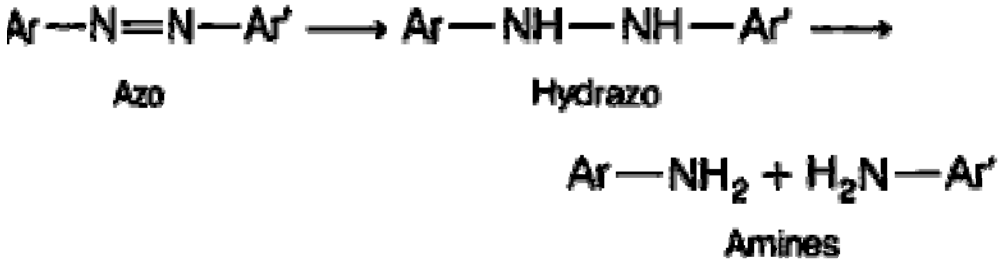


Clonex® Clonazepam, R = Cl
Nitrazepam, R = H

7-Amino Metabolite

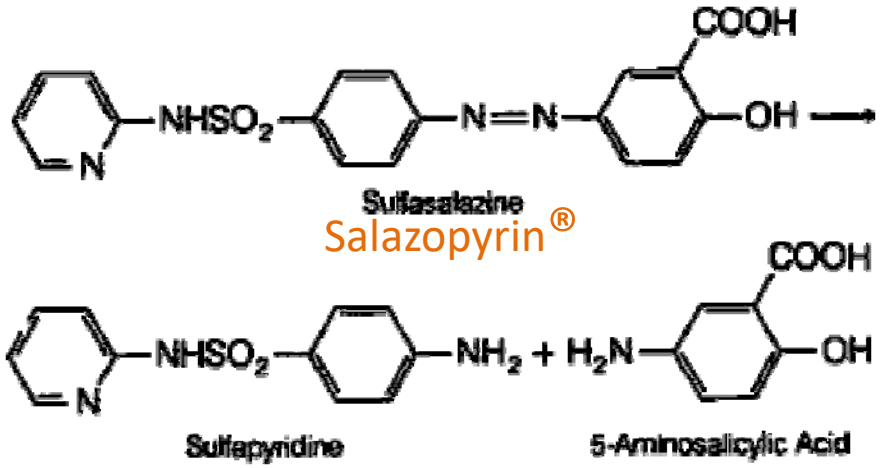
B- Azo reduction:

- It is proceeded via a hydrazo intermediate (-NH-NH-)
- This subsequently is cleaved reductively to yield the corresponding aromatic amines

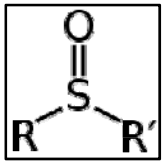


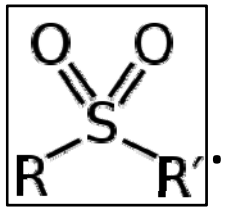
Reduction of azo groups by bacterial reductases

- They are present in the intestine
- They play a significant role in reducing azo xenobiotics particularly those that are absorbed poorly.
- Example of Intestinal reduction is the metabolism of sulfasalazine
- This drug is absorbed poorly
- It undergoes reductive cleavage of the azo linkage to yield sulfapyridine and 5-aminosalicylic acid.
- The reaction occurs primarily in the colon



4.2- Sulfoxide functionalities:



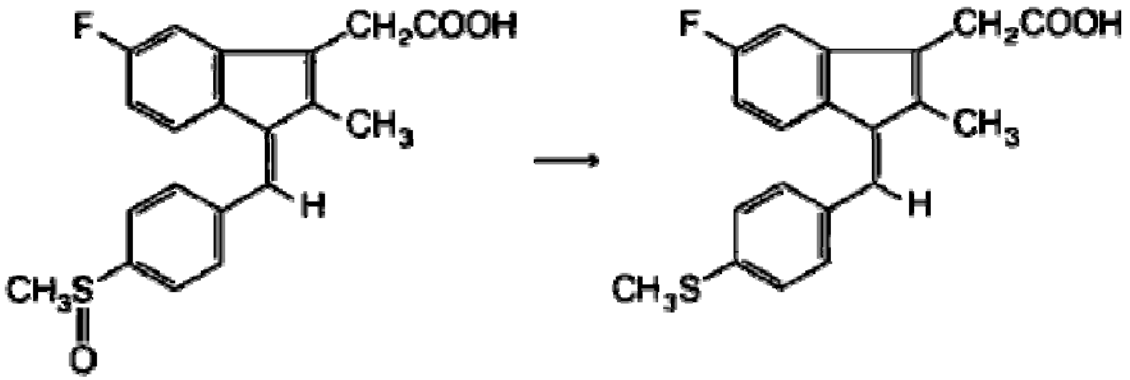
– They are oxidized mainly to sulfones 

.

– They sometimes undergo reduction to sulfides.

– This reductive pathway is seen in the metabolism of the anti-inflammatory agent sulindac .

- Sulindac undergoes reduction to an active sulfide
- This metabolite is responsible for the overall anti-inflammatory effect of the parent drug sulindac.



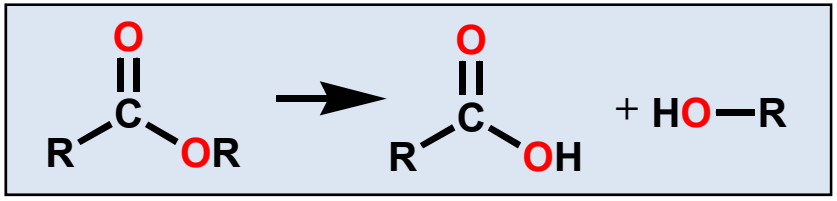
Sulindac

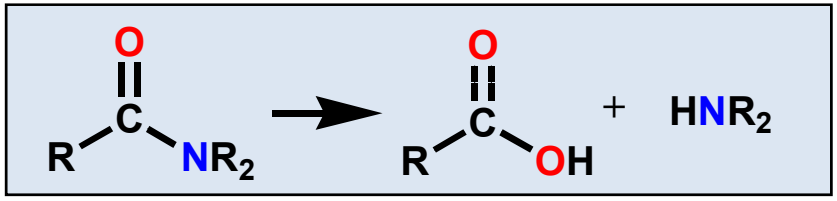
Mobicol®

Sulindac Sulfide Metabolite

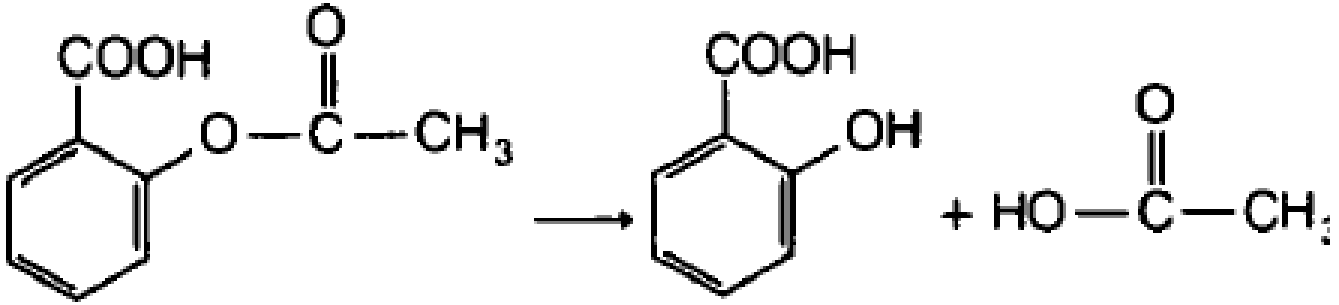
5) Hydrolysis of esters & amides is a common metabolic reaction catalysed by esterases & peptidases respectively.

• 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.



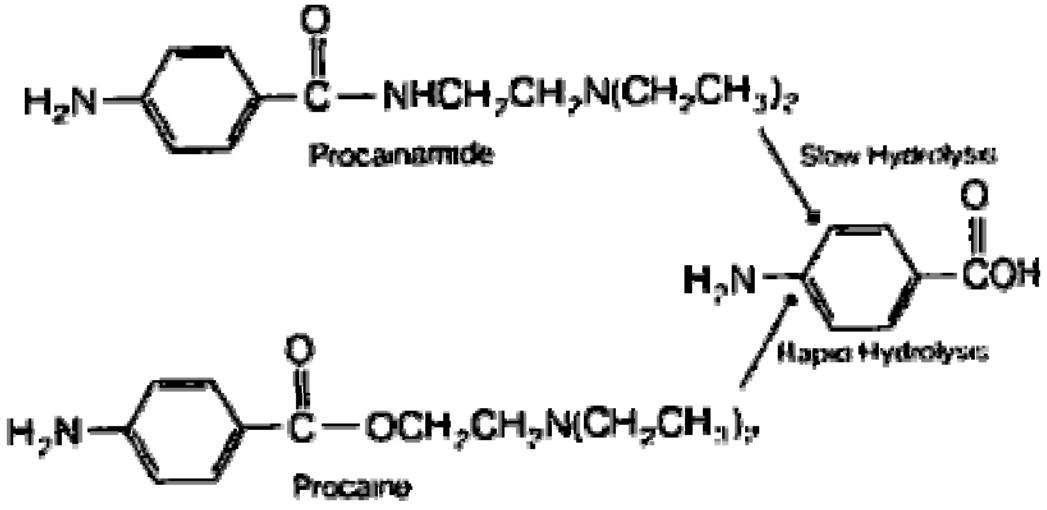


- The enzyme carrying out ester hydrolysis is esterases:
  - Found in the liver, kidney, intestine and plasma.
  - Hydrolysis is a major biotransformation pathway for drugs containing an ester functionality.
  - This is because of the relative ease of hydrolyzing the ester linkage.
- An example of ester hydrolysis:
  - The metabolic conversion of aspirin (acetylsalicylic acid) to salicylic acid.



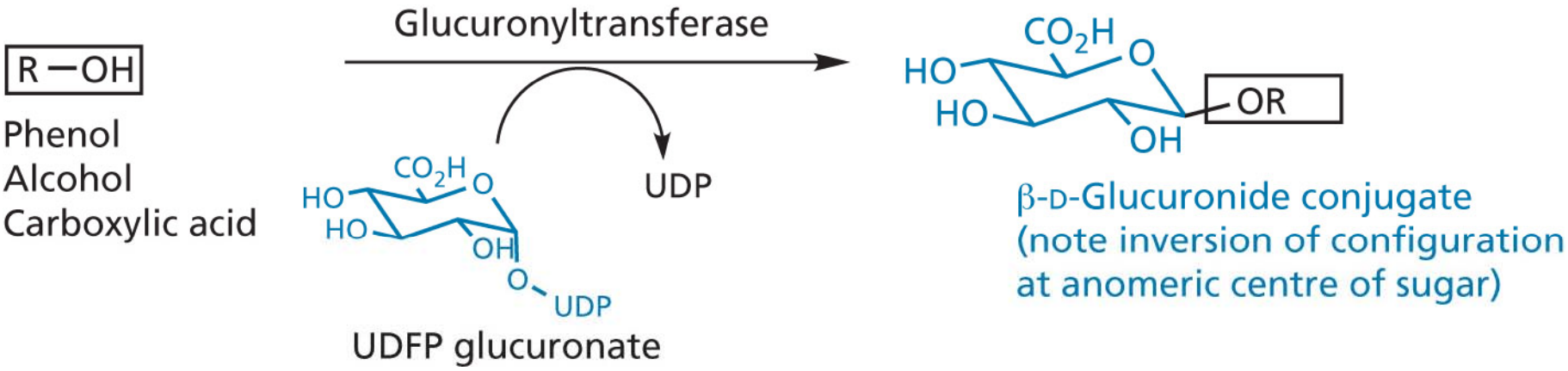
Aspirin (Acetylsalicylic acid) | Salicylic Acid | Acetic Acid

- Amides are more stable to esterase hydrolysis than are esters
  - So we find amides excreted largely unchanged.
- This fact has been exploited in developing the antiarrhythmic drug procainamide.
  - Procaine is not useful because of its rapid esterase hydrolysis,
  - But 60% of a dose of procainamide was recovered unchanged from the urine of humans.



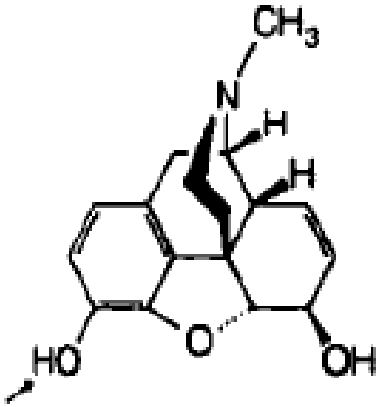
Phase II Reactions

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

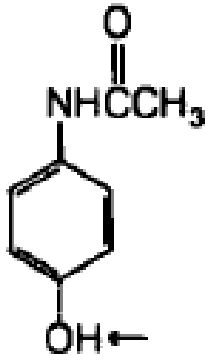


I. Hydroxyl Glucuronides:

A- phenols:

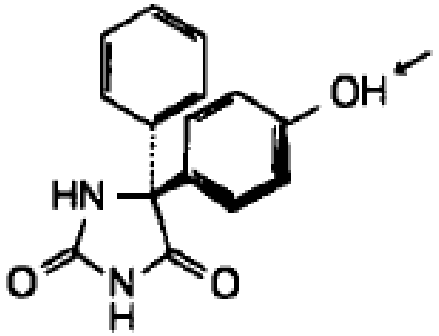


Morphine



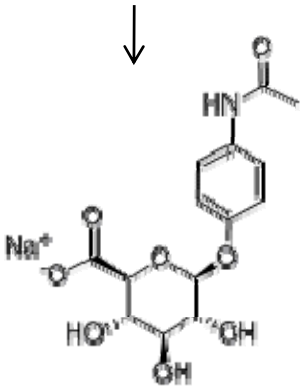
Acetaminophen

Acamol ®

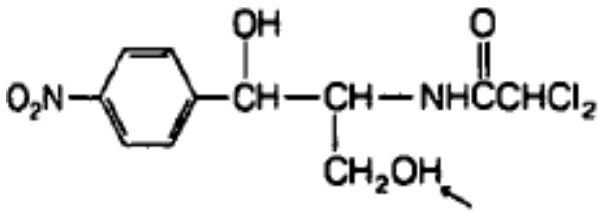


P-hydroxyphenytion

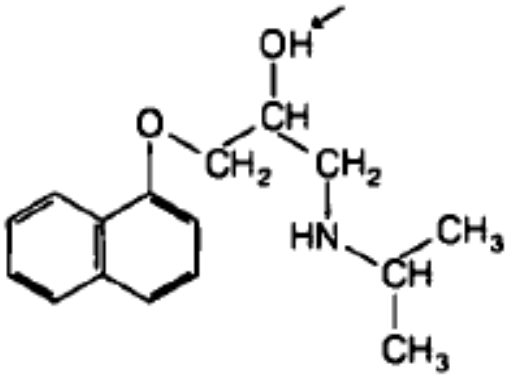
Epanutin ®



B- Alcohols:

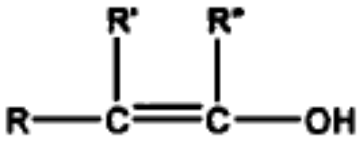


Chloramphenicol
Lomixin E/D®

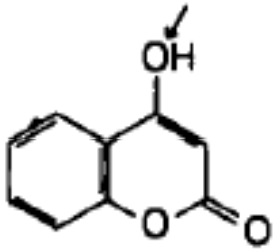


Propranolol
Deralin ®

C- Enols:

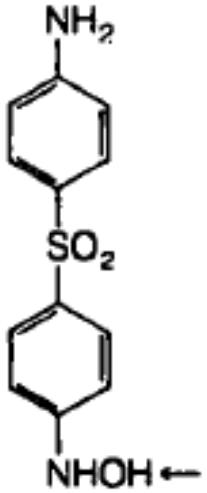


Enol



4-hydroxycoumarin

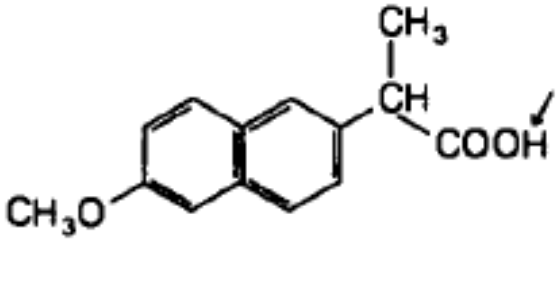
D- N-Hydoxyamines



N-hydroxydapsone

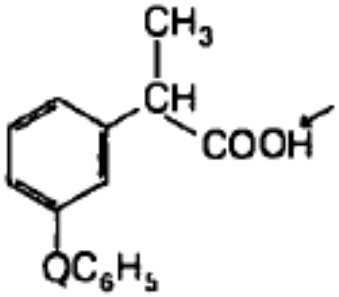
Used in the treatment of leprosy

E- Carboxyl compounds (Arylalkyl acids):



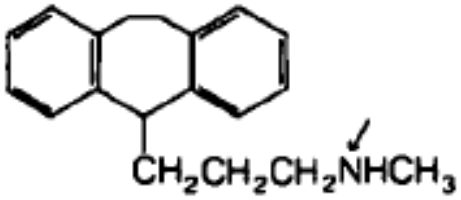
Naproxen

Naprex ®

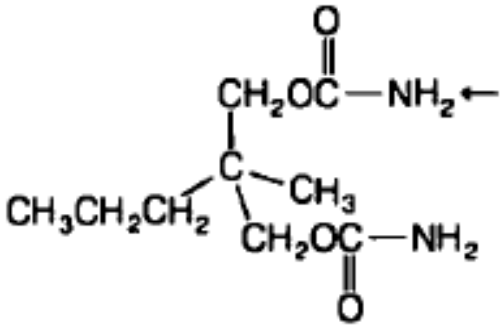


Fenoprofen

II. Nitrogen Glucuronides:



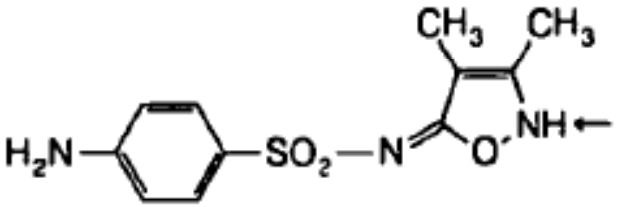
Desipramine



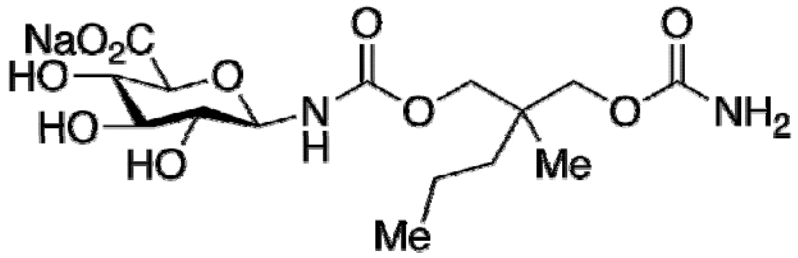
Meprobamate

Used as anxiolytic

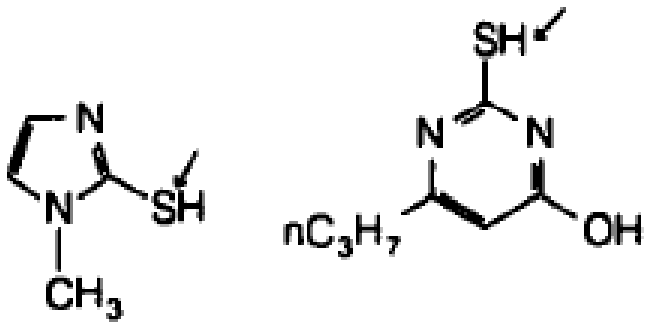
Mepro®



Sulfisoxazole



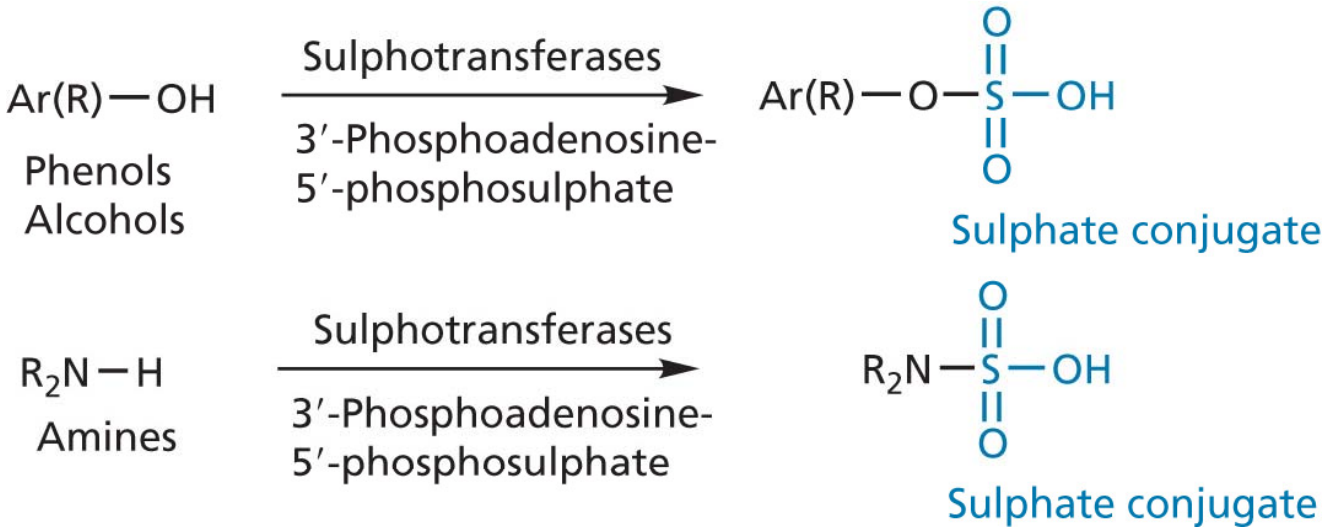
III. Sulphur Glucuronides



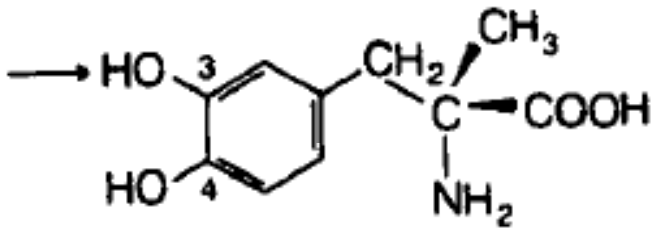
Methimazole
Mercaptizol ®

Propylthiouracil
Propyl-Thiocyl ®

2. Sulfate conjugates: it is restricted to phenols, alcohols, arylamines & *N*-hydroxy compounds.

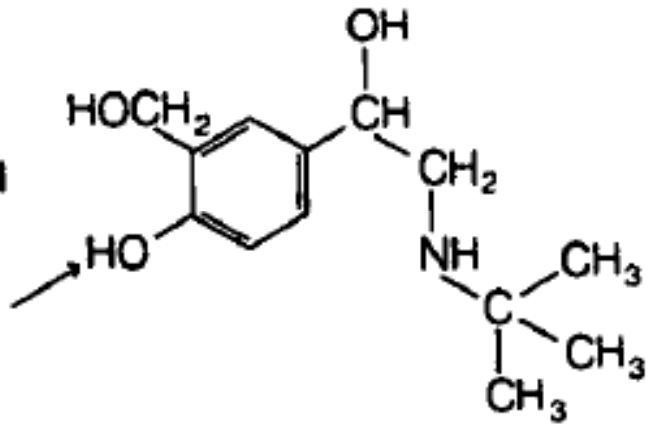


- Phenols are the main group of substrates undergoing sulphate conjugation.
- Drugs containing phenolic moieties are often susceptible to sulphate formation.
  - For example the antihypertensive agent:
    - α-Methyldopa is metabolised extensively to its 3-O-sulfate ester in humans.
  - The β-adrenergic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



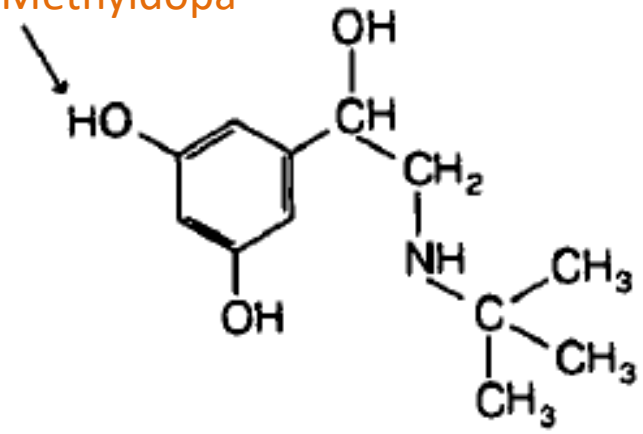
α-Methyldopa

Methyldopa®



Salbutamol
(Albuterol)

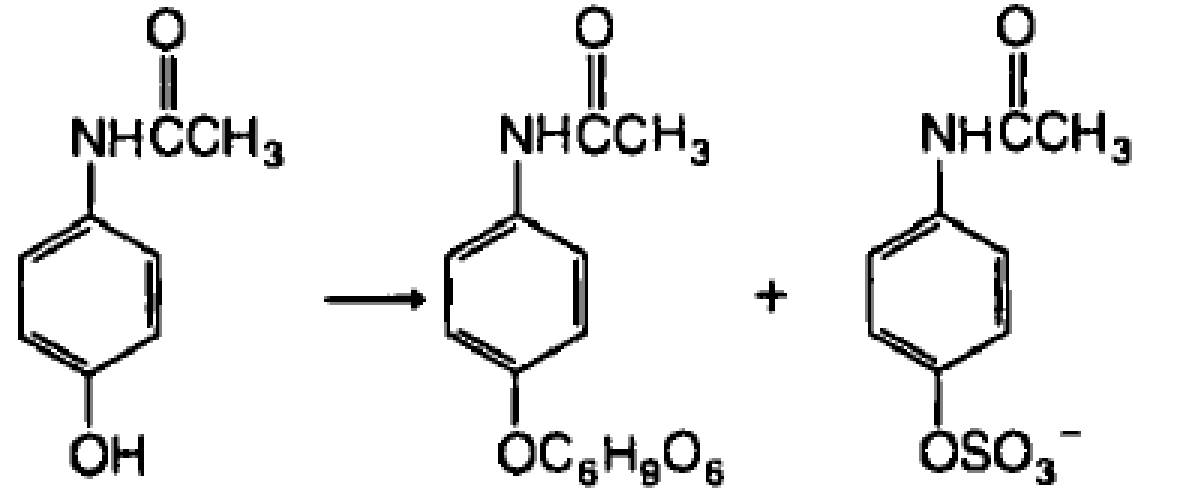
Ventocare®



Terbutaline

Bricalin ®

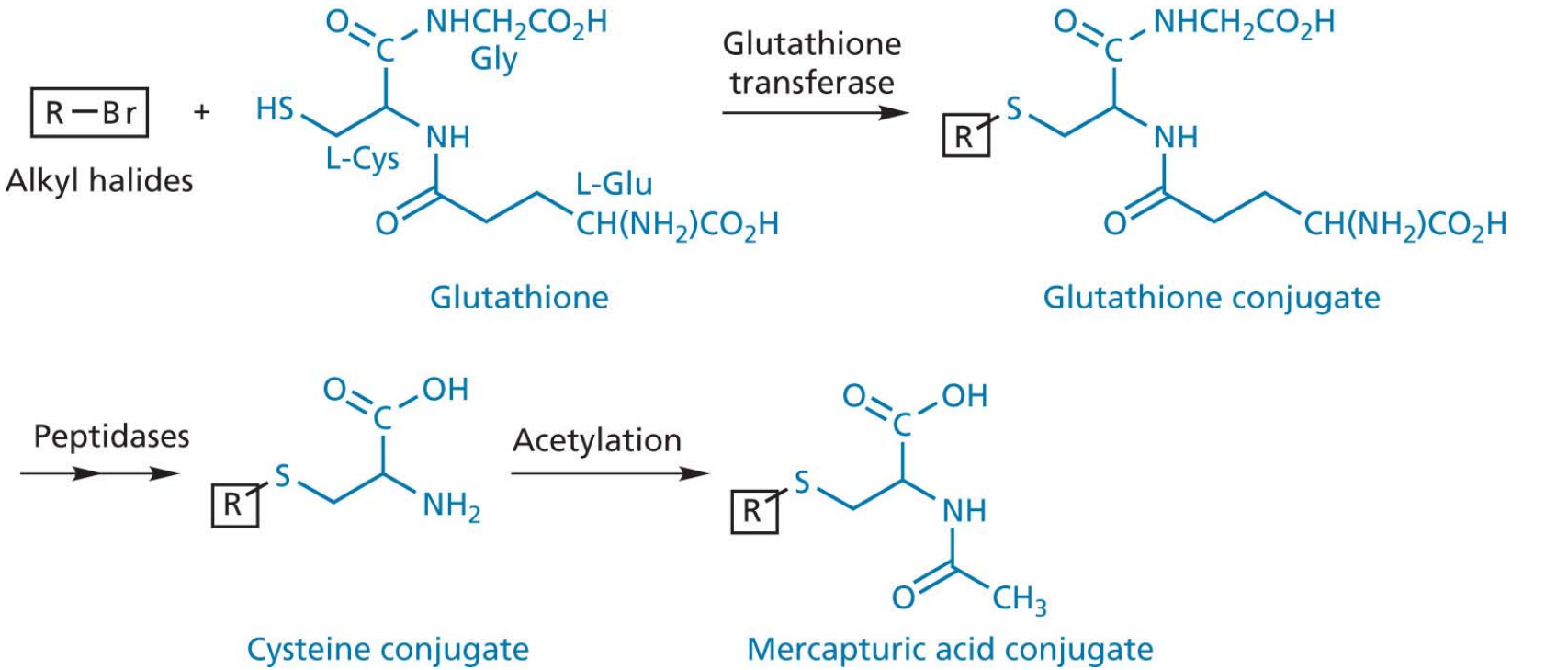
- For many phenols sulpho-conjugation is a minor pathway.
  - Glucuronidation of phenols is more frequent and predominant in phenolic drugs.
  - In adults, the major urinary metabolite of the analgesic acetaminophen is the O-glucuronide conjugate with small amount of O-sulphate conjugate
- In infants 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.

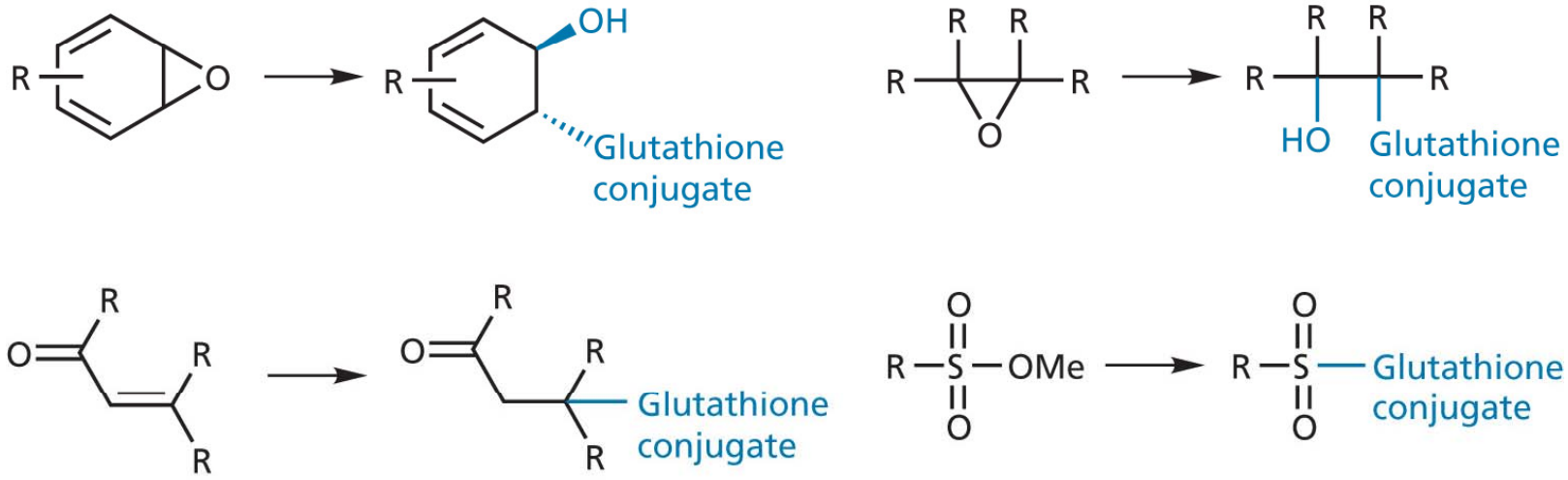

NHCCH3
O
OH
Acetaminophen
NHCCH3
O
OC6H9O6
O-Glucuronide Conjugate
+
NHCCH3
O
OSO3−
O-Sulfate Conjugate

Febramol ®

3. Electrophilic functional groups such as epoxides, alkyl halides, sulfonates, disulfides and radical species can react with the nuclephilic thiol group of the **tripeptide glutathione** to give glutathione conjugates which can be transformed to **mercapturic acid**.

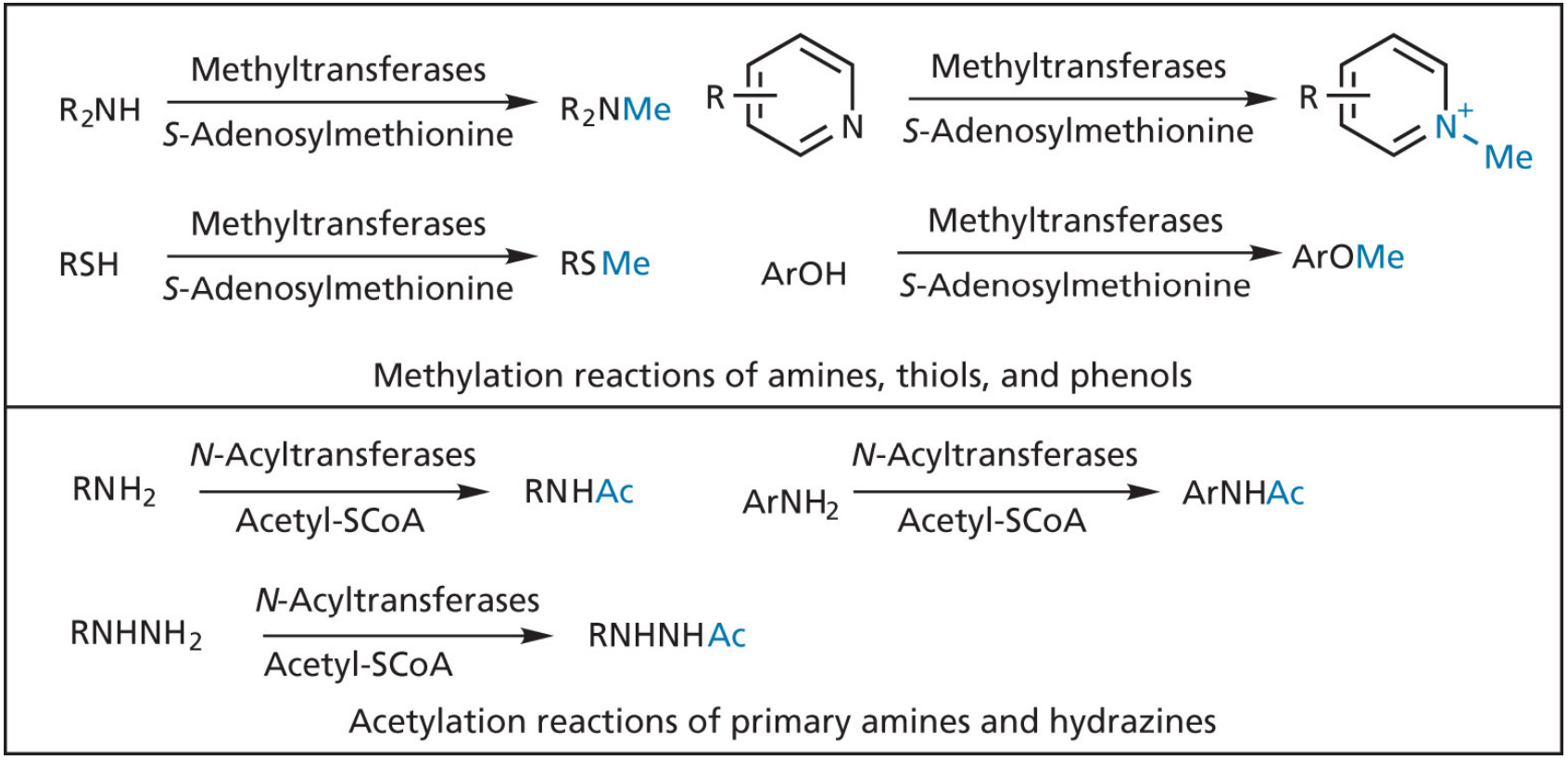
• it is catalyzed by **glutathione transferase**.

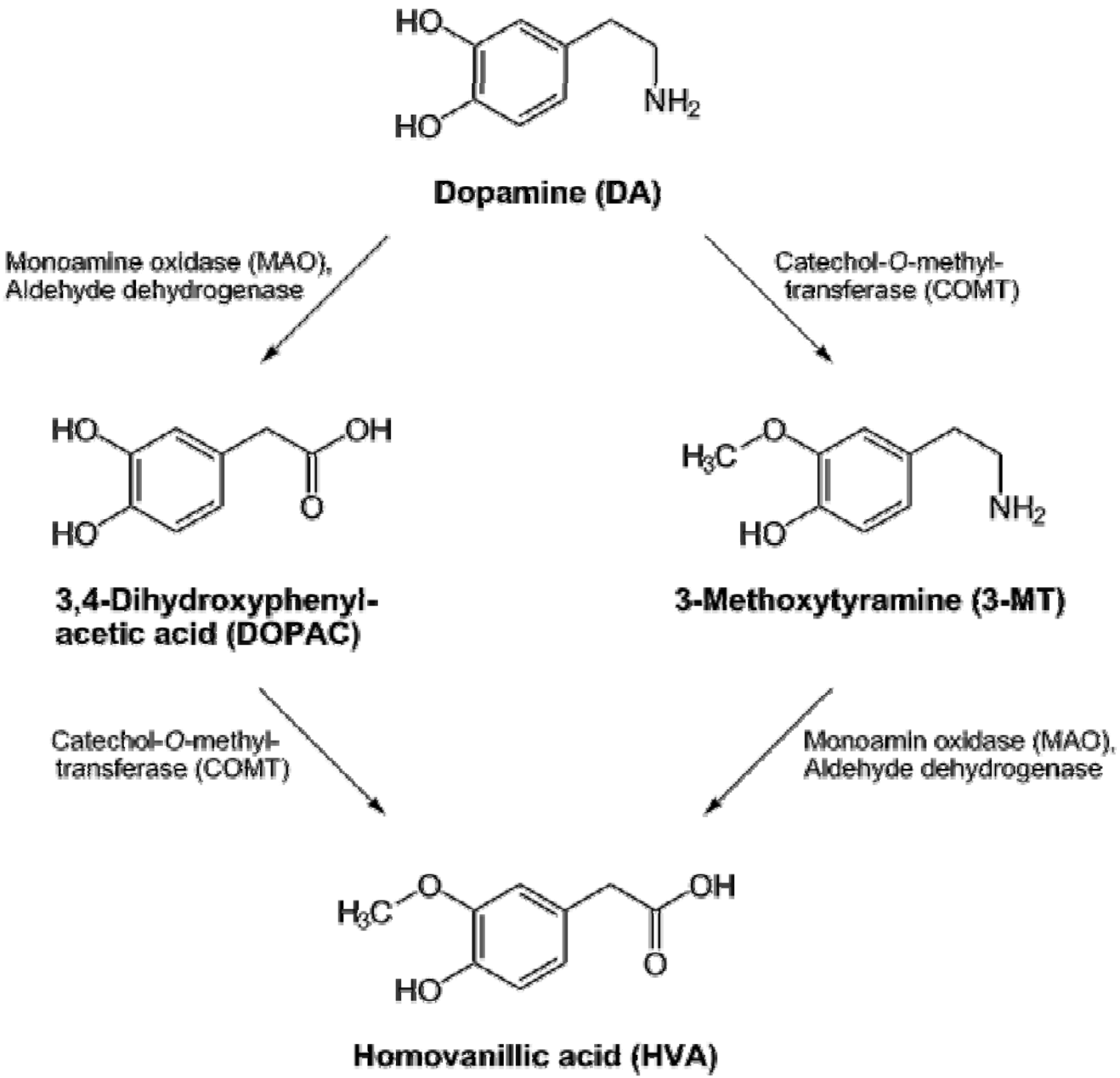

R—Br
Alkyl halides
+
HS
L-Cys
NH
Gly
L-Glu
Glutathione
Glutathione transferase
Glutathione conjugate
Peptidases
Cysteine conjugate
Acetylation
Mercapturic acid conjugate


Glutathione conjugate
Glutathione conjugate
Glutathione conjugate
Glutathione conjugate

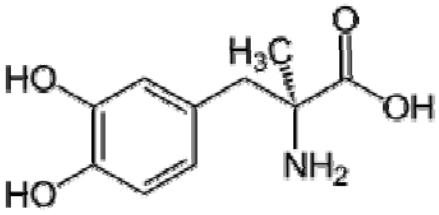
4. Methylation & acetylation: the enzyme cofactors involved in contributing the methyl group or acetyl group are ***S*-adenosyl methionine** and **acetyl SCoA** respectively.

• the most important enzyme for O-methyation is catechol O-methyltransferase (COMT) which methylates the *meta* position of catechols.



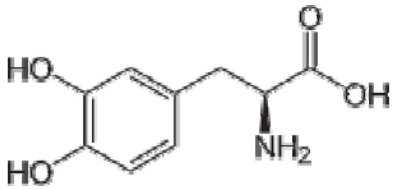

HO
HO
NH2
Dopamine (DA)
Monoamine oxidase (MAO),
Aldehyde dehydrogenase
Catechol-O-methyl-
transferase (COMT)
HO
HO
OH
O
3,4-Dihydroxyphenyl-
acetic acid (DOPAC)
H3C
O
HO
NH2
3-Methoxytyramine (3-MT)
Catechol-O-methyl-
transferase (COMT)
Monoamin oxidase (MAO),
Aldehyde dehydrogenase
H3C
O
HO
OH
O
Homovanillic acid (HVA)

- COMT is present in the central and peripheral nerves and also distributed in other mammalian tissues, particularly the liver and kidney.
- Catechol and catecholamine-like drugs are metabolized by COMT to inactive monomethylated catechol products.
- Examples of drugs that undergo significant O-methylation by COMT in humans include:
  - The antihypernensive methyldopa
  - The antiparkinsonism agent levodopa
  - Dobutamine
  - These drugs have structural similarities with the endogenous catecholamines such as norepinephrine and dopamine.



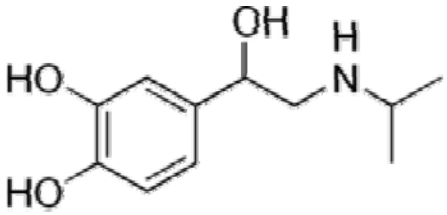
Methyldopa

Dopal®

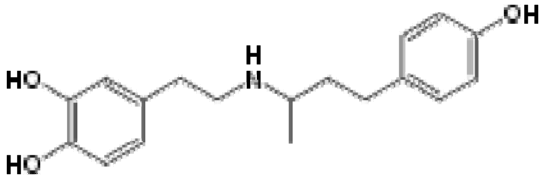


Levodeopa

Dopicar®



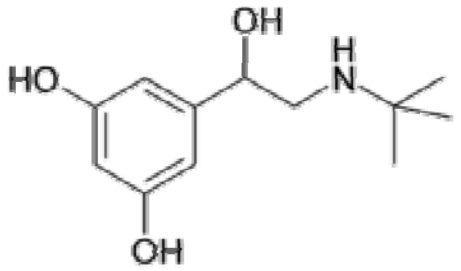
Isoproterenol (Isoprenaline)
(*non-selective beta-adrenergic agonist*)



Dobutamine

Butamine®

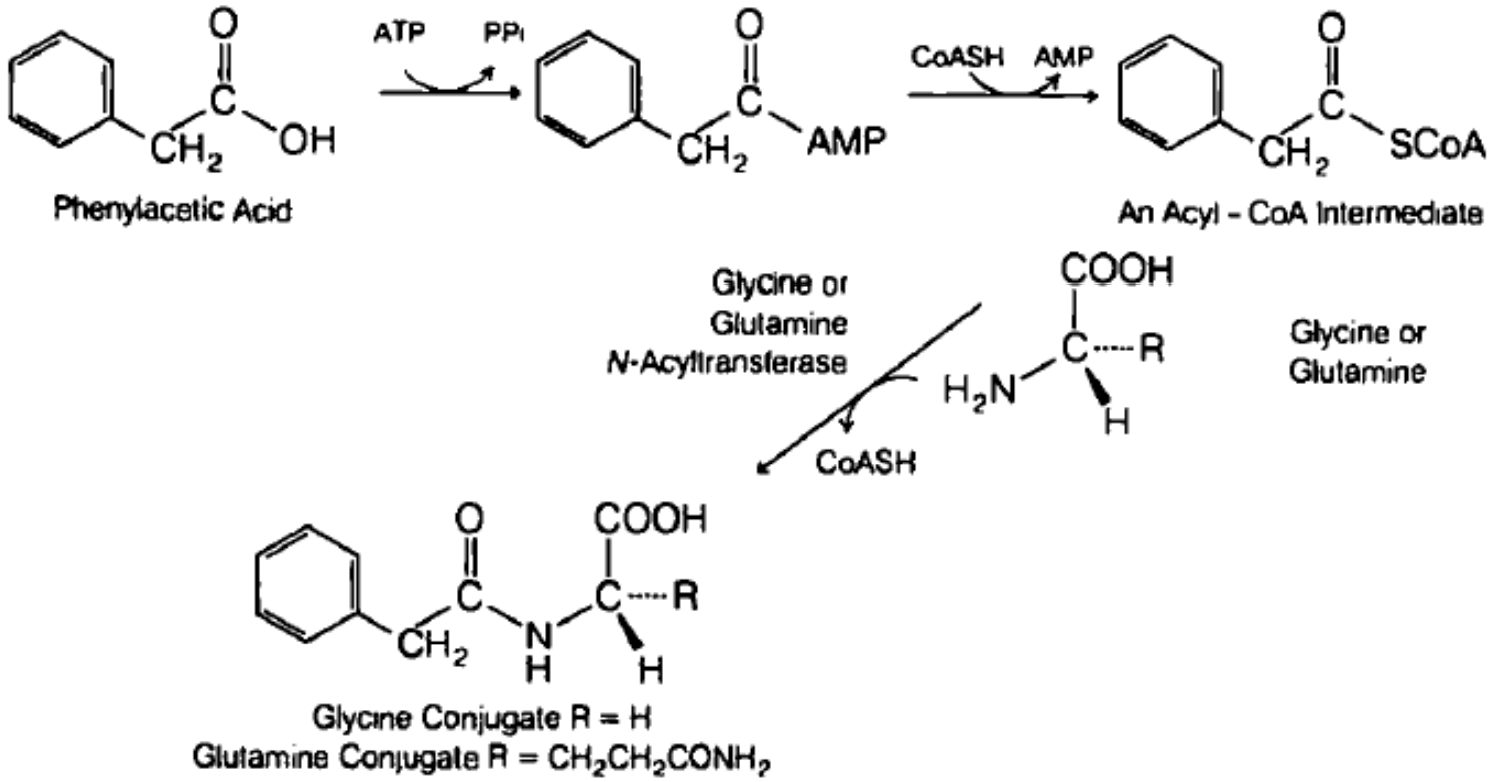
- **COMT:**
  - Selectively O-methylates only one the phenolic OH.
    - Bismethylation does not occur.
  - Substrates undergoing O-methylation by COMT must contain an aromatic 1,2-dihydroxy group (catechol group).
    - Resorcinol (I ,3-dihydroxybenzene) or *p*-hydroquinone (1,4-dihydroxybenzene) derivatives are not substrates for COMT.
    - This explains why isoproterenol undergoes extensive O-methylation but terbutaline (which contains a resorcinol moiety) does not.



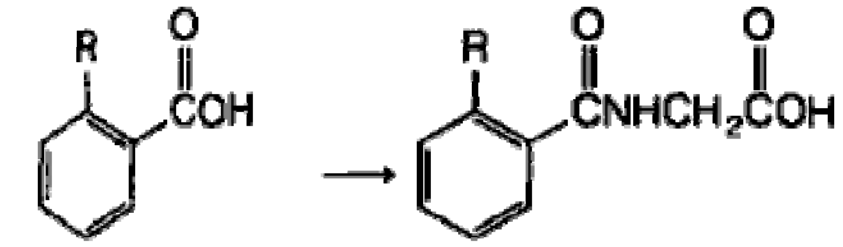
Terbutaline bricalin®

5. Conjugation with Glycine, Glutamine and other amino acids

- The amino acids glycine and glutamine:
  - Are used in the mammalian systems to conjugate carboxylic acids
  - Particularly aromatic acids and arylalkyl.
- The quantity of amino acid conjugates formed with xenobiotics is little because of:
  - The limited availability of amino acids in the body
  - And competition with glucuronidation for carboxylic acid substrates.
- Glycine and glutamine conjugation:
  - Unlike glucuronic acid and sulphate, they are not converted to activated coenzymes.
  - The carboxylic acid substrate is activated with adenosine triphosphate (ATP)
  - Then CoenzymeA (CoA) forms an acyl-CoA complex.
  - This acylates glycine or glutamine by the influence N-acyltransferase enzymes.


ATP
PPi
CoASH
AMP
Phenylacetic Acid
An Acyl - CoA Intermediate
Glycine or
Glutamine
N-Acyltransferase
CoASH
Glycine or
Glutamine
Glycine Conjugate R = H
Glutamine Conjugate R = CH2CH2CONH2

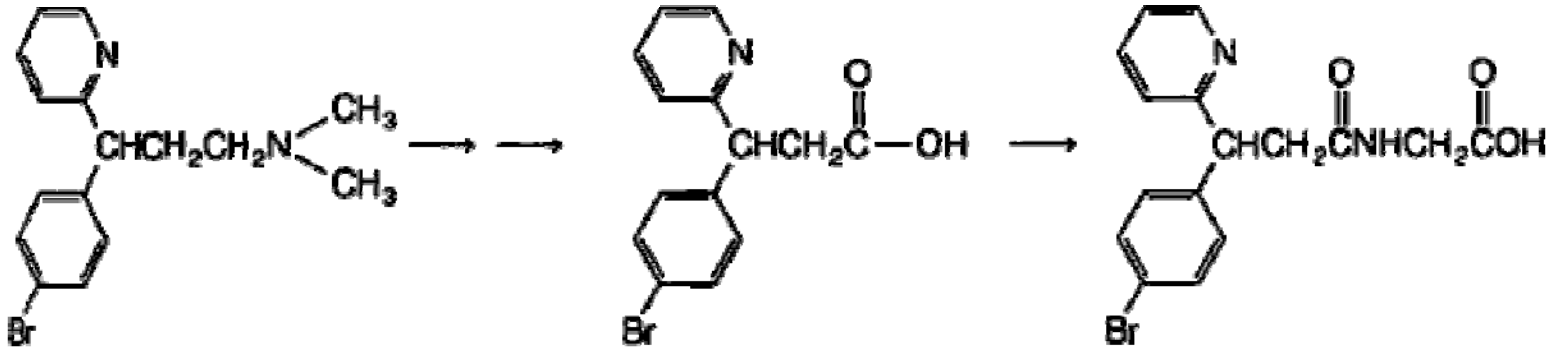
- Aromatic acids and arylalkyl acids are the major substrates undergoing glycine conjugation.
- The conversion of benzoic acid to its glycine conjugate hippuric acid, is a well-known metabolic reaction in many mammalian systems.
- The metabolism of salicylic acid (75% of dose) to salicyluric acid in humans is another example



Benzoic Acid, R = H
Salicylic Acid, R = OH

Hippuric Acid, R = H
Salicyluric Acid, R = OH

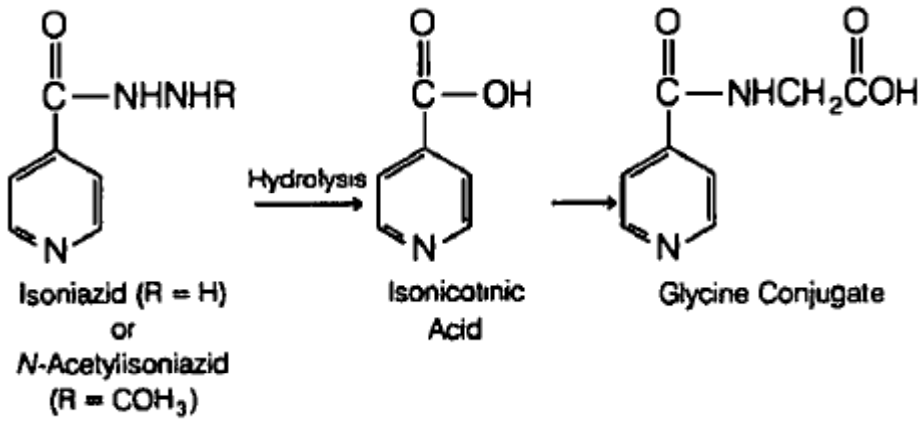
- Carboxylic acid metabolite resulting from oxidation or hydrolysis of many drugs are also susceptible to glycine conjugation.
- For example, the H1 histamine antagonist brompheniramine is oxidized to a propionic acid metabolite that is then conjugated with glycine.

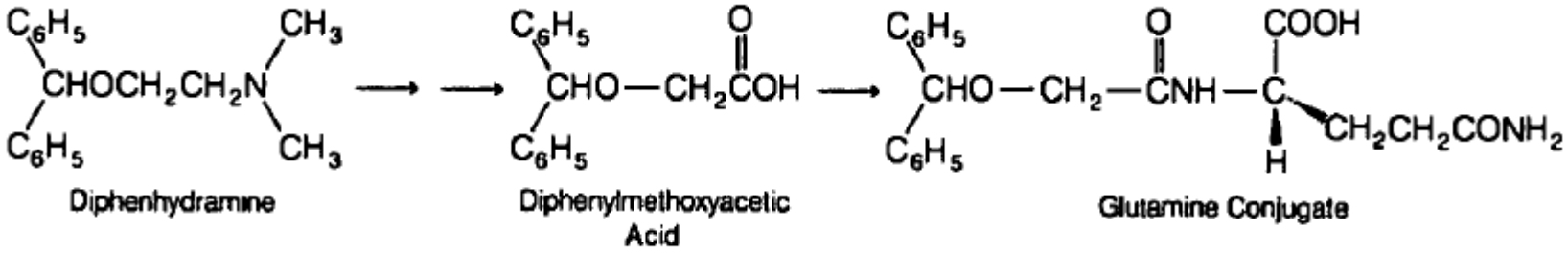


Pheneramine (Collihist) ®

Chlorpheramine (Allergon) ®

Another examples:





Hudu®

4. DRUG METABOLISM

• Individuals differ in types of CytP450 enzymes present

• Patient variability in drug metabolism complicates dose levels and leads to different susceptibilities to drugs

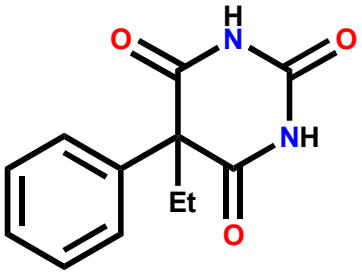
• **Pharmacogenomics** is the study of genetic variations between individuals and how these affect individual responses to drugs.

• In the future, it is possible that “fingerprints” of an individual´s genome may allow better prediction of which drugs would be suitable for individual and which drugs might produce unacceptable side effects. This known as **personalized medicine**.

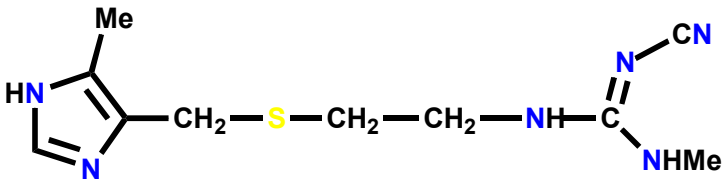
Drug-drug interactions

Some drugs affect the activity of cytochrome P450 enzymes

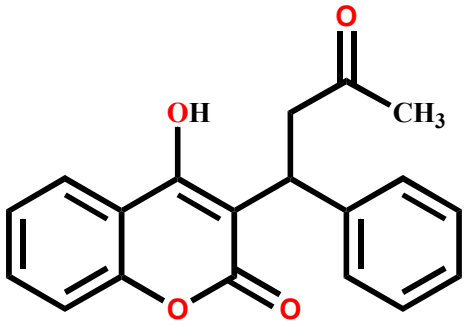
- phenobarbitone enhances activity
- cimetidine inhibits activity
- may affect metabolism of other drugs (e.g. warfarin)
- results in overdose or underdose of affected drug



Phenobarbitone



Cimetidine

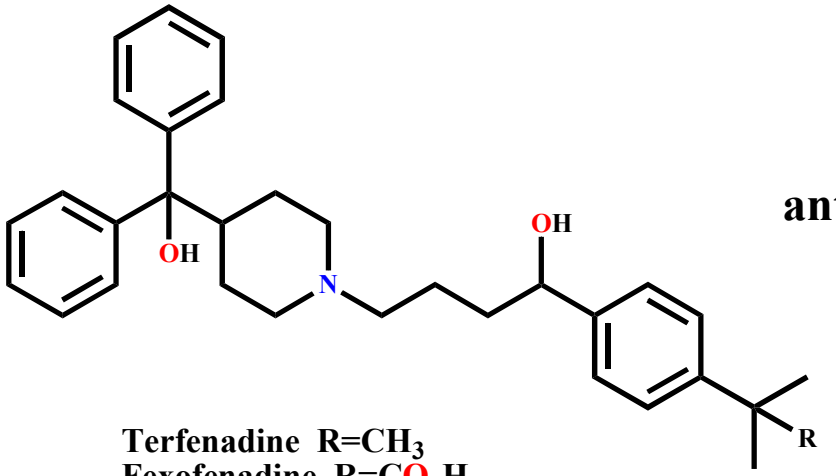


Warfarin

Drug-food interactions

Certain foods affect the activity of cytochrome P450 enzymes

- brussel sprouts & cigarette smoke enhance activity
- grapefruit juice inhibits activity



antihistamines

Terfenadine R=CH_3
Fexofenadine R=CO_2H

- Terfenadine (Seldane) - prodrug for Fexofenadine (Allegra)
- Metabolised by cytochrome P450 enzymes
- Metabolism slowed by grapefruit juice
- Build up of terfenadine leads to cardiac toxicity
- Fexofenadine favoured in therapy over terfenadine

5. DRUG EXCRETION

Routes of excretion

- **Lungs - general anaesthetics**
- **Skin (sweat)**
- **Breast milk - nicotine**
- **Bile duct - morphine**
- **Kidneys - major excretion route**