لجنة عمداء كليات الصيدلة

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Organic Pharmaceutical Chemistry I

المرحلة الثالثة

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تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي. لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتيبها وتنظيمها لتكون واضحة ويسيرة على طلبتنا الاعزاء. نأمل منكم اعزاءنا الطلبة الاستفادة منها في طريقكم الى النجاح والتفوق، والله الموفق.

Organic Pharmaceutical Chemistry I College of Pharmacy/3rd year Reference text: **Wilson and Gisvold's Textbook of Organic medicinal and pharmaceutical chemistry, John M. Beale & John H. Block; 12th edition, 2011**	
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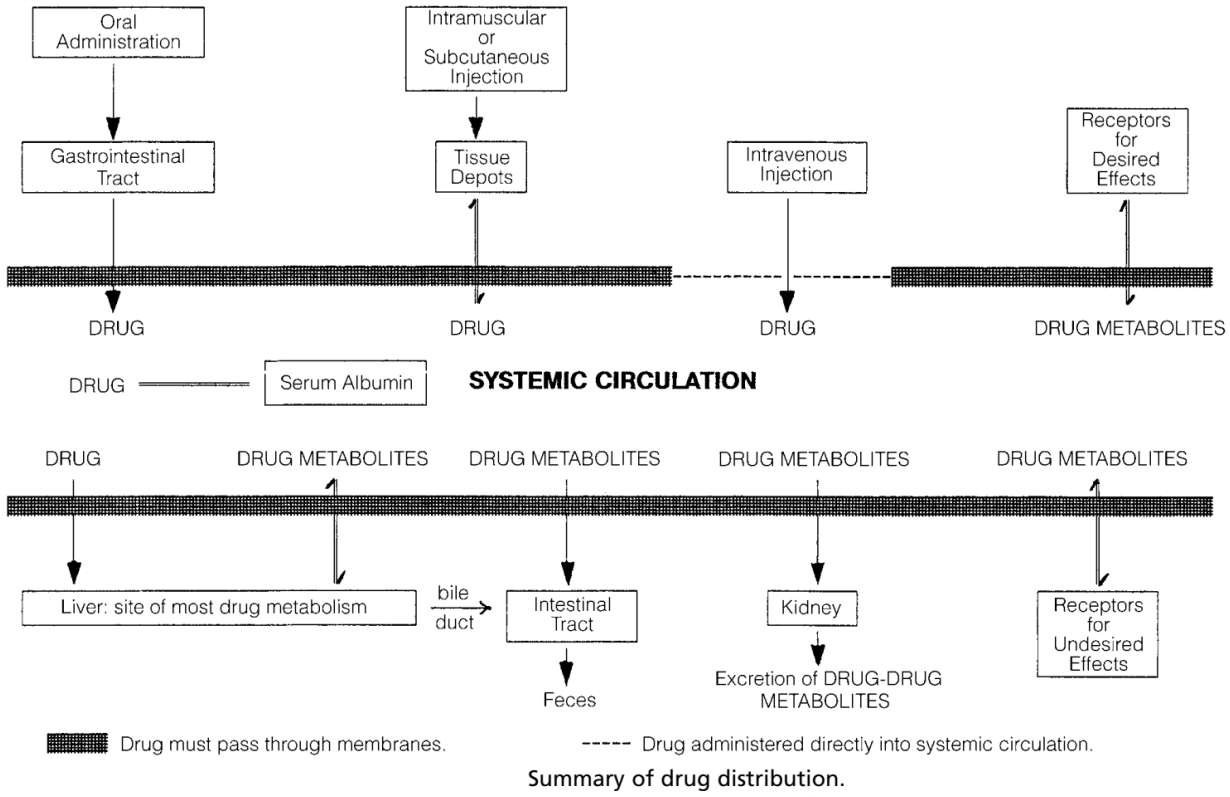
Drug Design Strategies

1. DRUG DISTRIBUTION

A drug is a chemical molecule. Following introduction into the body, a drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction before it reaches the site of action, usually a receptor on or in a cell.



Summary of drug distribution.

Distribution after Oral Administration

When the drug is administered orally, the drug must go into solution to pass through the gastrointestinal mucosa. Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract. The ability of the drug to dissolve is governed by several factors, including:

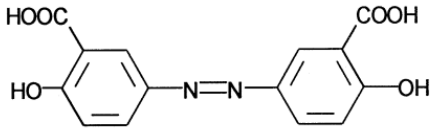
1. Its chemical structure.
2. Variation in particle size and particle surface area.
3. Nature of the crystal form.

4. Type of tablet coating.
5. Type of tablet matrix.

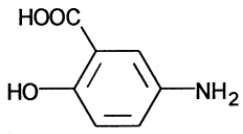
By varying the dosage form and physical characteristics of the drug, it is possible to have a drug dissolve quickly or slowly. Chemical modification is also used to a limited extent to facilitate a drug reaching its desired target.

Any compound passing through the gastrointestinal tract will encounter a large number and variety of digestive and bacterial enzymes, which, in theory, can degrade the drug molecule, therefore, a new drug molecule under investigation will likely be dropped from further consideration if it cannot survive in the intestinal tract or its oral bioavailability is low, leading to necessitating an alternate route, including parenteral, buccal, or transdermal, when there is no effective alternative for this new drug, or this new drug is more effective than existing products and can be administered by one of these alternate routes.

An example is **olsalazine**, used in the treatment of ulcerative colitis. This drug is a dimer of the pharmacologically active **mesalamine** (5-aminosalicylic acid). The latter is not effective orally because it is metabolized to inactive forms before reaching the colon. The dimeric form passes through a significant portion of the intestinal tract before being cleaved by the intestinal bacteria to two equivalents of mesalamine.

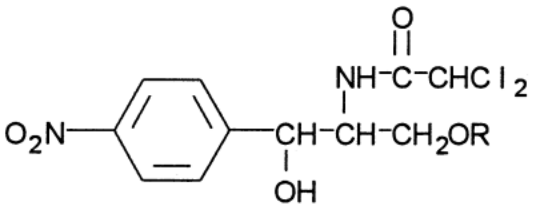


Olsalazine



Mesalamine

In contrast, these same digestive enzymes can be used to be advantageous. Example, **chloramphenicol** is water soluble enough (2.5 mg/mL) to come in contact with the taste receptors on the tongue, producing an unpalatable bitterness. To mask this intense bitter taste, the palmitic acid moiety is added as an ester of the primary hydroxyl of chloramphenicol (i.e. **chloramphenicol palmitate**). This reduces the parent drug's water solubility (1.05 mg/mL), enough so that it can be formulated as a suspension that passes over the bitter taste receptors on the tongue. Once in the intestinal tract, the ester linkage is hydrolyzed by the digestive esterases to the active antibiotic chloramphenicol and the very common dietary fatty acid palmitic acid.

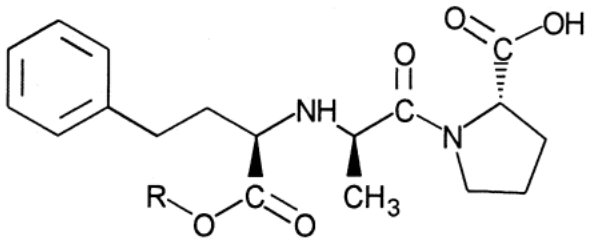


Chloramphenicol: R = H

Chloramphenicol Palmitate: R = $CO(CH_2)_{14}CH_3$

Olsalazine and chloramphenicol palmitate are examples of prodrugs. Most prodrugs are compounds that are inactive in their native form but are easily metabolized to the active agent. Olsalazine and chloramphenicol palmitate are examples of prodrugs that are cleaved to smaller compounds, one of which is the active drug.

Occasionally, the prodrug approach is used to enhance the absorption of a drug that is poorly absorbed from the gastrointestinal tract. **Enalapril** is the ethyl ester of **enalaprilic acid**, an active inhibitor of angiotensin-converting enzyme (ACE). The ester prodrug is much more readily absorbed orally than the pharmacologically active carboxylic acid.



Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

Unless the drug is intended to act locally in the gastrointestinal tract, it will have to pass through the gastrointestinal mucosal barrier into venous circulation to reach the site of the receptor. This journey involves distribution or partitioning between:

1. The aqueous environment of the gastrointestinal tract,
2. The lipid bilayer cell membrane of the mucosal cells,
3. Possibly the aqueous interior of the mucosal cells,
4. The lipid bilayer membranes on the venous side of the gastrointestinal tract,
5. The aqueous environment of venous circulation.

Parenteral Administration

Many times, there will be therapeutic advantages in bypassing the intestinal barrier by using parenteral (injectable) dosage forms. These include:

1. Patients who, because of illness, cannot tolerate or are incapable of accepting drugs orally.
2. Some drugs are so rapidly and completely metabolized to inactive products in the liver (first-pass effect) that oral administration is precluded.

This is does not mean the drug administered by injection is not opposed by some of the obstacles which can occur regardless to route of administration. These are:

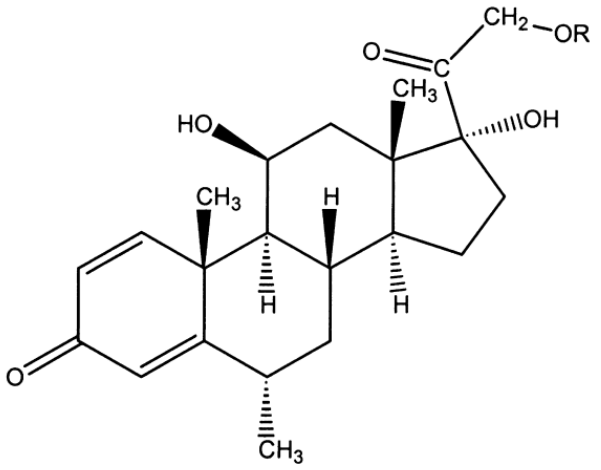
1. Intravenous administration places the drug directly into the circulatory system, where it will be rapidly distributed throughout the body, which can put the drug (in addition to the receptors) in to many unwanted places including tissue depots and the liver (where most biotransformations occur).
2. In comparison to intravenous administration, subcutaneous and intramuscular injections show slow distribution of the drug, because it must diffuse from the site of injection into systemic circulation. These parenteral routes produce a depot in the tissues from which the drug must reach the blood or lymph. Once in systemic circulation, the drug will undergo the same distributive phenomena as orally and intravenously administered agents before reaching the target receptor.
3. The blood-brain barrier, BBB, permeation: like other route of administration, parenterally administered drugs may not cross the BBB which is composed of membranes of tightly joined epithelial cells lining the cerebral capillaries which protects the brain from exposure to a large number of metabolites and chemicals. The net result is that the brain is not exposed to the same variety of compounds that other organs are. This makes it is possible to bypass the BBB by injecting the drug directly into specific organs or areas of the body. Intraspinal (ex. local anesthetics) and intracerebral routes will place the drug directly into the spinal fluid or brain, respectively.

The prodrug approach can also be used to alter the solubility characteristics, which, in turn, can increase the flexibility in formulating dosage forms.

For example, the solubility of **methylprednisolone** can be altered from one to another form as follow:

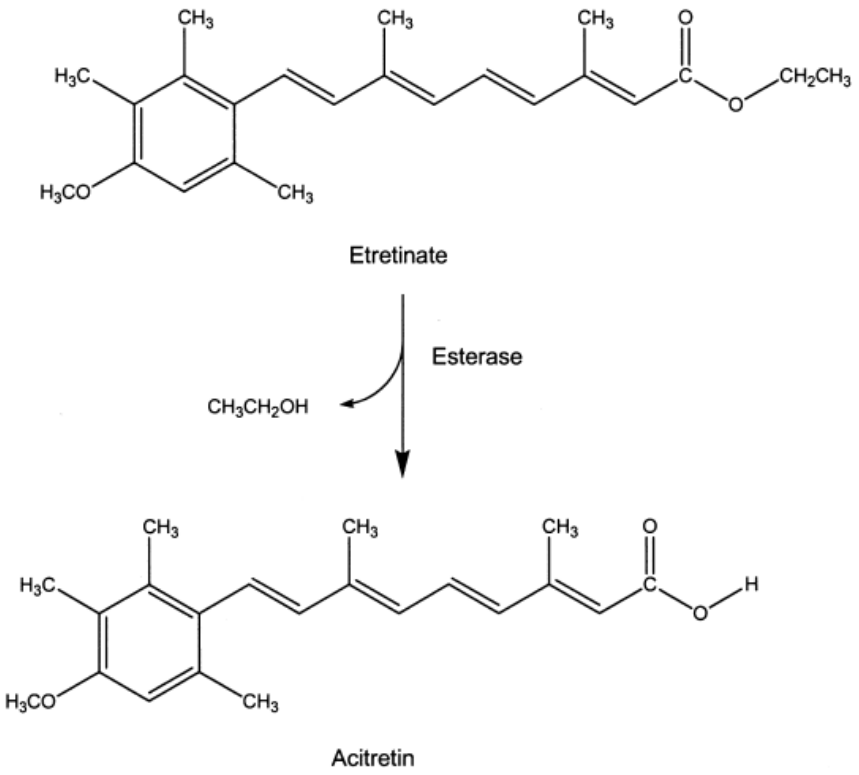
1. **Methylprednisolone:** it is slightly water-insoluble and is normally found in tablets.

2. **Methylprednisolone acetate:** it is essentially water-insoluble. This acetate ester is found in topical ointments and sterile aqueous suspensions for intramuscular injection. It is hydrolyzed to the active methylprednisolone by the patient's own systemic hydrolytic enzymes (esterases).
3. **Methylprednisolone sodium succinate:** it is water-soluble sodium salt of succinate ester. It is used in oral, intravenous, and intramuscular dosage forms. The succinate esters are hydrolyzed to the active methylprednisolone by the patient's own systemic hydrolytic enzymes (esterases).



Methylprednisolone: R = H
Methylprednisolone Acetate: R = $C(=O)CH_3$
Methylprednisolone Sodium Succinate: R = $C(=O)CH_2CH_2COO^-$ Na^+

Another example of how prodrug design can significantly alter biodistribution and biological half-life illustrated by the two drugs based on the **retinoic acid** structure used systemically to treat psoriasis, a nonmalignant hyperplasia. **Etretinate** has a 120-day terminal half-life after 6 months of therapy. In contrast, the active metabolite, **acitretin**, has a 33-96 hour terminal half-life. Both drugs are potentially teratogenic. Acitretin, with its shorter half-life, is recommended for a woman who would like to become pregnant, because it can clear from her body within a reasonable time frame.



Protein Binding

Once the drug enters the systemic circulation, it can undergo several events. It may stay in solution, but many drugs will be bound to the serum proteins, usually albumin. The drug can remain in systemic circulation bound to albumin for a considerable period and not be available to the sites of biotransformation, the pharmacological receptors, and excretion.

$$\text{Drug} + \text{Albumin} \rightleftharpoons \text{Drug-Albumin Complex}$$

Protein binding can have a profound effect on the:

1. **Drug's effective solubility.** A drug with such poor water solubility that therapeutic concentrations of the unbound (active) drug normally cannot be maintained still can be a very effective agent. The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.
2. **Drug's biodistribution.** Protein binding may also limit access to certain body compartments. The placenta is able to block passage of proteins from maternal to fetal circulation. Thus, drugs that normally would be expected to cross the placental barrier and possibly harm the fetus are retained in the maternal circulation, bound to the mother's serum proteins.

3. **Drug's half-life in the body and drug's duration of action.** The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor. The drug–protein complex is too large to pass through the renal glomerular membranes, preventing rapid excretion of the drug. Protein binding limits the amount of drug available for biotransformation and for interaction with specific receptor sites. For example, the large, polar trypanocide **suramin** remains in the body in the protein-bound form for as long as 3 months ($t_{1/2}$ = 50 days). The maintenance dose for this drug is based on weekly administration. At first, this might seem to be an advantage to the patient, but when the patient have serious adverse reactions, a significant length of time will be required before the concentration of drug falls below toxic levels.

4. **Interaction with other drugs.** The drug–protein binding phenomenon can lead to some clinically significant drug–drug interactions that result when one drug displaces another from the binding site on albumin. For example, a large number of drugs can displace the anticoagulant **warfarin** from its albumin-binding sites. This increases the effective concentration of warfarin at the receptor, leading to an increased prothrombin time (increased time for clot formation) and potential hemorrhage.

Tissue Depots

The drug can also be stored in tissue depots. Neutral fat constitutes some 20% to 50% of body weight and constitutes a depot of considerable importance. The more lipophilic the drug, the more likely it will concentrate in these pharmacologically inert depots. The ultra–short-acting, lipophilic barbiturate **thiopental's** concentration rapidly decreases below its effective concentration following administration. It disappears into tissue protein, redistributes into body fat, and then slowly diffuses back out of the tissue depots but in concentrations too low for a pharmacological response. Thus, only the initially administered thiopental is present in high enough concentrations to combine with its receptors. The remaining thiopental diffuses out of the tissue depots into systemic circulation, in concentrations too small to be effective, which then is metabolized in the liver, and is excreted.

In general, structural changes in the barbiturate series that favor partitioning into the lipid tissue stores decrease duration of action but increase central nervous system (CNS) depression. Conversely, the barbiturates with the slowest onset of action and longest duration of action contain the more polar side chains. This latter group of

barbiturates both enters and leaves the CNS more slowly than the more lipophilic thiopental.

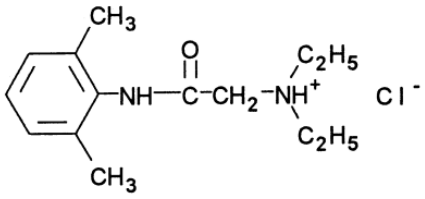
Drug Metabolism

All substances in the circulatory system, including drugs, metabolites, and nutrients, will pass through the liver.

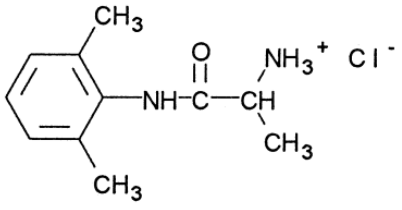
Most molecules absorbed from the gastrointestinal tract enter the portal vein and are initially transported to the liver. A significant proportion of a drug will partition or be transported into the hepatocyte, where it may be metabolized by hepatic enzymes to inactive chemicals during the initial trip through the liver, by what is known as the firstpass effect.

Lidocaine is a classic example of the significance of the first-pass effect. Over 60% of this local anesthetic antiarrhythmic agent is metabolized during its initial passage through the liver, resulting in it being impractical to administer orally. When used for cardiac arrhythmias, it is administered intravenously. This rapid metabolism of lidocaine is useful when stabilizing a patient with cardiac arrhythmias. Lidocaine should be administered intravenously in too much quantities where toxic responses will tend to decrease because of rapid biotransformation to inactive metabolites.

An understanding of the metabolic labile site on lidocaine led to the development of the primary amine analog **tocainide**. In contrast to lidocaine's half-life of less than 2 hours, tocainide's half-life is approximately 15 hours, with 40% of the drug excreted unchanged.



Lidocaine



Tocainide

A study of the metabolic fate of a drug is required for all new drug products.

Where we have different situation:

1. Active parent drug converted to inactive metabolites. Example **lidocaine**.

2. An inactive parent drug that is converted to an active metabolite ex. the nonsteroidal anti-inflammatory agent **sulindac** being reduced to the active sulfide metabolite, the immunosuppressant **azathioprine** being cleaved to the purine antimetabolite 6-mercaptopurine, and purine and pyrimidine antimetabolites and antiviral agent **acyclovir** being converted to their nucleotide form acyclovir triphosphate.
3. Often both the parent drug and its metabolite are active. Example about 75% to 80% of **phenacetin** (now withdrawn from the U.S. market) is converted to **acetaminophen**. In the tricyclic antidepressant series, **imipramine** and **amitriptyline** are N-demethylated to **desipramine** and **nortriptyline**, respectively.

Although a drug's metabolism can be a source of hindrance for the medicinal chemist, pharmacist, and physician and lead to inconvenience and compliance problems with the patient, it is fortunate that the body has the ability to metabolize foreign molecules (xenobiotics). Otherwise, many of these substances could remain in the body for years especially certain lipophilic chemical pollutants, including the once very popular insecticide dichlorodiphenyltrichloroethane (DDT). After entering the body, these chemicals reside in body tissues, slowly diffusing out of the depots and potentially harming the individual on a chronic basis for several years.

Excretion

The main route of excretion of a drug and its metabolites is

- Through the kidney.
- For some drugs, enterohepatic circulation, in which the drug reenters the intestinal tract from the liver through the bile duct and be excreted in the feces.
- Milk of nursing mothers and so they must be worried, because drugs and their metabolites can be excreted in human milk and be ingested by the nursing infant.

Several variables make dosing regimens must be more frequent:

- If the situation does not favor formation of the drug–receptor complex, higher and usually more frequent doses must be administered.
- If partitioning into tissue stores or metabolic degradation and/or excretion is favored, it will take more of the drug and usually more frequent administration to maintain therapeutic concentrations at the receptor.

The Receptors

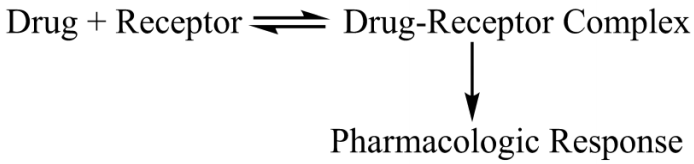
The receptor components appear to be mainly protein. The nature of the amide link in proteins provides a unique opportunity for the formation of multiple internal hydrogen bonds, as well as internal formation of hydrophobic, van der Waals, and ionic bonds by side chain groups, leading to such organized structures. An organized protein structure would hold the amino acid side chains at relatively fixed positions in space and available for specific interactions with a small molecule (ligands or drugs).

Pharmacological response consists of a drug binding to a specific receptor. Many drug receptors are the same as those used by endogenously produced ligands. Example cholinergic agents and synthetic corticosteroids interact with the same receptors as acetylcholine and cortisone bind to them.

Binding of drugs to receptors may produce desired or undesired effects. This is depending on

1. The biological distribution of these receptors. Example, the nonsteroidal anti-inflammatory drugs combine with the desired cyclooxygenase receptors at the site of the inflammation and the undesired cyclooxygenase receptors in the gastrointestinal mucosa, causing severe discomfort and sometimes ulceration.
2. Biological distribution of drugs, i.e. the organs and tissues that can be reached by the drug and contain these receptors. Unlike the first generation antihistamines, the second-generation antihistamines, like fexofenadine, are claimed to cause less sedation because it does not readily penetrate the blood-brain barrier.
3. Various receptors with similar structural requirements are found in several organs and tissues. Example, tamoxifen is an estrogen antagonist in the mammary gland and an agonist in the uterus and bone. In contrast, raloxifene does not appear to have much agonist property in the uterus but, like tamoxifen, are an antagonist in the breast and agonist in the bone.

Drug-receptor interaction is an equilibrium process, equation below. A good ability to fit the receptor favors binding and the desired pharmacological response. In contrast, a poor fit favors the reverse reaction and the amount of drug bound to the receptor is too small which leads to a much smaller pharmacological effect.



Many variables contribute to a drug's binding to the receptor. These include:

- The structural classes, since most drugs that belong to the same pharmacological class have certain structural features in common.
- The 3D shape of the molecule. Very slight changes in structure could cause significant changes in biological activity. These structural variations could increase or decrease activity or change an agonist into an antagonist.
- The types of chemical bonding involved in the binding of the drug to the receptor.

The initial receptor model was based on a rigid lock-and-key concept, with the drug (key) fitting into a receptor (lock). It has been used to explain why certain structural features produce a predictable pharmacological action.

Recent model must realize that both the drug and the receptor can have considerable flexibility. The receptor can undergo an adjustment in 3D structure when the drug makes contact, i.e. the drug docks with the receptor.

The fit of drugs onto or into macromolecules is not always an all-or-none process as pictured by the earlier lock-and-key concept of a receptor. Rather, it appears to be a continuous process, as indicated by regular increase and decrease in biological activity of a homologous series of drugs.

Drug-receptor association may produce productive changes in the configuration of the macromolecule, leading to agonist responses, an antagonistic or blocking response. Similarly, strong drug-receptor associations may lead to unproductive changes in the configuration of the macromolecule, leading to an antagonistic or blocking response.

Acid–Base Properties of Drugs

Most drugs used today can be classified as acids or bases. A drug's acid–base properties can greatly influence its biodistribution and partitioning characteristics.

In their definition, an acid is defined as a proton donor and a base is defined as a proton acceptor. Un-ionized acids, like carboxylic acids, donate their protons forming ionized conjugate bases, carboxylate. In contrast, ionized acids, like ammonium compounds, donate proton and yield un-ionized conjugate bases (amine derivatives). Similarly for un-ionized and ionized bases accept protons and yield their ionized and un-ionized conjugated acids respectively.

Acid/Conjugated Base and Base/Conjugated Acid Pairs

In biological systems, drug molecules face water everywhere and an acid-base reaction can occur. Water is an amphoteric molecule, can be either a weak base accepting a proton from acidic drugs to form the strongly acidic hydrated proton or hydronium ion (H_3O^+), or a weak acid donating a proton to a basic drug to form the strongly basic hydroxide anion (OH^-).

$$\text{Acid} + \text{Base} \rightleftharpoons \text{Conjuate Acid} + \text{Conjugate Base} \quad \text{-------- Eq.1}$$

$$\text{Acidic Drug} + \text{Water} \rightleftharpoons \text{Conjugate Base} + H_3O^+$$

$$\text{Basic Drug} + \text{Water} \rightleftharpoons \text{Conjuate Acid} + OH^-$$

Acid Strength

Two logical questions to ask at this point, these are:

- How one predicts in which direction an acid–base reaction lies? and
- To what extent the reaction goes to completion?

The common physicochemical measurement that contains this information is known as the pKa. The pKa is the negative logarithm of the modified equilibrium constant, Ka which can be calculated as follow (depending on Eq.1):

$$K_a = \frac{[\text{conj. acid}][\text{conj. base}]}{\text{acid}}$$

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

the Ka or pKa are modified equilibrium constants that indicate the extent to which the acid (proton donor) reacts with water to form conjugate acid and conjugate base. The equilibrium for a strong acid (low pKa) in water lies to the right, favoring the formation of products (conjugate acid and conjugate base). The equilibrium for a weak acid (high pKa) in water lies to the left, meaning that the conjugate acid is a better proton donor than the parent acid is or that the conjugate base is a good proton acceptor (table below).

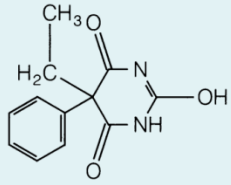
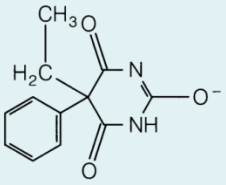
It is important to recognize that a pKa for a base (B) is in reality the pKa of the conjugate acid (acid donor or protonated form, BH^+) of the base, and the pKa for an acid (AH) is the pKa of its conjugate base (proton acceptor or deprotonated form, A^-).

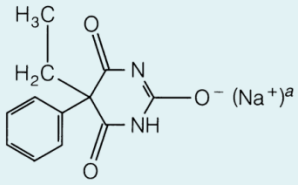
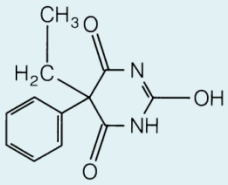
Examples of Acid–Base Reactions (with the Exception of Hydrochloric Acid, Whose Conjugate Base [Cl^-] Has No Basic Properties in Water, and Sodium Hydroxide, which Generates Hydroxide, the Reaction of the Conjugate Base in Water Is Shown for Each Acid)

Acid	+	Base	⇌	Conjugate Acid	+	Conjugate Base
Hydrochloric acid						
(a) HCl	+	H_2O	⟶	H_3O^+	+	Cl^-
Sodium hydroxide						
(b) H_2O	+	NaOH	⟶	H_2O	+	$OH^-(Na^+)^a$
Sodium dihydrogen phosphate and its conjugate base, sodium monohydrogen phosphate						
(c) $H_2PO_4^-(Na^+)^a$	+	H_2O	⇌	H_3O^+	+	$HPO_4^{2-}(Na^+)^a$
(d) H_2O	+	$HPO_4^{2-}(2Na^+)^a$	⇌	$H_2PO_4^-(Na^+)^a$	+	$OH^-(Na^+)^a$
Ammonium chloride and its conjugate base, ammonia						
(e) $NH_4^+(Cl^-)^a$	+	H_2O	⇌	$H_3O^+(Cl^-)^a$	+	NH_3
(f) H_2O	+	NH_3	⇌	NH_4^+	+	OH^-
Acetic acid and its conjugate base, sodium acetate						
(g) CH_3COOH	+	H_2O	⇌	H_3O^+	+	CH_3COO^-
(h) H_2O	+	$CH_3COO^-(Na^+)^a$	⇌	CH_3COOH	+	$OH^-(Na^+)^a$

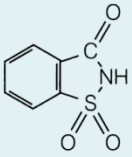
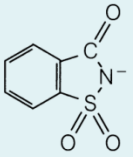
Indomethacin and its conjugate base, indomethacin sodium, show the identical acid–base chemistry as acetic acid and sodium acetate, respectively.

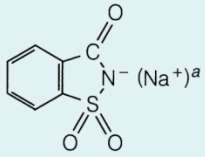
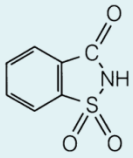
Phenobarbital and its conjugate base, phenobarbital sodium

(i)  + H_2O ⇌ H_3O^+ + 

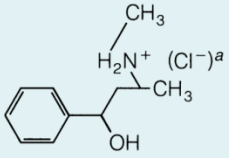
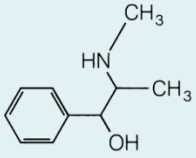
(j) H_2O +  ⇌  + $OH^-(Na^+)^a$

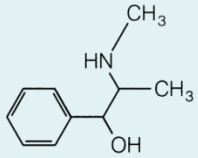
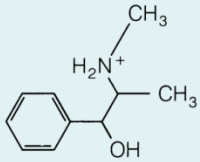
Saccharin and its conjugate base, saccharin sodium

(k)  + H_2O ⇌ H_3O^+ + 

(l) H_2O +  ⇌  + $OH^-(Na^+)^a$

Ephedrine HCl and its conjugate base, ephedrine

(m)  + H_2O ⇌ $H_3O^+(Cl^-)^a$ + 

(n) H_2O +  ⇌  + OH^-

[a]The chloride anion and sodium cation are present only to maintain charge balance. These anions play no other acid–base role.

Hydrochloric acid, a Ka of 1.26 x 10^6 means that the product of the molar concentrations of the conjugate acid, [H_3O^+], and the conjugate base, [Cl^-], is huge relative to the denominator term, [HCl]. In other words, there essentially is no unreacted HCl left in an aqueous solution of hydrochloric acid. At the other extreme is ephedrine HCl with a pKa of 9.6 or a Ka of 2.51 x 10^{10-}. Here, the denominator representing the concentration of ephedrine HCl greatly predominates over that of the products, which, in this example, is ephedrine (conjugate base) and H_3O^+ (conjugate acid). In other words, the protonated form of ephedrine is a very poor proton donor. Free ephedrine (the conjugate base in this reaction) is an excellent proton acceptor.

Representative K_a and pK_a Values

Hydrochloric acid	1.26×10^{6}	−6.1
Dihydrogen phosphate	6.31×10^{-8}	7.2
Ammonia (ammonium)	5.01×10^{-10}	9.3
Acetic acid	1.58×10^{-5}	4.8
Phenobarbital	3.16×10^{-8}	7.5
Saccharin	2.51×10^{-2}	1.6
Indomethacin	3.16×10^{-5}	4.5
Ephedrine (as the HCl salt)	2.51×10^{-10}	9.6

A general rule for determining whether a chemical is strong or weak acid or base is
- pKa < 2: strong acid; conjugate base has no meaningful basic properties in water
- pKa 4 to 6: weak acid; weak conjugate base
- pKa 8 to 10: very weak acid; conjugate base getting stronger
- pKa >12: essentially no acidic properties in water; strong conjugate base

Percent Ionization

Using the drug's pKa, we can adjust the pH to ensure maximum water solubility (ionic form of the drug) or maximum solubility in nonpolar media (un-ionic form). This is why understanding the drug's acid–base chemistry becomes important.

$$\underset{\text{Acid}}{HA_{(\text{un-ionized})}} + \underset{\text{Base}}{H_2O} \rightleftharpoons \underset{\text{Conj. Acid}}{H_3O^+} + \underset{\text{Conj. Base}}{A^-_{(\text{ionized})}}$$

$$\underset{\text{Acid}}{BH^+_{(\text{ionized})}} + \underset{\text{Base}}{H_2O} \rightleftharpoons \underset{\text{Conj. Acid}}{H_3O^+} + \underset{\text{Conj. Base}}{B_{(\text{un-ionized})}}$$

Acids can be divided into two types, HA and BH^+, on the basis of the ionic form of the acid (or conjugate base). HA acids go from un-ionized acids to ionized conjugate bases. In contrast, BH^+ acids go from ionized (polar) acids to un-ionized (nonpolar)

conjugate bases. In general, pharmaceutically important HA acids include the inorganic acids (e.g., HCl, H_2SO_4), enols (e.g., barbiturates, hydantoins), carboxylic acids, and amides and imides (e.g., sulfonamides and saccharin, respectively). The chemistry is simpler for the pharmaceutically important BH^+ acids: They are all protonated amines.

The percent ionization of a drug is calculated by using equations below:

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pK_a - pH)}}$$ for HA acids

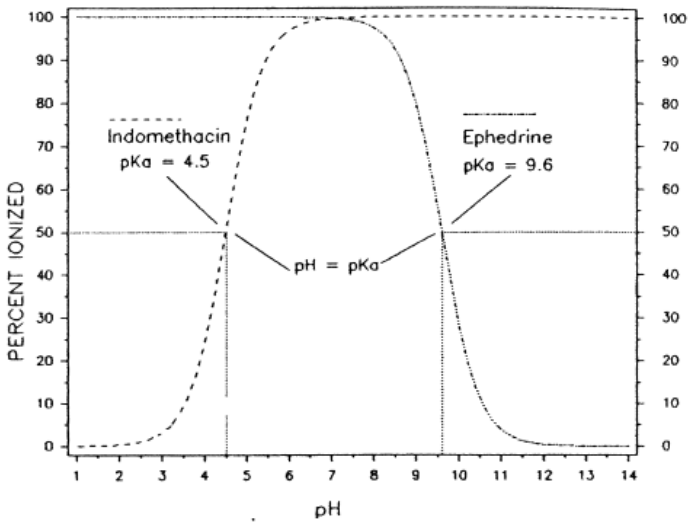
$$\% \text{ ionization} = \frac{100}{1 + 10^{(pH - pK_a)}}$$ for BH^+ acids

when pH = pKa, the compound is 50% ionized (or 50% un-ionized). In other words, when the pKa is equal to the pH, the molar concentration of the acid equals the molar concentration of its conjugate base. In the Henderson-Hasselbalch equation, pKa = pH when log [conjugate base]/[acid] = 1. An increase of 1 pH unit from the pKa (increase in alkalinity) causes an HA acid (ex. indomethacin) to become 90.9% in the ionized conjugate base form, but in a BH^+ acid (ex. ephedrine HCl) decreasing its percent ionization to only 9.1%. An increase of 2 pH units essentially shifts an HA acid to complete ionization(99%) and a BH^+ acid to the nonionic conjugate base form (0.99%).

Just the opposite is seen when the medium is made more acidic relative to the drug's pKa value. Increasing the hydrogen ion concentration (decreasing the pH) will shift the equilibrium to the left, thereby increasing the concentration of the acid and decreasing the concentration of conjugate base. Table below summarizes the relation of percent ionization and the pKa.

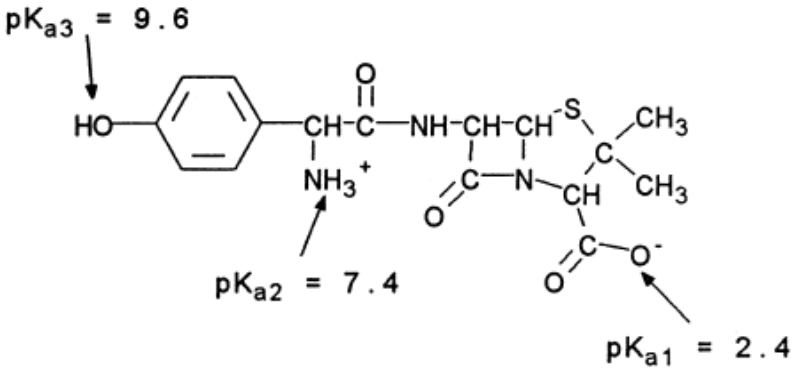
Percentage Ionization Relative to the pK_a

	Ionization (%)	
	HA Acids	BH Acids
pK_a − 2 pH units	0.99	99.0
pK_a − 1 pH unit	9.1	90.9
pK_a = pH	50.0	50.0
pK_a + 1 pH unit	90.9	9.1
pK_a + 2 pH units	99.0	0.99



Percent ionized versus pH for indomethacin (pK_a 4.5) and ephedrine (pK_a 9.6).

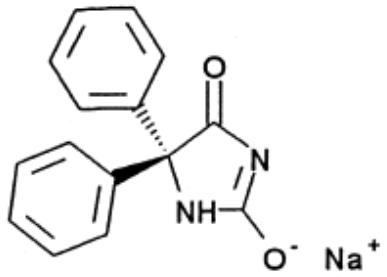
A polyfunctional drug can have several pKa's (e.g., amoxicillin). At physiological pH, the carboxylic acid (HA acid; pKa_1 2.4) will be in the ionized carboxylate form, the primary amine (BH^+ acid; pKa_2 7.4) will be 50% protonated and 50% in the free amine form, and the phenol (HA acid; pKa_3 9.6) will be in the un-ionized protonated form.



Amoxicillin

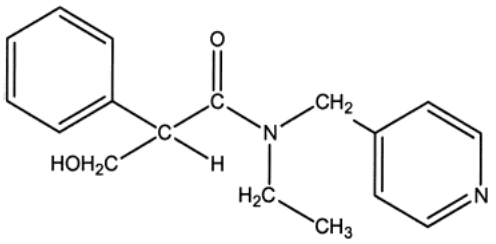
Knowledge of percent ionization makes it easier to explain and predict why the use of some preparations can cause problems and discomfort as a result of pH extremes.

Phenytoin (HA acid; pKa 8.3) injection must be adjusted to pH 12 with sodium hydroxide to ensure complete ionization and maximize water solubility. In theory, a pH of 10.3 will result in 99.0% of the drug being an anionic water-soluble conjugate base. To lower the concentration of phenytoin in the insoluble acid form even further and maintain excess alkalinity, the pH is raised to 12 to obtain 99.98% of the drug in the ionized form. This highly alkaline solution is irritating to the patient and generally cannot be administered as an admixture with other intravenous fluids that are buffered more closely at physiological pH 7.4. This decrease in pH would result in the parent unionized phenytoin precipitating out of solution.



Phenytoin Sodium

Tropicamide is an anticholinergic drug administered as eye drops for its mydriatic response during eye examinations. With a pKa of 5.2, the drug has to be buffered near pH 4 to obtain more than 90% ionization. The acidic eye drops can sting. Some ophthalmologists use local anesthetic eye drops to minimize the patient's discomfort.



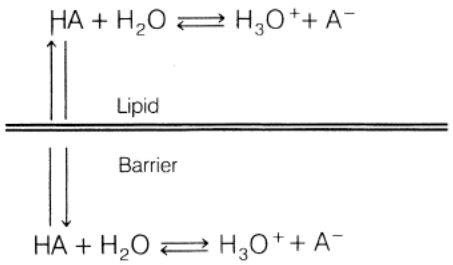
Tropicamide

The only atom with a meaningful pKa is the pyridine nitrogen. The amide nitrogen has no acid–base properties in aqueous media.

Adjustments in pH to maintain water solubility can sometimes lead to chemical stability problems. An example is indomethacin (HA acid; pKa 4.5), which is unstable in alkaline media. Therefore, the preferred oral liquid dosage form is a suspension buffered at pH 4 to 5. Because this is near the drug's pKa, only 50% will be in the water-soluble form. There is a medical indication requiring intravenous administration of indomethacin to premature infants. The intravenous dosage form is the sodium salt, which is reconstituted just prior to use.

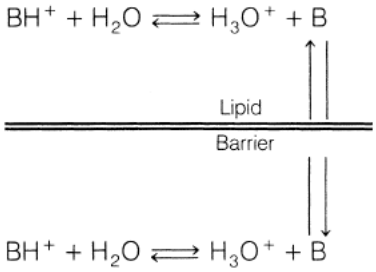
Drug Distribution and pKa

The pKa can have a pronounced effect on the pharmacokinetics of the drug. Drugs are transported in the aqueous environment of the blood. Those drugs in an ionized form will tend to distribute throughout the body more rapidly than will un-ionized (nonpolar) molecules. then, the drug must leave the polar environment of the plasma to reach the site of action by passing through the nonpolar membranes of capillary walls, cell membranes, and the blood-brain barrier in the un-ionized (nonpolar) form. For HA acids, it is the parent acid that will readily cross these membranes.



Passage of HA acids through lipid barriers

The situation is just the opposite for the BH^+ acids. The unionized conjugate base (B, free amine) is the species most readily crossing the nonpolar membranes.



Passage of BH^+ acids through lipid barriers.

For drug molecules orally administered. The drug first encounters the acidic stomach, where the pH can range from 2 to 6 depending on the presence of food. HA acids with pKa's of 4 to 5 will tend to be nonionic and be absorbed partially through the gastric mucosa. (The main reason most acidic drugs are absorbed from the intestinal tract rather than the stomach is that the microvilli of the intestinal mucosa provide a large surface area relative to that found in the gastric mucosa of the stomach.) In contrast, amines (pKa 9–10) will be protonated (BH^+ acids) in the acidic stomach and usually will not be absorbed until reaching the mildly alkaline intestinal tract (pH 8).

Once in systemic circulation, the plasma pH of 7.4 will be one of the determinants of whether the drug will tend to remain in the aqueous environment of the blood or partition across lipid membranes into hepatic tissue to be metabolized, into the kidney for excretion, into tissue depots, or to the receptor tissue.

Of course, the effect of protein binding, discussed previously, can greatly alter any prediction of biodistribution based solely on pKa.

COMPUTER AIDED DRUG DESGIN CADD

A. Early Methods

Drug design is the process of finding new medicines for treating diseases. There are two main approaches to drug design:

1. The first one is based on modifying existing molecules, usually from natural sources, to make them more effective or less toxic. This approach has produced many important drugs, such as antibiotics, hormones, and painkillers.

2. The second one is based on understanding the cause of the disease and the structure of the target where the drug will bind. This approach uses computer tools to predict the biological activity and the best fit of potential drugs. This approach is called quantitative structure–activity relationships (QSAR).

   QSAR plays a crucial role in drug design and discovery by establishing mathematical relationships between the chemical structure of compounds (through certain structural parameters) and their biological activities. The main QSAR parameters include:

   1. **Molecular Weight:** Influences pharmacokinetic properties, such as absorption, distribution, metabolism, and excretion (ADME).
   2. **Partition Coefficient:** Partitioning between octanol and water. It reflects the compound's hydrophobicity and membrane permeability.
   3. **Number of Hydrogen Bond Donor/Acceptor:** Indicates the potential for forming hydrogen bonds. It influences the molecule's ability to form specific interactions with biomolecules (ex. Receptors).
   4. **Polar Surface Area:** The surface area of a molecule that is polar and capable of forming hydrogen bonds. It affects interactions with biological targets and influences the compound's permeability

   Some pharmacological concepts (biological activities parameters) that are useful for drug design are:

   - The **ED50**, which is the dose of the drug that produces the desired effect in half of the subjects. The lower the ED50, the more potent the drug is.
   - The **ED90**, which is the dose of the drug that produces the desired effect in 90% of the subjects.
   - The **LD50**, which is the dose of the drug that kills half of the subjects. The lower the LD50, the more toxic the drug is.

- The **MIC**, which is the lowest concentration of the drug that inhibits the growth of bacteria. The lower the MIC, the more effective the drug is against infections.

Partition Coefficient

The most common physicochemical descriptor is the molecule's partition coefficient in an octanol/water system. As emphasized previously, the drug will go through a series of partitioning steps: (a) leaving the aqueous extracellular fluids, (b) passing through lipid membranes, and (c) entering other aqueous environments before reaching the receptor.

In this sense, a drug is undergoing the same partitioning phenomenon that happens to any chemical in a separatory funnel containing water and a nonpolar solvent such as hexane, chloroform, or ether. The **partition coefficient (P)** is the ratio of the molar concentration of chemical in the nonaqueous phase (usually 1-octanol) versus that in the aqueous phase (Equation below).

$$P = \frac{[\text{chemical}]_{oct}}{[\text{chemical}]_{aq}}$$

To obtain a linear correlation between partition coefficient and concentrations, it is more common to use the logarithmic expression (Equation below).

$$\log P = \log\left(\frac{[\text{solute}]_{oct}}{[\text{solute}]_{aq}}\right)$$

A large percentage of drugs are amines whose pKa is such that at physiological pH 7.4, a significant percentage of the drug will be in its protonated, ionized form (BH^+). A similar statement can be made for the HA acids (carboxyl, sulfonamide, imide) in that at physiological pH, a significant percentage will be in their anionic forms(A^-). An assumption is made that the ionic form is water-soluble and will remain in the water phase of an octanol/water system. This reality has led to the use of **log D**, which is defined as the equilibrium ratio of both the ionized and un-ionized species of the molecule in an octanol/water system (Equation below). The percent ionization of ionized HA acids and BH protonated amines and acids can be estimated from previous equations and the log D become as follow:

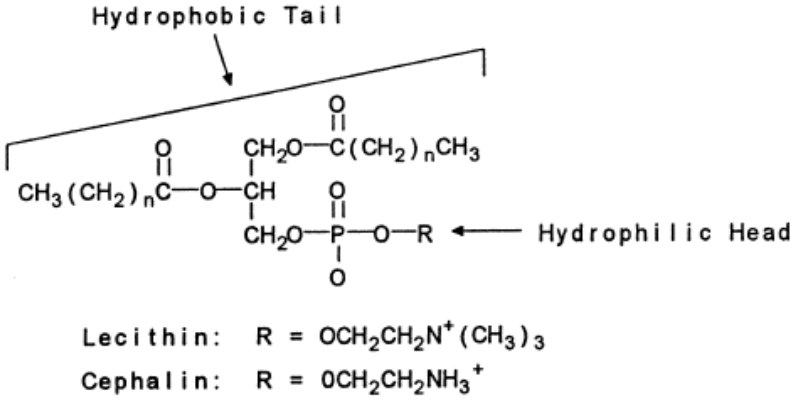
$$\log D = \log\left(\frac{[\text{solute}]_{oct}}{[\text{solute}]_{aq}^{ionized} + [\text{solute}]_{aq}^{nonionized}}\right)$$

$$\log D_{acids} = \log P + \log\left[\frac{1}{(1 + 10^{(pH - pK_a)})}\right]$$

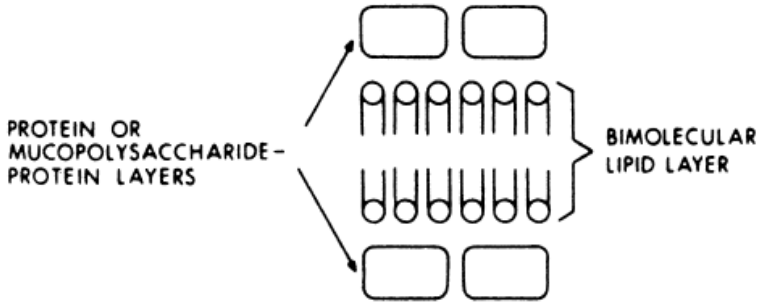
$$\log D_{bases} = \log P + \log\left[\frac{1}{(1 + 10^{(pK_a - pH)})}\right]$$

Because much of the time the drug's movement across membranes is a partitioning process, the partition coefficient has become the most common physicochemical property. The question that now must be asked is what immiscible nonpolar solvent system best mimics the water/lipid membrane barriers found in the body? It is now realized that the **n-octanol/water** system is an excellent estimator of drug partitioning in biological systems.

To appreciate why this is so, one must understand the chemical nature of the lipid membranes. These membranes are not exclusively anhydrous fatty or oily structures. As a first approximation, they can be considered bilayers composed of lipids consisting of a polar cap and large hydrophobic tail. **Phosphoglycerides** are major components of lipid bilayers (Fig. below). Other groups of bifunctional lipids include the **sphingomyelins**, **galactocerebrosides**, and **plasmalogens**. The hydrophobic portion is composed largely of unsaturated fatty acids, mostly with *cis* double bonds. In addition, there are considerable amounts of cholesterol esters, protein, and charged mucopolysaccharides in the lipid membranes. The final result is that these membranes are highly organized structures composed of channels for transport of important molecules such as metabolites, chemical regulators (hormones), amino acids, glucose, and fatty acids into the cell and removal of waste products and biochemically produced products out of the cell. The cellular membranes are dynamic, with the channels forming and disappearing depending on the cell's and body's needs (Fig. below).



General structure of a bifunctional phospholipid



Schematic representation of the cell membrane

For this cell membrane, the two outer layers, one facing the interior and the other facing the exterior of the cell, consist of the polar ends of the bifunctional lipids. These surfaces are exposed to an aqueous polar environment. The polar ends of the charged phospholipids and other bifunctional lipids are solvated by the water molecules. There are also considerable amounts of charged proteins and mucopolysaccharides present on the surface. In contrast, the interior of the membrane is populated by the hydrophobic aliphatic chains from the fatty acid esters.

A partial explanation can be presented as to why the n-octanol/water partitioning system seems to mimic the lipid membranes/water systems found in the body. Water-saturated octanol contains 2.3 M water because the small water molecules easily cluster around octanol's hydroxy moiety. The water in the n-octanol phase apparently approximates the polar properties of the lipid bilayer, whereas the lack of octanol in the water phase mimics the physiological aqueous compartments, which are relatively free of nonpolar components.

In contrast, partitioning systems such as hexane/water and chloroform/water contain so little water in the organic phase that they are poor models for the lipid bilayer/water

system found in the body. At the same time, remember that the n-octanol/water system is only an approximation of the actual environment found in the interface between the cellular membranes and the extracellular/intracellular fluids.

B. Newer Methods

Computational chemistry methods in drug design involve the application of computational techniques and softwares to model and analyze the chemical interactions between drugs and their biological targets. These methods are used to:

1. **Generating pharmacophores:** A pharmacophore is a theoretical framework that represents the essential structural and chemical features necessary for a molecule to interact with a specific biological target and exhibit a particular biological activity. These features include hydrogen bond donors/acceptors, hydrophobic regions, aromatic moieties, and the relative spatial arrangement.
2. **Virtual High Throughput Screening (vHTS):** is a computational approach used in drug discovery to rapidly assess large databases of chemical compounds in silico (using computer simulations), rather than through traditional experimental methods, to identify potential lead compounds with desired biological activity.
3. **Lead Compound Optimization:** A lead compound is an actual chemical entity identified during the early stages of drug discovery that exhibits promising biological activity against a specific target. The lead compound serves as a starting point for further optimization and development into a potential therapeutic agent. Lead compounds are selected based on their ability to interact with a target and their potential for further modification to enhance properties like potency, selectivity, and pharmacokinetics.
4. **In Silico ADME Modeling:** Predicts the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of drugs using computational methods.

Forces Involved in Drug–Receptor Interactions

Keep in mind that it is desirable for most drug to have reversible effects. Therefore, most useful drugs are held to their receptors by ionic or weaker bonds. When relatively long-lasting or irreversible effects are desired (e.g., antibacterial, anticancer), drugs that form covalent bonds with the receptor are effective and useful.

When relatively long-lasting or irreversible effects are desired (e.g., antibacterial, anticancer), drugs that form covalent bonds with the receptor are effective and useful. These compounds carry reactive groups capable of forming covalent bonds and may be irreversibly bound to the receptor by covalent bond formation with reactive groups adjacent to the active site. The diuretic drug ethacrynic acid is an α,β-unsaturated

ketone, thought to act by covalent bond formation with sulfhydryl groups of ion transport systems in the renal tubules. Other examples involve the acylation of bacterial cell wall constituents by penicillin, and the phosphorylation of the serine hydroxyl moiety at the active site of cholinesterase by organic phosphates.

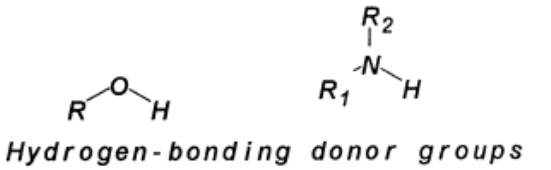
Therefore, relatively weak forces must be involved in the drug–receptor complex yet be strong enough that other binding sites will not competitively deplete the site of action. Compounds with high structural specificity may orient several weakly binding groups so that the summation of their interactions with specifically oriented complementary groups on the receptor provides total bond strength sufficient for a stable combination. Consequently, most drugs acting by virtue of their structural specificity will bind to the receptor site by:

1. Hydrogen bonds,
2. Ionic bonds,
3. Ion–dipole and dipole–dipole interactions.
4. van der Waals and
5. hydrophobic forces.

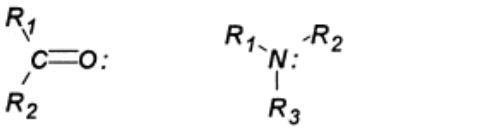
Considering the wide variety of functional groups found on a drug molecule and receptor, there will be a variety of secondary bonding forces. **Ionization** at physiological pH would normally occur with the **carboxyl**, **sulfonamido**, and **aliphatic amino** groups, as well as the **quaternary ammonium** group at any pH. These sources of potential ionic bonds are frequently found in active drugs.

Differences in electro-negativity between carbon and other atoms, such as oxygenand nitrogen, lead to an asymmetric distribution of electrons (dipoles) that are alsocapable of forming weak bonds with regions of high or low electron density, such asions or other dipoles (dipole-dipole or ion-dipole). **Carbonyl**, **ester**, **amide**, **ether**, **nitrile**, and related groups that contain such dipolar functions, are frequently found instructurally specific drugs.

Many drugs possess groups such as carbonyl, hydroxyl, amino, and imino, with the structural capabilities of acting as acceptors or donors in the formation of **hydrogen bonds**. However, in a drug–receptor combination, several forces could be involved, including the hydrogen bond, which would contribute to the stability of the interaction.



Hydrogen-bonding donor groups



Hydrogen-bonding acceptor groups

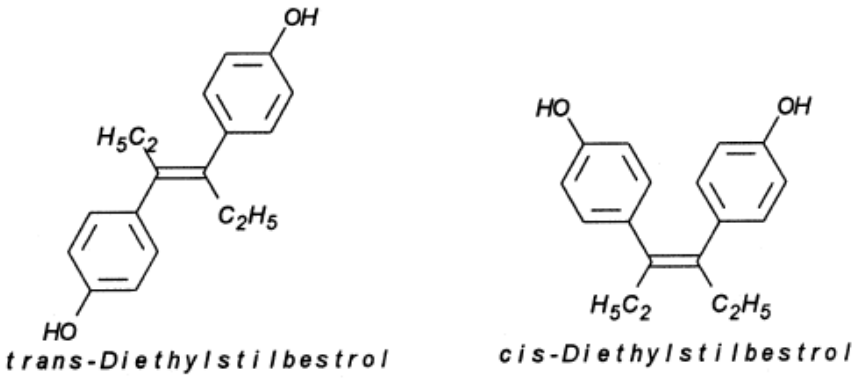
Van der Waals forces are attractive forces created by the polarizability of molecules and exerted when any two uncharged atoms approach each other very closely. Although individually weak, the summation of their forces provides a significant bonding factor in higher molecular-weight compounds.

The hydrophobic bond is a concept used to explain attractive interactions between nonpolar regions of the receptor and the drug. Examples such as the isopropyl moiety of the drug fits into a hydrophobic cleft on the receptor composed of the hydrocarbon side chains of the amino acids valine, isoleucine, and leucine are commonly used to explain why a nonpolar substituent at a particular position on the drug molecule is important for activity.

Steric Features of Drugs

To produce its effects, the drug must approach the receptor and fit closely to its surface. Steric factors determined by the stereochemistry of the receptor site surface and that of the drug molecules are, therefore, of primary importance in determining the nature and theefficiency of the drug–receptor interaction.

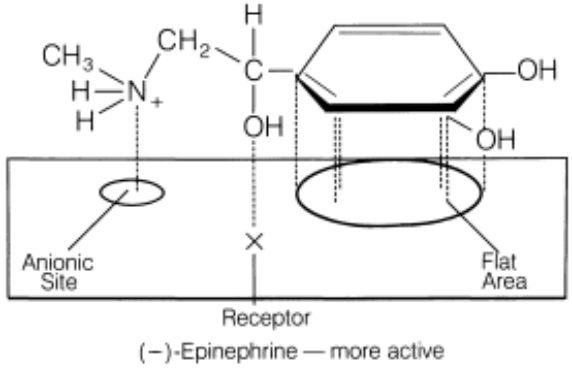
Some structural features contribute a high structural rigidity to the molecule. Example groups attached to aromatic ring will be restricted to the plane of this ring. Also the relative positions of atoms attached directly to multiple bonds are also fixed. For the double bond, *cis*- and *trans*-isomers result. For example, **diethylstilbestrol** exists in two fixed stereoisomeric forms: *trans*-diethylstilbestrol is estrogenic, whereas the *cis*-isomer is only 7% as active.



Geometric isomers (cis-trans isomerism or E-Z isomerism) of drugs not only differ in capabilities for interacting with a biological receptor, but also in their distribution, metabolism and excretion of the molecules because of the related changes in pKa values and rate of lipid solubility characteristics.

Like geometric isomers, conformational isomers (anti, eclipsed, and gauche) exist due to rotation the atoms or groups of atoms around a single bond. This rotation about bonds allows interconversion of conformational isomers. Differences in reactivity of functional groups or interaction with biological receptors may be caused by differences in steric requirements of the receptors. In certain semirigid ring systems, conformational isomers show significant differences in biological activities.

A postulated fit to epinephrine's receptor can explain why (-)-epinephrine exhibits 12 to 15 times more vasoconstrictor activity than (+)-epinephrine. This is the classical three-point attachment model. For epinephrine, the benzene ring, benzylic hydroxyl, and protonated amine must have the stereochemistry seen with the (-) isomer to match up with the hydrophobic or aromatic region, anionic site, and a hydrogen-bonding center on the receptor. The (+) isomer (the mirror image) will not align properly on the receptor.



(−)-Epinephrine — more active

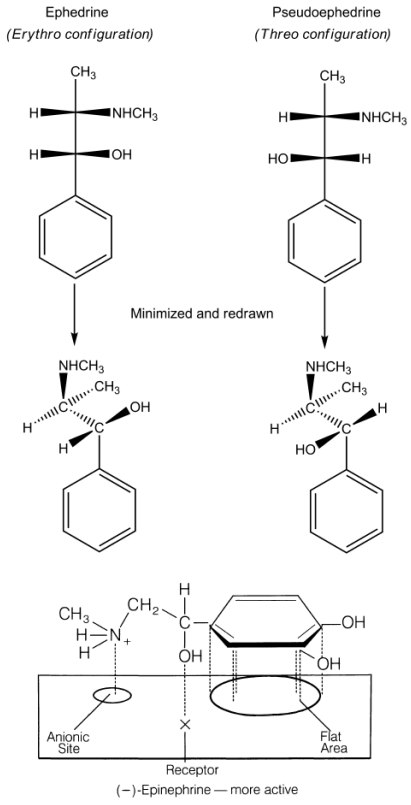
Conformational Flexibility and Multiple Modes of Action

It has been proposed that the conformational flexibility of most open-chain neurohormones, such as acetylcholine, epinephrine, serotonin, histamine, and related physiologically active biomolecules, permits multiple biological effects to be produced by each molecule, by virtue of their ability to interact in a different and unique conformation with different biological receptors. Thus, it has been suggested that acetylcholine may interact with the muscarinic receptor of postganglionic parasympathetic nerves and with acetylcholinesterase in the fully extended conformation and, in a different, more folded structure, with the nicotinic receptors at ganglia and at neuromuscular junctions.

Optical Isomerism and Biological Activity

The *optical activities* has been of particular importance in drug–receptor interactions. Most commercial drugs are asymmetric, meaning that they cannot be divided into symmetrical halves (i.e. optically active).

A large number of drugs are *diastereomeric*, meaning that they have two or more asymmetric centers. Diastereomers have different physical properties. Examples are the diastereomers **ephedrine** and **pseudoephedrine**. The former has a melting point of 79° and is soluble in water, whereas pseudoephedrine's melting point is 118°, and it is only sparingly soluble in water.

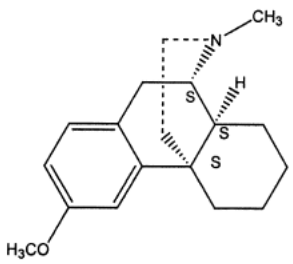


Optical isomers will also have different biological properties. Well known examples of this phenomenon include (-)-hyoscyamine, which exhibits 15 to 20 times more mydriatic activity than (+)-hyoscyamine, and (-)-ephedrine, which shows three times more pressor activity than (+)-ephedrine, five times more pressor activity than (+)-pseudoephedrine, and 36 times more pressor activity than (-)-pseudoephedrine.
All of ascorbic acid's antiscorbutic properties reside in the (-) isomer. A postulated fit to epinephrine's receptor can explain why (-)-epinephrine exhibits 12 to 15 times more vasoconstrictor activity than (+)-epinephrine.
Frequently, the generic name indicates a specific stereoisomer. Examples include levodopa, dextroamphetamine, dextromethorphan, levamisole, dexmethylphenidate, levobupivacaine, dexlansoprazole, and levothyroxine.
Sometimes, the difference in pharmacological activity between stereoisomers is dramatic. The dextrorotatory isomers in the morphine series are cough suppressants with less risk of substance abuse, whereas the levorotatory isomers contain the analgesic activity and significant risk of substance abuse. Dextropropoxyphene contains the analgesic activity, and the *levo*-isomer contains antitussive activity.
More recently drugs originally marketed as racemic mixtures are reintroduced using the active isomer. Examples include racemic citalopram and its S-enantiomer escitalopram; racemic omeprazole and its S-enantiomer esomeprazole.

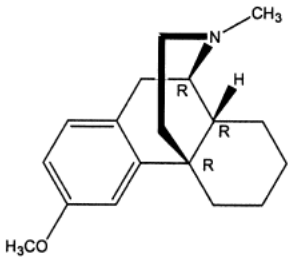
Some drugs were originally approved as racemic mixtures, and later a specific isomer was marketed with claims of having fewer adverse reactions in patients. An example of the latter is the local anesthetic **levobupivacaine**, which is the *S*-isomer of bupivacaine. Both the *R*- and *S*-isomers have good local anesthetic activity, but the *R*-isomer may cause depression of the myocardium leading to decreased cardiac output, heart block hypotension, bradycardia, and ventricular arrhythmias. In contrast, the *S*-isomer shows less cardiotoxic responses but still with good local anesthetic activity.

Escitalopram is the *S*-isomer of the antidepressant citalopram. There is some evidence that the *R*-isomer, which contains little of the desired selective serotonin reuptake inhibition, contributes more to the adverse reactions than does the *S*-isomer.

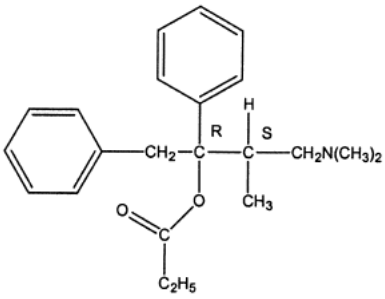
Sometimes it may not be cost-effective to resolve the drug into its stereoisomers. An example is the calcium channel antagonist **verapamil**, which illustrates why it is difficult to conclude that one isomer is superior to the other. *S-v*erapamil is a more active pharmacological stereoisomer than *R*-verapamil, but the former is more rapidly metabolized by the first-pass effect.



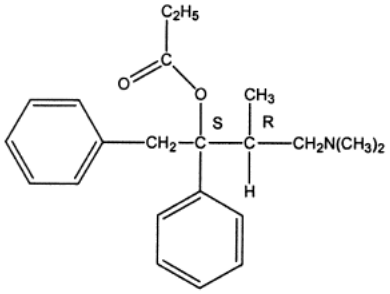
Dextromethorphan



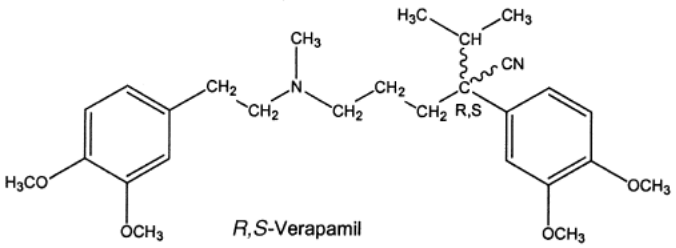
Levomethorphan



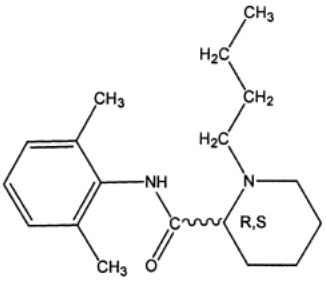
Levopropoxyphene



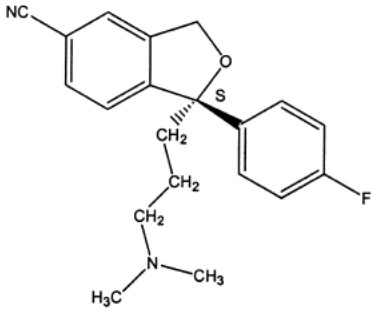
Dextropropoxyphene



R,S-Verapamil

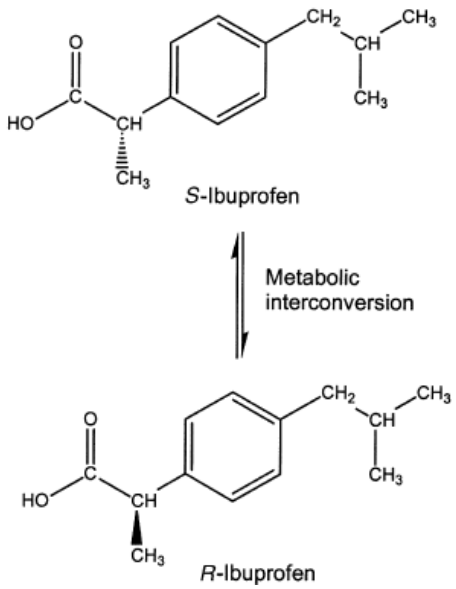


R,S-Bupivacaine



Escitalopram

Because of biotransformations after the drug is administered, it sometimes makes little difference whether a racemic mixture or one isomer is administered. The popular nonsteroidal anti-inflammatory drug (NSAID) **ibuprofen** is sold as the racemic mixture. The S-enantiomer contains the anti-inflammatory activity by inhibiting cyclooxygenase. The *R*-isomer does have centrally acting analgesic activity, but it is converted to the *S* form in vivo.



There are many reasons why stereoisomers show different biological responses, these includes:

1. Most receptors are asymmetric, that could accept one stereoisomer of drug rather than the other.
2. Active transport mechanisms involve asymmetric carrier molecules, which means that there will be preferential binding of one stereoisomer over others.
3. When differences in physical properties exist, the distribution of isomers between body fluids and tissues where the receptors are located will differ.
4. The enzymes responsible for drug metabolism are asymmetric, which means that biological half-lives will differ among possible stereoisomers of the same molecule. This is may be a very important variable because the metabolite may actually be the active molecule.

Chemical databases can contain hundreds of thousands of molecules that could be suitable ligands for a receptor. It is no matter how good the fit is to the receptor, the candidate molecule is of no use if the absorption is poor or if the drug is excreted too slowly from the body. Analysis of drugs has led to a set of "rules" called the *Lipinski Rule of Five* which states that a candidate molecule is more likely to have poor absorption or permeability if:

1. The molecular weight exceeds 500.
2. The calculated octanol/water partition coefficient exceeds 5.
3. There are more than 5 H-bond donors expressed as the sum of O–H and N–H groups.
4. There are more than 10 H-bond acceptors expressed as the sum of N and O atoms.

Isosterism

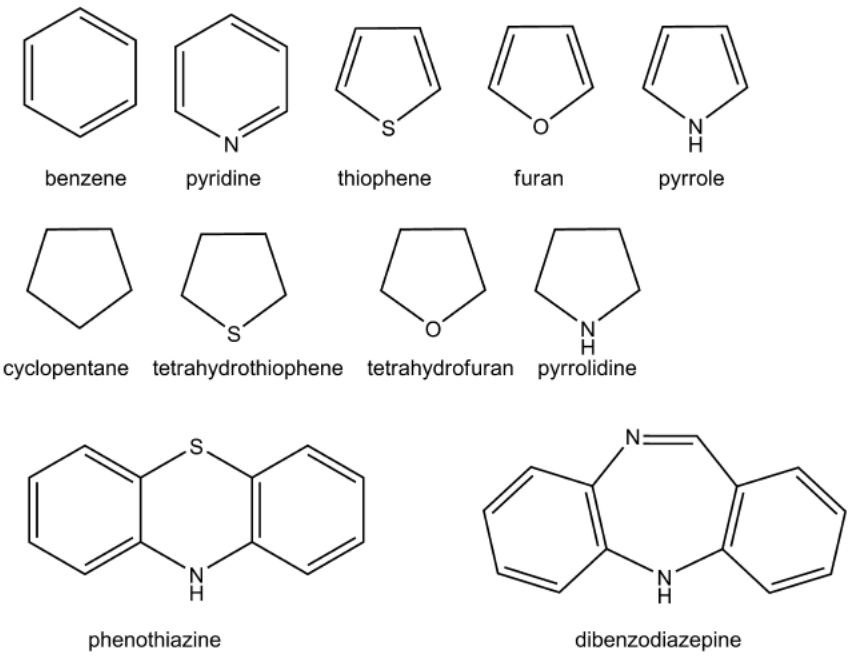
In the process of designing new pharmacologically active compounds, it is important to not restrict the definition of the structures to specific atoms. An important concept is ***isosterism***, a term that has been used widely to describe the selection of structural components—the steric, electronic, and solubility characteristics that make them interchangeable in drugs of the same pharmacological class.

Isosteres are compounds or groups of atoms having the same number and arrangement of electrons. Isosteres that were isoelectric (i.e., with the same total charge as well as the

same number of electrons) would possess similar physical properties. For example, the molecules N_2 and CO both possess 14 total electrons and no charge and show similar physical properties. Related examples were CO_2, N_2O, N_3^-, and NCO^- (Table below).

Groups of atoms that impart similar physical or chemical properties to a molecule because of similarities in size, electronegativity, or stereochemistry are now frequently referred to by the general term of *isostere*.

Commonly Used Alicyclic Chemical Isosteres					
A. Univalent atoms and groups					
(1)	$-CH_3$	$-NH_2$	—OH	—F	—Cl
(2)	—Cl	—SH			
(3)	—Br	—*i*—Pr			
B. Bivalent atoms and groups					
(1)	$-CH_2-$	—NH—	—O—	—S—	
(2)	$-COCH_2R$	—CONHR			
(3)	$-CO_2R$	—COSR			
C. Trivalent atoms and groups					
(1)	—CH═	—N═			



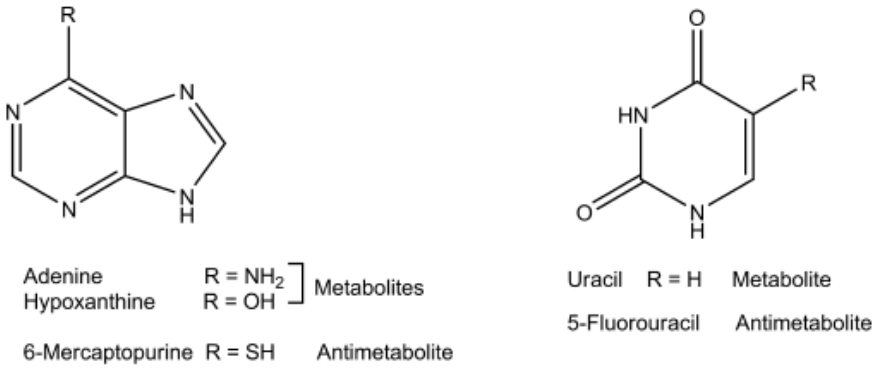
Examples of isosteric ring systems

Examples of isosteric pairs that possess similar steric and electronic configurations are the carboxylate (COO^-) and sulfonamide ($SO_2NR\_$) ions; ketone (C=O) and sulfone (O=S=O); chloride (Cl^-) and trifluoromethyl (CF_3); hydrogen (-H) and fluorine (-F); hydroxy (-OH) and amine ($-NH_2$); hydroxy (-OH) and thiol (-SH). Divalent ether (-O-), sulfide (-S-), amine (-NH-), and methylene ($-CH_2-$) groups, although dissimilar electronically, they are sufficiently alike in their steric nature to be frequently interchangeable in designing new drugs. Compounds may be altered by isosteric replacements of atoms or groups, to develop analogs with select biological effects or to act as antagonists to normal metabolites, but there are no general rules that predict whether biological activity will be increased or decreased.

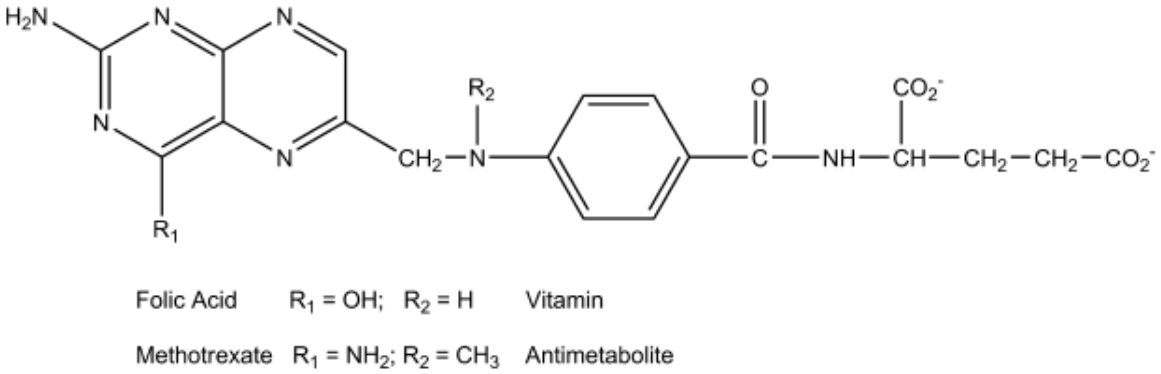
When a group is present in a part of a molecule in which it may be involved in an essential interaction or may influence the reactions of neighboring groups, isosteric replacement sometimes produces analogs that act as antagonists. The 6-NH_2 and 6-OH

groups appear to play essential roles in the hydrogen-bonding interactions of base pairs during nucleic acid replication in cells (Fig. below).

Adenine, **hypoxanthine** and the **antineoplastic 6-mercaptopurine** illustrate how substitution of the significantly weaker hydrogen-bonding isosteric sulfhydryl groups results in a partial blockage of this interaction and a decrease in the rate of cellular synthesis. Similarly, replacement of the hydroxyl group of pteroylglutamic acid (**folic acid**) by the isosteric amino group and addition of the methyl group to the *p*-aminobenzoate leads to the widely used **methotrexate**, a folate antimetabolite. Replacement of the hydrogen at the 5-position of **uracil** with the isosteric fluorine producing **5-fluorouracil** blocks the methylation step leading to thymine.



Examples of how isosterism produces drugs that inhibit the activity of the native metabolite



Examples of how isosterism produces drugs that inhibit the activity of the native metabolite

As a better understanding of the nature of the interactions between drug-metabolizing enzymes and biological receptors develops, selection of isosteric groups with particular electronic, solubility, and steric properties should permit the rational preparation of drugs that act more selectively. At the same time, results obtained by the systematic application of the principles of isosteric replacement are aiding in the understanding of the nature of these receptors.

METABOLIC CHANGES OF DRUGS AND RELATED ORGANIC COMPOUNDS

Metabolism plays a central role in the elimination of drugs and other foreign compounds (*xenobiotics*) from the body.

Most organic compounds entering the body are relatively lipid soluble (*lipophilic*). To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract. Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions.

Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine. Xenobiotics then meet their metabolic fate through various enzyme systems that change the parent compound to render it more water soluble (*hydrophilic*). Once the metabolite is sufficiently water soluble, it may be excreted from the body.

If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects. Thus, the formation of water-soluble metabolites not only enhances drug elimination, but also leads to compounds that are generally pharmacologically inactive and relatively nontoxic.

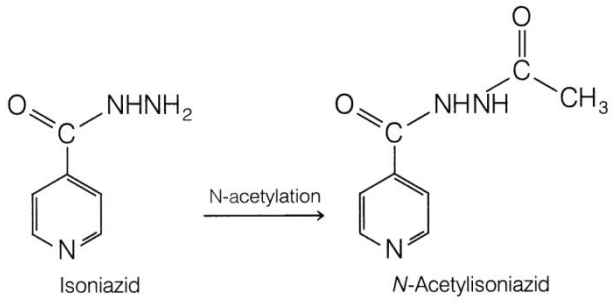
Detoxication (or *detoxification*) processes is regarded as drug metabolism reactions. It is incorrect to assume that drug metabolism reactions are always detoxifying since many drugs are biotransformed to pharmacologically active metabolites, and these metabolites may have significant pharmacological or toxicological effect(s) attributed to the parent

drug, whereas other parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite). These types of compounds are referred to as *prodrugs*.

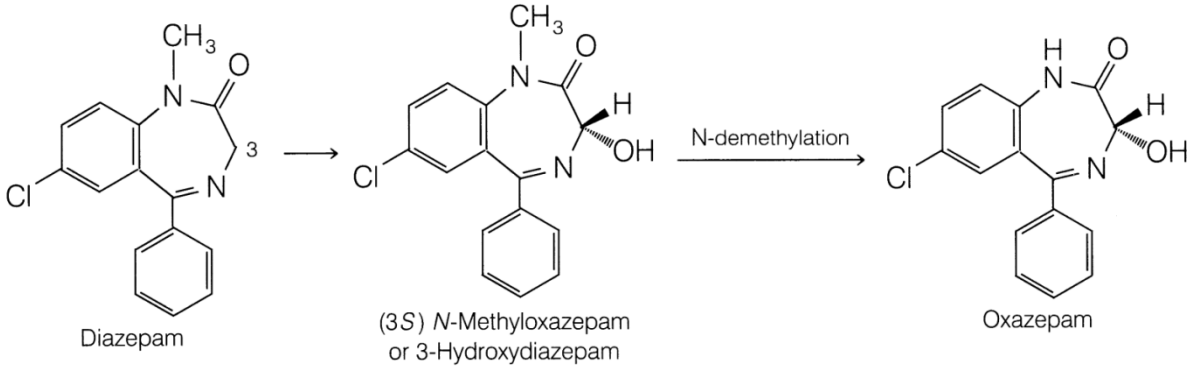
Indeed, many adverse effects (e.g., tissue necrosis, carcinogenicity, teratogenicity) of drugs and environmental contaminants can be attributed directly to the formation of chemically reactive metabolites that are highly detrimental to the body. This concept is more important when the patient has a disease state that inhibits or accelerates xenobiotic metabolism.

Purposes of metabolism in regarding to drug molecule

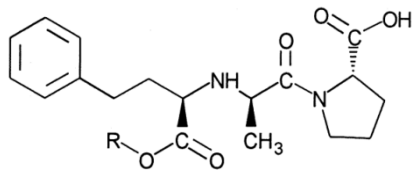
1. Inactivation of drug: example isoniazide used as antituberculosis can be inactivated by acetylation, by addition of acetyl derivation to produce inactive compound.



2. Maintain or enhance of drug activity: example diazepam this drug is active undergo several steps of metabolism, like demethylation of amine and hydroxylation of third position of the compound convert it from active compound to more active form.



3. Initiate activity of some drugs: when drug taken is inactive, but is activated inside the body called (prodrug). Example enalapril. It is taken in ester form, when reached to liver, deesterification occurs, turning it to active form.



Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

General Pathways of drug metabolism:

Drug metabolism reactions have been divided into two categories: phase I (*functionalization*) and phase II (*conjugation*) reactions.

1. Phase I, or functionalization reactions,:

include oxidative, reductive, and hydrolytic biotransformations (Table 3.1). The purpose of these reactions is to introduce a functional polar group(s) (e.g., OH, COOH, NH_2, SH) into the xenobiotic molecule to produce a more water-soluble compound. This can be achieved by

a. direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation)
b. By modifying or "unmasking" existing functionalities e.g.
    1. reduction of ketones and aldehydes to alcohols;
    2. oxidation of alcohols to acids;
    3. hydrolysis of ester and amides to yield COOH, NH_2, and OH groups;
    4. reduction of azo and nitro compounds to give NH_2 moieties;
    5. oxidative *N*-, *O*-, and *S*-dealkylation to give NH2, OH, and SH groups.

Although phase I reactions may not produce sufficiently hydrophilic or inactive metabolites, they generally tend to provide a functional group that can undergo subsequent phase II reactions.

2. phase II reactions:

The purpose of phase II reactions is to form water-soluble conjugated products by attaching small, polar, and ionizable endogenous compounds such as **glucuronic acid**, **sulfate**, **glycine**, and other amino acids to the functional groups of phase I metabolites or parent compounds that

already have suitable existing functional groups. Conjugated metabolites are readily excreted in the urine and are generally devoid of pharmacological activity and toxicity in humans.

Other phase II pathways, such as **methylation** and **acetylation**, terminate or attenuate biological activity, whereas **glutathione** (GSH) conjugation protects the body against chemically reactive compounds or metabolites. Thus, phase I and phase II reactions complement one another in detoxifying, and facilitating the elimination of, drugs and xenobiotics.

General Summary of Phase I and Phase II Metabolic Pathways

Phase I or Functionalization Reactions

Oxidative Reactions
Oxidation of aromatic moieties
Oxidation of olefins
Oxidation at benzylic, allylic carbon atoms, and carbon atoms α to carbonyl and imines
Oxidation at aliphatic and alicyclic carbon atoms
Oxidation involving carbon–heteroatom systems:
- Carbon–nitrogen systems (aliphatic and aromatic amines; includes *N*-dealkylation, oxidative deamination, *N*-oxide formation, *N*-hydroxylation)
- Carbon–oxygen systems (*O*-dealkylation)
- Carbon–sulfur systems (*S*-dealkylation, *S*-oxidation, and desulfuration)

Oxidation of alcohols and aldehydes
Other miscellaneous oxidative reactions

Reductive Reactions
Reduction of aldehydes and ketones
Reduction of nitro and azo compounds
Miscellaneous reductive reactions

Hydrolytic Reactions
Hydrolysis of esters and amides
Hydration of epoxides and arene oxides by epoxide hydrase

Phase II or Conjugation Reactions

Glucuronic acid conjugation
Sulfate conjugation
Conjugation with glycine, glutamine, and other amino acids
Glutathione or mercapturic acid conjugation
Acetylation
Methylation

Sites of Drug Biotransformation:

Liver is the most important organ in drug metabolism and detoxification of endogenous and exogenous compounds. Liver, a well-perfused organ, is particularly rich in almost all of the drug-metabolizing enzymes. Orally administered drugs that are absorbed into the bloodstream through the GI tract must pass through the liver before being further distributed into body compartments.

Therefore, they are susceptible to hepatic metabolism known as the ***first-pass effect*** before reaching the systemic circulation. Depending on the drug, this metabolism can sometimes be quite significant and results in decreased oral bioavailability. For example, in humans, several drugs are metabolized extensively by the first-pass effect. Some of those drugs are:

Isoproterenol, **Morphine**, **Propoxyphene**, **Lidocaine (**not effective orally**),** **Nitroglycerin (**given bucally or sublingually**)**, **Propranolol**, **Meperidine**, **Pentazocine**, and **Salicylamide**.

Another important site, especially for orally administered drugs, is the **intestinal mucosa**. Intestinal mucosa contains the CYP3A4 isozyme and P-glycoprotein that can capture the drug and secrete it back into the **intestinal tract**.

- For example, in humans, orally administered **isoproterenol** undergoes considerable sulfate conjugation in the intestinal wall. Several other drugs (e.g., **levodopa**, **chlorpromazine**, and **diethylstilbestrol**) are also metabolized in the GI tract.
- **Esterases** and **lipases** present in the intestine may be particularly important in carrying out hydrolysis of many ester prodrugs.
- Bacterial flora present in the intestine and colon appear to play an important role in the reduction of many aromatic azo and nitro drugs (e.g., sulfasalazine).
- Intestinal-glucuronidase enzymes can hydrolyze glucuronide conjugates excreted in the bile, thereby liberating the free drug or its metabolite for possible reabsorption (enterohepatic circulation or recycling).

  Although other tissues, such as **kidney**, **lungs**, **adrenal glands**, placenta, **brain**, and **skin**, have some drug metabolizing capability, the biotransformations that they carry out are often more substrate selective and more limited to particular types of reaction (e.g., oxidation and glucuronidation).

Role of Cytochrome P_{450} monooxygenase in Oxidative Biotransformation:

Oxidative biotransformation processes are the most common and important in drug metabolism. The enzyme systems carrying out this biotransformation are referred to as *mixed-function oxidases* or *monooxygenases*.

Nomenclature of these enzymes is as the following:

There are four components to the name.

- CYP refers to the cytochrome system.
- This is followed by the number that specifies the cytochrome family (CYP1, CYP2, CYP3, etc.).
- Next is a capital letter that represents the subfamily (CYP1A, CYP1B, CYP2A, CYP2B, CYP3A, CYP3B, etc.).
- Finally, the cytochrome name ends with another number that specifies the specific enzyme responsible for a particular reaction (CYP1A2, CYP2C9, CYP2C19, CYP3A4, etc.).

$$\underset{\text{Xenobiotic}}{RH} + NADPH + O_2 \longrightarrow H^+ + \underset{\substack{\text{oxidized}\\\text{metabolite}}}{ROH} + NADP + H_2O$$

The reaction requires both molecular oxygen and the reducing agent NADPH (reduced form of nicotinamide adenosine dinucleotide phosphate). During this oxidative process, one atom of molecular oxygen (O2) is introduced into the substrate R-H to form R-OH and the other oxygen atom is incorporated into water. The mixed-function oxidase system is actually made up of several components, the most important being the superfamily of CYP oxidase enzymes which are responsible for transferring an *oxygen atom* to the substrate RH.

Other important components of this system include the NADPH-dependent CYP reductase and the NADH-linked cytochrome b5. These two components, along with the cofactors NADPH and NADH, supply the reducing equivalents (electrons) needed in the overall metabolic oxidation of foreign compounds.

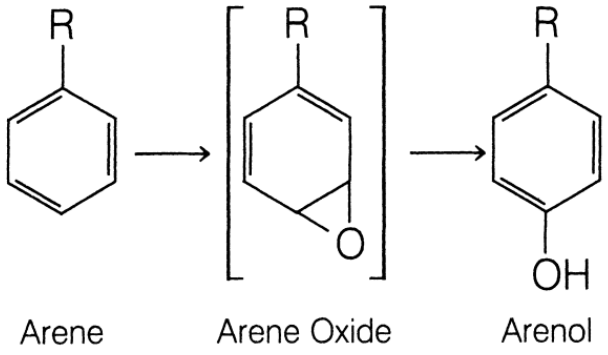
The CYP enzymes are heme proteins. The heme portion is an iron-containing porphyrin called *protoporphyrin IX*, and the protein is called the *apoprotein*. CYP is found in high concentrations in the liver, the major organ involved in the metabolism of xenobiotics. The presence of this enzyme in many other tissues (e.g., lung, kidney, intestine, skin, placenta, adrenal cortex) shows that these tissues have drug-oxidizing capability too. The name *cytochrome P450* is derived from the fact that the reduced (Fe^{+2}) form of this enzyme binds with carbon monoxide to form a complex that has a distinguishing spectroscopic absorption maximum at 450 nm.

One important feature of the hepatic CYP mixed function oxidase system is its ability to metabolize an almost unlimited number of diverse substrates by various oxidative transformations. This versatility is believed to be a result of the substrate nonspecificity of CYP as well as the presence of multiple forms of the enzyme. Some of these P450 enzymes are selectively inducible by various chemicals.

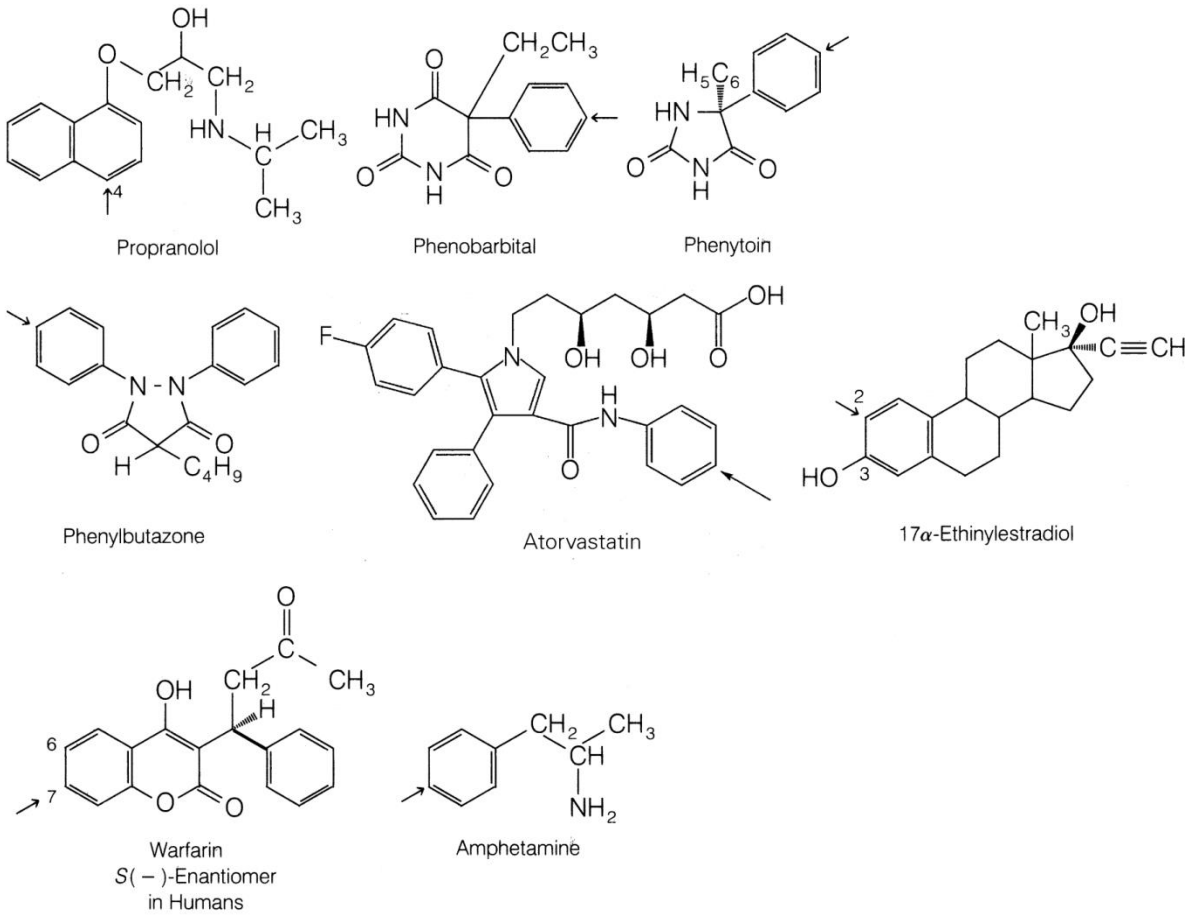
Phase I Oxidation reaction

1. Oxidation of Aromatic Moieties

Aromatic hydroxylation refers to the mixed-function oxidation of aromatic compounds (arenes) to their corresponding phenolic metabolites (arenols). Almost all aromatic hydroxylation reactions are believed to proceed initially through an epoxide intermediate called an "arene oxide," which rearranges rapidly and spontaneously to the arenol product in most instances.



Most foreign compounds containing aromatic moieties are susceptible to aromatic oxidation. In humans, aromatic hydroxylation is a major route of metabolism for many drugs containing phenyl groups. Important therapeutic agents such as propranolol, phenobarbital, phenytoin and atorvastatin, undergo extensive aromatic oxidation. In most of these drugs hydroxylation occurs at the para position.



Examples of drugs and xenobiotics that undergo aromatic hydroxylation in humans. *Arrow* indicates site of aromatic hydroxylation.

Factors affecting aromatic oxidation:

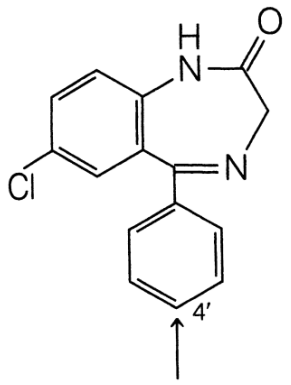
The substituents attached to the aromatic ring may influence the ease of hydroxylation.

Types of substitutions are classified to

- Activated group: like hydroxyl, amine, alkyl, etc. (electron-donating group). Cause ring activation, in this case oxidation is characterized by rapid metabolism and position of OH group at para position.
- Deactivation group: like halogens, NO_2, ammonium ion, COOH, SO_2NHR, etc. (electron-withdrawing group) are generally slow or resistant to hydroxylation.

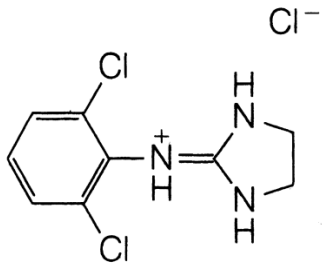
Examples:

e.g.1: Diazepam, compounds with two aromatic rings, hydroxylation occurs preferentially in the more electron-rich ring.



Diazepam

e.g.2: The deactivating groups (Cl, $-N^+H=C$) present in the antihypertensive clonidine may explain why this drug undergoes little aromatic hydroxylation in humans.



Clonidine Hydrochloride

Arene oxide intermediates are formed when a double bond in aromatic moieties is epoxidized. Arene oxides are of significant toxicologic concern because these intermediates are electrophilic and chemically reactive (because of the strained three-membered epoxide ring).

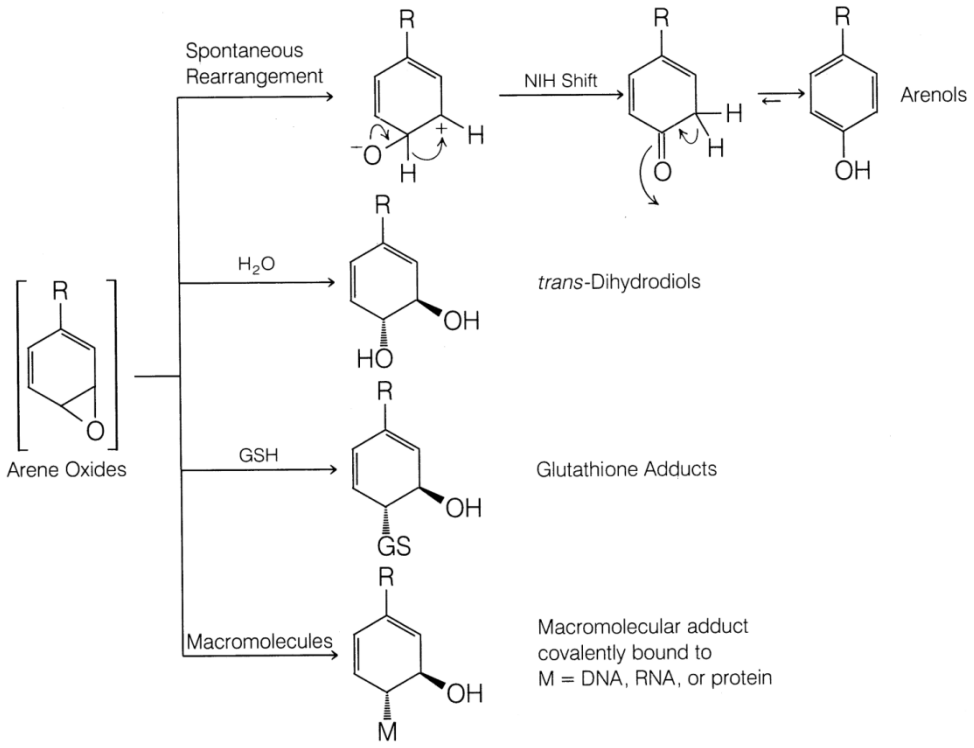
Arene oxides are mainly detoxified by the following possible reaction pathways:

a- The most important detoxification reaction for arene oxides is the spontaneous rearrangement to corresponding arenols. Often, this rearrangement is accompanied by a novel intramolecular hydride migration called the “NIH shift.”

b- Enzymatic hydration to trans-dihydrodiols. (i.e., nucleophilic attack of water on the epoxide). Transdiol may undergo further oxidation to give catechol derivative. This reaction is catalyzed by microsomal enzymes called epoxide hydrases.

c- Enzymatic conjugation with (GSH) in the presence of glutathione S-trnsferase enzyme to give glutathione derivatives, which undergo further metabolism to give mercapturic derivative.

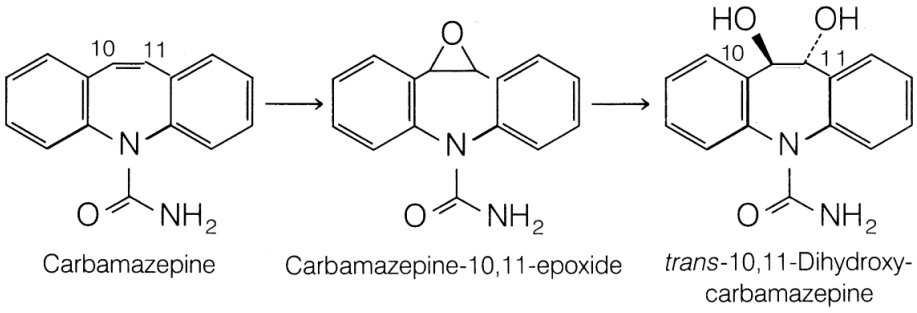
If not effectively detoxified by the first three pathways, arene oxides will bind covalently with nucleophilic groups present on proteins, (DNA), and (RNA), thereby leading to serious cellular damage. This, in part, helps explain why benzene can be so toxic to mammalian systems.



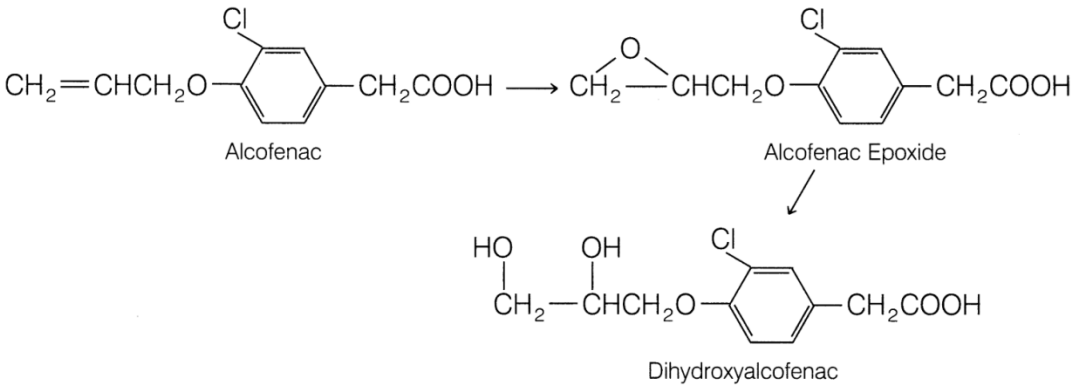
Possible reaction pathways for arene oxides

2. Oxidation of Olefin

The metabolic oxidation of olefinic carbon-carbon double bonds leads to the corresponding epoxide (or oxirane). Epoxides are susceptible to enzymatic hydration by epoxide hydrase to form *trans*-dihydrodiols. In addition, several epoxides undergo GSH conjugation. **E.g.** The anticonvulsant drug Carbamazepine (Tegretol) and Alcofenac.

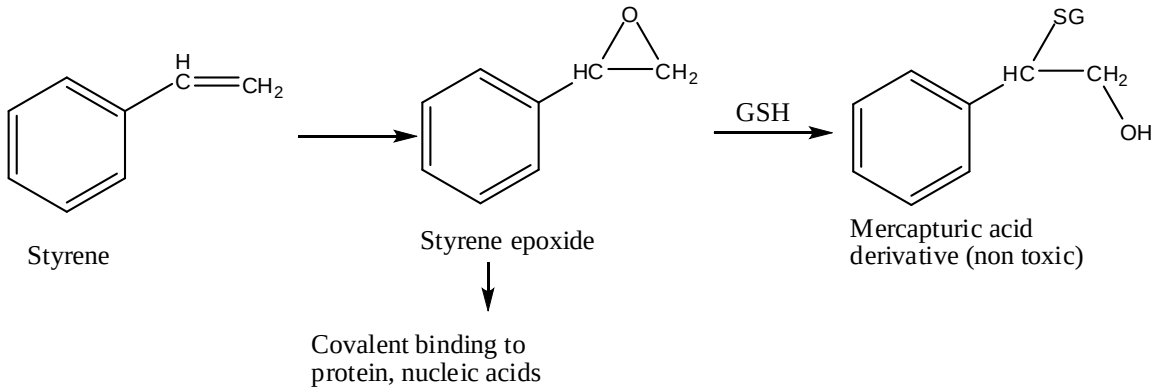


Carbamazepine → Carbamazepine-10,11-epoxide → *trans*-10,11-Dihydroxy-carbamazepine



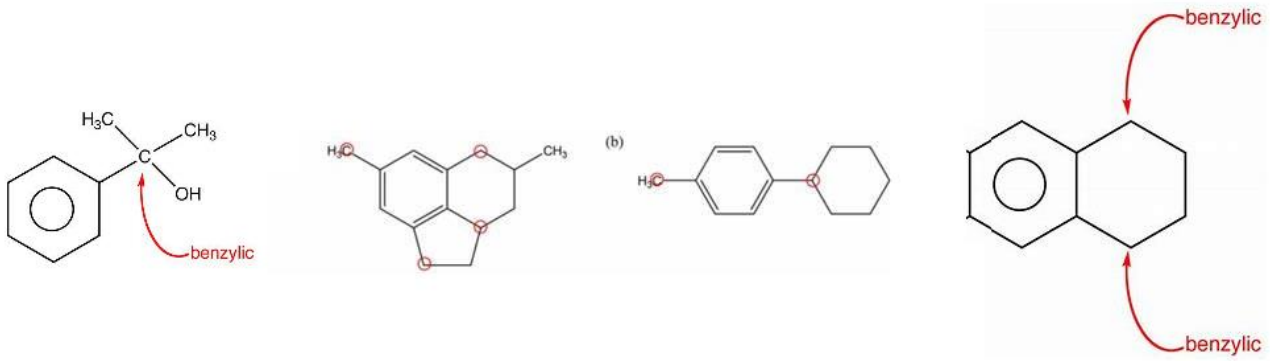
Alcofenac → Alcofenac Epoxide → Dihydroxyalcofenac

Other olefinic compounds, such as vinyl chloride, stilbene undergoes metabolic epoxidation. The corresponding epoxide metabolites may be the reactive species responsible for the cellular toxicity seen with these compounds.



Some of olefin-containing compounds causes the destruction of CYP. Such compounds are secobarbital and the volatile anesthetic agent fluroxene. It is believed that the olefinic moiety present in these compounds is activated metabolically by CYP to form a very reactive intermediate that covalently binds to the heme portion of CYP. Long-term administration of the above-mentioned agent is expected to lead to inhibition of oxidative drug metabolism, potential drug interactions, and prolonged pharmacological effects.

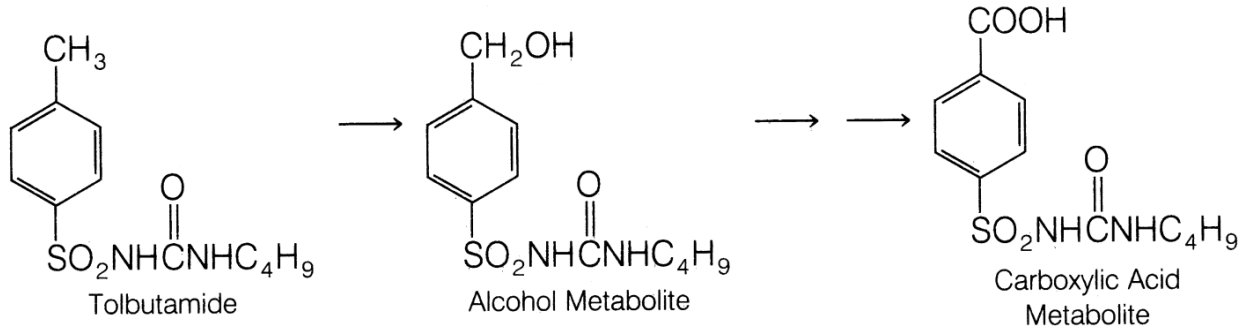
3. Oxidation at Benzyl Carbon Atoms



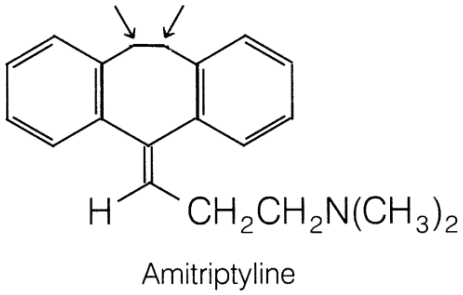
Carbon atoms attached to aromatic rings (benzylic position) are susceptible to oxidation, thereby forming the corresponding alcohol (or carbinol) metabolite.
Primary alcohol metabolites are often oxidized further to aldehydes and carboxylic acids

(-CH_2OH ⟶ -CHO → -COOH), and secondary alcohols are converted to ketones by soluble alcohol and aldehyde dehydrogenases. Alternatively, the alcohol may be conjugated directly with glucuronic acid.

E.g. the benzylic carbon atom present in the oral hypoglycemic agent tolbutamide is oxidized extensively to the corresponding alcohol and carboxylic acid. Both metabolites have been isolated from human urine.

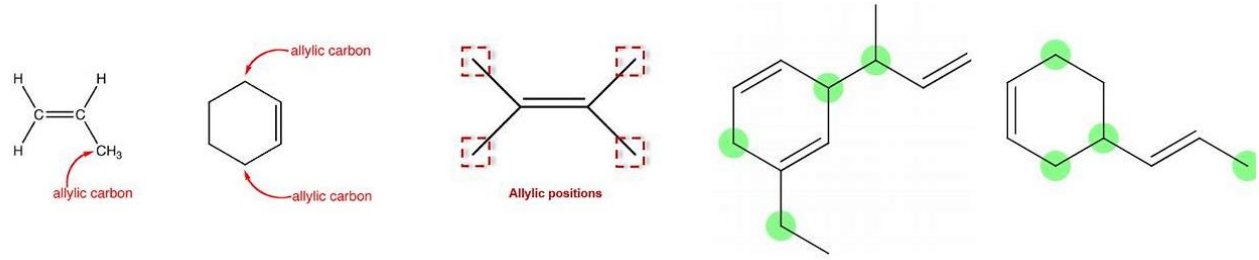


E.g. Amitriptyline



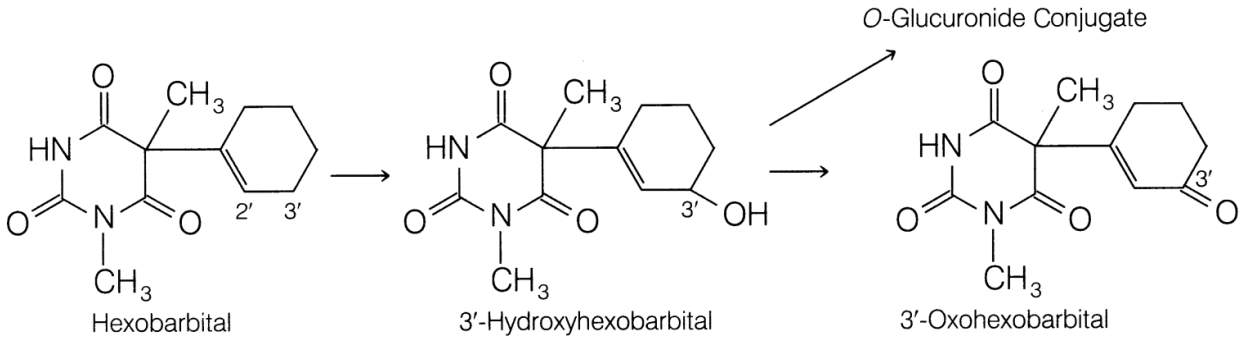
4. Oxidation at Allylic Carbon Atoms

Microsomal hydroxylation at allylic carbon atoms is commonly observed in drug metabolism.



Examples of allylic oxidation include the sedative-hypnotic hexobarbital.

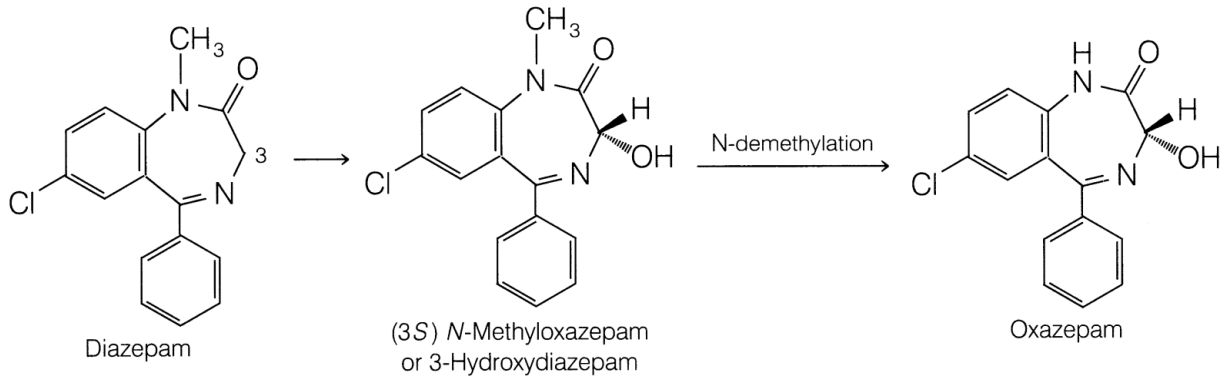
The 3′-hydroxylated metabolite formed from hexobarbital is susceptible to glucuronide conjugation as well as further oxid



ation to the 3′-oxo compound.

5. Oxidation at Carbon Atoms α to Carbonyls and Imines

The mixed-function oxidase system also oxidizes carbon atoms adjacent (i.e., α) to carbonyl and imino functionalities. An important class of drugs undergoing this type of oxidation is the benzodiazepines. Example diazepam (Valium)**.**



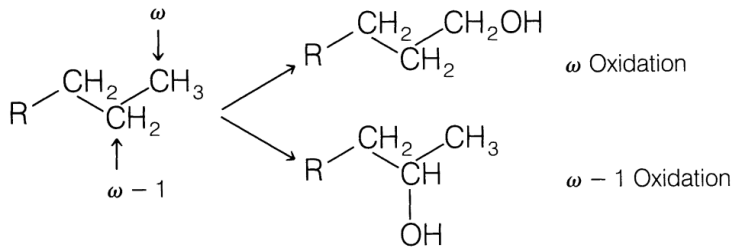
6. Oxidation of Aliphatic and Alicyclic Carbon Atom

Compounds contain straight or branched chain undergoes 2 types of oxidation:

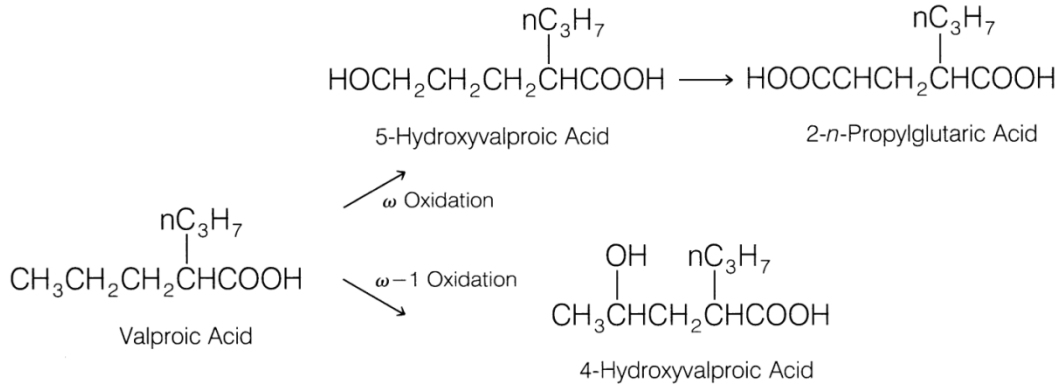
●oxidation takes place at terminal methyl group (ꝺ-oxidation).

●oxidation takes place at carbon atom before the last carbon (ꝺ-1oxidation)

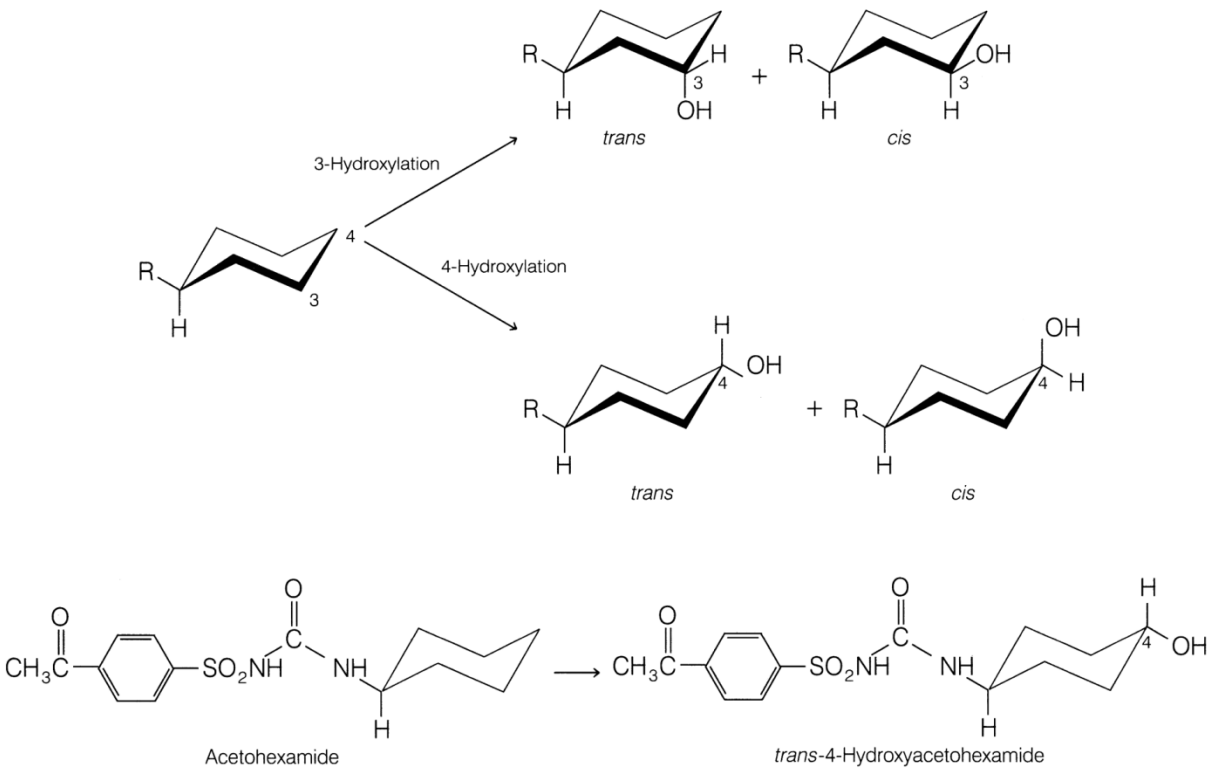
The initial alcohol metabolites formed from these enzymatic ω and ω-1 oxidations are susceptible to further oxidation to yield aldehyde, ketones, or carboxylic acids. Alternatively, the alcohol metabolites may undergo glucuronide conjugation.



E.g. the antiepileptic agent valproic acid (Depakene) undergoes both ω and ω-1 oxidation to the 5-hydroxy and 4-hydroxy metabolites, respectively. Further oxidation of the 5-hydroxy metabolite yields 2-n-propylglutaric acid.



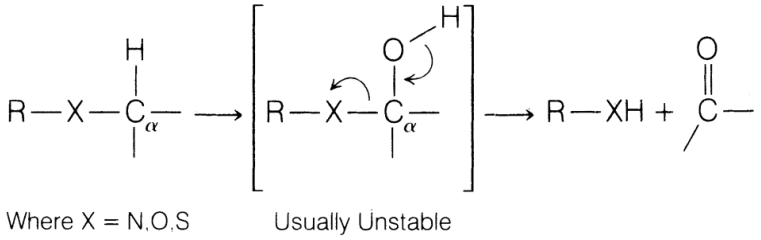
The cyclohexyl group is commonly found in many medicinal agents, and is also susceptible to mixed-function oxidation (alicyclic hydroxylation).114,115 Enzymatic introduction of a hydroxyl group into a monosubstituted cyclohexane ring generally occurs at C-3 or C-4 and can lead to cis and trans conformational stereoisomers, as shown in the following scheme. E.g. the oral hypoglycemic agent acetohexamide.



7. Oxidation Involving Carbon–Heteroatom Systems

Nitrogen and oxygen functionalities are commonly found in most drugs and foreign compounds; sulfur functionalities occur only occasionally. Metabolic oxidation of carbon–nitrogen, carbon–oxygen, and carbon–sulfur systems principally involves two basic types of biotransformation processes:

1. Hydroxylation of the -carbon atom attached directly to the heteroatom (N, O, S). The resulting intermediate is often unstable and decomposes with the cleavage of the carbon–heteroatom bond. Oxidative N-, O-, and S-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.



2. Hydroxylation or oxidation of the heteroatom (N, S only, e.g., N-hydroxylation, N-oxide formation, sulfoxide, and sulfone formation).

a. Oxidation involving carbon–nitrogen systems

Metabolism of nitrogen functionalities (e.g., amines, amides) is important because such functional groups are found in many natural products (e.g., morphine, cocaine, nicotine) and in numerous important drugs (e.g., phenothiazines, antihistamines, tricyclic antidepressants, β-adrenergic agents, sympathomimetic phenylethylamines, benzodiazepines).

Nitrogen-containing compounds are divided into three basic classes:

1. Aliphatic (primary, secondary, and tertiary) and alicyclic (secondary and tertiary) amines.

2. Aromatic and heterocyclic nitrogen compounds.

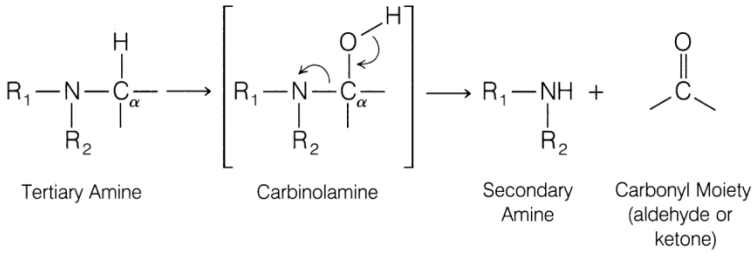
3. Amides.

1. Tertiary Aliphatic and Alicyclic Amines

a. Oxidative N-dealkylation

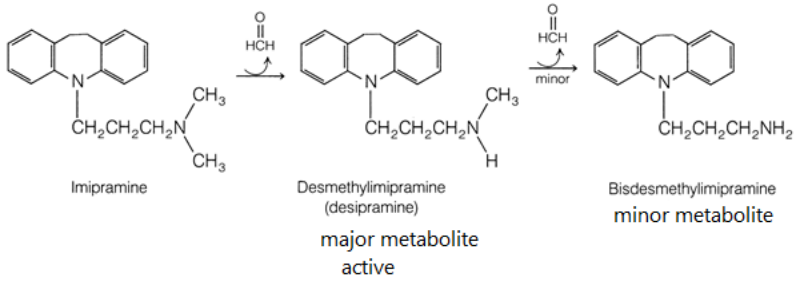
It is the oxidative removal of alkyl groups (particularly methyl groups) from tertiary aliphatic and alicyclic amines which is carried out by hepatic CYP mixed-function oxidase enzymes.

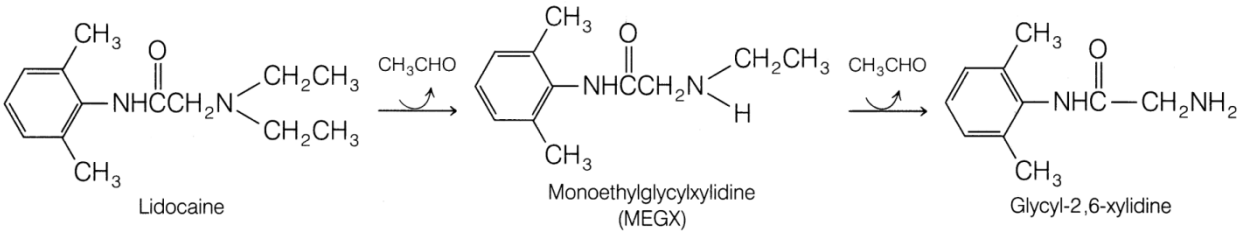
The initial step involves α-carbon hydroxylation to form a carbinolamine intermediate, which is unstable and undergoes spontaneous heterolytic cleavage of the C–N bond to give a secondary amine and a carbonyl moiety (aldehyde or ketone).



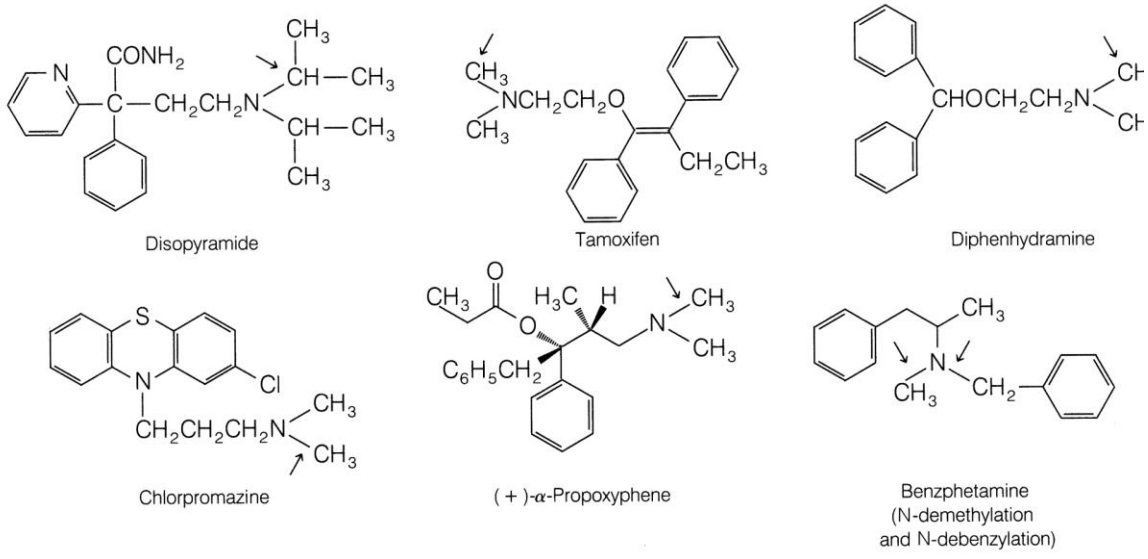
In general, small alkyl groups, such as methyl, ethyl, and isopropyl, are removed rapidly. N-dealkylation of the t-butyl group is not possible by the carbinolamine pathway because α-carbon hydroxylation cannot occur. E.g. the N-t-butyl group present in many β-adrenergic antagonists, such as terbutaline and salbutamol, remains intact and does not appear to undergo any significant metabolism.

The first alkyl group from a tertiary amine is removed more rapidly than the second alkyl group. In some instances, bisdealkylation of the tertiary aliphatic amine to the corresponding primary aliphatic amine occurs very slowly. E.g.imipramine (Tofranil ®) and lidocaine.

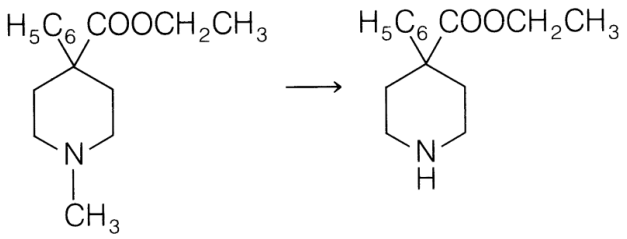




Other examples of tertiary aliphatic amine drugs which are metabolized principally by oxidative N-dealkylation:



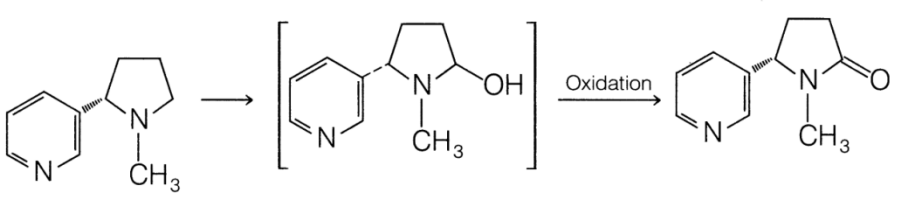
Like their aliphatic counterparts, alicyclic tertiary amines are susceptible to oxidative N-dealkylation reactions. For example, the analgesic drug meperidine.



Meperidine Normeperidine

b. Formation of lactam metabolites

Alicyclic tertiary amines often generate lactam metabolites by α-carbon hydroxylation reactions at the ring carbon atom α to the nitrogen which further oxidized to lactam metabolites. E.g. nicotine undergoes this reaction.



Nicotine Carbinolamine Cotinine

c. N-oxidation

Tertiary amines possibly undergo N-oxidation leading to formation of the active N-oxide metabolite. E.g. the tricyclic antidepressants imipramine.

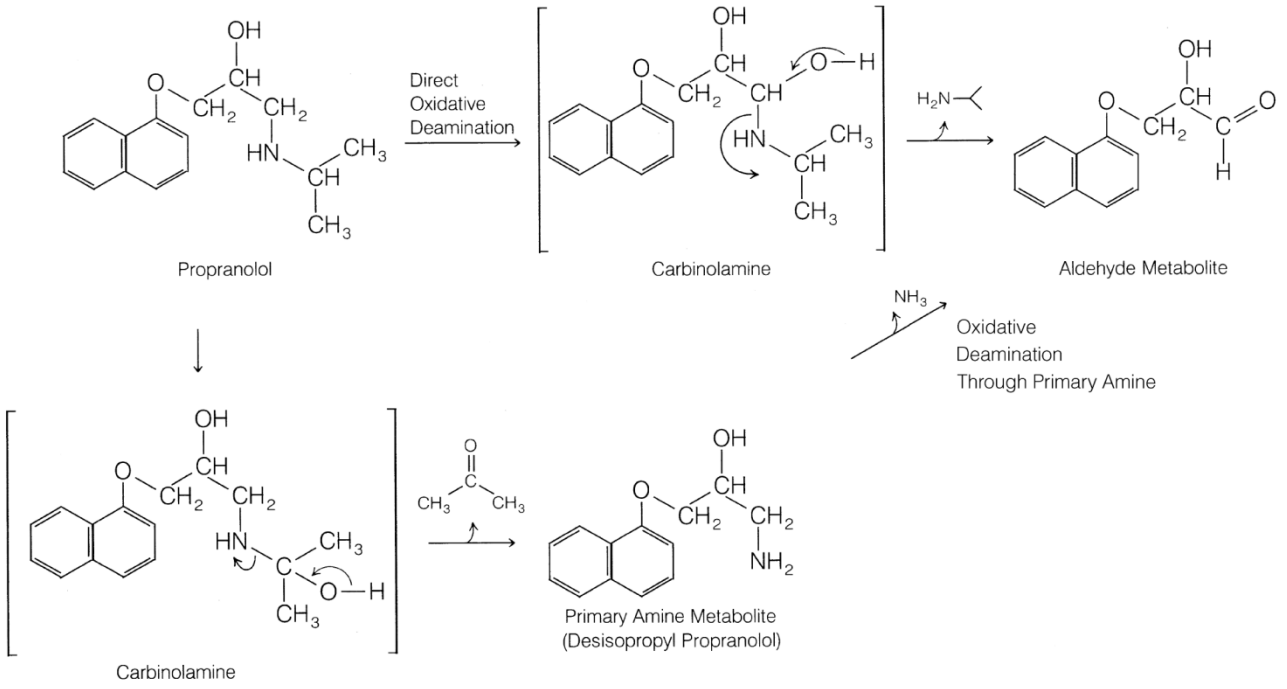
2. Secondary and Primary Amines.

a. Secondary amines (either parent compounds or metabolites) are susceptible to

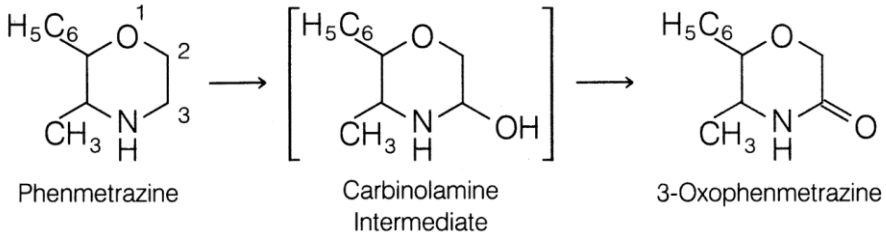
- oxidative N-dealkylation,
- oxidative deamination, and
- N-oxidation reactions.

- As in tertiary amines, N-dealkylation of secondary amines proceeds by the carbinolamine pathway. Dealkylation of secondary amines gives rise to the corresponding **primary amine metabolite**. For example, the β-adrenergic blocker propranolol.
- The primary amine metabolites formed from oxidative dealkylation are susceptible to oxidative deamination. This process is similar to N-dealkylation, in that it involves an initial α-carbon hydroxylation reaction to form a carbinolamine intermediate, which then undergoes subsequent carbon–nitrogen cleavage to the **carbonyl metabolite** and **ammonia**.

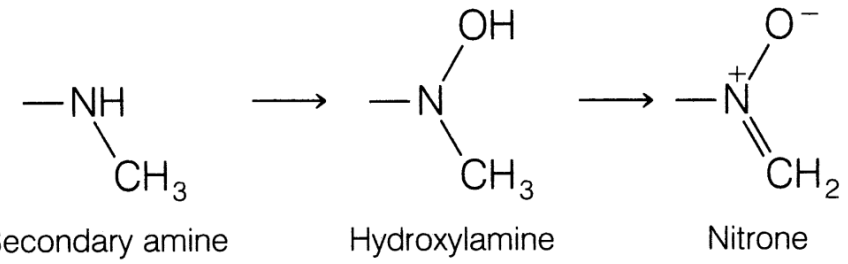
- Direct deamination of the secondary amine (ex. Propranolol) also has occurred. In addition to undergoing deamination after oxidative N-dealkylation, propranolol can undergo a direct oxidative deamination reaction (also by α-carbon hydroxylation) to yield the **aldehyde metabolite** and **alkylamine** (isopropylamine).

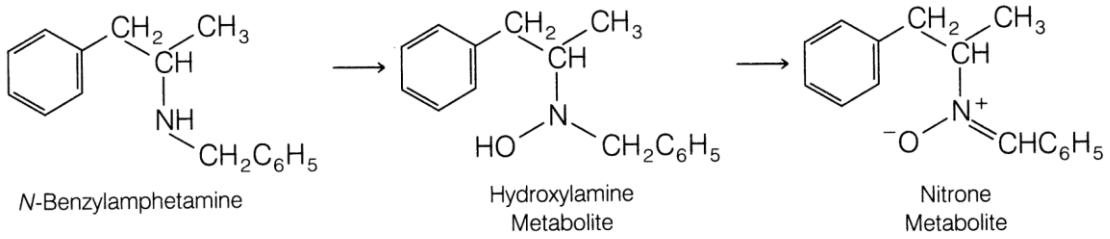


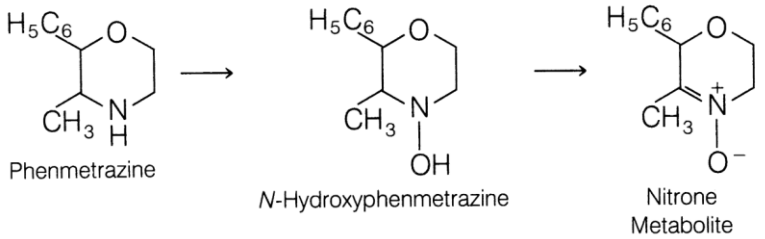
- Some secondary alicyclic amines, like their tertiary amine analogs, are metabolized to their corresponding **lactam derivatives**. For example, the anorectic agent phenmetrazine.



- Metabolic N-oxidation of secondary aliphatic and alicyclic amines leads to several N-oxygenated products. N-hydroxylation of secondary amines generates the corresponding N-hydroxylamine metabolites. These hydroxylamine products are susceptible to further oxidation (either spontaneous or enzymatic) to the corresponding nitrone derivatives. E.g. N-benzylamphetamine and phenmetrazine.

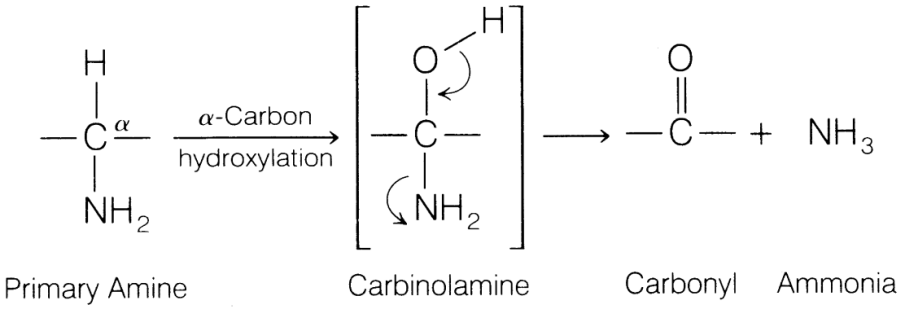




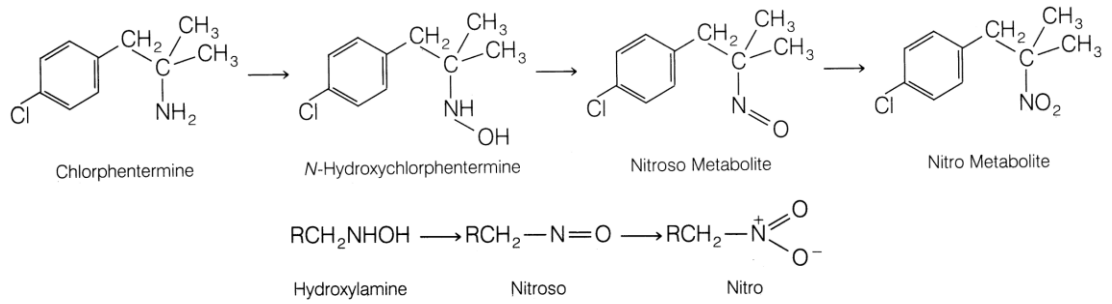


b. Primary aliphatic amines (whether parent drugs or metabolites) are biotransformed by:

- Oxidative deamination (through the carbinolamine pathway) by CYP which leads to the formation of carbonyl metabolites and ammonia.



- N-oxidation which leads to the formation of N-hydroxyl amine metabolites which are susceptible to further oxidation to yield other *N*-oxygenated products like nitroso (N=O) and the nitro (nitrogen dioxide).

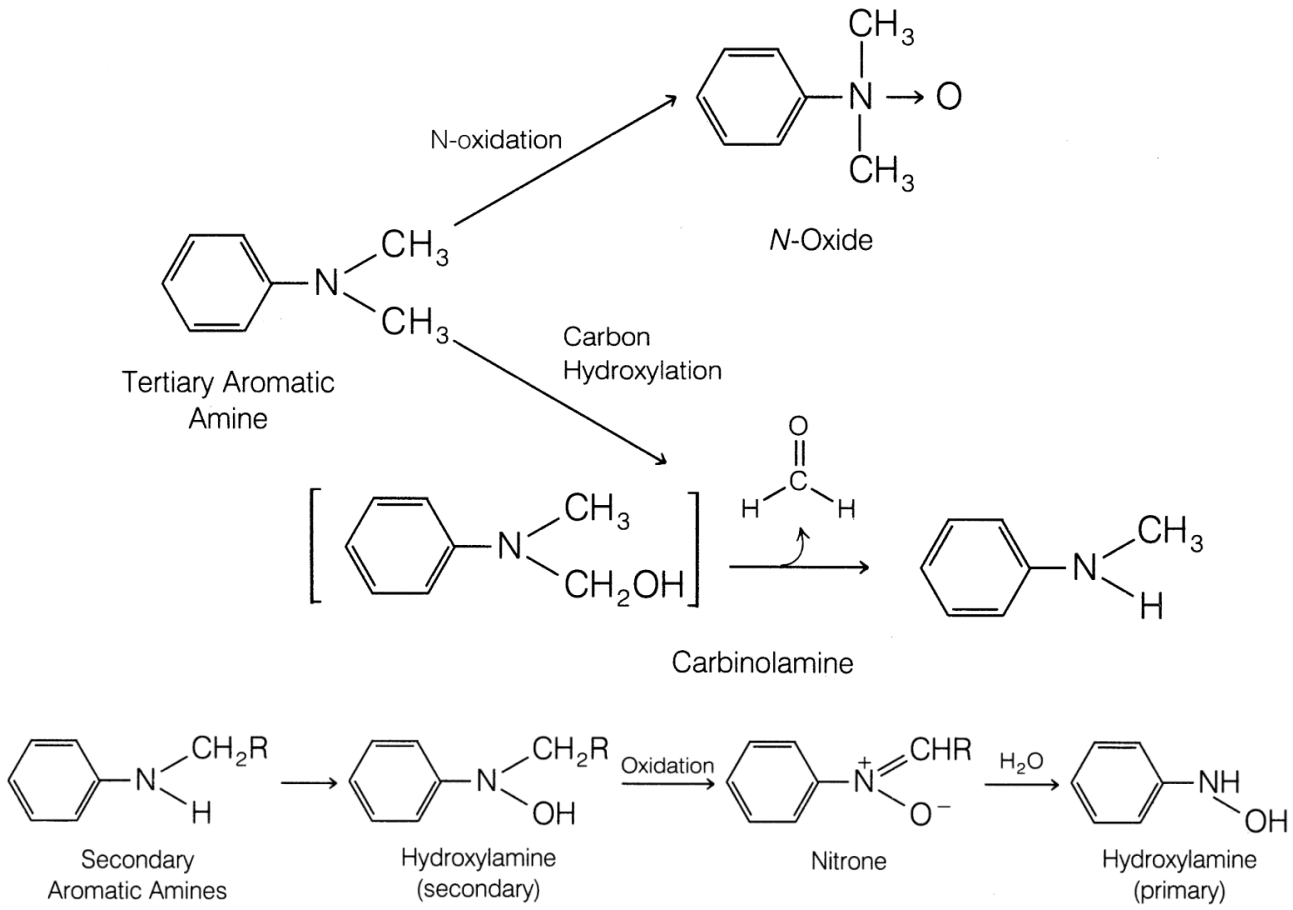


N-Oxidation of Primary Amines

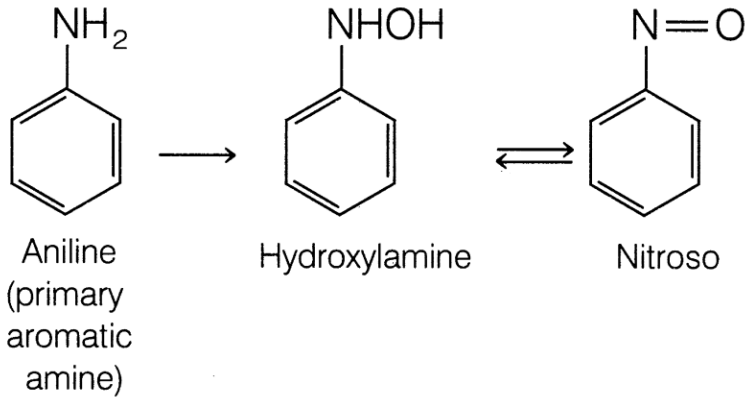
3. Tertiary aromatic amines

tertiary aromatic amines (such as *N*,*N*-dimethylaniline) and secondary aromatic amines can undergo oxidative *N*-dealkylation as well as *N*-oxide formation take place. Further

oxidation of the *N*-hydroxylamine leads to nitrone products, which in turn may be hydrolyzed to primary hydroxylamines.

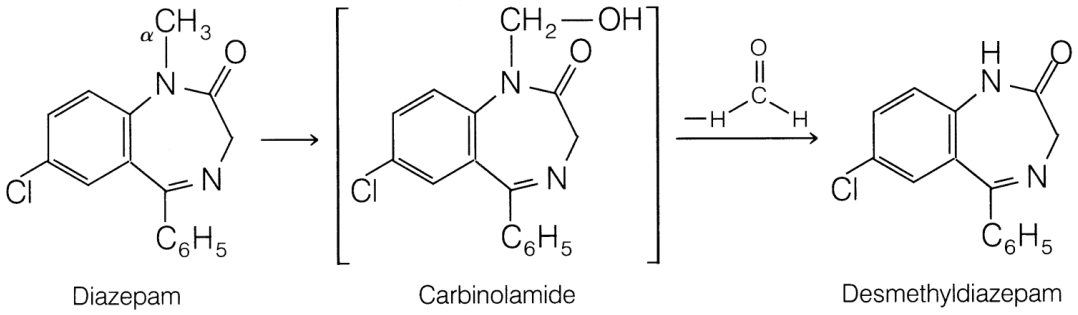


N-oxidation of primary aromatic amines generates the N-hydroxylamine metabolite. One such case is aniline, which is metabolized to the corresponding N-hydroxy product.223 Oxidation of the hydroxylamine derivative to the nitroso derivative also can occur.

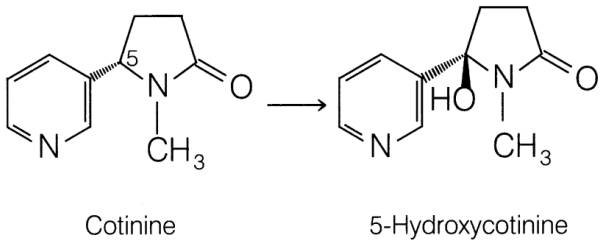


4. Amides

Amide functionalities are susceptible to oxidative carbon–nitrogen bond cleavage (via -carbon hydroxylation) and N-hydroxylation reactions. Oxidative dealkylation proceeds via an initially formed carbinolamide, which is unstable and fragments to form the N-dealkylated product. For example, diazepam undergoes extensive N-demethylation to the pharmacologically active metabolite desmethyldiazepam.

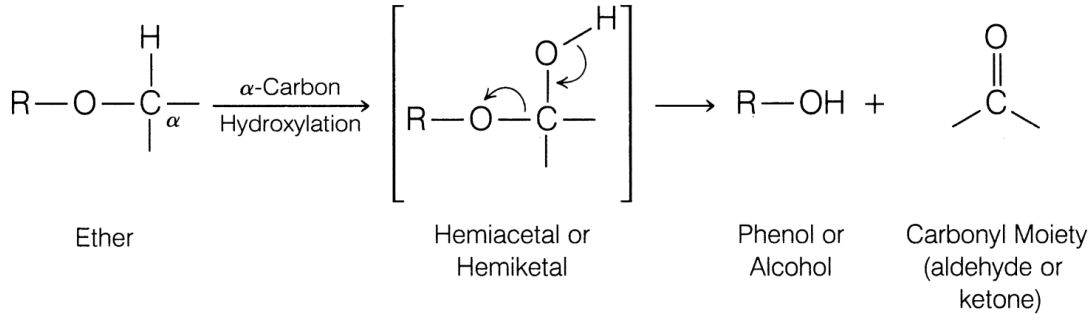


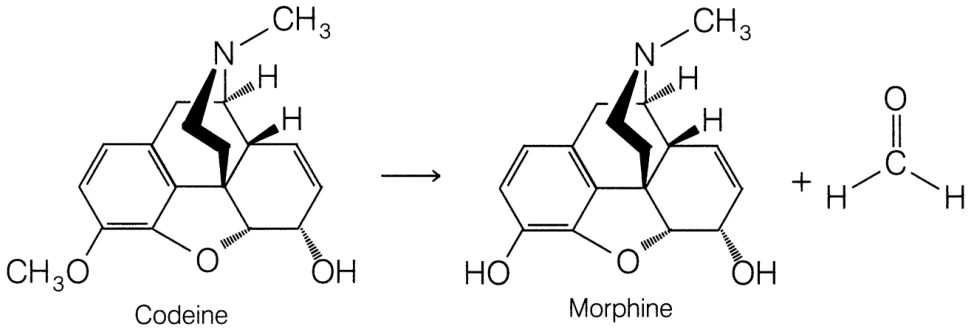
In the cyclic amides or lactams, hydroxylation of the alicyclic carbon to the nitrogen atom also leads to carbinolamides. An example of this pathway is the conversion of cotinine to 5-hydroxycotinine.



b. Oxidation Involving Carbon-Oxygen (ethers)

The biotransformation of ethers involves an initial α-carbon hydroxylation to form either hemiacetal or hemiketal, which undergoes spontaneous carbon-oxygen bond cleavage to yield the dealkylated oxygen species (phenol or alcohol) and a carbonyl moiety (aldehyde or ketone).

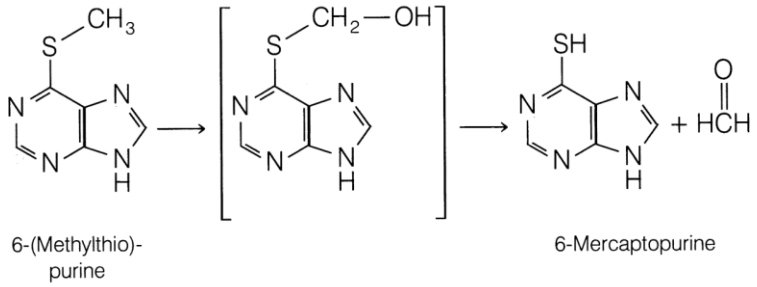




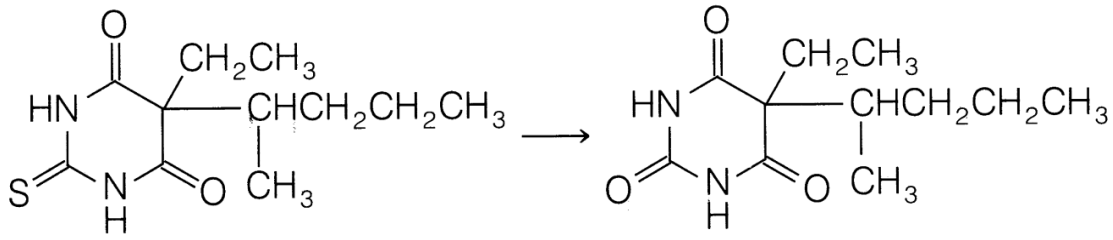
c. Oxidation Involving Carbon-Sulfur

Several drugs containing Carbon-Sulfur functional group are susceptible to

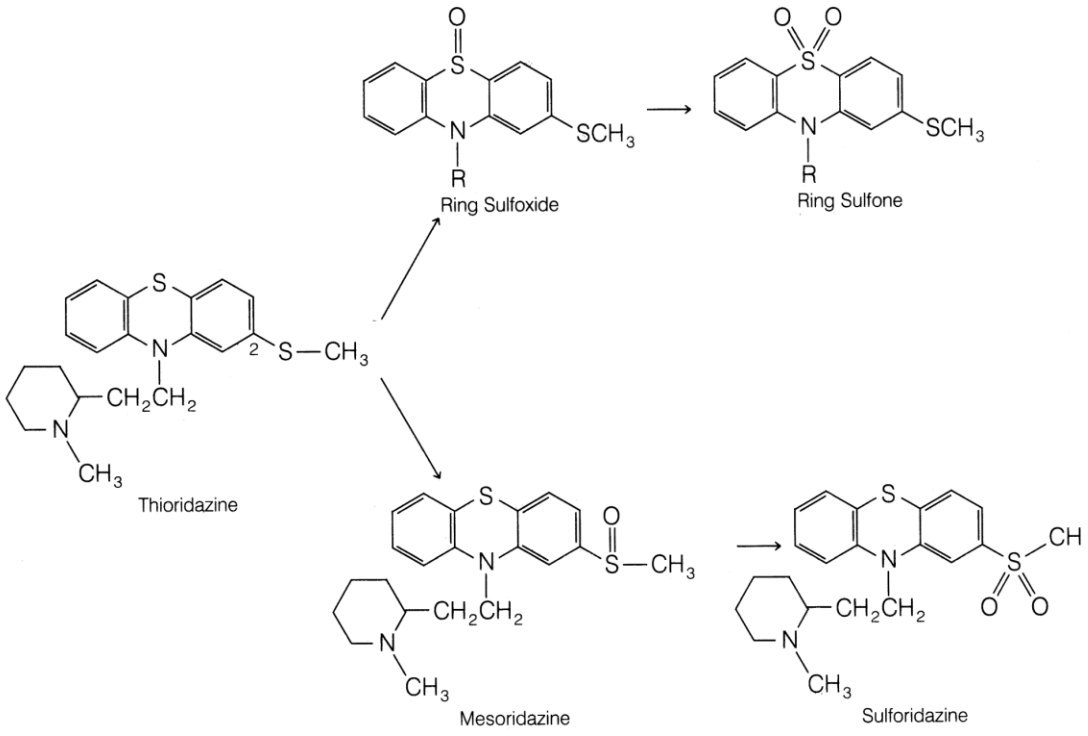
1. S-dealkylation: Similar to N- and O-dealkylation and involves oxidative carbon-sulfur bond cleavage.



2. Desulfuration: Oxidative conversion of carbon-sulfur double bonds (C=S) (thiono) to the corresponding carbon-oxygen double bond (C=O) is called desulfuration.



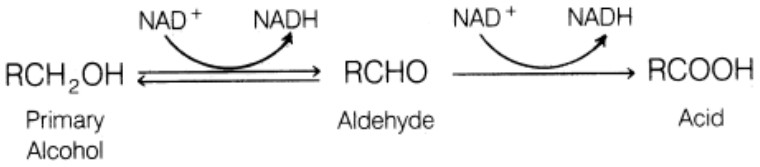
3. S-oxidation: S-oxidation yields the corresponding sulfoxide derivatives. Sulfoxide drugs/metabolites may further oxidised to sulfones (-SO2).



Oxidation of Alcohols and Aldehydes

Many oxidative processes (e.g., benzylic, allylic, alicyclic, or aliphatic hydroxylation) generate alcohol or carbinol metabolites as intermediate products. If not conjugated, these alcohol products are further oxidized to aldehydes (if primary alcohols) or to ketones (if secondary alcohols).

Aldehyde metabolites resulting from oxidation of primary alcohols or from oxidative deamination of primary aliphatic amines often undergo oxidation to generate polar carboxylic acid derivatives.



The bioconversion of alcohols to aldehydes and ketones is catalyzed by soluble alcohol dehydrogenases present in the liver and other tissues.

Oxidation of secondary alcohol to ketones is NOT often important as it reduces back to secondary alcohol. Secondary alcohol group being more polar and functionalized, is more likely to be conjugated than the ketone moiety.

Other Oxidative Biotransformation Pathways

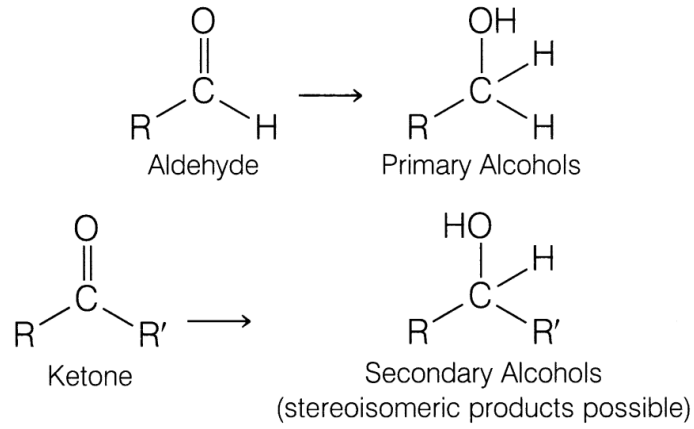
1. Oxidative aromatization reactions ex, the progesterone derivative norgestrel.
2. Oxidative dehalogenation reactions ex, volatile anesthetic agent halothane.

Reduction Reactions

Reductive process play an important role in the metabolism of many compounds containing carbonyl, nitro and azo groups. Bioreduction of carbonyl compounds generates alcohol derivatives, whereas nitro and azo reductions lead to amino derivatives. The hydroxyl and amino moieties of the metabolites are much more susceptible to conjugation than the functional groups of the parent compounds. Therefore, reductive processes, as such, facilitate drug elimination.

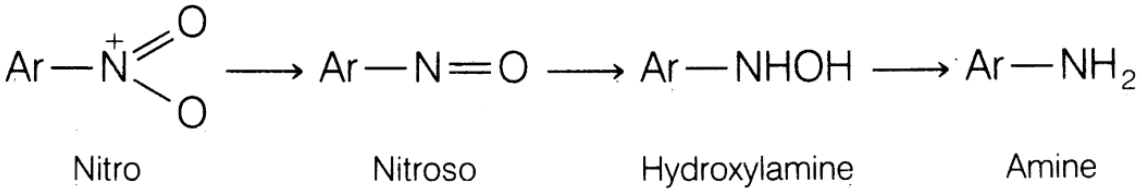
Reduction of Aldehydes and Ketones

- Aldehydes reduced to primary alcohols.
- Ketones reduced to secondary alcohols.
- Reactions mediated by *Aldo-Keto reductase* enzymes
- Bioreduction of ketones often leads to the creation of an asymetric center and thereby produces two possible stereoisomeric alcohols.
- One of the stereoisomer may preferentially form predominantly over other stereoisomer and thus shows product stereo selectivity in drug metabolism.

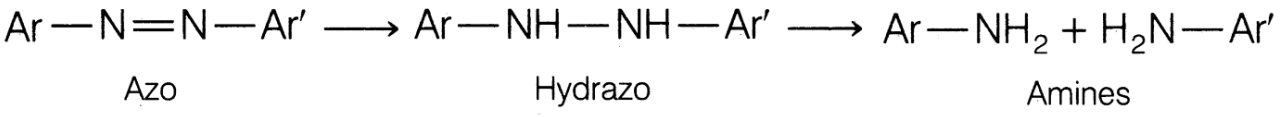


Reduction of Nitro and Azo Compounds

- Bioreduction of aromatic nitro and azo compounds leads to aromatic primary amine metabolites.
- Aromatic nitro compounds are reduced initially to the nitroso and ydroxylamine intermediates that subsequently further reduced to amine.



- Azo reduction proceed via hydrazo intermediate (-NH-NH-) that subsequently cleaved reductively to yield the corresponding amines.

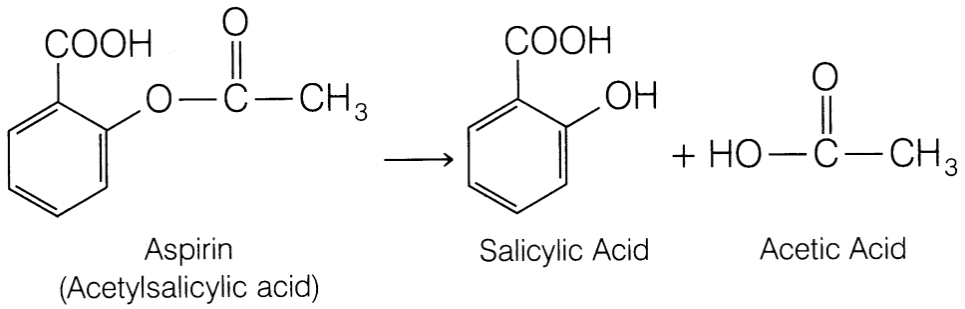


Phase I Hydrolytic reaction:

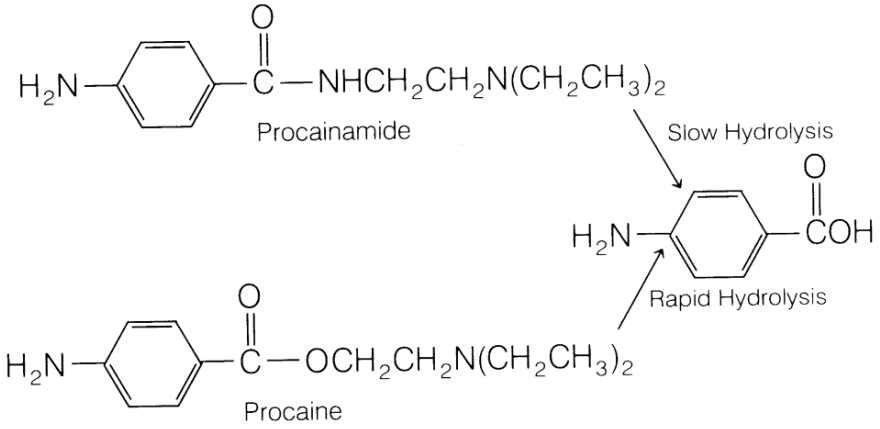
Hydrolysis of Esters and Amides

The metabolism of ester and amide linkages in many drugs is catalyzed by hydrolytic enzymes present in various tissues and in plasma. The metabolic products formed (carboxylic acids, alcohols, phenols, and amines) generally are polar and functionally more susceptible to conjugation and excretion than the parent ester or amide drugs. The enzymes carrying out ester hydrolysis include several nonspecific esterases found in the liver, kidney, and intestine as well as the pseudocholinesterases present in plasma. Amide hydrolysis appears to be mediated by liver microsomal amidases, esterases, and deacylases.

Hydrolysis is a major biotransformation pathway for drugs containing an ester functionality. This is because of the relative ease of hydrolyzing the ester linkage. A classic example of ester hydrolysis is the metabolic conversion of aspirin (acetylsalicylic acid) to salicylic acid.



Amides are hydrolyzed slowly in comparison to esters.337 Consequently, hydrolysis of the amide bond of procainamide is relatively slow compared with hydrolysis of the ester linkage in procaine.



Miscellaneous Hydrolytic Reactions

1. Hydrolysis of recombinant human peptide drugs and hormones at the N- or C-terminal amino acids by carboxypeptidase and aminopeptidase and proteases in blood and other tissues. Examples of peptides or protein hormones undergoing hydrolysis include human insulin, growth hormone (GH), prolactin, parathyroid hormone (PTH) Examples of peptides or protein hormones undergoing hydrolysis include human insulin, growth hormone (GH), prolactin and parathyroid hormone (PTH).
2. The hydrolysis of phosphate esters (e.g., diethylstilbestrol diphosphate), sulfonylureas, cardiac glycosides, carbamate esters, and organophosphate compounds.
3. Glucuronide and sulfate conjugates also can undergo hydrolytic cleavage by β-glucuronidase and sulfatase enzymes.

Phase II (Conjugation) Reactions.

Introduction

- Phase I or functionalization reactions do not always produce hydrophilic or pharmacologically inactive metabolites and nontoxic.
- 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.
- The role of **GSH** is to combine with chemically reactive compounds to prevent damage to important biomacromolecules, such as DNA, RNA, and proteins.
- Thus, phase II reactions can be regarded as truly **detoxifying pathways** in drug metabolism, with a **few exceptions.**
- A distinguishing feature of most phase II reactions is that the conjugating group (glucuronic acid, sulfate, methyl, and acetyl) is activated initially in the form of a coenzyme before transfer or attachment of the group to the accepting substrate by the appropriate transferase enzyme.
- In other cases, such as glycine and glutamine conjugation, the substrate (amino acid) is activated initially.
    - All of the conjugating groups need to be activated to react with drug molecule
    - The activation process is carried out by enzyme using two main approaches:

Reactions	Enzymes	Drug Functional Groups	Activated Coenzyme
Glucuronidation	UDP-glucuronyltransferase	OH, SH, COOH, NH_2	Uridine diphosphate glucuronic acid (UDPGA).
Sulfation	Sulfotransferase	OH, NH_2, SH	3-Phosphoadenosine5—phosphosulfate(PAPS)
Methylayion	Methyl transferase	OH, NH_2, SH	S-Adenosinemethaionine(SAM)
Acetylation	Acetyl transferase	OH, NH_2	Acetyl-CoA
Amino acid conjugation	Acetylcoenzyme A (ATP)	COOH	Substrate derivative of AMP&CoASH
Glutathione conjugation	Glutathione-S-transferase	Epoxide, organic halides	No Activation

Phase II reactions include:

1. Conjugation; it includes:

A. Glucuronic acid (GUA) conjugation.

B. Sulfate conjugation.

C. Amino acid(a.a.) conjugation (glycine, and glutamine).

D. Glutathione (GSH) reaction.

2. Acetylation.

3. Methylation.

- Other minor conjugative pathways are conjugation with glycosides, phosphate, and other amino acids and conversion of cyanide to thiocyanate.

1. Conjugation

A. Glucuronic Acid (GUA) Conjugation

- Glucuronidation is the major phase II metabolic path way for drugs, xenobiotics and endogenous compounds for the following reasons:

a) A readily available supply of D-glucuronic acid (derived from D-glucose),

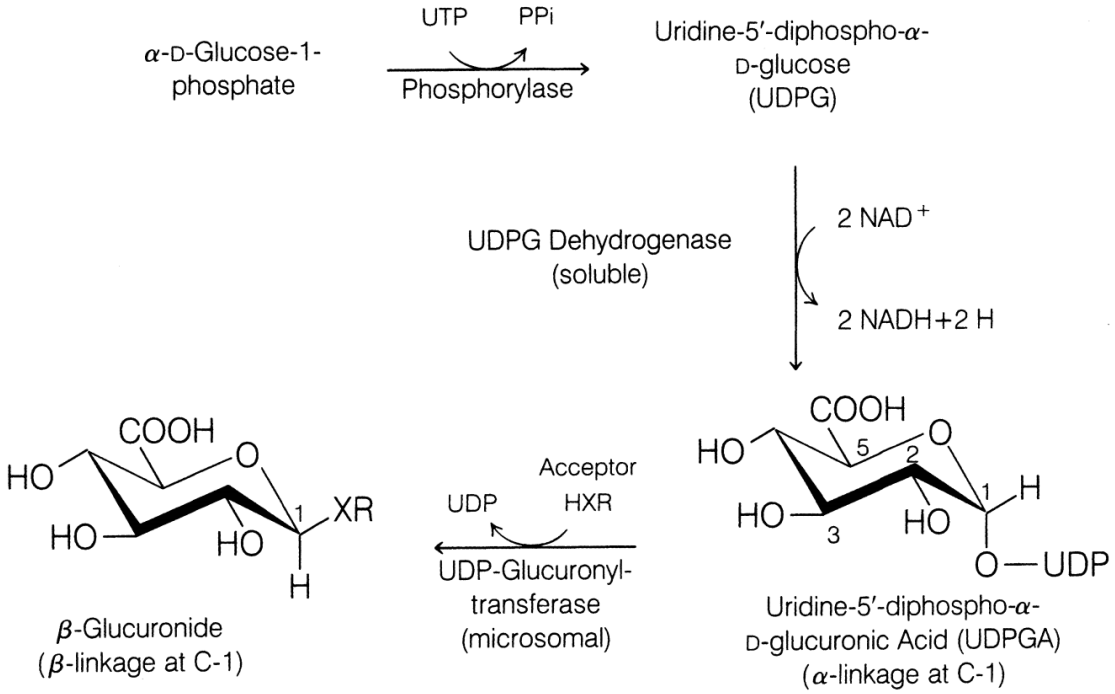
b) Numerous functional groups that can combine enzymatically with glucuronic acid,

c) The glucuronyl moiety (with its ionized carboxylate [pKa 3.2] and polar Hydroxyl groups), which, when attached to xenobiotic substrates greatly increases the water solubility of the conjugated product.

- Formation of β-glucuronides involves two steps:

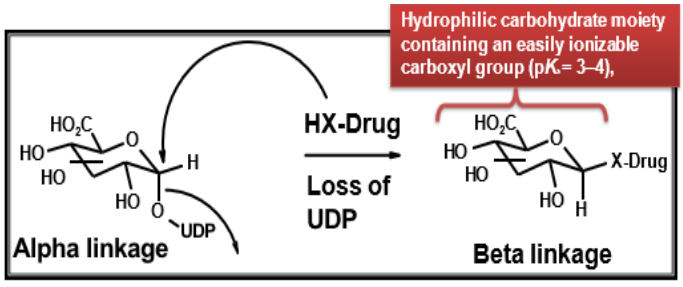
a. Synthesis of an activated coenzyme, uridine-5-diphospho-α-D-glucuronic acid (UDPGA),

b. Subsequent transfer of the glucuronyl group from UDPGA to an appropriate substrate. This step is catalyzed by microsomal enzymes called *UDP-glucuronyltransferases*.



Formation of UDPGA and β-glucuronide conjugates. The synthesis of the coenzyme UDPGA uses α-D-glucose- 1-phosphate as its initial precursor

- All glucuronide conjugates have the β-configuration or β-linkage at C-1 (hence, the term β-*glucuronides*).
- In contrast, the coenzyme UDPGA has an α-linkage, the above enzymatic transfer step, is nucleophilic displacement of the α-linked UDP moiety from UDPGA by the substrate RXH (X = O, N, S &C) proceeds with complete inversion of configuration at C-1 to give the β-glucuronide (SN^2).



- Diglucuronide conjugates do not usually occur, because glucuronidation of one functional group is sufficient for the excretion of the conjugated metabolite (in urine).
- β-Glucuronides are classified according to the heteroatom attached to the C-1 atom of the glucuronyl group. into:
  i). O-β-Glucuronides.

  ii). N-β-Glucuronides.

  iii). S-β-Glucuronides.

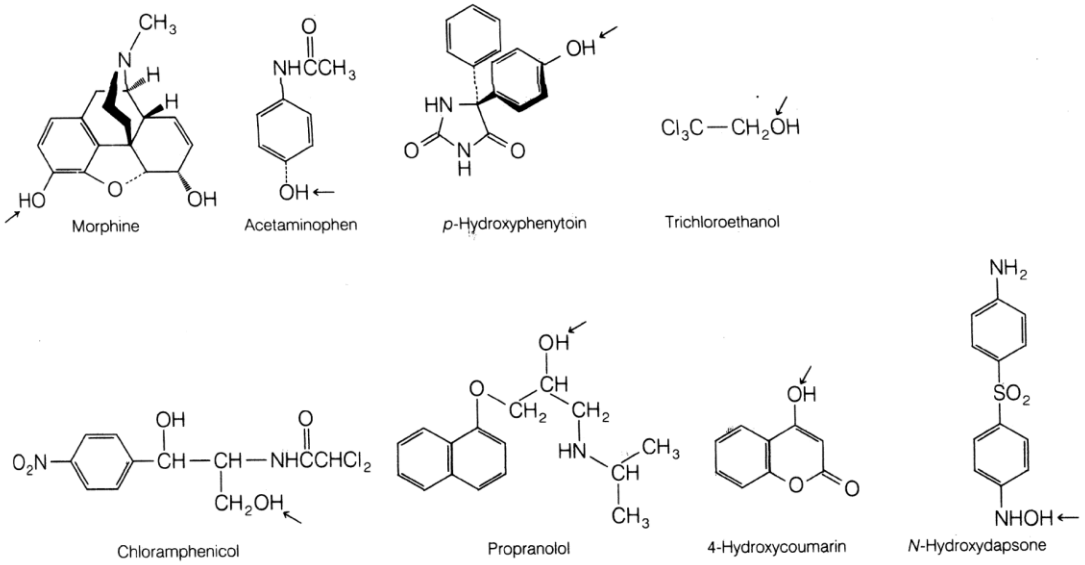
  iv). C-β-Glucuronide.

- The functional groups undergoing glucuronidation in drug metabolism are hydroxy (phenolic and alcoholic hydroxyls) and carboxy, amino, thiol and even Carbone in some cases as illustrated below
- Several endogenous substrates, e.g., bilirubin and steroids are eliminated as glucuronide conjugates, which are excreted primarily in the urine.
- Due to the large size of some glucuronide conjugates (>300 Da), they are excreted to bile (e.g., steroids).
- However, in the intestine, the conjugates are hydrolyzed by β-glucuronidase enzymes and release drug which may be reabsorbed (entero-hepatic circulation that increases half-life of drug)

i). O-β-Glucuronides.

The most common functional groups undergoing glucuronidation in drug metabolism to form *O*-glucuronides, are hydroxy (phenolic and alcoholic hydroxyls) and carboxy.

Examples for drugs undergo O-glucuronidation: at phenolic and alcoholic hydroxyl groups as well as at the carboxylic group are illustrated below:

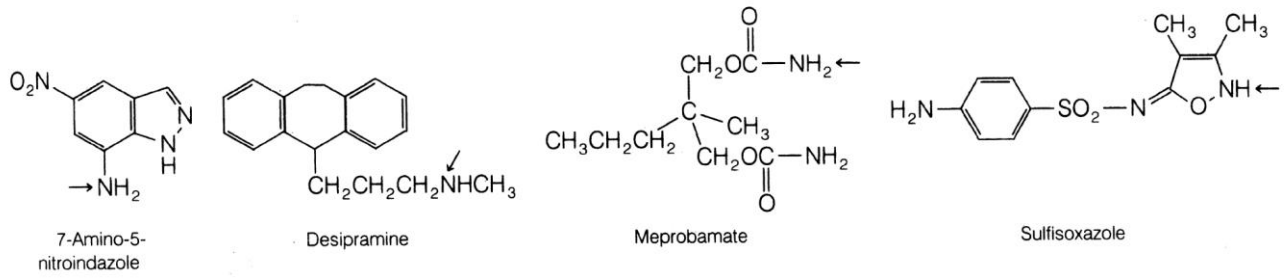


ii). N-β-Glucuronides.

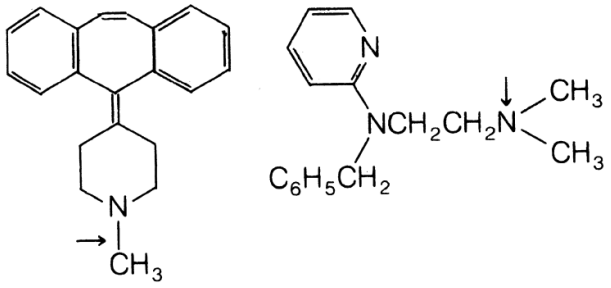
The most common functional groups undergoing glucuronidation in drug metabolism to form *N*-glucuronides, are: Aromatic & aliphatic amines, ($PhNH_2$, RNH_2, RNHR & R_3N); Amides ($RCONH_2$) & Sulfonamides (RSO_2NH_2).

Examples for drugs undergo N-glucuronidation are illustrated below:

- Glucuronidation of aromatic and aliphatic amines is generally a minor pathway in comparison with *N*-acetylation (for aromatic) or oxidative processes (e.g., oxidative deamination for aliphatic**).**



- Tertiary amines, such as the cyproheptadine quaternary ammonium glucuronide metabolites as in these examples.

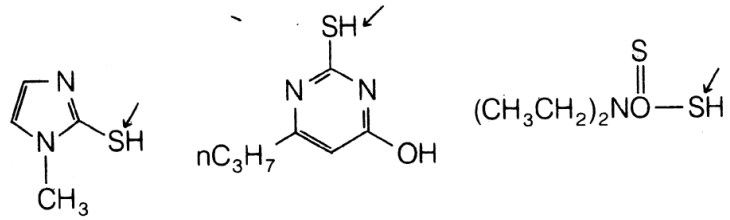


Cyproheptadine Tripelennamine

iii). S-β-Glucuronides.

This pathway is very minor metabolic pathway. The functional groups undergoing S-glucuronidation are compounds with free SH group.

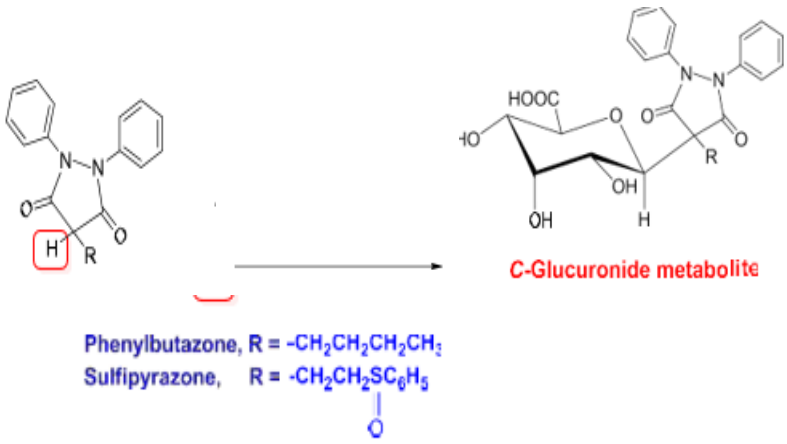
- Examples for drugs undergo S-glucuronidation are illustrated below:



Methimazole Propylthiouracil Diethylthio-carbamic Acid

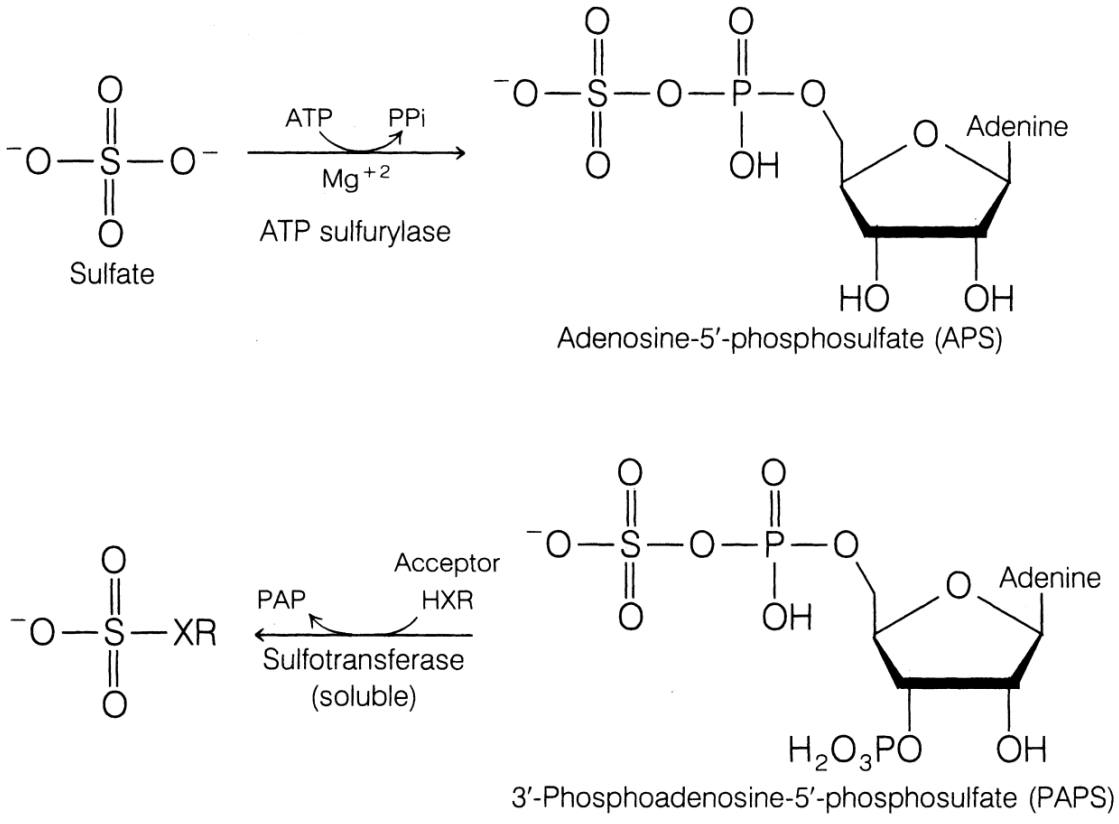
iv. C-β-Glucuronide.

This pathway is relatively rare pathway in drug metabolism as shown in the following example:



B. Sulfate (SO4) Conjugation

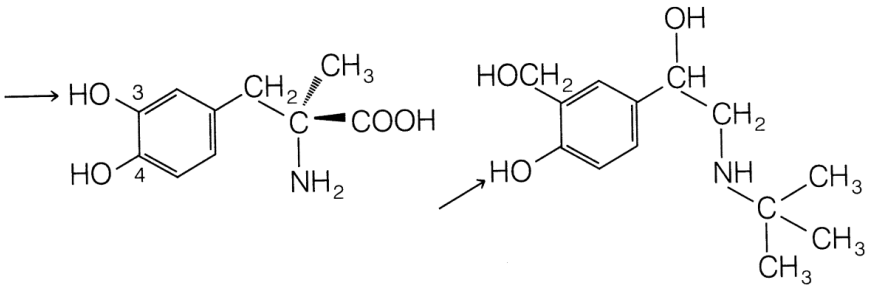
- Sulfate conjugation (Sulfation) is less frequent than glucuronide conjugation (glucuronidation).
- The most common functional groups undergoing sulfation are free OH, NH_2 & NHOH, it occurs mainly for phenols > alcohols > aromatic amines > N-hydroxyl.
- Sulfation is mainly used to conjugate endogenous compounds such as steroids, heparin, chondroitin, catecholamines, and thyroxine.
- The sulfate conjugation process involves activation of inorganic sulfate (SO_4) to the coenzyme 3′-phosphoadenosine- 5′-phosphosulfate (PAPS).
- Subsequent transfer of the sulfate group from PAPS to the accepting substrate is catalyzed by sulfotransferases.



Formation of PAPS and sulfate conjugates

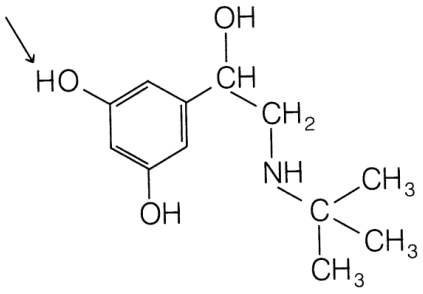
- Sulfate conjugation generally leads to water-soluble and inactive metabolites.
- However, the *O*-sulfate conjugates of some *N*-hydroxy compounds give rise to chemically reactive intermediates that are toxic.

- Phenols are the main group of substrates which undergo sulfate conjugation.
- Examples for phenol containing drugs being conjugated by sulfation include α-methyldopa, salbutamol and terbutaline as shown below.



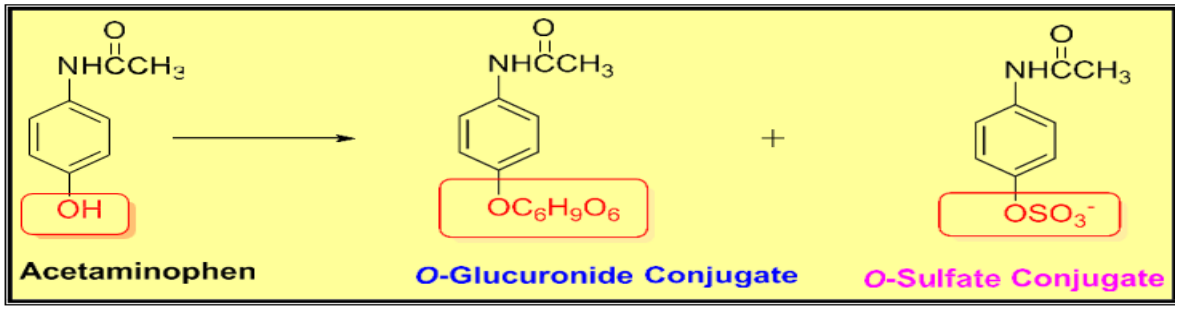
α-Methyldopa

Salbutamol
(Albuterol)



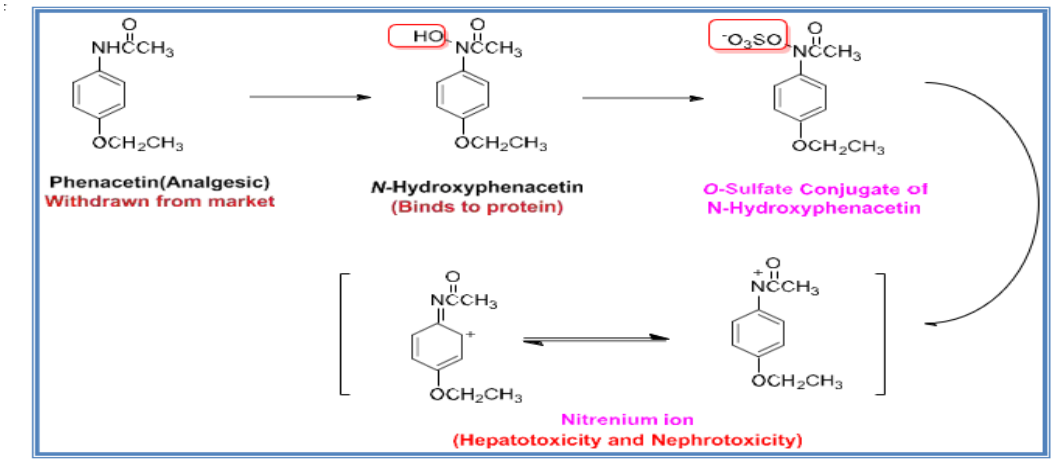
Terbutaline

- Glucuronidation of phenols is frequently a competing reaction to sulfation, the major urinary metabolite acetaminophen is the O-glucuronide conjugate, with the *O*-sulfate conjugate being formed in small amounts (minor) as shown below.
- Exception neonates and young children (ages 3–9 years) have a decreased glucuronidating capacity because of undeveloped glucuronyltransferases or low levels these enzymes. Sulfate conjugation, however, is well developed and becomes the major route of acetaminophen conjugation in these children as shown below.



Although sulfate-conjugation is a detoxification reaction, it may produce reactive toxic molecule if it occurs on some N-OH containing compounds.

The hepatotoxicity and nephrotoxicity associated with phenacetin is due to its metabolism to *N*-hydroxyphenacetin and subsequently conjugated with sulfate. The *O*-sulfate conjugate of *N*-hydroxyphenacetin generates chemically reactive electrophile (nitrenium ion) binds covalently to proteins as shown below.

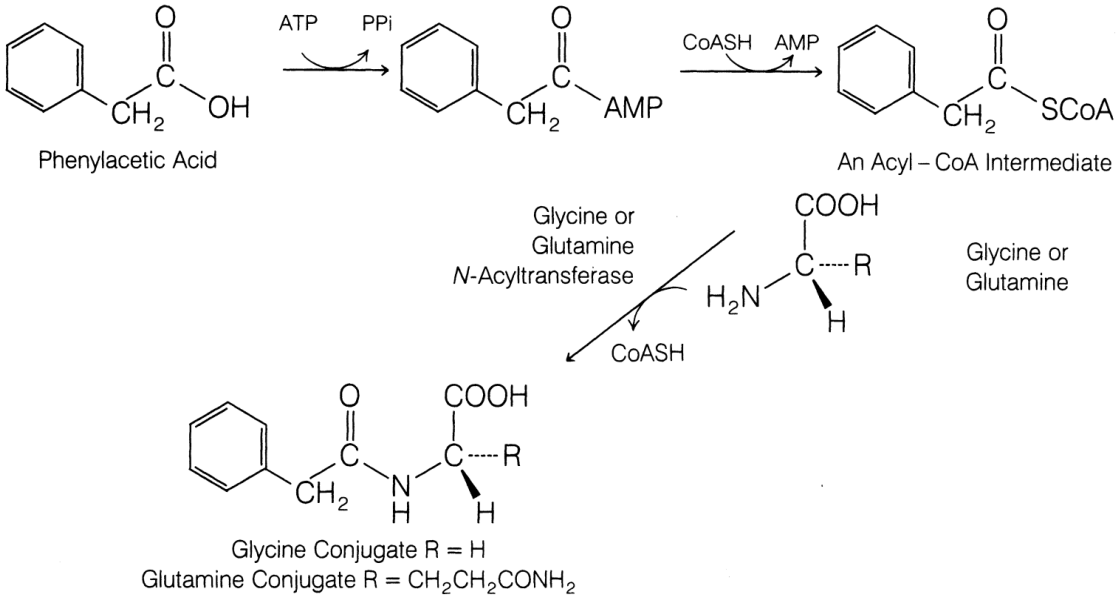


This pathway and arene oxides pathway represent metabolic pathways lead to reactive intermediates that are responsible toxicity associated with some drugs and xenobiotics.

C.Amino Acids Conjugation(Glycin&Glutamine)

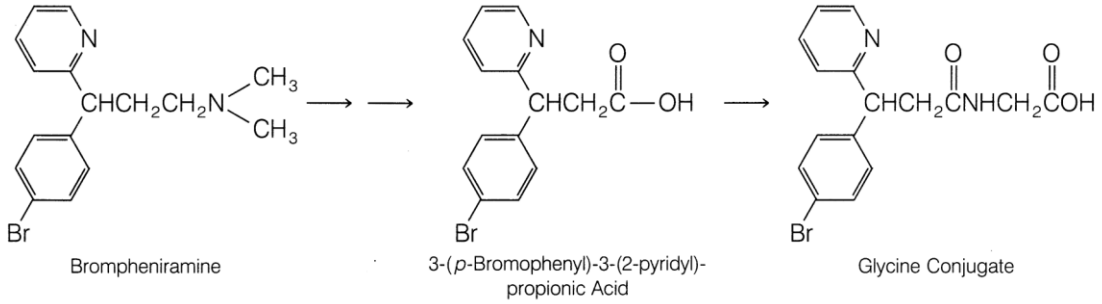
Amino acids conjugation is less frequent than glucuronide conjugation (glucuronidation). The functional group undergoing amino acids conjugation is carboxyl group (COOH) particularly aromatic acids and arylalkyl acids.

In contrast with glucuronic acid and sulfate, glycine and glutamine are not converted to activated coenzymes, instead, the carboxylic acid (substrate) is activated with adenosine triphosphate (ATP) and coenzyme A (CoA) to form an acyl-CoA complex. This complex (intermediate), in turn, acylates glycine or glutamine by the aid of glycine or glutamine *N*-acyltransferase enzymes.

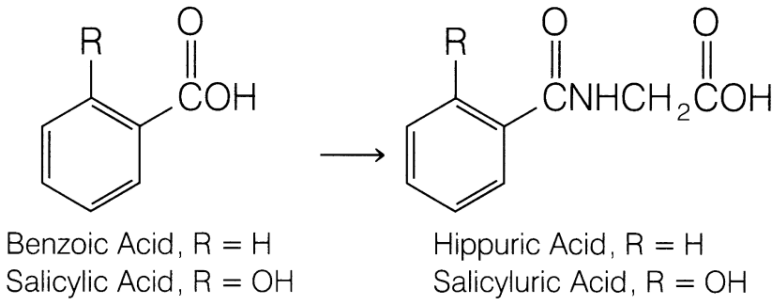


Formation of glycine and glutamine conjugates of phenylacetic acid

For example, brompheniramine is oxidized to a propionic acid metabolite that is conjugated with glycine as follows:



Benzoic acid and salicylic acid undergo glycine conjugate as shown below:



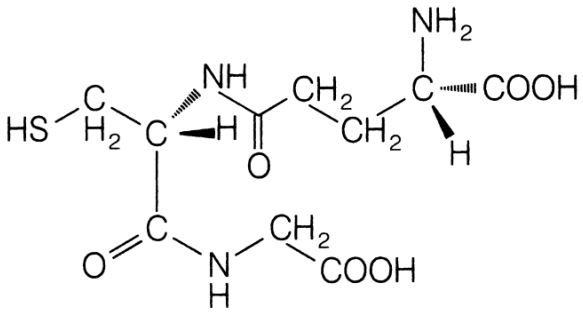
D. Glutathione (GSH) or Mercapturic Acid Conjugates (Conjugation)

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

Reactive electrophilic species exert their toxicity (e.g., tissue necrosis, carcinogenicity, mutagenicity, teratogenicity) by combining covalently with nucleophilic groups present in vital cellular proteins and nucleic acids.

GSH protects vital cellular constituents against chemically reactive species by its nucleophilic SH group. The SH group reacts with electron-deficient compounds to form *S*-substituted GSH adducts

GSH is a tripeptide (γ-glutamyl-cysteinyl glycine, structure below.



Glutathione

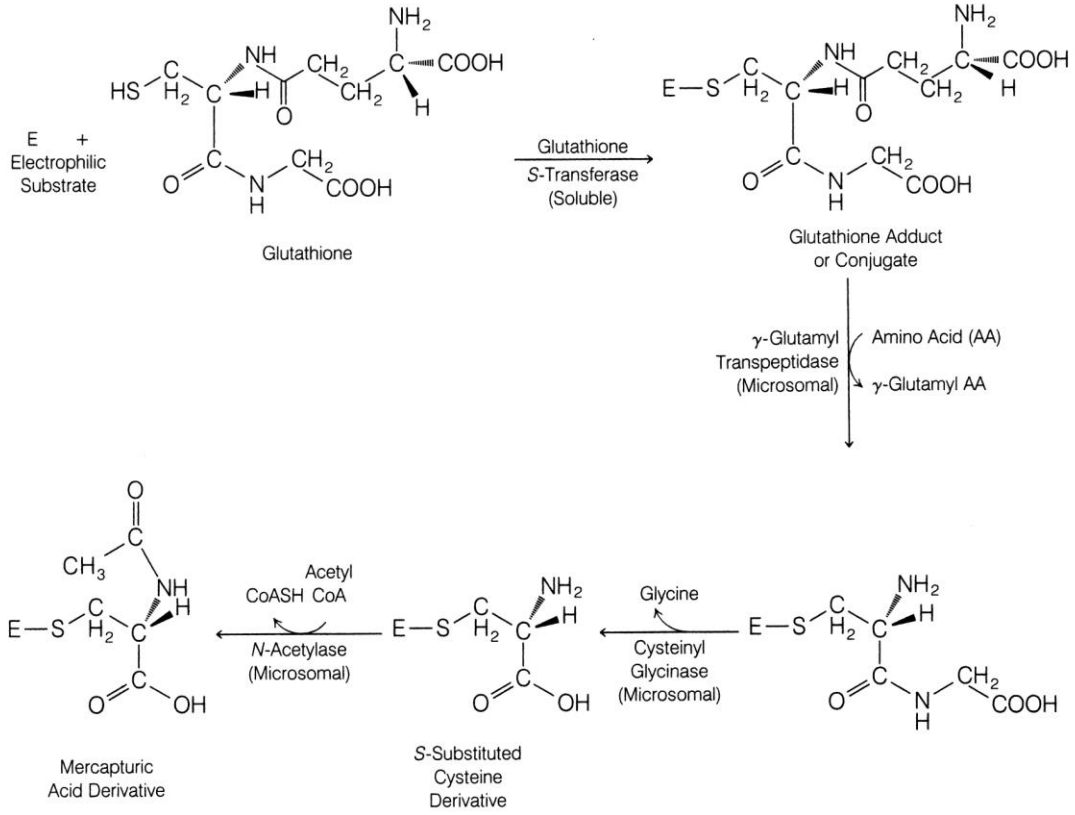
Xenobiotics conjugated with GSH usually are not excreted as such, but undergo further biotransformation to give *S*-substituted *N*-acetylcysteine products called mercapturic acids.

This process involves enzymatic cleavage of two amino acids (namely, glutamic acid and glycine) from the initially formed GSH adduct and subsequent N-acetylation of the remaining *S*-substituted cysteine residue.

Conjugation of substrates with GSH is catalyzed by enzymes known as GSH *S*-transferases.

Unlike other conjugative phase II reactions, GSH conjugation does not require the initial formation of an activated coenzyme or substrate. The inherent reactivity of the nucleophilic GSH toward an electrophilic substrate usually provides sufficient driving force.

A major structural requirement for the substrates susceptible to GSH conjugation is to be sufficiently electrophilic.



Formation of GSH conjugates of electrophilic xenobiotics or metabolites (E) and their conversion to mercapturic acids

As discussed previously, arene oxides and epoxides are intermediary products formed from CYP oxidation of aromatic compounds (arenes) and olefins, respectively are "neutralized" or detoxified by GSH *S*-conjugation.

2. Acetylation

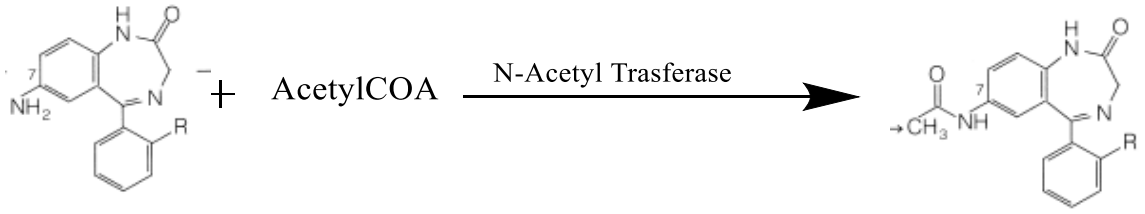
The objective of this metabolic pathway is to terminate the biological activity and detoxification of drugs and xenobiotics.

The functional group undergoing acetylation is primary amino group (NH_2), this includes:

a. Primary aromatic amines ($ArNH_2$),
b. Sulfonamides ($H_2NC_6H_4SO_2NHR$).

c. Hydrazines (-$NHNH_2$).
d. Hydrazides (-$CONHNH_2$).
e. Primary aliphatic amines (RNH_2; $PhNH_2$).

The amide derivatives formed from acetylation of these amino functionalities are generally inactive and nontoxic. A few reports indicate, that acetylated metabolites may be as active as parent compounds (e.g., *N*-acetylprocainamide), or more toxic than parent compounds (e.g., *N*-acetylisoniazid). Water solubility is not enhanced greatly by *N*-acetylation. The activated coenzyme is Acetyl-CoA, and the catalytic enzymes are N-acetyltransferases as shown below.



The acetylation pattern of several drugs (e.g., isoniazid, hydralazine, procainamide) in the human population displays a bimodal character in which the drug is conjugated either rapidly or slowly with acetyl-CoA. This phenomenon is termed acetylation polymorphism. This variation is genetic and is caused mainly by differences in *N*-acetyltransferase activity.

Individuals are classified as either:

a. Slow acetylator (e.g., Egyptians and some Western European groups)
b. Rapid acetylator (e.g., Eskimos and Asians)
c. Other populations are intermediate between these two extremes.

Because of the bimodal distribution of the human population into rapid and slow acetylators, there is a significant individual variation in therapeutic and toxicological responses to drugs displaying acetylation polymorphism.

Slow acetylators seem more likely to develop adverse reactions, whereas rapid acetylators are more likely to show an inadequate therapeutic response to standard drug doses.

The antituberculosis drug isoniazid illustrates an example on acetylation polymorphism.

3. Methylation

The objective of this metabolic pathway is to:

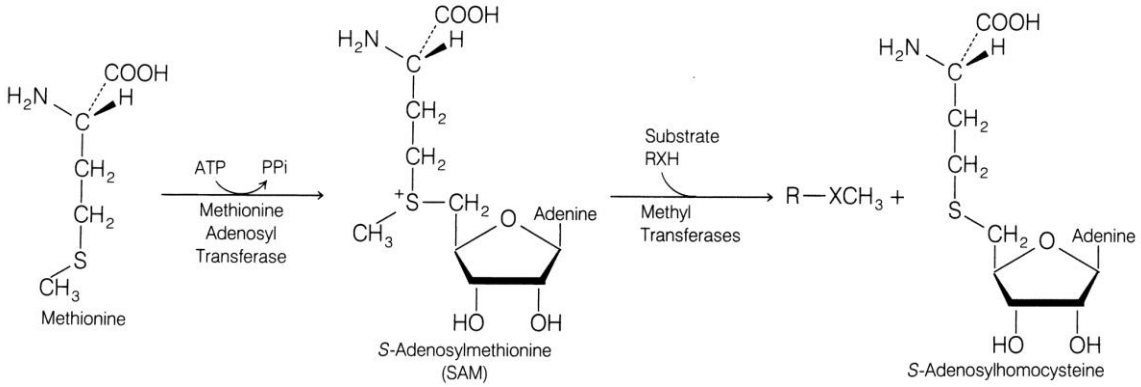
a) Terminate the biological activity of biogenic amines (e.g., norepinephrine , dopamine, serotonin, and histamine).
b) The biosynthesis of many endogenous compounds (e.g., epinephrine and melatonin).

Methylation, represents only a minor pathway for the metabolism of drugs and xenobiotics.

Methylation generally does not lead to polar or water-soluble metabolites, except when it creates a quaternary ammonium derivative.

Most methylated products tend to be pharmacologically inactive, although there are a few exceptions.

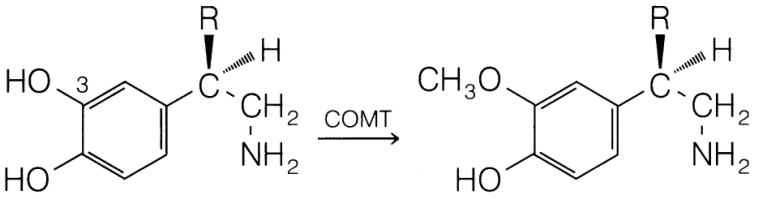
The activated coenzyme involved in methylation reactions is *S*-adenosylmethionine (SAM). Methylation is catalyzed by various Methyltransferases (MTs) as shown below:



MTs importances in the metabolism of xenobiotics include:

catechol-*O*-methyltransferase (COMT), phenol-*O*-methyltransferase, nonspecific *N*-methyltransferases and *S*-methyltransferases.

The enzymes, COMT carries out *O*-methylation of important neurotransmitters as norepinephrine and dopamine and thus terminates their activity.

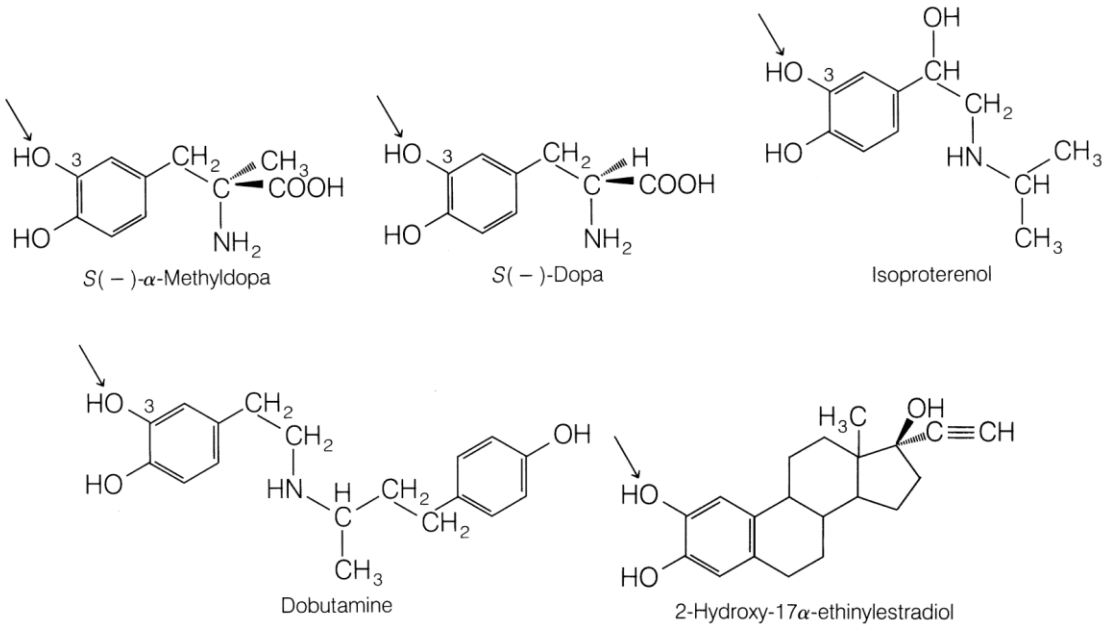


Norepinephrine, R = OH
Dopamine, R = H

Normetanephrine, R = OH
3-Methoxytyramine, R = H

Transferases that specifically methylate histamine, serotonin, and epinephrine are not usually involved in the metabolism of xenobiotics**.**

Examples of drugs that undergo significant *O*-methylation by COMT are illustrated below:



S(−)-α-Methyldopa

S(−)-Dopa

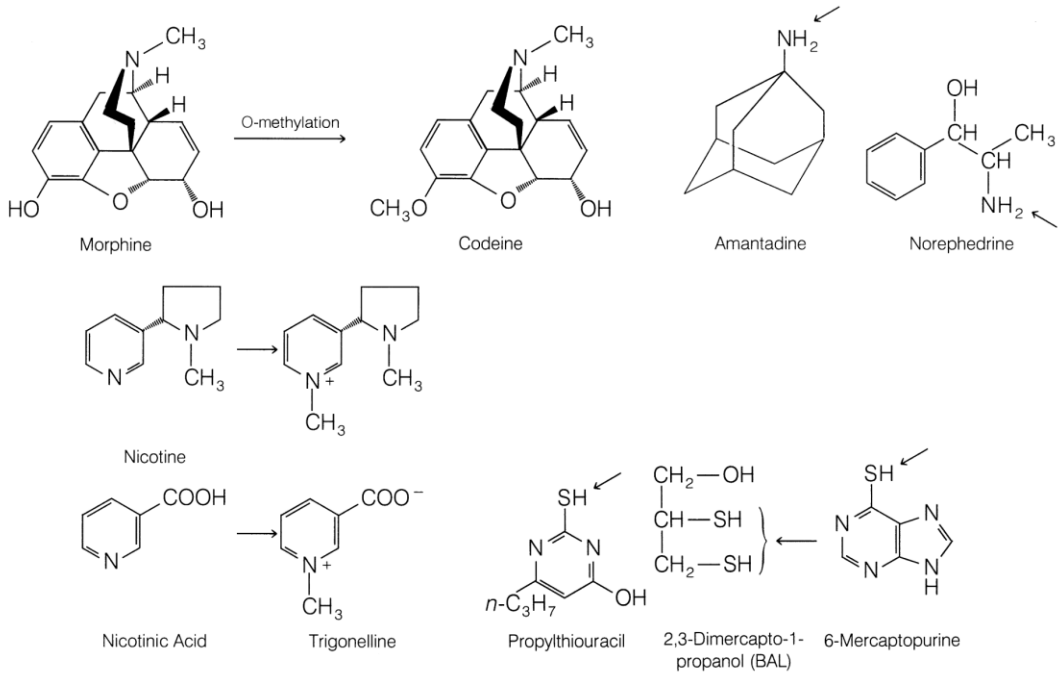
Isoproterenol

Dobutamine

2-Hydroxy-17α-ethinylestradiol

In the above four drugs, COMT selectively *O*-methylates only the phenolic OH at C-3. Bismethylation does not occur. COMT needs catecholic functionality to carry out methylation as above.

Other examples of drugs that undergo significant *O*-methylation, N- methylation & S-methylation are illustrated below:



Factors Affecting Drug Metabolism

Drugs and xenobiotics often are metabolized by several different phase I and phase II pathways to give several metabolites.

The relative amount of any particular metabolite is determined by the concentration and activity of the enzyme(s) responsible for the biotransformation.

The rate of metabolism of a drug is particularly important for its pharmacological action as well as its toxicity.

If the rate of metabolism of a drug is decreased, this generally, increases the intensity and duration of the drug action. In addition, decreased metabolic elimination may lead to accumulation of toxic levels of the drug and vis-versa.

An increased rate of metabolism decreases the intensity and duration of action as well as the drug's efficacy.

In addition to the concentration and activity of the enzyme(s), many other factors may affect drug metabolism. These are

1. **Chemical factor (Chemical Structure):**
2. **Biological factors:** Age, species and strain, genetic or hereditary factors, sex, enzyme induction, enzyme inhibition, physiological or disease state, drug dosing, nutritional status and drug route of administration.

Stereochemical Aspects of Drug Metabolism

The preferential interaction of one stereoisomer with drug-metabolizing enzymes may lead differences in metabolic pathways and the amount of metabolites for the two enantiomers

This is due to many factors which include:

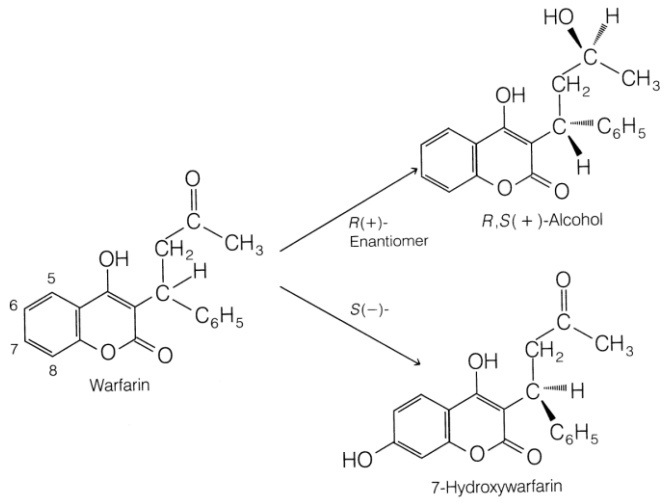
a. **Substrate stereoselectivity.**
b. **Product stereoselectivity.**
c. **Regioselectivity**

a. Substrate stereoselectivity

The term ***substrate stereoselectivity*** is used to denote a preference for one stereoisomer as a substrate for a metabolizing enzyme or metabolic process.

For instance, the (+) enantiomer of propranolol undergoes more rapid metabolism than the corresponding (-) enantiomer.

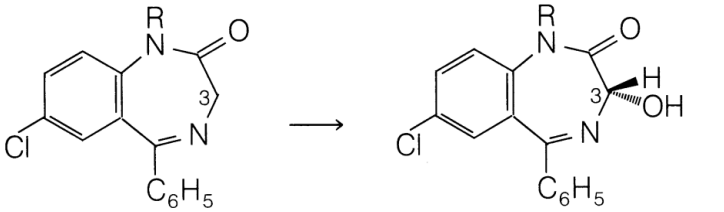
Dramatic differences in the metabolic profile of two enantiomers of warfarin also have been noted. The (*S*) (-)-isomer is 7-hydroxylated (aromatic hydroxylation), whereas the (*R*)(+)-isomer undergoes keto reduction to yield the (*R,S*) warfarin alcohol as the major plasma metabolite as shown below:



b. product stereoselectivity.

It means the preferential metabolic formation of a stereoisomeric product (formation of one stereoisomer as predominant metabolic product).

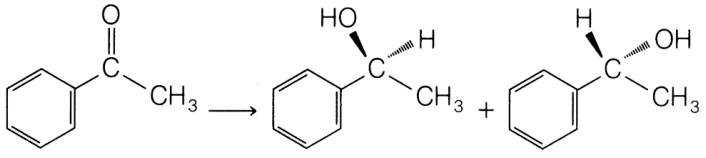
Oxidative biotransformations display product stereoselectivity as shown below:



Diazepam, R = CH_3
Desmethyldiazepam, R = H

(3*S*) *N*-Methyloxazepam, R = CH_3
S(+)-Oxazepam, R = H

The, bio reduction of ketone xenobiotics, as a general rule, produces predominantly one stereoisomeric (*S*) (-)- alcohol as shown below:



Acetophenone

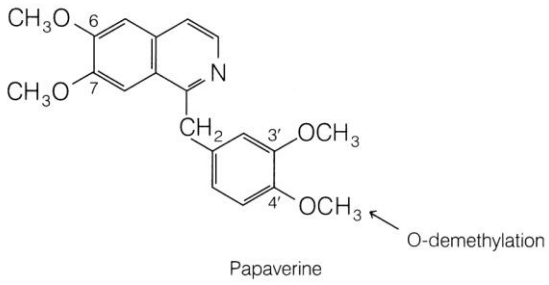
S(−)-Methyl Phenyl Carbinol (75%)

R(+)-Methyl Phenyl Carbinol (25%)

c. Regioselectivity

The term **regioselectivity** describes the selective metabolism of two or more similar functional groups (e.g., OCH3, OH, NO2) or two or more similar atoms that are positioned in different regions of a molecule.

For example, of the four methoxy groups present in papaverine, the 4-OCH3 group is regioselectively O-demethylated alcohol as shown below:



Papaverine

Pharmacologically Active Metabolites

The traditional idea that drugs metabolites are inactive and insignificant in drug therapy has changed dramatically in recent years. Increasing evidence indicates that many drugs are biotransformed to pharmacologically active metabolites that contribute to the therapeutic as well as toxic effects of the parent compounds. Prodrugs (pharmacologically inactive) are bioactivated enzymatically to the pharmacologically active drug as in chloramphenicol palmitate which is ester prodrug hydrolyzed by esterase to the active drug (chloramphenicol).