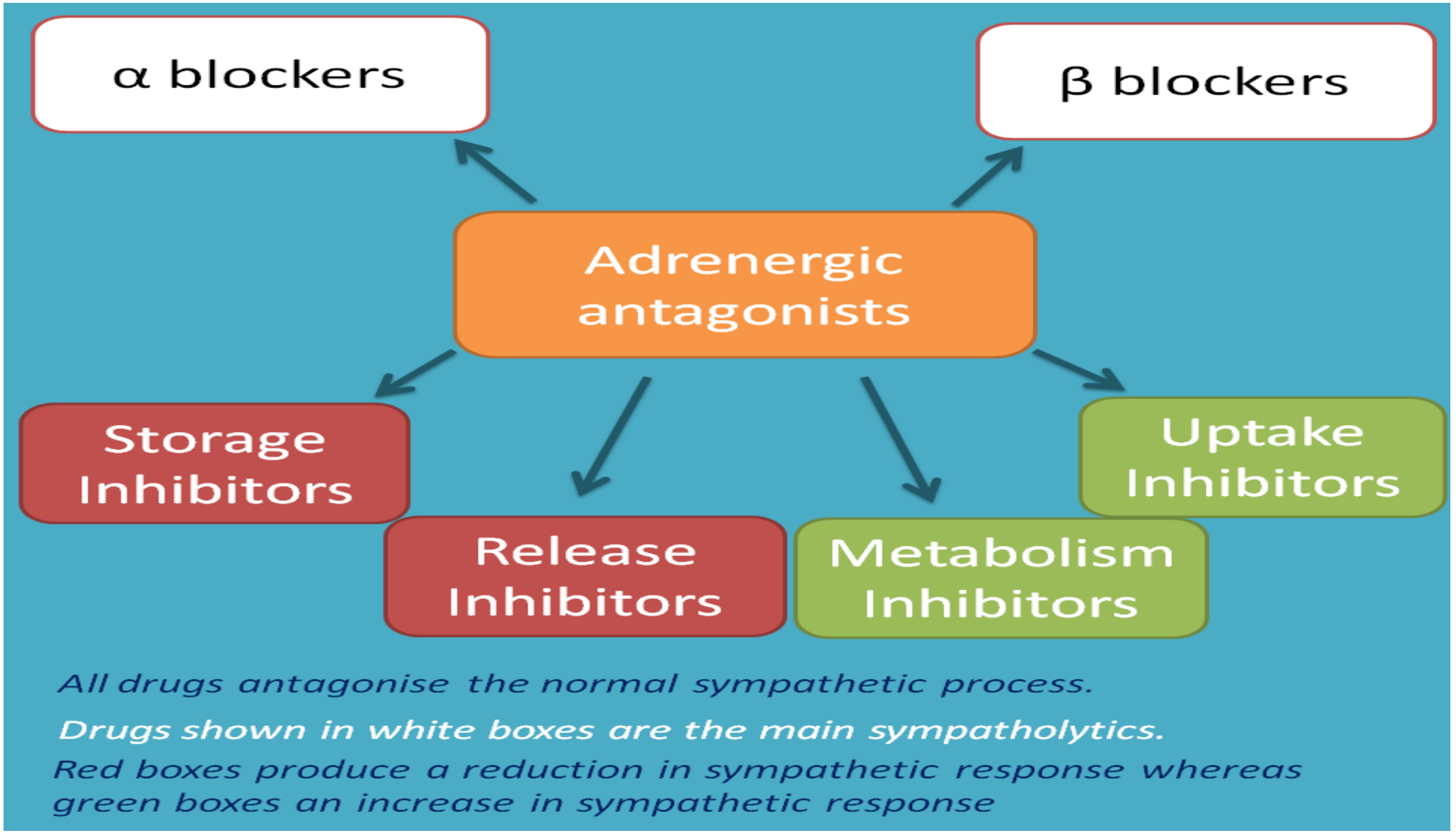
ADRENERGIC ANTAGONISTS
α and β BLOCKERS
Sympatholytics


α blockers
β blockers
Adrenergic antagonists
Storage Inhibitors
Release Inhibitors
Metabolism Inhibitors
Uptake Inhibitors
All drugs antagonise the normal sympathetic process.
Drugs shown in white boxes are the main sympatholytics.
Red boxes produce a reduction in sympathetic response whereas green boxes an increase in sympathetic response

α-BLOCKERS

- These α-agonists cause vasoconstriction and raise blood pressure.
- Therefore, α-antagonists (α-blockers) should be therapeutically used as antihypertensive agents.
- The α-antagonists are structurally diverse with little resemblance to α-agonists.
- **Classification:**
- 1. Non-selective α-blockers:

  Tolazoline and Phentolamine

- 2. Irreversible α-blockers:

  Phenoxybenzamine.

- 3. Selective α1-blockers:

  Prazosin, Terazosin, Doxazosin, Alfuzosin and Tamsulosin.

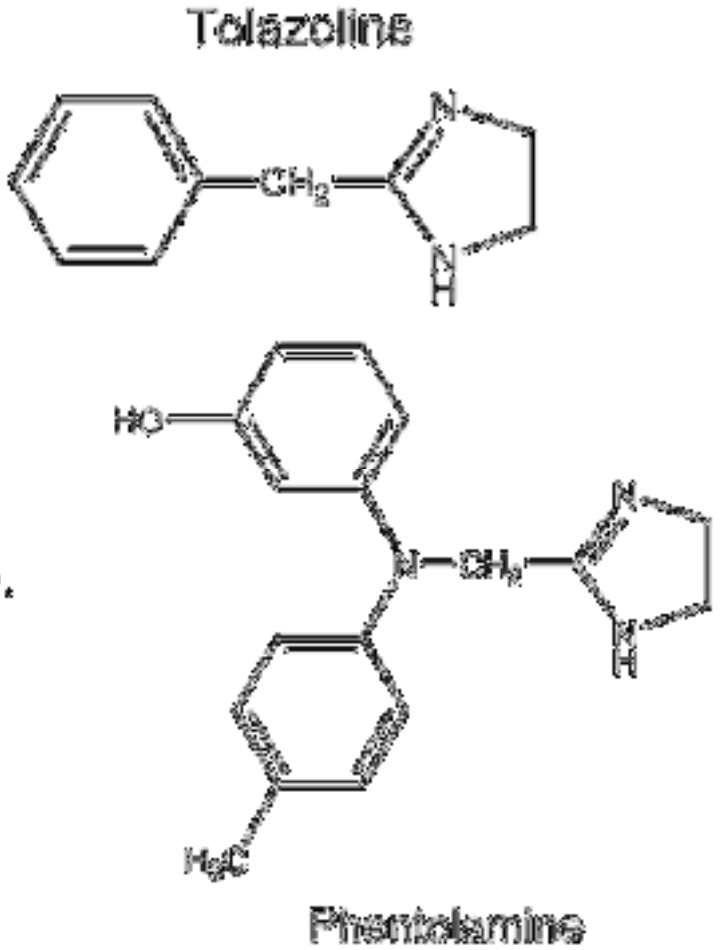
- 4. Selective α2-blockers:

  Yohimbine, Corynanthine, Mirtazapine, Methysergide and Dihydroergotamine.

https://youtu.be/41Xloc_vvX8

TOLAZOLINE AND PHENTOLAMINE

- Both are imidazoline derivatives.
- Competitive nonselective α-blockers.
- The structure of **tolazoline** is similar to the imidazoline α 1-agonists like naphazoline oxymetazoline,tetrahydrozoline & xylometazoline.
- But it does not have the lipophilic substituents required for agonist activity.



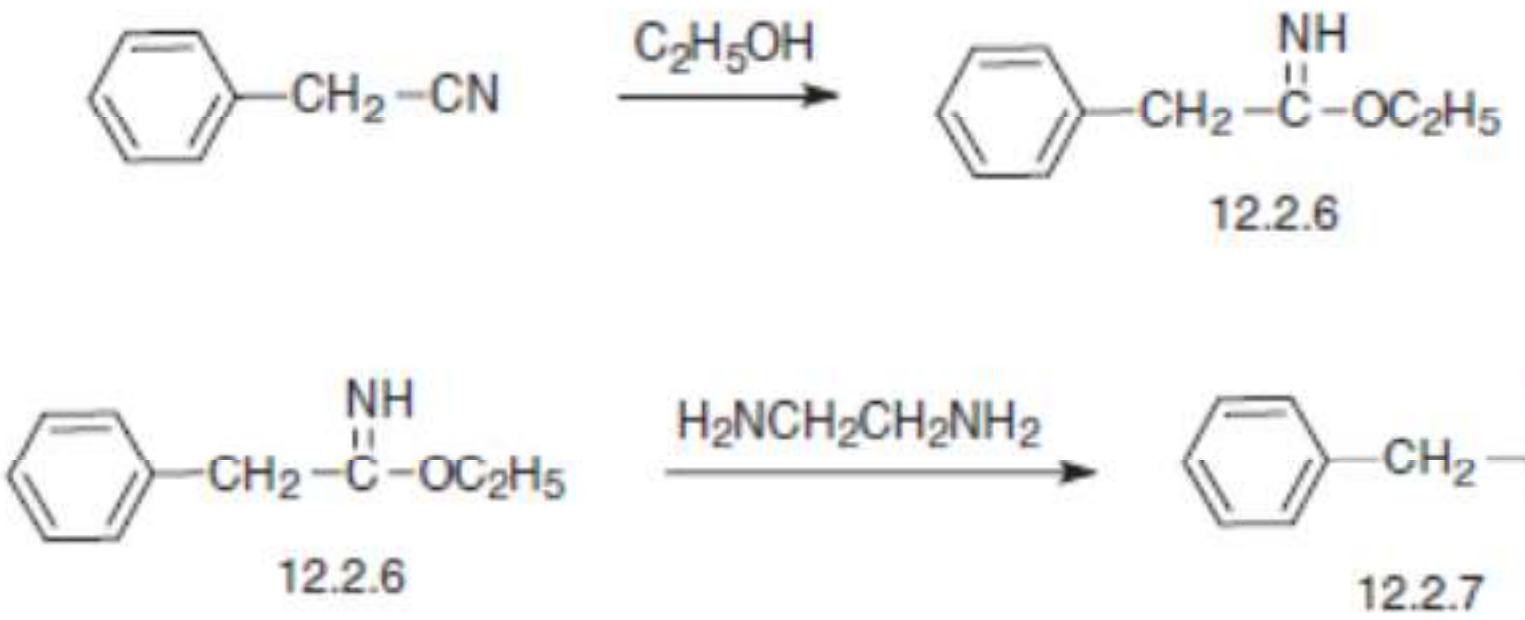
- The type of group attached to the imidazoline ring dictates whether an imidazoline is an agonist or a blocker.
- But neither drug is useful in treating essential hypertension for following reasons.
- (a) Tolazoline and phentolamine have both α1- and α2-blocking activity and produce tachycardia.
- (b) The blocking actions of these agents at presynaptic α2-receptors contribute to their cardiac stimulatory effects by releasing norepinephrine.

- The blocking action of **tolazoline** is relatively weak.
- Its histamine-like and acetylcholine-like agonistic actions contribute to its vasodilatory activity.
- Its histamine-like effects include stimulation of gastric acid secretion.
- It is inappropriate for administration to patients who have gastric or peptic ulcers.
- It has been used to treat Raynaud syndrome and other conditions involving peripheral vasospasm.

- Tolazoline is available in an injectable form and is indicated for use in persistent pulmonary hypertension of the newborn when supportive measures are not successful.
- Phentolamine is the more effective α-blocker.
- Phentolamine is used to prevent or control hypertensive episodes that occur in patients with pheochromocytoma.
- It also has been used in combination with papaverine to treat impotence.

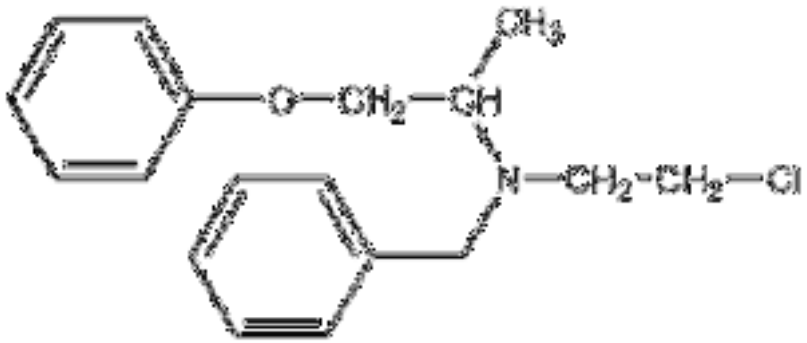
Synthesis of Tolazoline

- Tolazoline, 2-benzyl-2-imidazoline (12.2.7), is synthesized by the heterocyclation of the ethyl ester of iminophenzylacetic acid with ethylendiamine (12.2.6), which forms the desired product (12.2.7).

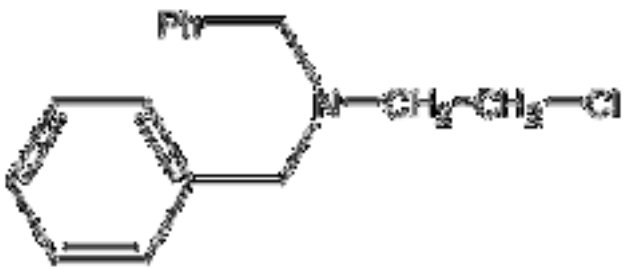


PHENOXYBENZAMINE

- Haloalkylamine derivative.
- Old but powerful α–blocker.
- Irreversible blocker of α1- and α2-receptors.
- Dibenamine is the prototypical drug but currently not in therapeutic use.

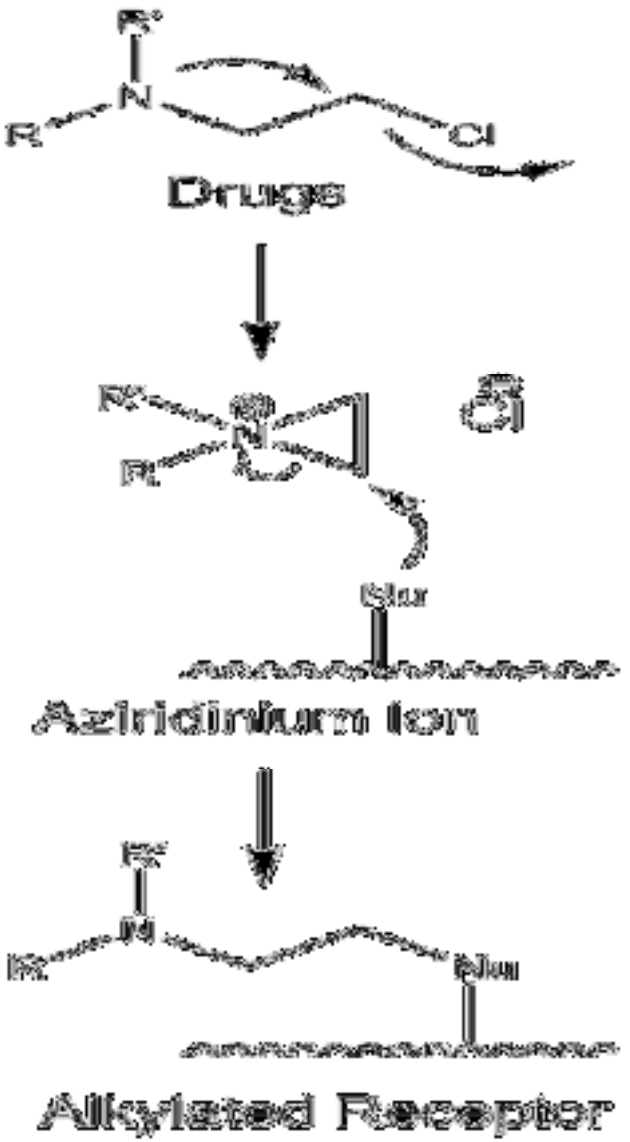


Phenoxybenzamine



Dibenamine

- **General mechanism:**
- The initial step involves the formation of an intermediate aziridinium ion (ethylene iminium ion).
- The positively charged aziridinium ion is electrophilic.
- It reacts with a nucleophilic group on the α-receptors to form a covalent bond between the drug and the receptor.
- Unfortunately, these nonselective drugs alkylate not only α-receptors but also other biomolecules, leading to their toxicity.
- It is thus used only to relieve the sympathetic effects of pheochromocytoma.



- Slow onset of action.
- The effects of a single dose may last 3 to 4 days.
- Only about 20% to 30% of an oral dose is absorbed.
- **The principal peripheral effects are-**

➢ an increase in systemic blood flow,

➢ an increase in skin temperature,

➢ a lowering of blood pressure.

- It has no effect on the parasympathetic system and little effect on the gastrointestinal tract.
- The **most common side effects** are miosis, tachycardia, nasal stuffiness, and postural hypotension.
- **Therapeutic Uses:**
- Oral phenoxybenzamine is used for the **preoperative management of patients with pheochromocytoma** and in the **chronic management of patients whose tumors are not amenable to surgery**.

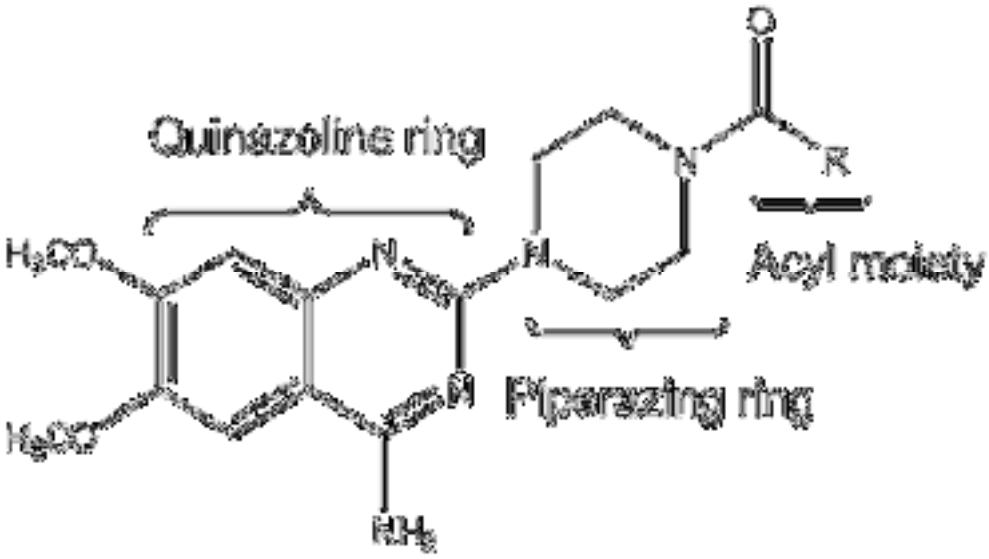
PRAZOSIN , TERAZOSIN, AND DOXAZOSIN

- **These are Quinazoline derivatives.**
- **Selective α1-blockers.**
- They exhibits greater clinical utility due to α1 selectivity.
- They replaced the nonselective haloalkylamine and imidazoline α-blockers.
- **SAR:**
- These agents consist of three components:

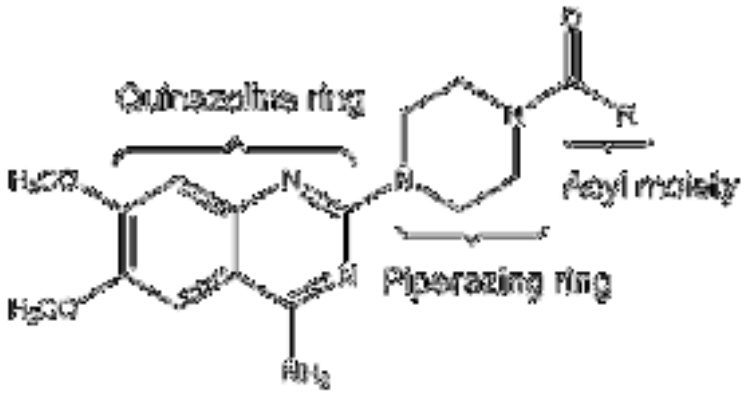
➢ the quinazoline ring,

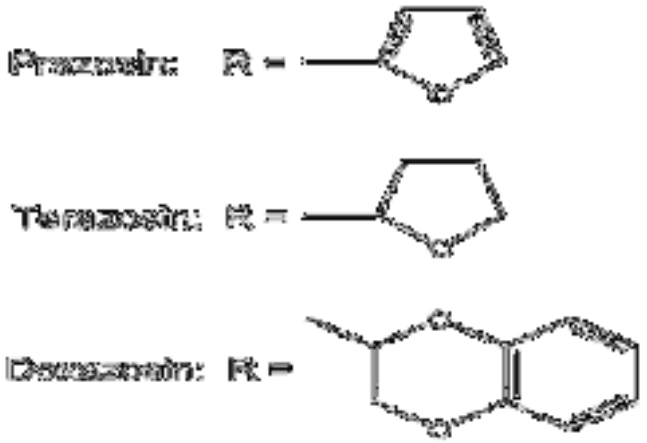
➢ the piperazine ring,

➢the acyl moiety.



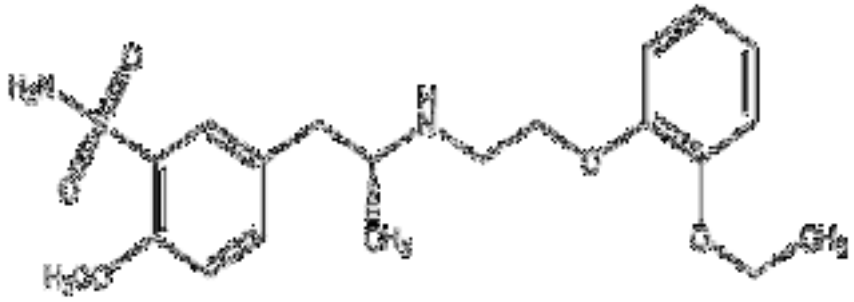
- The 4-amino group on the quinazoline ring is very important for α1-receptor affinity.
- Although they possess a piperazine moiety attached to the quinazoline ring, this group can be replaced with other heterocyclic moieties (e.g., piperidine moiety) without loss of affinity.
- The nature of of the acyl group has a significant effect on the pharmacokinetic properties.





- **Therapeutic Uses:**
- These drugs dilate both arterioles and veins and are thus used in the **treatment of hypertension**.
- They offer distinct **advantages over the other α-blockers**, because they produce peripheral vasodilation without an increase in heart rate or cardiac output.
- This advantage is due to prazosin's ability to block postjunctional α1-receptors selectively without blocking presynaptic α2-receptors.
- Contraction of the smooth muscle of prostate gland, prostatic urethra, and bladder neck is mediated by α1- adrenoceptors, with α1A being predominant, and blockade of these receptors relaxes the tissue.
- For this reason, these agents are also used in the **treatment of BPH**, where they help improve urination flow rates.

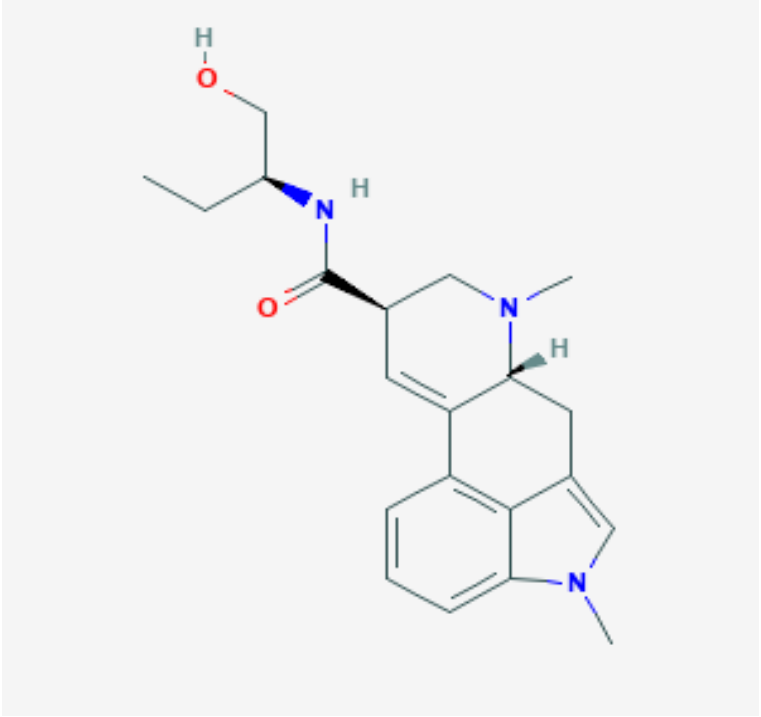
- **Adverse effects:**
- ***First-dose phenomenon*** produces **postural hypotension** which can be minimized by giving low dose at bed time.
- **Uroselective α1-blockers:**
- The single α1A-adrenoceptor subtype is found in the prostatic and urethral smooth muscle cells.
- Blocking these receptors will control **Bening Prostate Hyperplasia.**
- Thus, **alfuzosin and tamsulosin** are **uroselective α1-blockers** and **first-line drugs for treatment of BPH** without utility in treating hypertension.



Tamsulosin

METHYSERGIDE

- An ergot derivative that is a congener of LYSERGIC ACID DIETHYLAMIDE.
- It antagonizes the effects of serotonin in blood vessels and gastrointestinal smooth muscle, but has few of the properties of other ergot alkaloids.
- Methysergide is used prophylactically in migraine and other vascular headaches and to antagonize serotonin in the carcinoid syndrome.
- It is serotonin antagonist and Vasoconstrictor.



- **Mechanism:**
- Methysergide has been shown, in vitro and in vivo, to inhibit or block the effects of serotonin, a substance which may be involved in the mechanism of vascular headaches.
- **Methysergide** interacts with the serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{5A}, 5-HT_{6}, and 5-HT_{7} **receptors** and the α_{2A}-, α_{2B}-, and α_{2C}-**adrenergic receptors**.

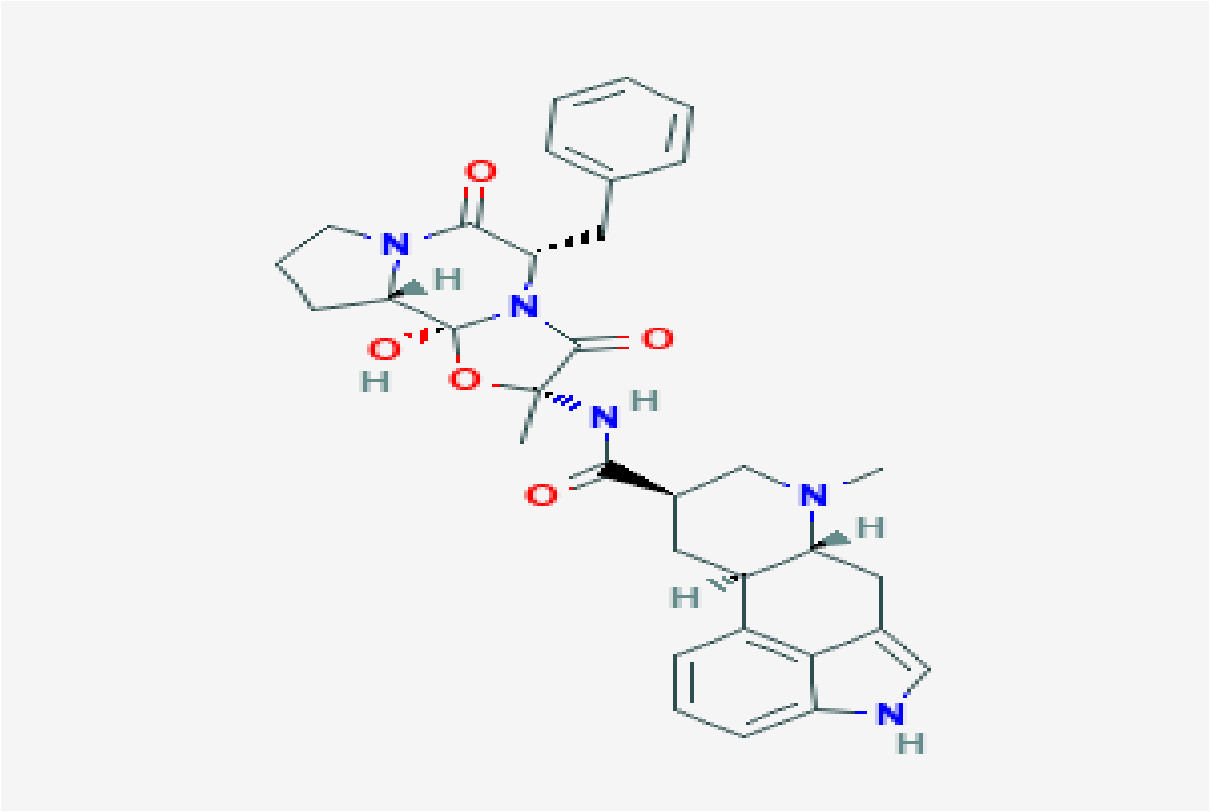
- **Therapeutic Uses:**
- For the prevention or reduction of intensity and frequency of vascular headaches in the following kinds of patients:
- Patients suffering from one or more severe vascular headaches per week; Patients suffering from vascular headaches that are uncontrollable.
- Sometimes useful in suppression of GI hypermotility and spasm and cardiovascular disorders that occur in patients with carcinoid tumor.
- These tumors release large amounts of serotonin into blood stream, and antiserotonin actions of drug are responsible for beneficial effects.

- **Adverse effects and Contraindications:**
- Retroperitoneal fibrosis, pleuropulmonary fibrosis and fibrotic thickening of cardiac valves may occur in patients receiving long-term methysergide maleate therapy. Therefore, this preparation must be reserved for prophylaxis in patients whose vascular headaches are frequent and/or severe and uncontrollable and who are under close medical supervision.
- Contraindications of methysergide therapt include:/ Hypersensitivity to the drug or to tartrazine (FD&C Yellow #5) or any other components of the formulation, pregnancy, lactation, peripheral vascular disease, severe arteriosclerosis, severe hypertension, coronary artery disease, phlebitis or cellulitis of the lower limbs, pulmonary disease, collagen diseases or fibrotic processes, impaired liver or renal function, valvular heart disease, debilitated states and serious infections.

DIHYDROERGOTAMINE

- Dihydroergotamine is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes.
- Dihydroergotamine binds with high affinity to 5-HT_{1D}a and 5-HT_{1D}b receptors.
- It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α2A, α2B and α receptors, and dopamine D2L and D3 receptors.
- The therapeutic activity of Dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT_{1D} receptors.

- The major excretory route of dihydroergotamine is via the bile in the feces.
- Only 6%-7% of unchanged dihydroergotamine is excreted in the urine after intramuscular injection.



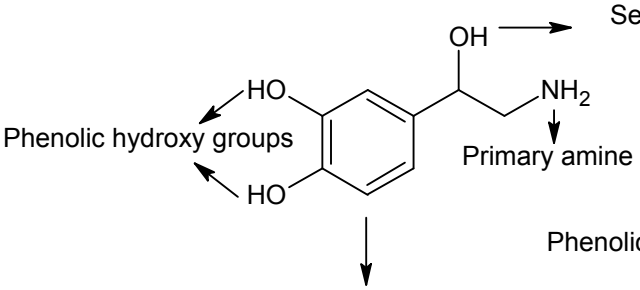
ADRENERGIC DRUGS

INTRODUCTION:

Norepinephrine (Noradrenaline) is the neurotransmitter in adrenergic or sympathetic nervous system. Epinephrine (Adrenaline) also acts similarly in this nervous system, but it is considered as neurohormone rather than neurotransmitter.

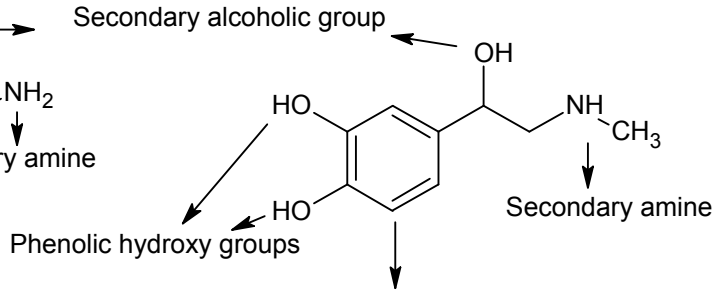
Both are chemically CATECHOLAMINES. Norepinephrine is a primary amine synthesized and released in sympathetic nerves and epinephrine is a secondary amine secreted from adrenal medulla.

Norepinephrine



Ortho dihydroxy benzene
CATECHOL

Epinephrine



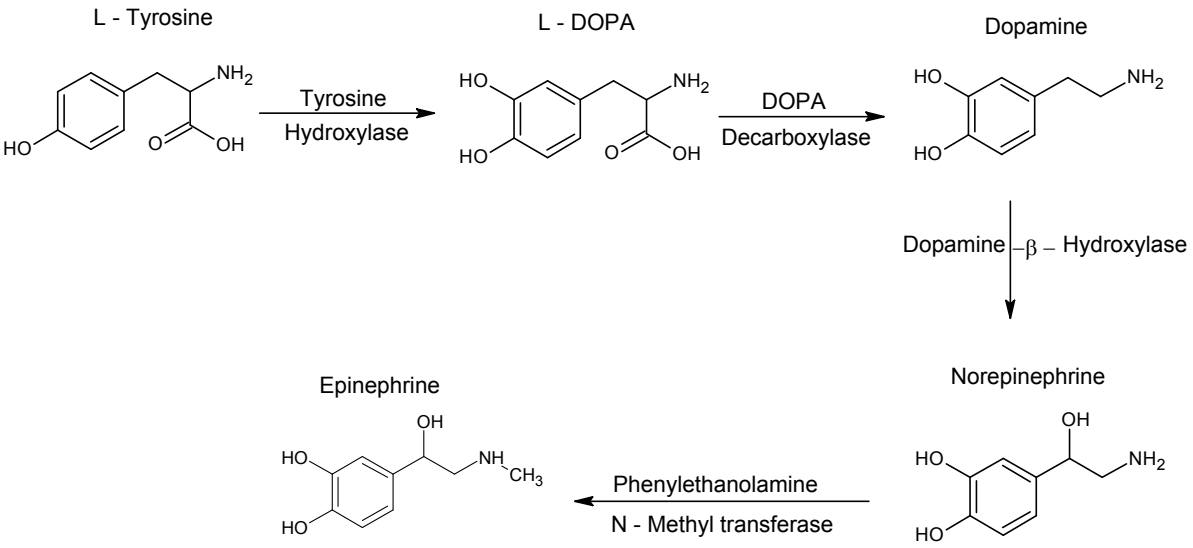
Ortho dihydroxy benzene
CATECHOL

BIOSYNTHESIS:

Norepinephrine is biosynthesized in sympathetic nerve cells and stored in storage vesicles. It is biosynthesized from L-Tyrosine, an aromatic aminoacid.

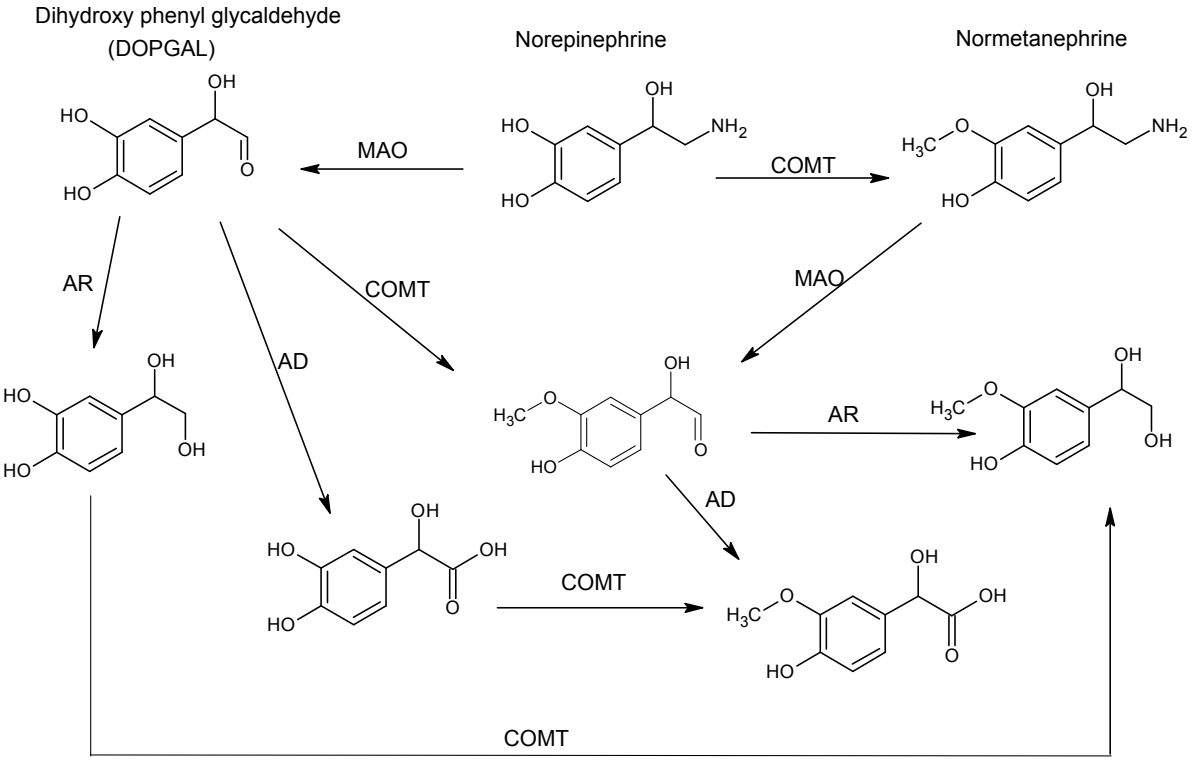
Tyrosine undergoes aromatic hydroxylation catalyzed by tyrosine hydroxylase enzyme resulting in the formation of L-DOPA. Then decarboxylation of L-DOPA catalyzed by DOPA decarboxylase or aromatic –L-aminoacid decarboxylase enzyme forms dopamine. Hydroxylation of dopamine by dopamine –β-hydroxylase enzyme finally gives norepinephrine.

In adrenal medulla also norepinephrine is biosynthesized similarly from L-Tyrosine. But, it undergoes N-methylation rapidly to give adrenaline. This reaction is catalyzed by phenylethanolamine-N-methyl transferase enzyme.



METABOLISM OF NOREPINEPHRINE:

Catecholamines undergo metabolic inactivation by the action of two important enzymes namely COMT (Catecholamine-O-Methyl Transferase) and MAO (MonoAmineOxidase). Norepinephrine, being a catecholamine, undergoes metabolic inactivation by these two enzymes. COMT converts norepinephrine in to normetanephrine and MAO converts norepinephrine in to dihydroxy phenylglycaldehyde (DOPGAL).



AD = Aldehyde dehydrogenase , AR = Aldehyde reductase

“FIGHT” OR “FLIGHT” RESPONSES:

Stimulation of sympathetic nervous system causes “fight” or “flight” responses. These include :-

- Increased rate and force of heart contraction.
- Increased blood pressure.
- Shift of blood flow to skeletal muscles(Adrenaline flush).
- Dilation of bronchioles and pupils.
- Increased blood glucose levels due to increased gluconeogenesis & glycogenolysis.

If a mammalian animal is enraged, it prepares to FIGHT. If it is frightened, it prepares to FLEE.

SELECTED RESPONSES TO STIMULATION OF ADRENORECEPTOR SUBTYPES:

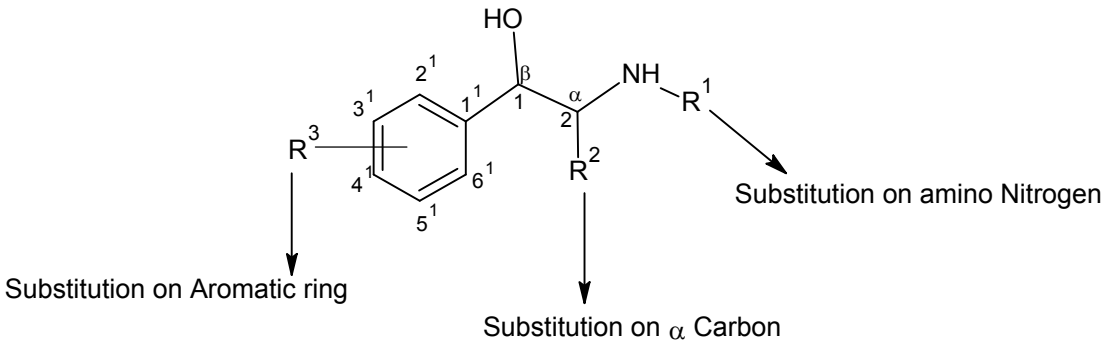
ORGAN / TISSUE	MAJOR RECEPTOR TYPE	RESPONSE
Arterioles, vessels to skeletal muscles.	α-1,α-2. β-2.	Constriction. Dilation.
Eye (radial muscles)	α-1.	Contraction.
Heart	β-1.	Increased rate & force.
Lungs	β-2.	Ralaxation(Bronchodilation).
Fat cells(adipose tissue)	α-1,β-3	Lipolysis.
Liver	α-1,β-2	Increased gluconeogenesis & glycogenolysis.
Uterus(Pregnant)	α-1. β-2.	Contraction. Relaxation.
Intestine	α-1,β-2.	Decreased motility.

SAR OF ADRENERGIC AGONISTS:

Phenylethanolamine agonists:

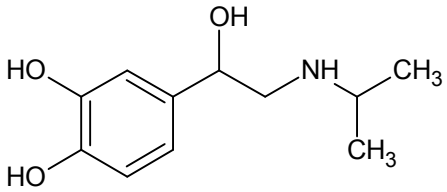
1. A primary or secondary aliphatic amine separated by two carbons from a substituted benzene ring is required for high agonist activity.
2. Hydroxyl substituted carbon (β to the amine or 1st carbon atom) must be in the "R" (rectus) absolute configuration.
   Both norepinephrine and epinephrine shows this rectus configuration. But, most of the commercially available drugs are racemic mixtures ie "R & S" mixtures.
3. Effect of Substitution:
   The effect of various substituents on activity can be studied in 3 different ways.

Phenylethanolamine Agonists



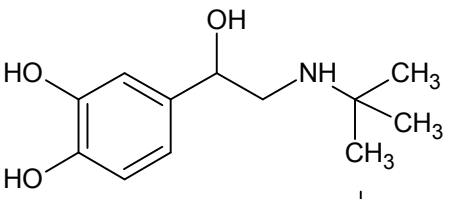
A. Substitution on amino Nitrogen R^1:
   Increase in size of R^1 decreases agonist activity at α-receptors and increase agonist activity at β-receptors.
   Eg: In norepinephrine, R^1 is a hydrogen atom and it is equally active at both α and β receptors.
   In epinephrine, R^1 is a methyl group and it is more active at β receptors.
   In isoproterenol, R^1 is an isopropyl group and it is only active at β-receptors and nonselective at α-receptors.

Isoproterenol



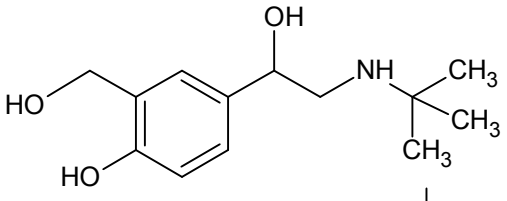
If R^1 is a t-butyl group then selectivity for β-2 receptors increases. Eg: Colterol and albuterol are selective β-2 agonists and are clinically useful bronchodilators.

Colterol



tertiary - Butyl group

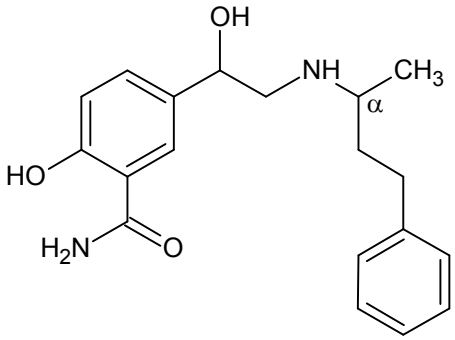
Albuterol



tertiary - Butyl group

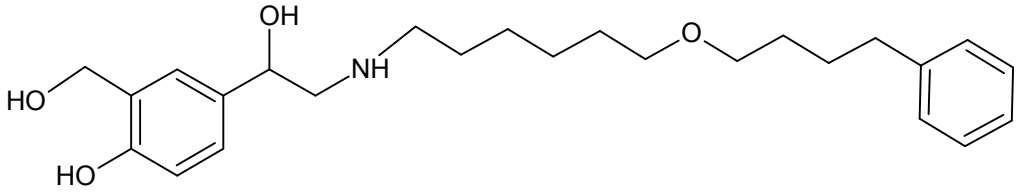
If R^1 becomes larger than t-butyl into aryl-α-methyl alkyl group, then the activity turns to antagonist at both α and β receptors. Eg: Labetalol – mixed α/β antagonist.

Labetalol



If R^1 is an aryl alkyl group with 2-11 carbon/oxygen atoms, β-2 selectivity increases. This structural modification also increases lipophilicity, cell penetration and duration of action. Eg: Salmeterol has more activity on β-2 receptors than β-1 receptor. It is a longer acting drug.

Salmeterol



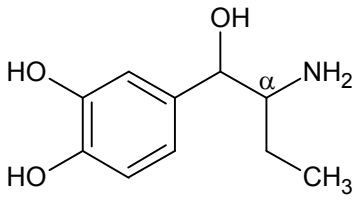
B. Substitution on α-Carbon atom R^2:

Small alkyl groups like methyl or ethyl may be present on the α-Carbon atom. This slows down the metabolism by MAO enzyme but cannot resist COMT metabolism.

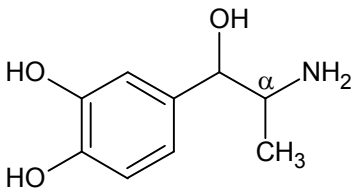
An ethyl group on α-Carbon atom increases β-activity but decreases α-activity. Eg: Ethylnorepinephrine is more active on β-receptors than α-receptors. It undergoes very slow metabolic oxidative deamination catalyzed by MAO but cannot resist metabolism by COMT.

α-Methylnorepinephrine exists in 4 different diastereomeric forms. But, only one isomer 1R,2S erythro isomer is more active on α-receptors. It is more selective on α-2 receptors than α-1 receptors. Therefore it is more suitable for treatment of hypertension.

Ethylnorepinephrine

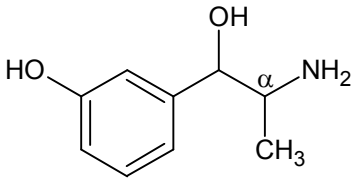


α – Methylnorepinephrine

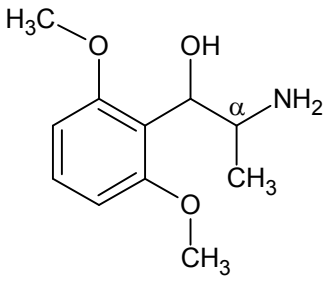


Metaraminol and methoxamine are more α-receptor selective and do not have any activity on β-receptors.

Metaraminol



Methoxamine



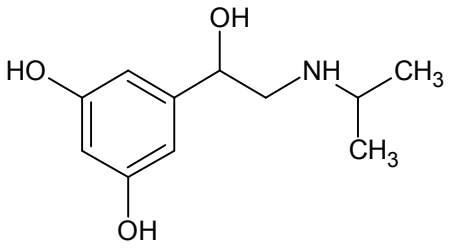
C. Substitution on Aromatic ring R^3:

Dihydroxy substitution on 3rd &4th positions of aromatic ring provides excellent receptor activity for both α & β receptors. But, these drugs are orally inactive due to rapid metabolic inactivation by COMT.

Eg: Norepinephrine & epinephrine are orally inactive.

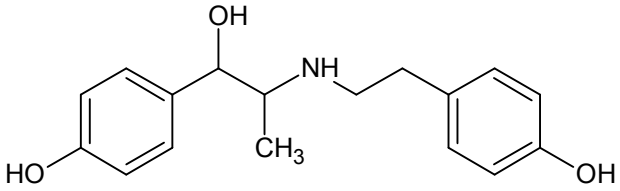
Dihydroxy substitution on 3rd & 5th positions of aromatic ring increases resistance to metabolic inactivation by COMT and also increases β-2 receptor selectivity.
Eg: Metaproterenol is orally active bronchodilator (β-2 receptor selectivity) with very little cardiovascular side effects(β-1 receptor inactivity).

Metaproterenol



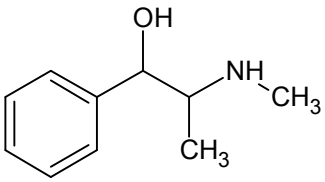
Hydroxymethyl group at 3rd position and hydroxyl group at 4th position of aromatic ring greatly enhance oral activity and β-2 receptor selectivity. Eg: Albuterol.
Atleast one hydrogen bond forming group must be at 4th position of aromatic ring to retain β-receptor activity. Eg: Ritodrine has only one hydroxyl group at 4th position with large substitution on nitrogen atom. It is a β-2 receptor selective and is used to prevent premature labor in pregnant women(β-2 receptor activity relaxes uterus).

Ritodrine



When the aromatic ring has no phenolic hydroxyl substituents, then the drugs may have both direct and indirect activity.
Direct activity is stimulation of an adrenoreceptor by the drug itself. Indirect activity is the result of norepinephrine release or reuptake inhibition.
Eg: Ephedrine

Ephedrine



ADRENERGIC AGONISTS(SYMPATHOMIMETICS):

1. α-1 AGONISTS:
   A. Phenylethanolamines:

   These are selective for α-1 receptors and have minimal cardiac stimulatory properties. They do not undergo metabolism by COMT and so longer acting than norepinephrine. They are strong vasoconstrictors and used in the treatment of shock and hypotension during surgeries.

   Eg: Metaraminol & Methoxamine.

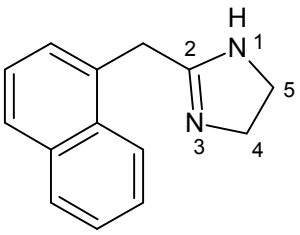
   B. 2-Arylimidazolines:

   These drugs contain a one carbon bridge between 2nd position of imidazoline and a phenyl ring. The general skeleton of phenylethylamine structure is maintained.

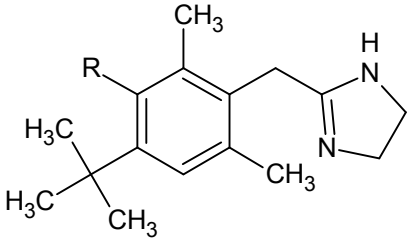
   A bulky alkyl group on phenyl ring improves lipophilicity and selectivity for α-1 receptor and decrease affinity for α-2 receptors.

   They are used only in topical preparations as nasal decongestants and eye drops.

Naphazoline



Xylometazoline R = -H
Oxymetazoline R= -OH



2. α-2 RECEPTOR AGONISTS:
   A. 2-Aminoimidazolines:

   2-Aminoimidazolines structurally resemble 2-arylimidazolines and differ only in having an amino group in the methylene place. This modification gives them guanidine like structure.

   Clonidine and tizanidine are two clinically important drugs of this class. They act specifically on α-2 receptors and are powerful agonists.

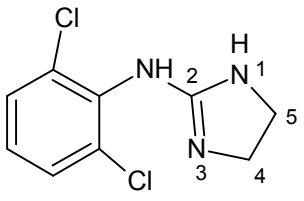
Clonidine acts through α-2A receptor subtype present in CNS and so considered as centrally acting antihypertensive. It also has some α-1 agonist property (vasoconstriction) in periphery, but its central action dominates.

It is a derivative of 2-aminoimidazoline and carries two chlorine atoms on phenyl ring system. These two chlorine atoms enhance lipophilicity and selectivity for α-2 receptors.

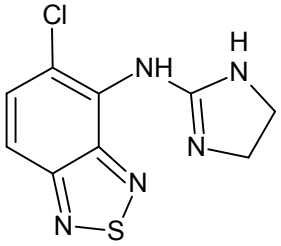
Clonidine is used as an antihypertensive drug. It posses sedative properties and used to treat attention-deficit hyperactivity disorder and nicotine & opiate withdrawal symptomps.

Tiazanidine is a centrally acting muscle relaxant analogue of clonidine. It is used to treat spasm associated with cerebral or spinal cord injury. It acts on α-2c receptor subtype and so has little antihypertensive action. It shows analgesic and antispasmodic activity.

Clonidine



Tizanidine

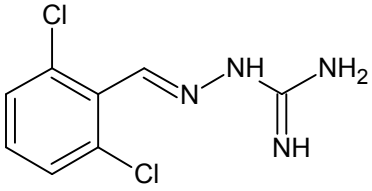


B. Guanidines:

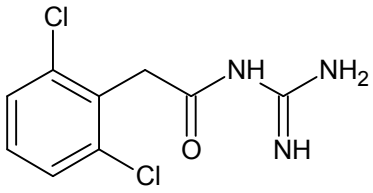
Guanabenz and guanfacine are guanidine derivatives. They are ring opened analogues of clonidine and their mechanism of action is same as that of clonidine.

They are used to treat hypertension.

Guanabenz



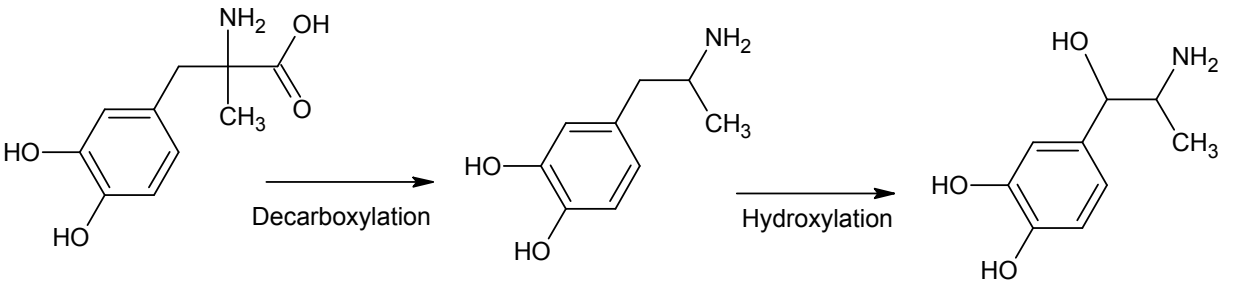
Guanfacine



C. Miscellaneous drugs:

Methyldopa is a prodrug structurally unrelated to clonidine and guanabenz. It is an α-2 agonist acting through its active metabolite α-methylnorepinephrine in CNS. It crosses BBB and undergoes decarboxylation and hydroxylation to give α-methylnorepinephrine in CNS. α-Methyldopamine and α-methylnorepinephrine cannot cross BBB and therefore given in prodrug form. It is used as antihypertensive agent.

Methyldopa — α – Methyldopamine — α – Methylnorepinephrine



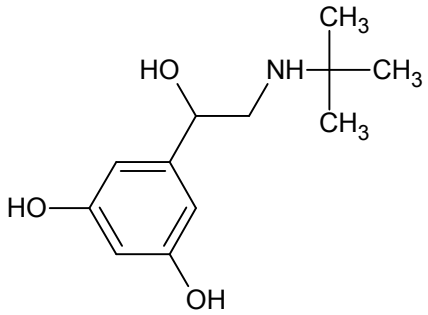
3. β-AGONISTS:

A. β-2 Agonists-Phenylethanolamines:

Most of these Phenylethanolamine β-2 agonists are clinically used as antiasthma drugs (bronchodilators). Eg: Isoproterenol,Colmetrol,Albuterol,Salmeterol and Terbutaline.

Now a day, isoproterenol is not used clinically to treat asthma due to side effects. Remaining drugs are short acting bronchodilators except salmeterol which is a longer acting bronchodilator.

Terbutaline



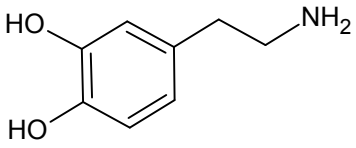
B. β-1 Agonists-Catecholamines:

Dopamine and dobutamine are two clinically used catecholamine derivatives that act through β-1 receptors.

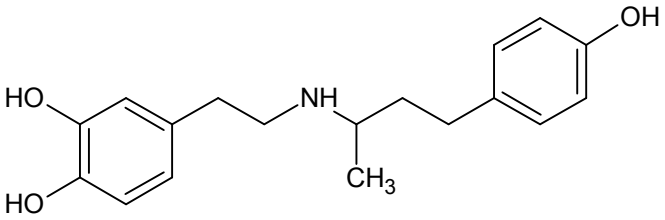
Dopamine stimulates cardiac β-1 receptors through both direct and indirect mechanisms. It is used in the treatment of shock,myocardial infarction and CHF.

Dobutamine is also a cardiac stimulant and used in CHF. It carries a bulky aryl alkyl group on nitrogen atom. It is commercially available as racemate.

Dopamine



Dobutamine



4. MIXED ACTING SYMPATHOMIMETICS:

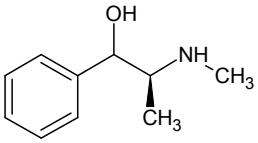
A. Phenyl propanolamines:

(-) Ephedrine is a natural product obtained from ephedra plant. It doesnot have phenolic substituents on phenyl ring but contain an alcoholic hydroxyl group in the side chain. This structural feature gives it a mixed-acting response and good oral activity. It do not undergo metabolic inactivation by COMT.

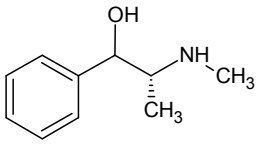
Clinically it is used as bronchodilator , vasopressor , cardiac stimulant and nasal decongestant.

(+) Pseudoephedrine is the threo diastereomer of ephedrine. It causes few CNS side effects than ephedrine. It is widely used as a nasal decongestant.

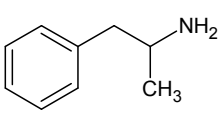
(-) Ephedrine



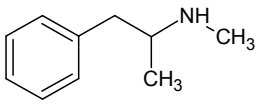
(+) Pseudoephedrine



Amphetamine



Metamphetamine



B. Phenyl isopropylamines:

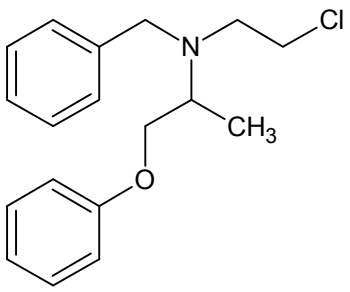
Both amphetamine and methamphetamine do not contain phenolic hydroxyl groups and alcoholic hydroxyl group in side chain. They easily crosses BBB and shows CNS stimulant action.They have central appetite suppressant actions and mostly abused.

Clinically they are used to treat attention-deficit disorder.

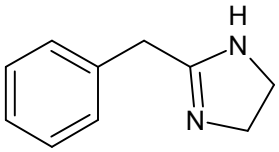
ADRENERGIC ANTAGONISTS:

1. Non-selective α-antagonists:
   Phenoxybenzamine is an old and powerful α-antagonist. Chemically it is a β-halo alkyl amine and alkylates α-receptors. It is a highly reactive alkylating agent. Because of its toxicity , its use is limited to treat pheochromocytoma.
   Both tolazoline and phentolamine are imidazoline derivatives. Once used to treat hypertension but now their use is also limited to treat pheochromocytoma.

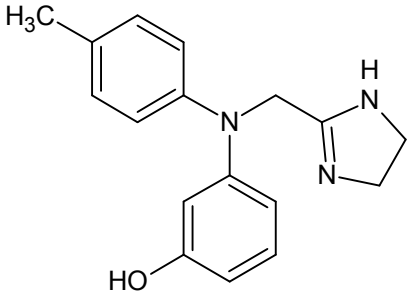
Phenoxy Benzamine



Tolazoline

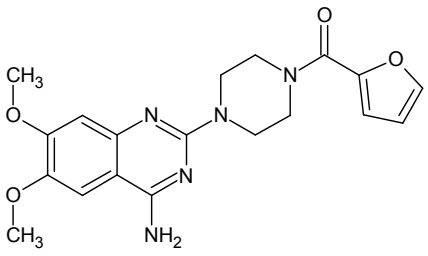


Phentolamine

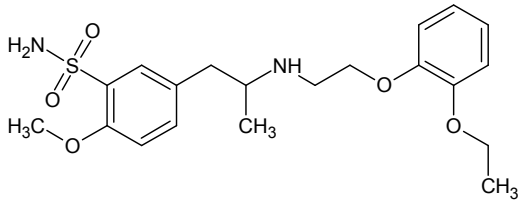


2. Selective α-1-Antagonists:
   Prazosin is the 1st known selective α-1-antagonist. It belongs to quinazoline antihypertensive class that also includes terazosin and doxazosin. These drugs are clinically used to treat hypertension. Terazosin and doxazosin can block α-1-receptor in prostate gland and therefore used in the treatment of Benign Prostate Hyperplasia.
   Tamsulosin is a benzene sulfonamide derivative and do not have any use in the treatment of hypertension. But it is the drug of choice in the treatment of Benign Prostate Hyperplasia.

Prazosin



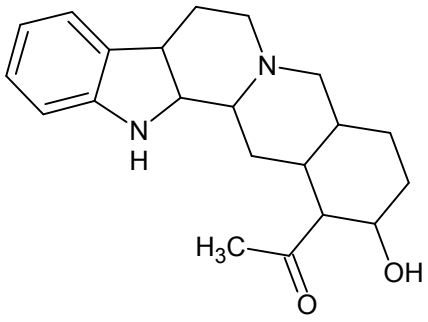
Tamsulosin



3. Selective α-2-antagonist:

   Yohimbine is an indole alkaloid. It has ability to block α-2-receptors and serotonin(5-HT) receptors. It induces hypertension and increases heart rate. It has been used to treat male impotence and postural hypotension.

Yohimbine

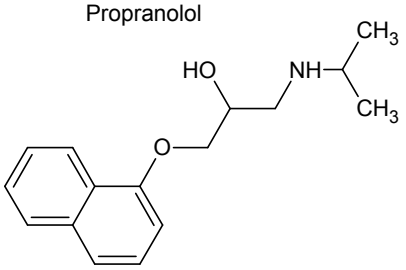


4. Non-selective β-receptor antagonists:

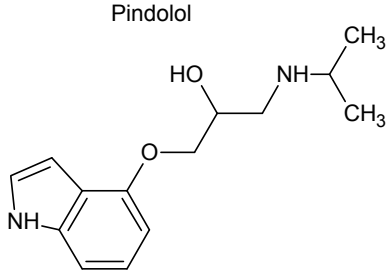
   Propranolol is a prototypical drug with ability to block both β-1 and β-2 receptors. It is an aryloxy propanolamine derivative and is used widely as an antihypertensive drug. It is also used in the treatment of arrhythmiasis , angina pectoris and other cardiac disorders.

   Other drugs in this class are pindolol, sotalol, bunolol,penbutolol and timolol.

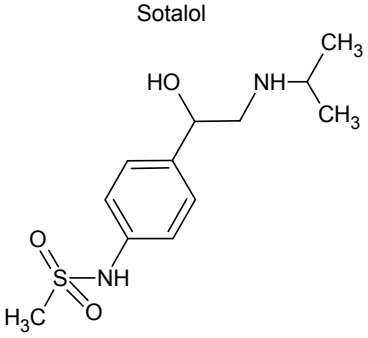
Propranolol



Pindolol



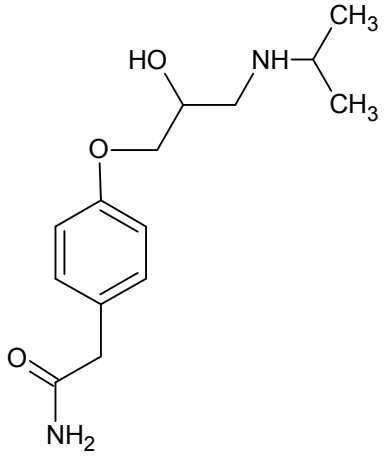
Sotalol



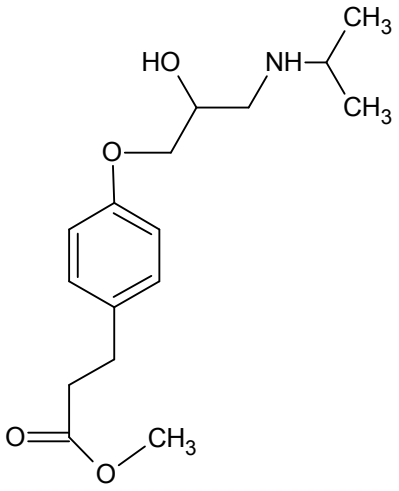
5. Selective β-1 antagonists:

   These drugs are selective blockers of β-1 receptors. They are used in the treatment of hypertension and glaucoma. Eg: Atenolol,Esmolol and Metoprolol.

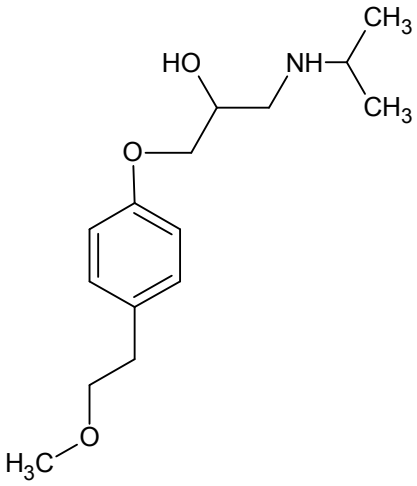
Atenolol



Esmolol



Metoprolol



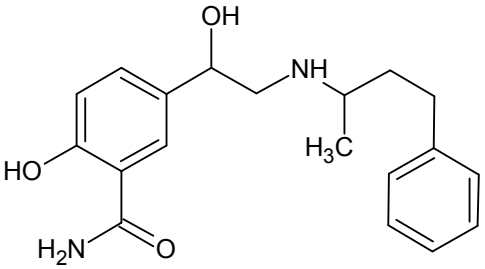
6.Mixed α/β-antagonists:

Labetalol and carvediol are mixed α/β-antagonists. They are used as antihypertensives.

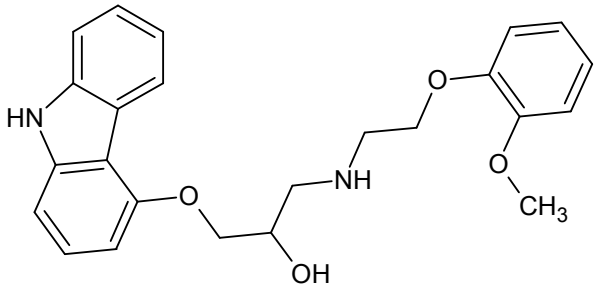
Labetalol is a phenylethanolamine derivative and its β-receptor blocking activity is 1.5 times more than α-receptor blocking activity.

Carvediol is an aryloxy propanolamine derivative and its β-receptor blocking activity is 10-100 times more than α-receptor blocking activity.

Labetalol



Carvediol



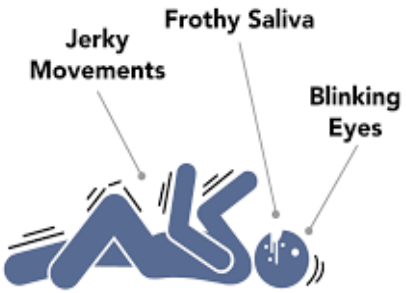
ANTICONVULSANTS

ANTICONVULSANTS

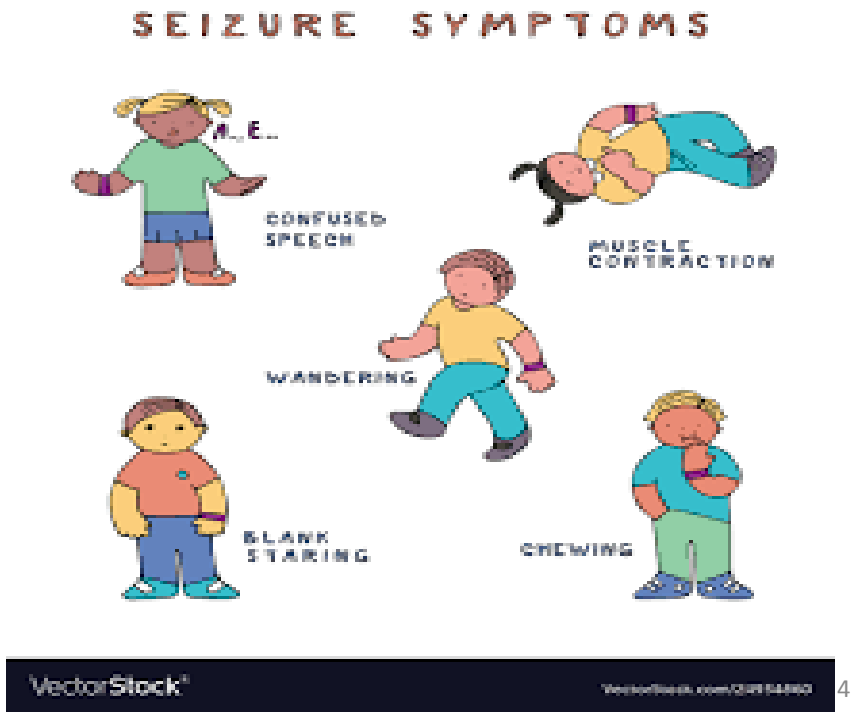
- The terms *anticonvulsant* and *antiepileptic* drug (AED) are used interchangeably to describe a diverse group of medications used clinically to provide seizure control in patients with epilepsies.
- Epilepsy is the most prevalent neurological disorder.
- It is characterized by recurrent seizures.
- The etiology of epilepsy is largely unknown.
- But literature suggests that it may have a genetic component associated.

- Seizures are symptoms of disturbed electrical activity in the brain.
- They are characterized by episodes of abnormal, excessive, and synchronous discharge of a group of neurons that cause involuntary movement, sensation, or thought.
- Seizures may result from primary or acquired neurological disturbances of brain function as a result of an imbalance between excitatory and inhibitory neurotransmitters / processes in the brain.

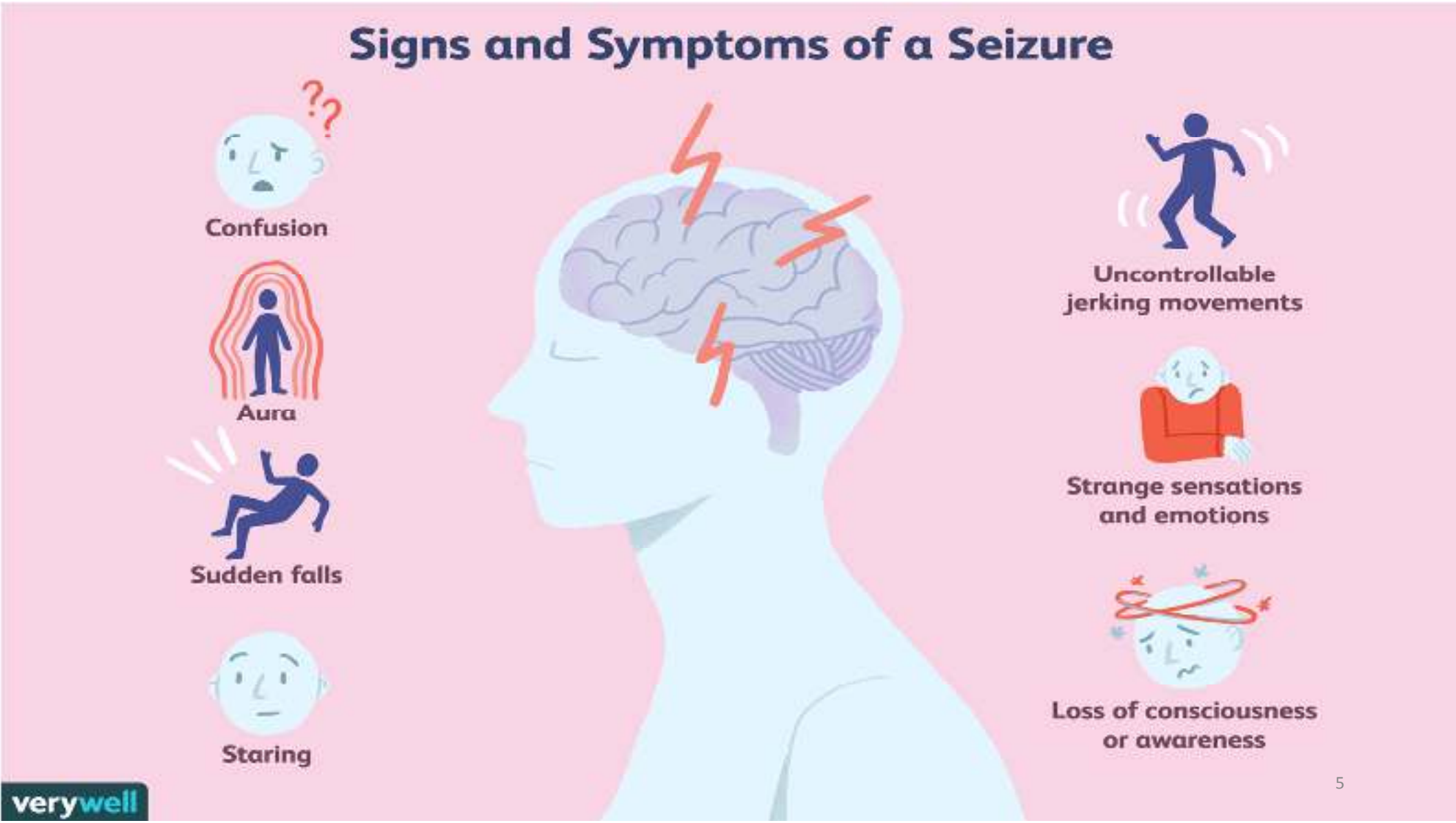
- There are many possible causes of seizures including-

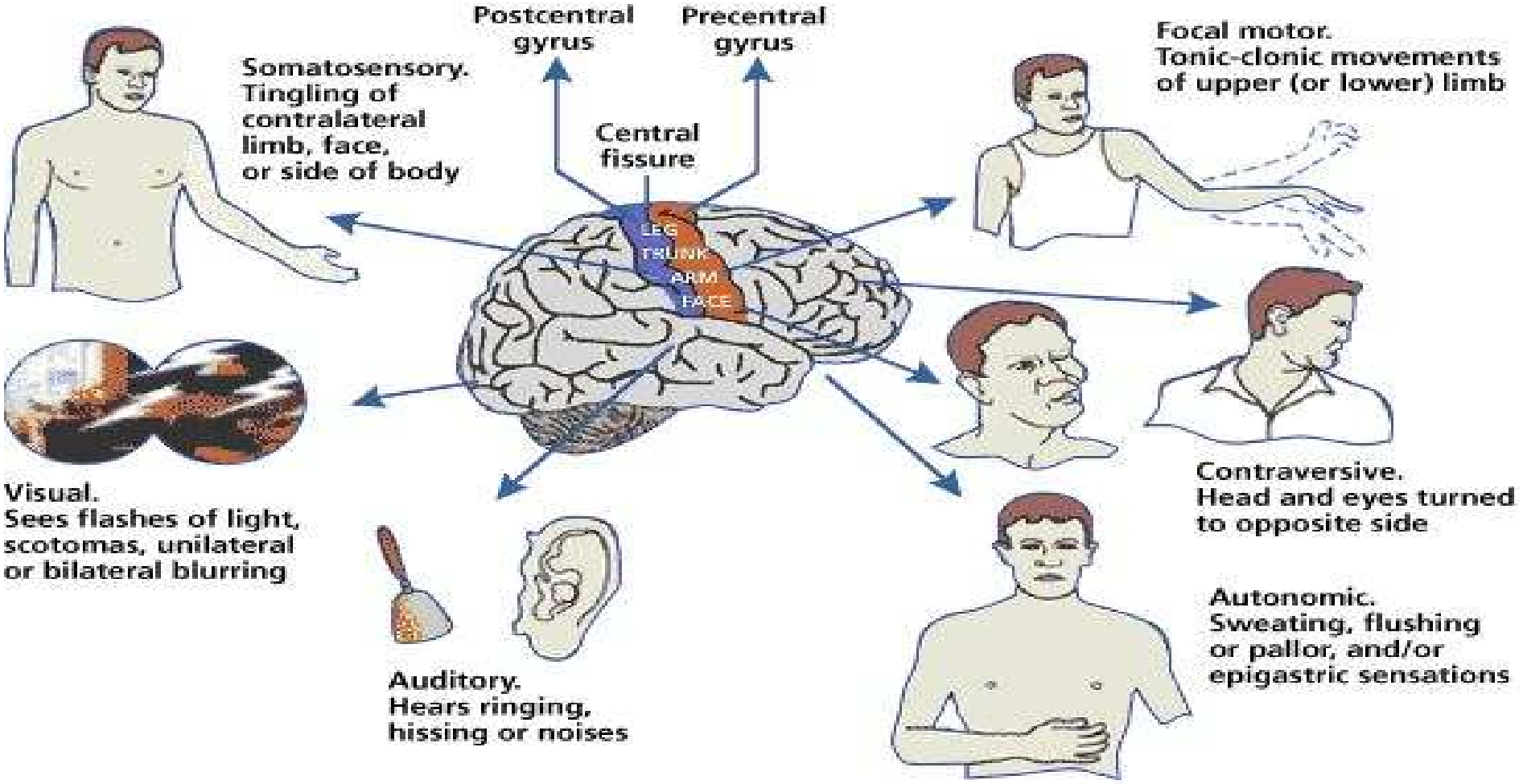


- ➢ brain tumors or infections,
- ➢ head trauma,
- ➢ neurological diseases,
- ➢ systemic or metabolic disorders,
- ➢ alcohol abuse,
- ➢ drug overdose, or toxicities.

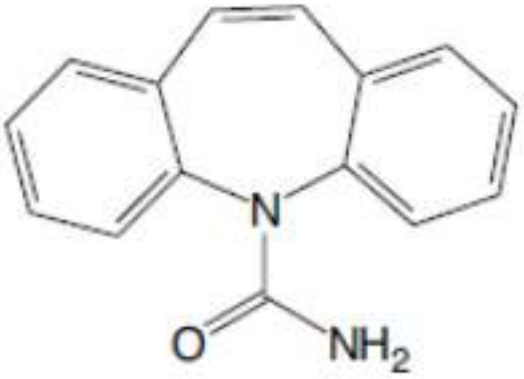


Signs and Symptoms of a Seizure

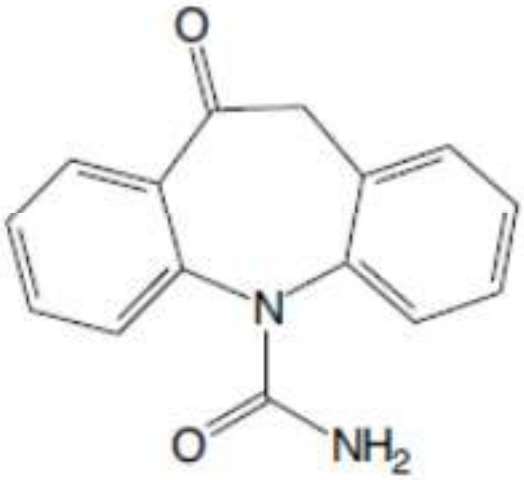



Postcentral gyrus
Precentral gyrus
Somatosensory. Tingling of contralateral limb, face, or side of body
Central fissure
Focal motor. Tonic-clonic movements of upper (or lower) limb
LEG
TRUNK
ARM
FACE
Visual. Sees flashes of light, scotomas, unilateral or bilateral blurring
Contraversive. Head and eyes turned to opposite side
Autonomic. Sweating, flushing or pallor, and/or epigastric sensations
Auditory. Hears ringing, hissing or noises

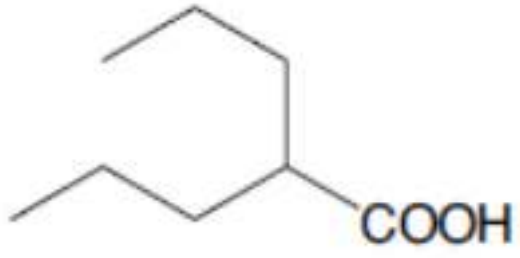
- **Types of Seizures:**
- **Primarily generalized tonic–clonic seizures (grand mal).**
- A series of bilateral muscular jerks followed by loss of consciousness, which in turn is followed by a series of tonic and then clonic spasms.
- The recommended initial monotherapy for patients with generalized seizures are carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine, valproic acid (VPA), phenytoin, and topiramate (TPM).



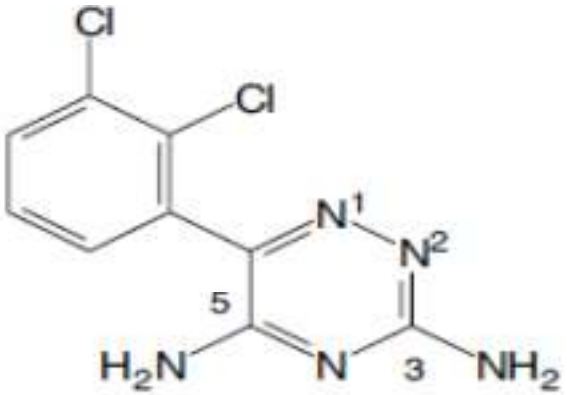
Carbamazepine (CBZ)



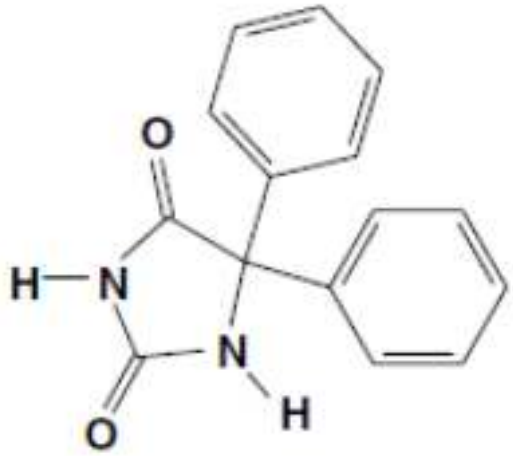
Oxcarbazepine (OXC)



Valproic acid (VPA)

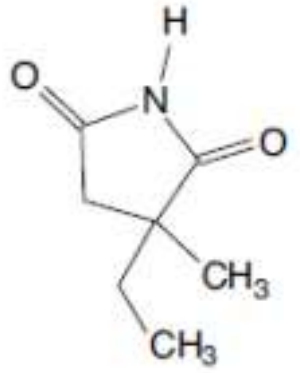


Lamotrigine

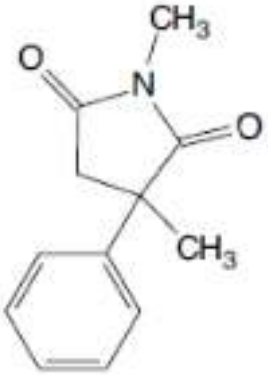


Phenytoin

- **Absence (petit mal) seizures.**
- Sudden brief loss of consciousness (approximately 10 seconds), sometimes with no motor activity, although often some minor clonic motor activity exists.
- The recommended initial monotherapy for children with absence seizures are lamotrigine, VPA, or ethosuximide.



Ethosuximide



Methsuximide

Seizure First Aid

What to do if a child has a convulsive seizure

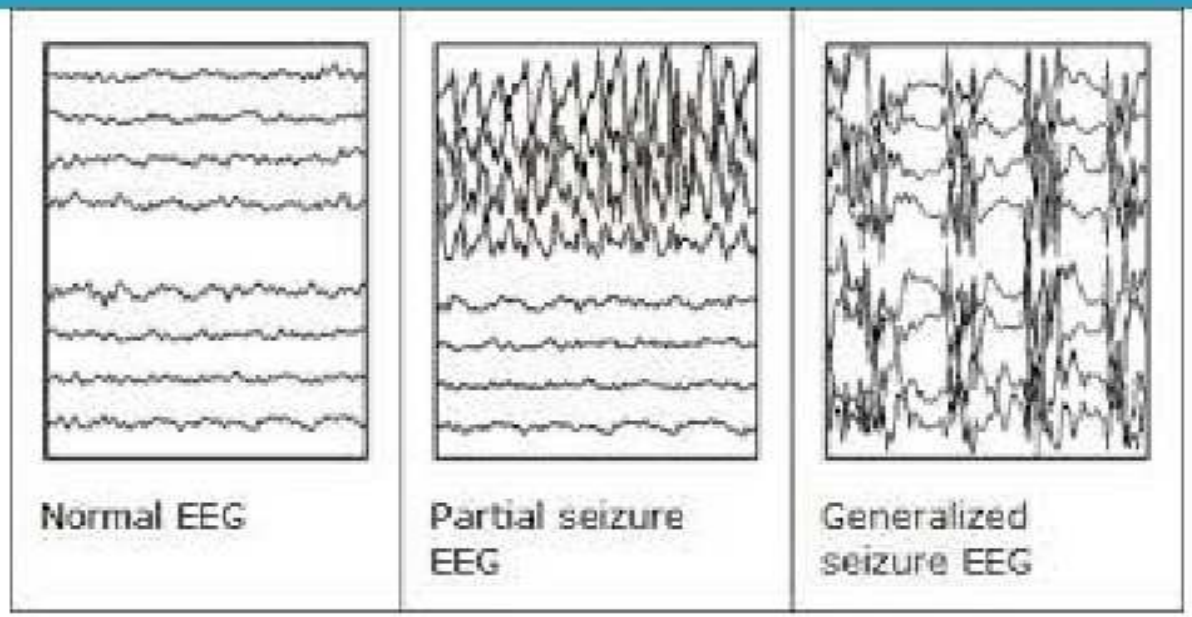
1. Do not panic
2. Turn on their side and start timing the seizure
3. Stay with child, do not restrain
4. Place something soft under head
5. Do NOT put anything in mouth
6. Call if seizure lasts longer than 5 minutes

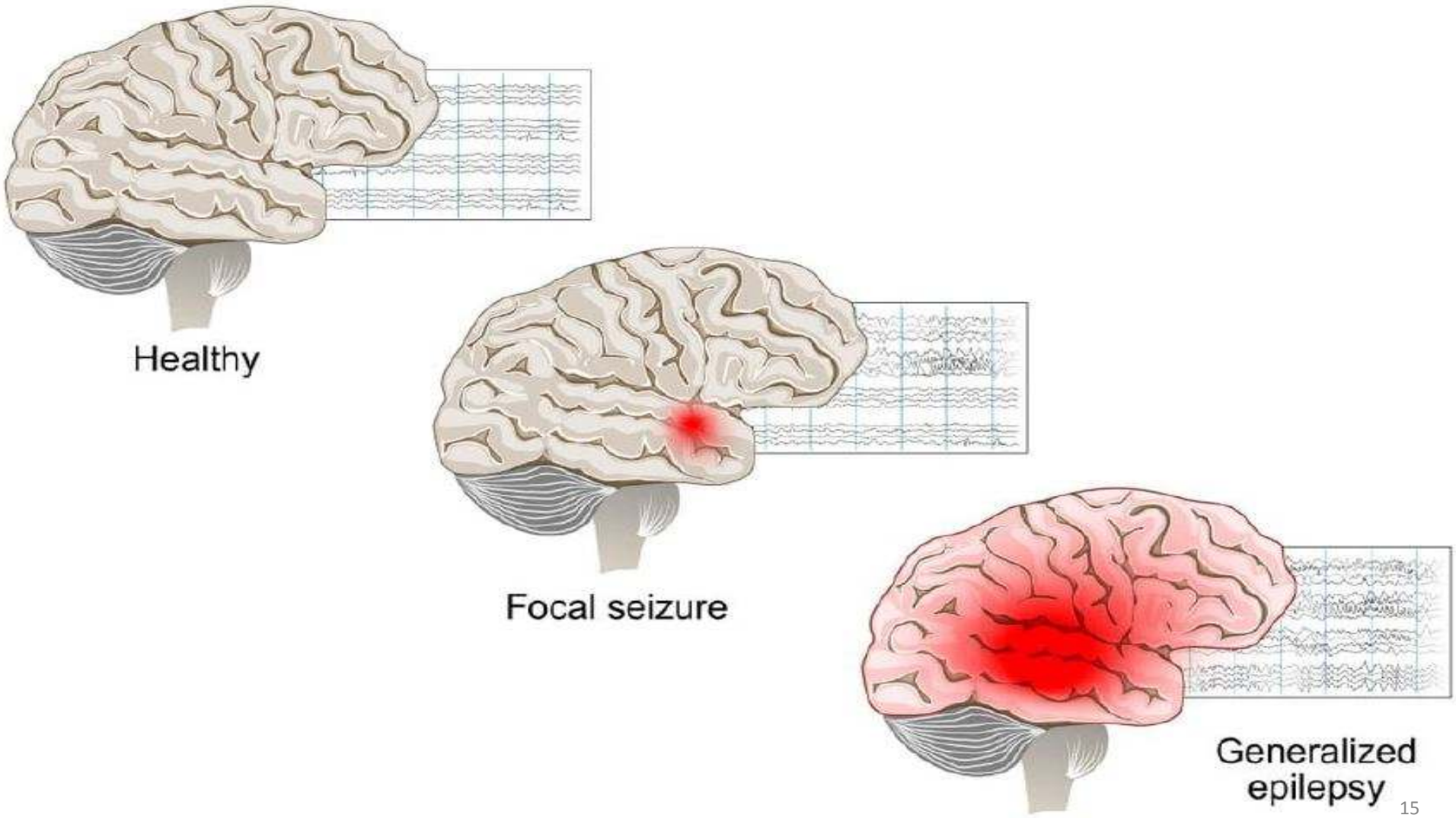
children's health

- **Partial Seizures:**
- Major types of partial seizure are simple partial seizures (focal) and complex partial seizures (temporal lobe or psychomotor).
- Approximately 60% to 70% of the adult patients develop partial seizures.
- A prototypic simple partial seizure is Jacksonian motor epilepsy in which the Jacksonian march may be seen.

- Partial seizures, if not controlled, may progress to another seizure type known as the **secondarily generalized partial seizures (tonic–clonic or grand mal)**.
- The first-line treatment for patients with newly diagnosed or untreated simple partial seizures are CBZ or phenytoin for adults, lamotrigine or gabapentin for elderly adults, and OXC for children.

- **The complex partial seizure** is represented by the psychomotor or temporal lobe seizure.
- There is an aura, then a confused or bizarre but seemingly purposeful behavior lasting 2 to 3 minutes, often with no memory of the event.
- The seizure may be misdiagnosed as a psychotic episode.
- Although the initial treatment is the same, it is much harder to control complex partial seizures.


Normal EEG
Partial seizure EEG
Generalized seizure EEG


Healthy
Focal seizure
Generalized epilepsy

First Aid: Convulsions

A.D.A.M.

- **Mechanism of Action of Anticonvulsants:**

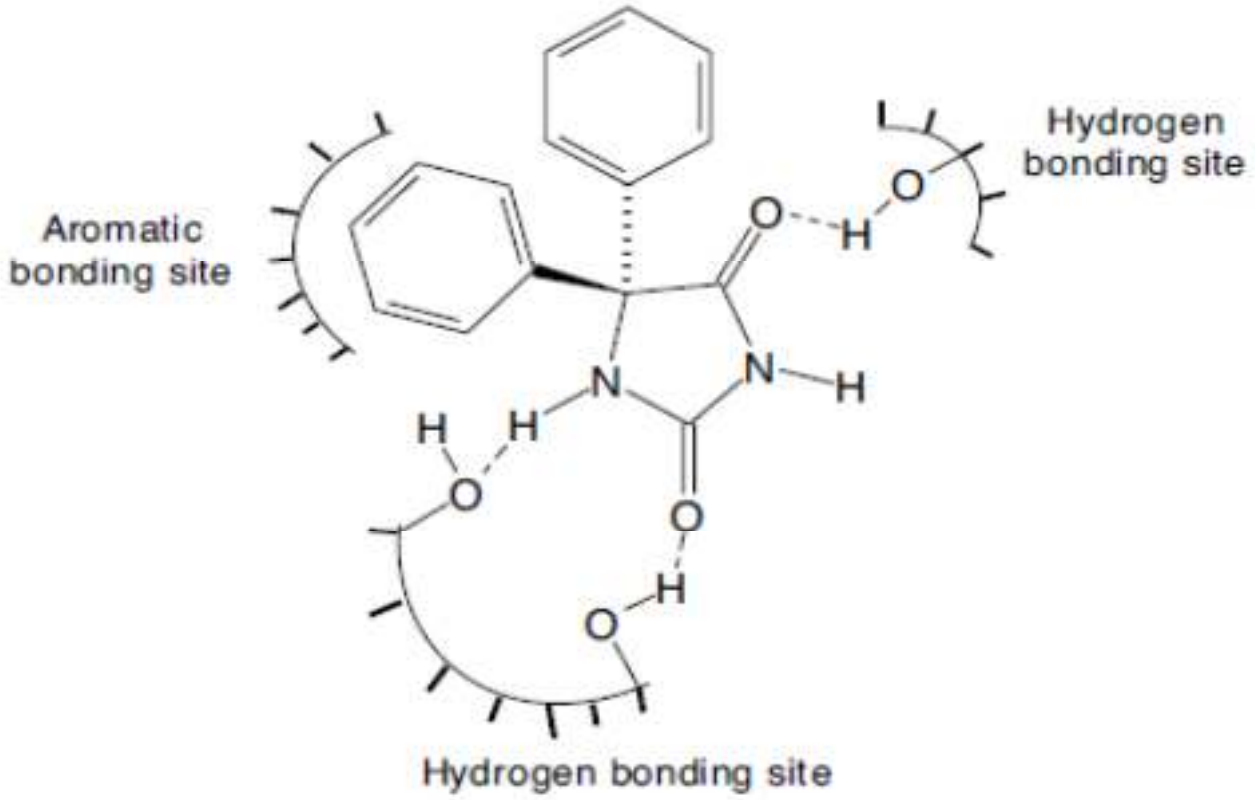
➢ Modulation of voltage-gated ion channels (Na+, Ca2+, and K+),

➢ Enhancement of ϒ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission,

➢ Attenuation of excitatory (particularly glutamate-mediated) neurotransmission in the brain.

- **Many of AEDs, especially the newer drugs, work by more than one of the above mechanisms of actions, therefore possessing a broader spectrum of antiepileptic action.**

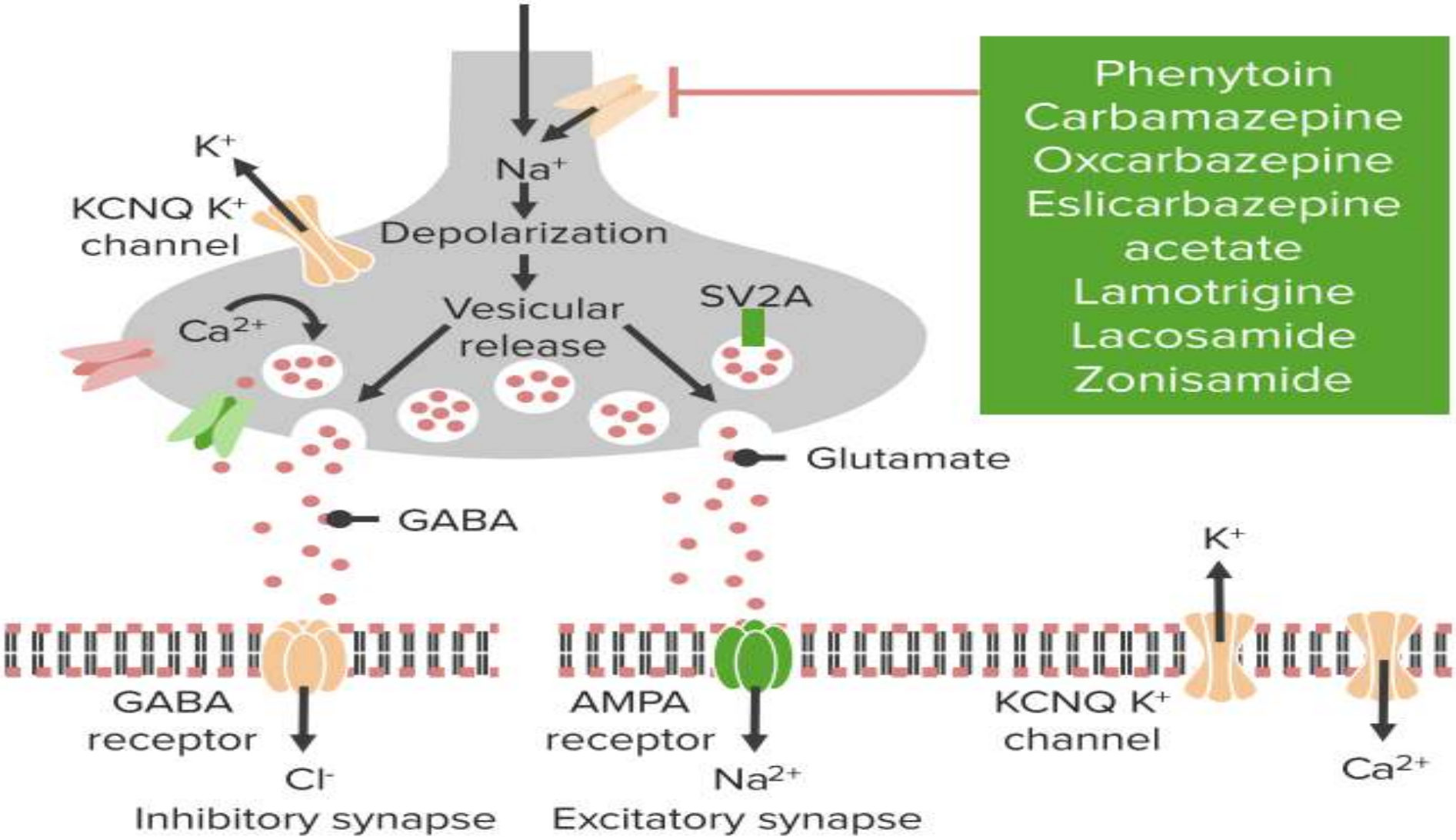
- **Voltage-gated sodium channels (VGSCs)** in the presynaptic nerve terminal of the excitatory glutamate receptors are the molecular target for phenytoin, CBZ, and lamotrigine as well as some of the newer AEDs, such as OXC, felbamate (FBM), and zonisamide.



- **The voltage-gated calcium channels (VGCCs)** are essential in regulating Ca2 signaling, which is associated with many important cellular events such as the release of excitatory glutamate neurotransmitters, the plasticity changes of long-term potentiation in learning and memory, and the maintenance of homeostasis of nerve cells.
- Excessive influx of Ca2+ plays a critical role in the induction and progression of epileptic seizures.

- The high-threshold **L-type Ca2+ channels** in the presynaptic glutaminergic receptors require strong depolarization and are the primary molecular targets of **gabapentin and pregabalin**, both of which are effective in **refractory partial seizures**.
- The low-threshold **T-type Ca2+ channels** require only weak depolarization for activation and are the molecular targets of AEDs such as **ethosuximide and zonisamide**.

- Potentiation of the **voltage-gated K channels** is another attractive target for designing of newer AEDs.
- Because they are intimately associated with the membrane repolarization processes.
- **Levetiracetam (LEV)** works by reducing the voltage-operated A-type potassium currents as one of its mechanism of actions.
- Levetiracetam (LEV) is a novel AED recently marketed for the adjunctive therapy of **refractory partial seizures in adults**.


Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
K+
KCNQ K+ channel
Na+
Depolarization
Ca2+
Vesicular release
SV2A
Glutamate
GABA
K+
GABA receptor
Cl-
Inhibitory synapse
AMPA receptor
Na2+
Excitatory synapse
KCNQ K+ channel
Ca2+

- **GABA-A Receptors as Targets for Anticonvulsants**

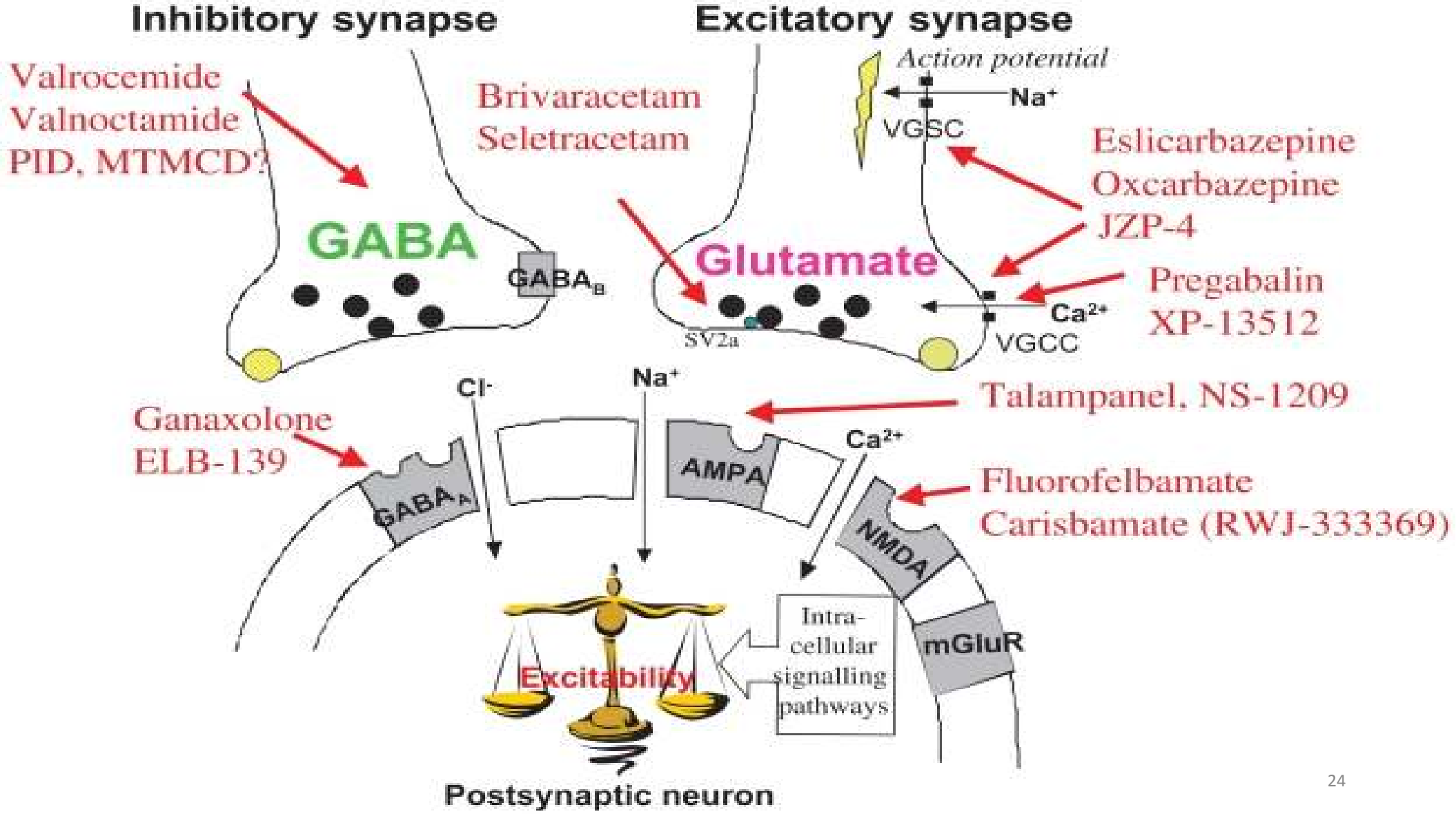
- The potential targets for AED's action on the GABAergic inhibitory synapses include-

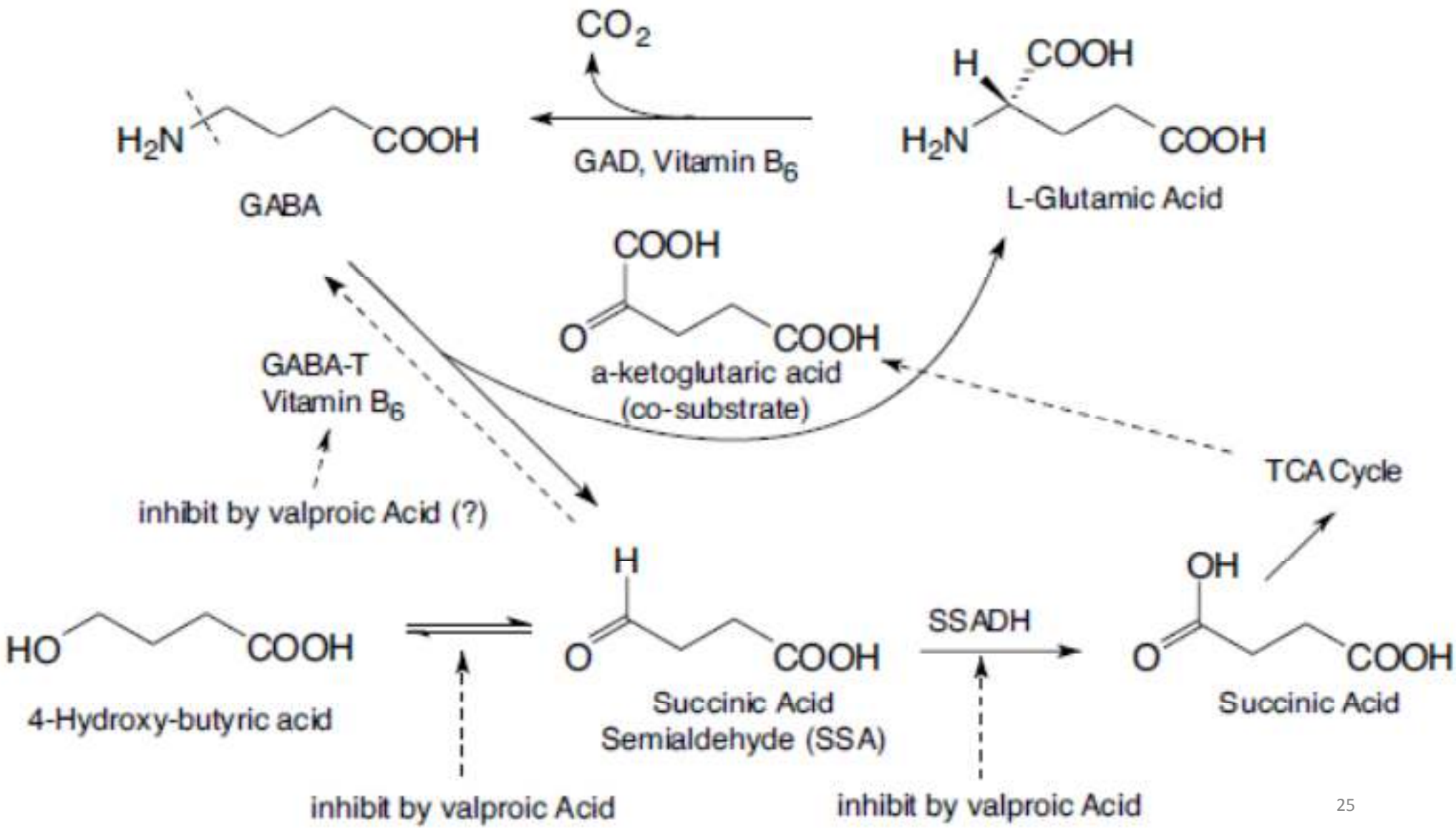
(a) drugs that enhance the biosynthesis of GABA (gabapentin, pregabalin, and VPA),

(b) drugs that inhibit GABA degradation (vigabatrin),

(c) drugs that inhibit the reuptake of GABA (tiagabine), and

(d) drugs that bind to an allosteric site on the postsynaptic GABA-A receptor complex that increase chloride conductance (barbiturates, BZDs, neurosteroids).

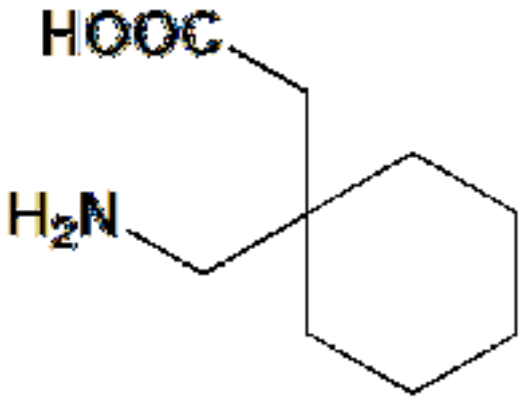

Inhibitory synapse
Excitatory synapse
Valrocemide
Valnoctamide
PID, MTMCD?
Brivaracetam
Seletracetam
Action potential
Na+
VGSC
Eslicarbazepine
Oxcarbazepine
JZP-4
GABA
GABA_B
Glutamate
Pregabalin
XP-13512
Ca2+
SV2a
VGCC
Cl-
Na+
Talampanel, NS-1209
Ganaxolone
ELB-139
Ca2+
AMPA
Fluorofelbamate
Carisbamate (RWJ-333369)
GABA_A
NMDA
mGluR
Intra-
cellular
signalling
pathways
Excitability
Postsynaptic neuron


CO_2
H_2N
COOH
GAD, Vitamin B_6
H
COOH
H_2N
COOH
GABA
L-Glutamic Acid
COOH
O
COOH
a-ketoglutaric acid
(co-substrate)
GABA-T
Vitamin B_6
inhibit by valproic Acid (?)
TCA Cycle
HO
COOH
4-Hydroxy-butyric acid
H
O
COOH
Succinic Acid
Semialdehyde (SSA)
SSADH
OH
O
COOH
Succinic Acid
inhibit by valproic Acid
inhibit by valproic Acid

- **DRUGS THAT ENHANCE THE BIOSYNTHESIS OF GABA:**
- GABA (the major inhibitory neurotransmitter in the brain) is biosynthesized by the decarboxylation of the L-glutamic acid (an excitatory amino acid neurotransmitter in the brain).
- The rate-limiting enzyme that catalyzes this conversion is L-glutamic acid decarboxylase (GAD).
- The essential cofactor for this reaction is pyridoxal phosphate (vitamin B6).

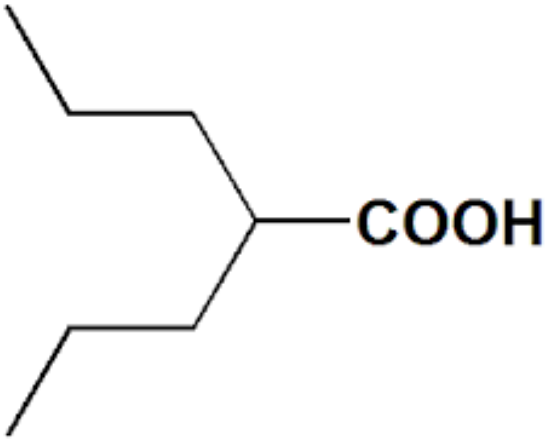
- **GABA is degraded by the GABA transaminase (GABA-T), which transfers an amino group from GABA to α–ketoglutarate producing L-glutamic acid and succinic acid semialdehyde (SSA).**
- **GABA-T enzyme requires pyridoxal phosphate for activation.**
- **SSA is oxidized by the enzyme succinic semialdehyde dehydrogenase (SSADH) to succinic acid.**
- **Succinic acid can enter the TCA cycle for the production of additional α-ketoglutarate or be further reduced by SSA reductase (an alcohol dehydrogenase that catalyzes the interconversion of SSA and 4-hydroxybutyric acid).**

- Both **Gabapentin** and **Pregabalin** are 3-substituted GABA derivatives.
- Both of these drugs are weak activators of GAD.
- Their major anticonvulsant action is due to blockade of the L-type Ca2+ channels in the presynaptic glutaminergic receptors.
- **Valproic acid** inhibits SSADH, the enzyme responsible for conversion of SSA to succinic acid.
- This results in an indirect stimulation of GAD and an inhibition of GABA-T.
- VPA elevates GABA levels by reversing the **transamination** mediated by GABA-T.

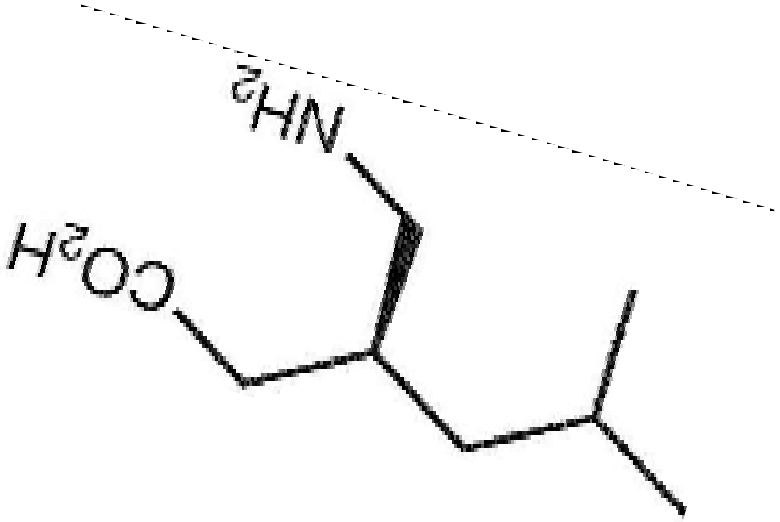


Gabapentin

PREGABALIN

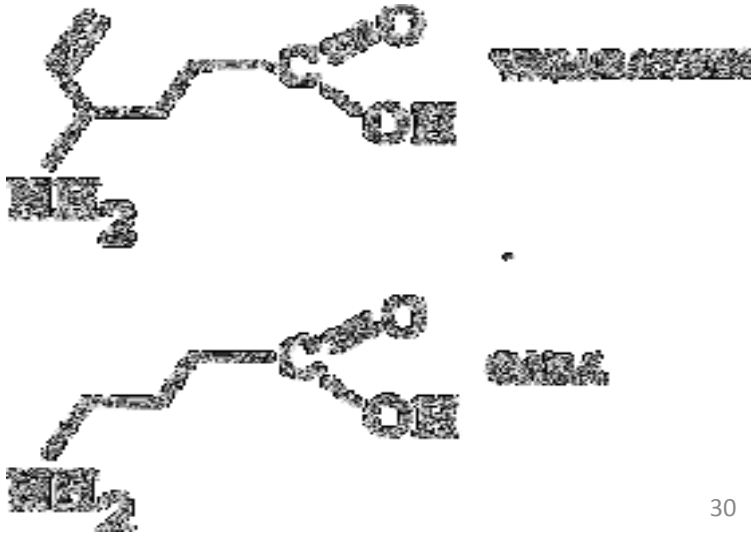


Valproic acid



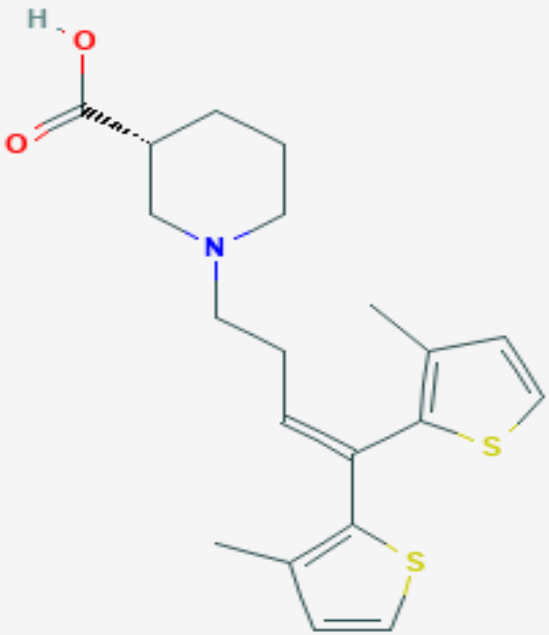
DRUGS THAT INHIBIT GABA DEGRADATION

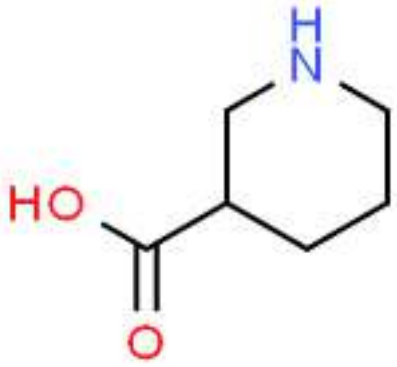
- **Vigabatrin** (ϒ-vinyl-GABA) is an irreversible inhibitor of GABA-T.
- Vigabatrin, because of its structural similarity, competes with GABA for binding to GABA-T and forms a Schiff base intermediate with the cofactor, pyridoxal phosphate similar to GABA.
- A reactive intermediate is formed by vigabatrin that immediately attaches to the active site of the enzyme, thereby irreversibly inhibiting GABA-T and increasing GABA levels in the brain.

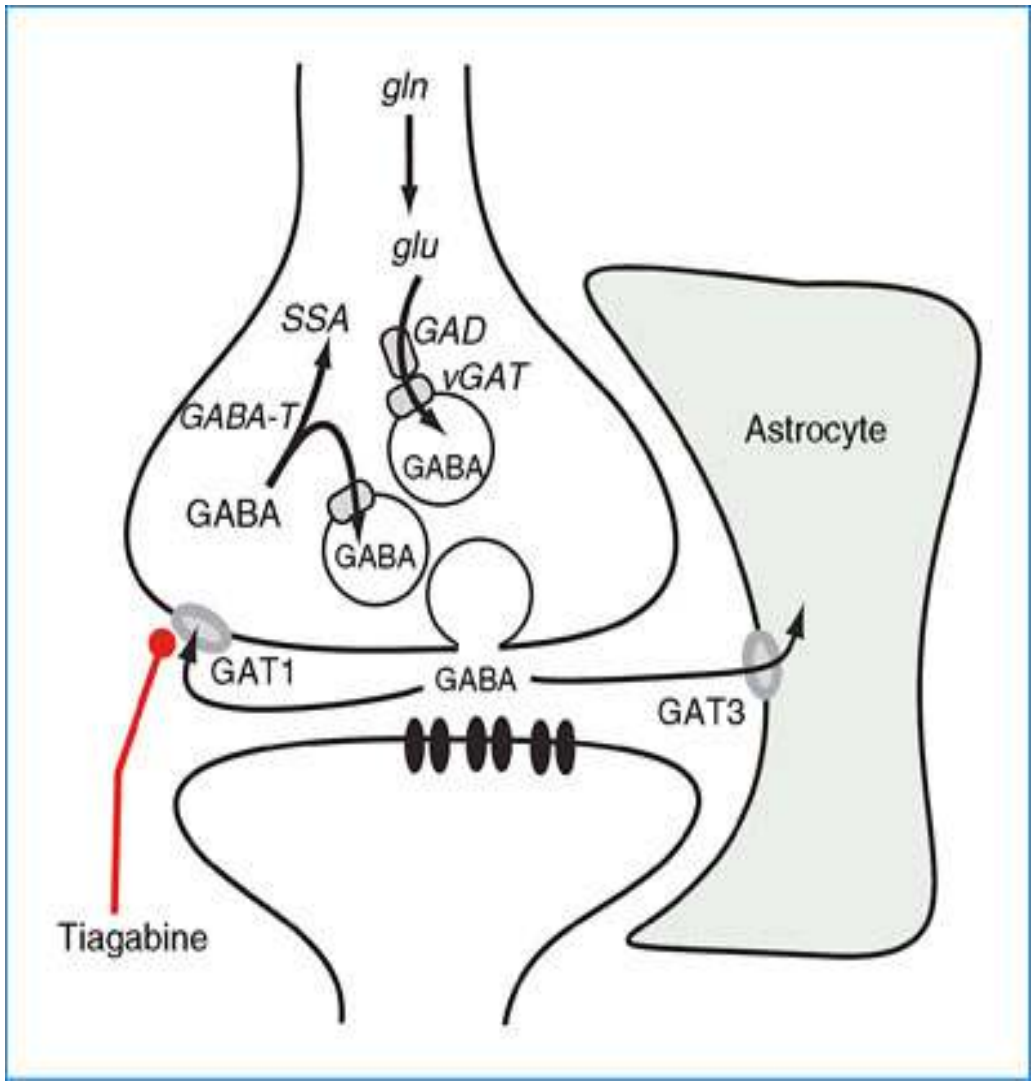


- **DRUGS THAT INHIBIT REUPTAKE OF GABA**

- Released GABA is actively taken back into the GABAergic neurons or glial cells in the brain by GABA transporters (GATs).
- **Tiagabine,** structurally related to nipecotic acid, is a selective inhibitor of the neuronal and glial GAT1 at the GABAergic neurons and an effective drug for the treatment of patients with refractory epilepsy.
- Addition of two lipophilic heterocyclic rings to the nicopetic acid moiety did not interfere with its ability to bind GAT1 but actually allows tiagabine to cross into the brain freely and also more selectively than nicopetic acid toward GAT1.


H
O
O
N
S
S

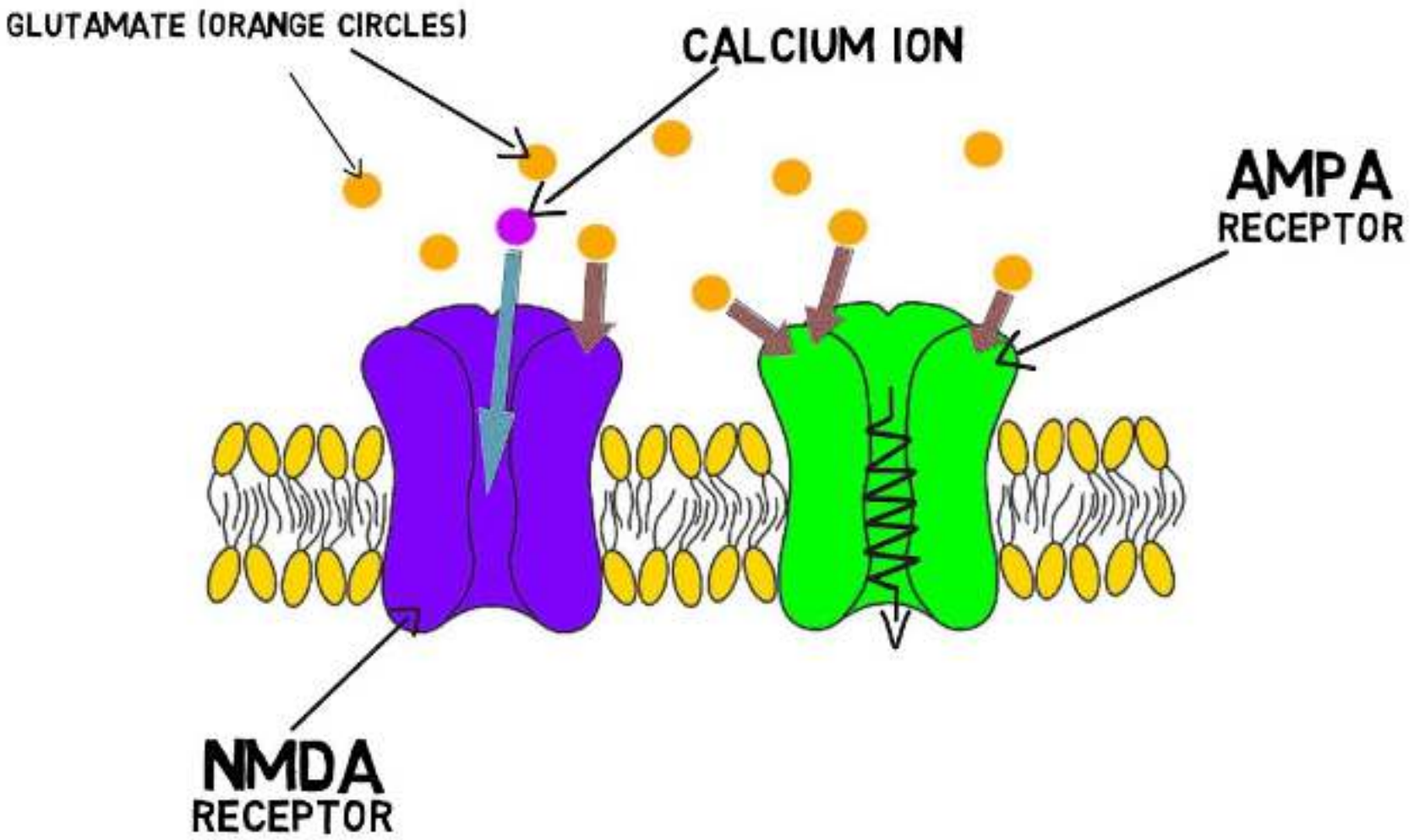

HN
HO
O

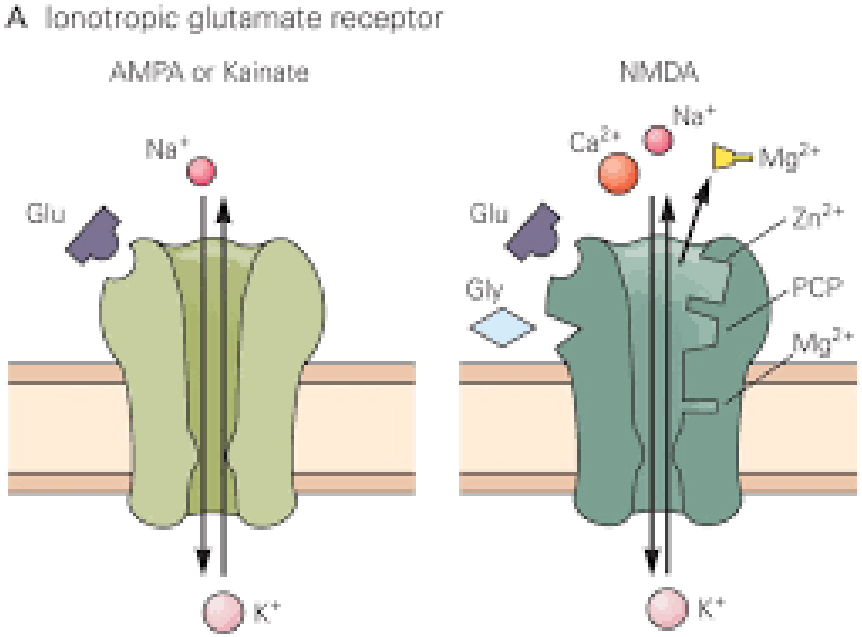

gln
glu
SSA
GAD
vGAT
GABA-T
GABA
GABA
GABA
Astrocyte
GAT1
GABA
GAT3
Tiagabine

- **DRUGS THAT BIND TO GABA-A RECEPTOR & MODULATE CHLORIDE INFLUX**

- Many clinically useful anxiolytic hypnotic–sedatives and some AED drugs such as BZDs, and barbiturates (e.g., phenobarbital) exert their pharmacological actions by interacting with GABAA-BZD receptor chloride channel complex.

- **Excitatory Glutamate-Mediated Receptors as Target**
- The acidic amino acids, L-glutamate and L-aspartate, are the most important excitatory neurotransmitters in the brain acting through two distinct families of glutamate receptors, the ligand-gated, ionotropic receptors and the G-protein–coupled metabotropic receptors.
- The ligand-gated glutamate receptors such as ***N*-methyl-D-aspartic acid (NMDA) / α-amino-3- hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA)** receptors modulate sodium and calcium influx and are involved in mediating excitatory synaptic transmission including the initiation and spread of seizure activity.


GLUTAMATE (ORANGE CIRCLES)
CALCIUM ION
AMPA
RECEPTOR
NMDA
RECEPTOR



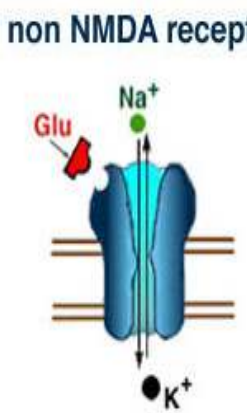


Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more perm eable to Na+ and K+ ions tha Ca+2 (from Kandel et al,.1991).

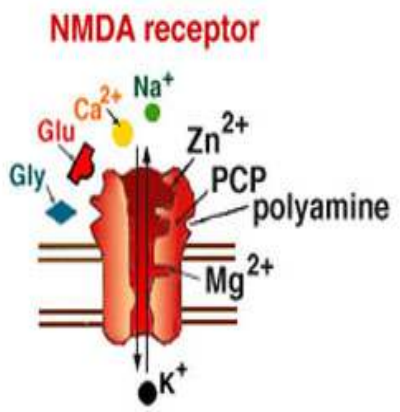
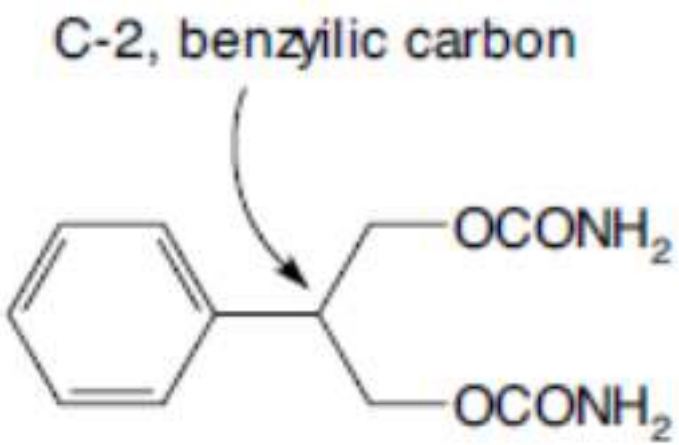
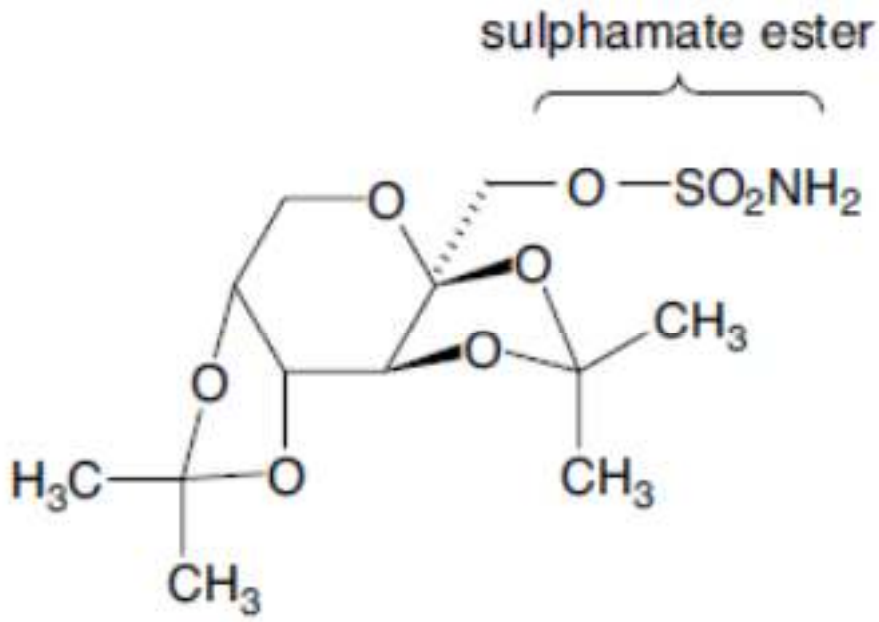


Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).

- Activation of these receptors is responsible for important functions in the brain including long-term potentiation in **memory acquisition, learning**, and some **neurodegenerative disorders**.
- These receptors are potential therapeutic targets for epilepsy and other neurodegenerative disorders such as stroke and head injury, Alzheimer, and other chronic debilitating disorders.
- **Felbamate** (NMDA receptor blocker) and **topiramate** (AMPA receptor blocker) can block these excitatory receptors.

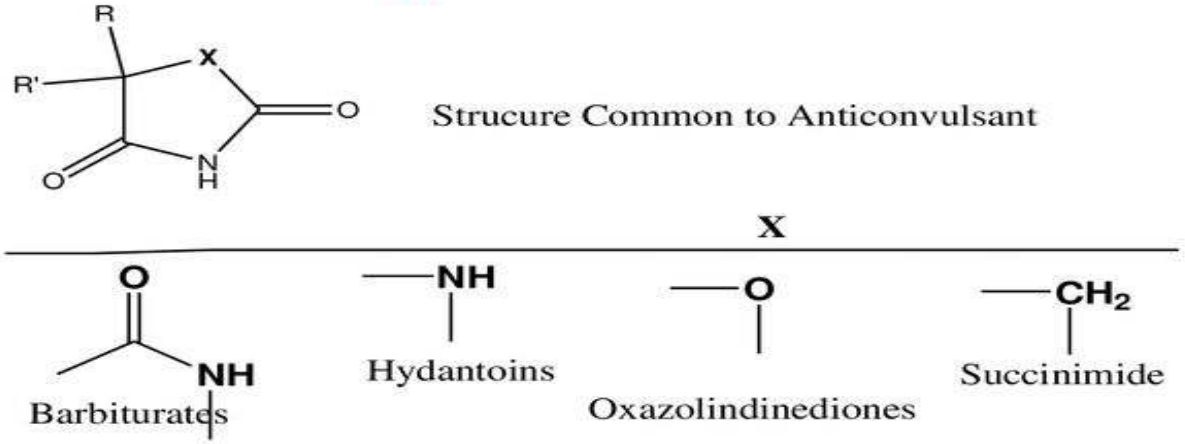


Felbamate (FBM)



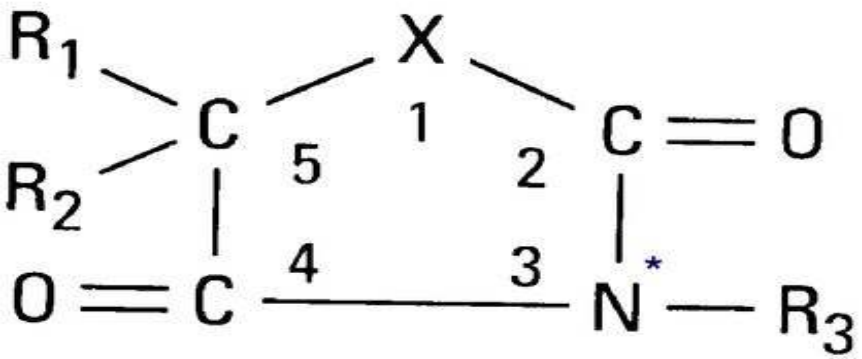
Topiramate

SARs among Anticonvulsants



- R and R' should both be hydrocarbon side chain.
- If both R and R' are lower alkyls, the tendency is to be active against absence seizures (petit mal) and not active against generalized tonic-clonic (grand mal) or partial seizures.
- If one of the hydrocarbon substituents is an aryl group, activity tends to be directed toward generalized tonic-clonic and partial seizures and not antiabsence activity.
- A conformational analysis of the aryl-containing antigeneralized tonic-clonic agents indicates that the conformational arrangement of the hydrophobic groups is important.

Chemical Structure of Classical Antiseizure Agents



X may vary as follows:

Barbiturates	**O= C – N**
Hydantoins	**- N –**
Oxazolidinediones	**– O –**
Succinimides	**– C –**
Acetylureas	**- NH_2 –**

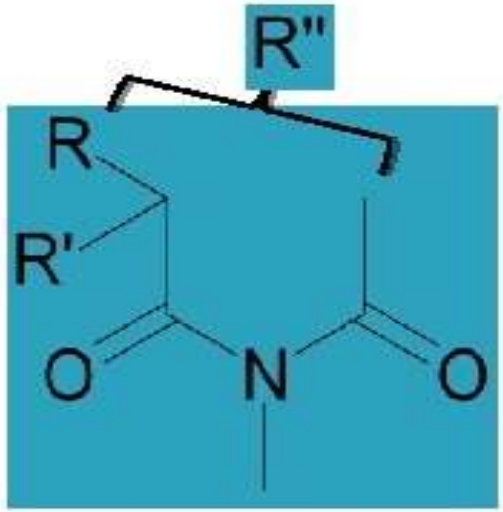
***(N connected to C_2)**

SARs among Anticonvulsants

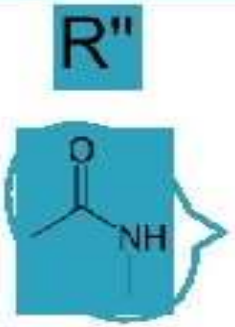
- A conformational analysis of the aryl-containing antigeneralized tonic-clonic agents indicates that the conformational arrangement of the hydrophobic groups is important.

R and R'	absence (petit mal)	generalized tonic-clonic (grand mal) or partial
Alkyl Groups	active	inactive
Aryl Groups	inactive	active

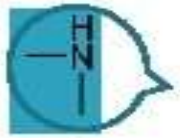
Antiepiletic agents: SAR



Structure common to anticonvulsant drugs.

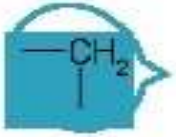


Barbiturates



Hydantoins

Oxazolidinediones



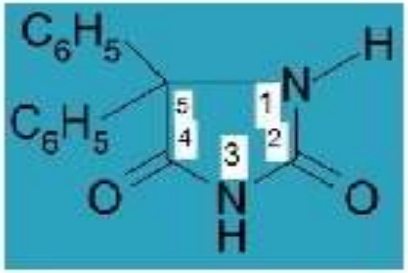
Succinimides

Phenacemide

Antiepileptic agents: SAR

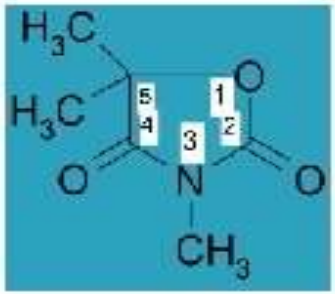
- R and R' should both be hydrocarbon radicals.

Phenytoin



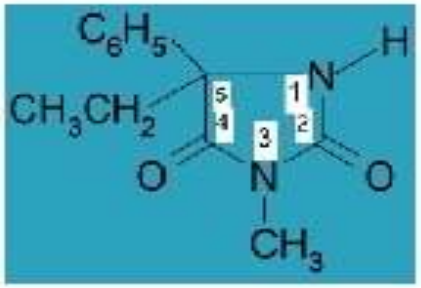
- R and R' are lower alkyls, the agent is active against absence seizures(petit mal) and not active against generalized tonic-clonic(grand mal) or partial seizures .

Trimethadione

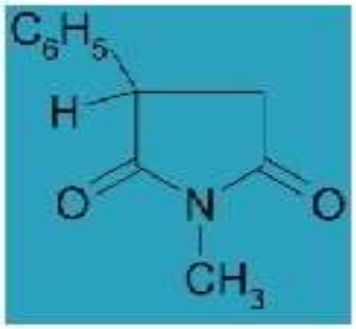


Antiepileptic agents: SAR

- If one of the hydrocarbon substituent is an aryl group, activity tends to be directed towards generalized tonic-clonic and partial seizures, and not towards antiabsence activity.



Mephenytoin



Phensuximide

- The conformational arrangement of hydrophobic group is important for antigeneralized tonic-clonic activity.

1. Hydantoins

- Phenylethylhydation
  $R_1 = H \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Phenytoin
  $R_1 = H \quad R_2 = R_3 = C_6H_5$
- Mephenytoin
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Ethotoin
  $R_1 = C_2H_5 \quad R_5 = H \quad R_5 = C_6H_5$

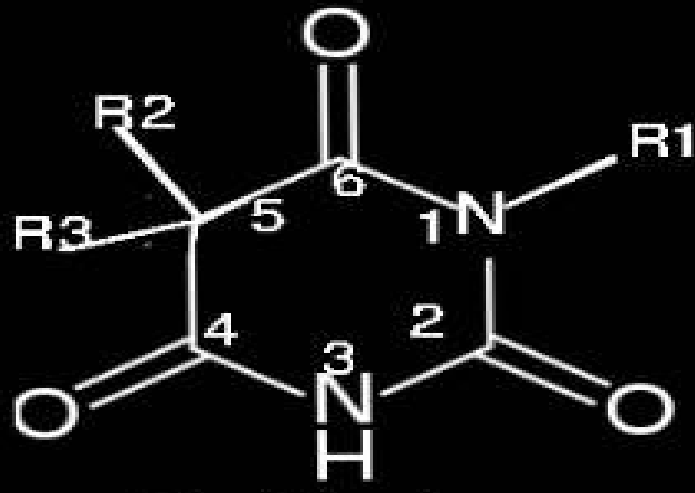
Contd..

- A phenyl or other aromatic substituents at C_5 is essential for the activity.
- Alkyl substituents at position 5 may contribute to sedation, a property absent in phenytoin. Hydantoin

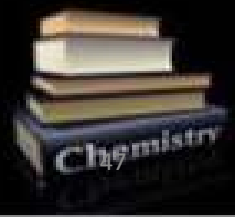
Hydantoin

2. Barbiturates

- Phenobarbitone
  $R_1 = H \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Mephobarbitone
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Metharbital
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_2H_5$

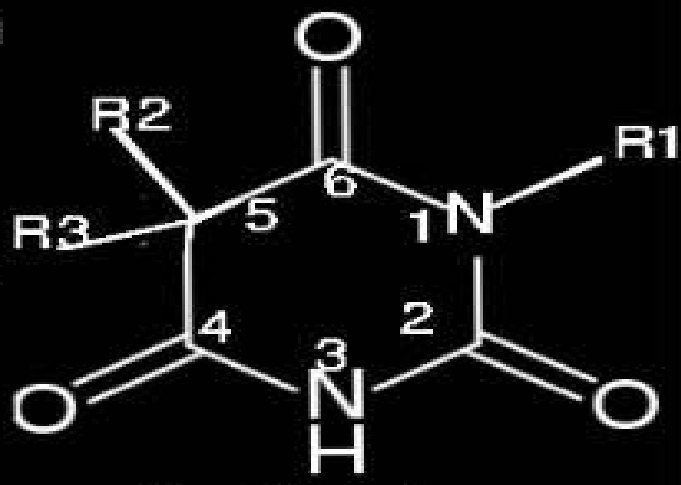


Barbiturates



Contd..

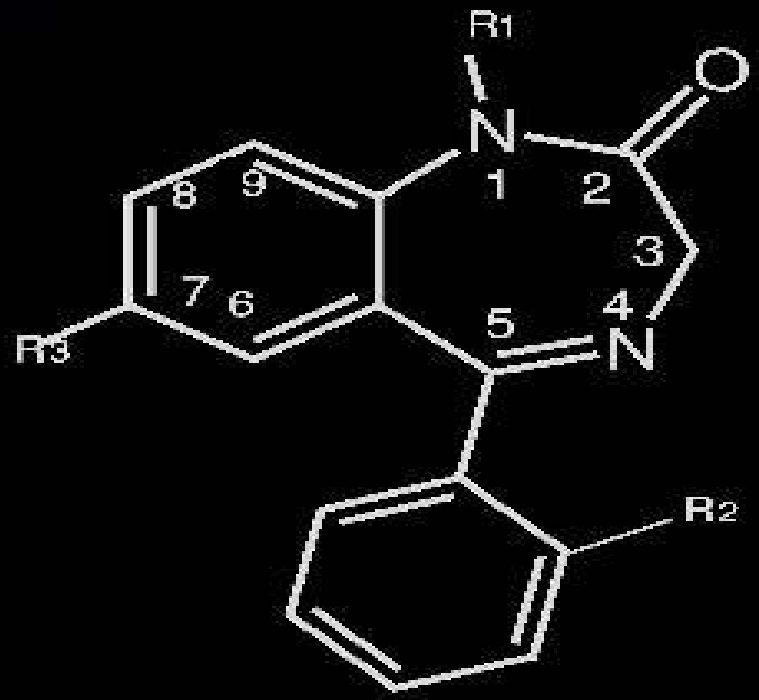
- Optimum activity is observed when one of the substituents at C_5 is phenyl.
- The 5, 5-diphenyl derivatives have less activity than phenobarbitone.
- N2 and N3 substituents, in some cases also results in an increased activity.
- 5, 5-dibenzyl barbituric acid causes convulsions.



Barbiturates

3. Benzodiazepines

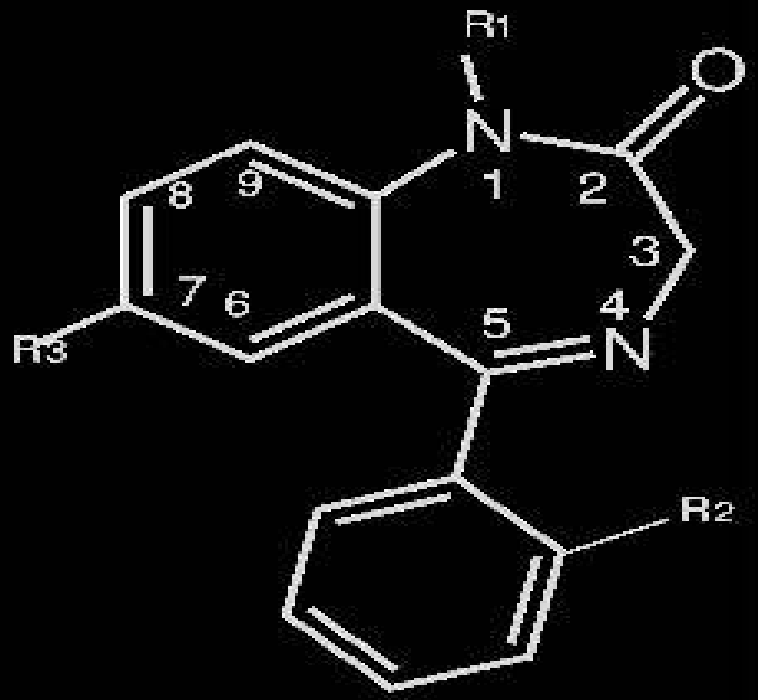
- Diazepam
  $R_1 = CH_3$ $R_2 = H$ $R_3 = Cl$
- Nitrazepam
  $R_1 = H$ $R_2 = H$ $R_3 = NO_2$
- Clonazepam
  $R_1 = H$ $R_2 = Cl$ $R_3 = NO_2$



Benzodiazepines

Contd..

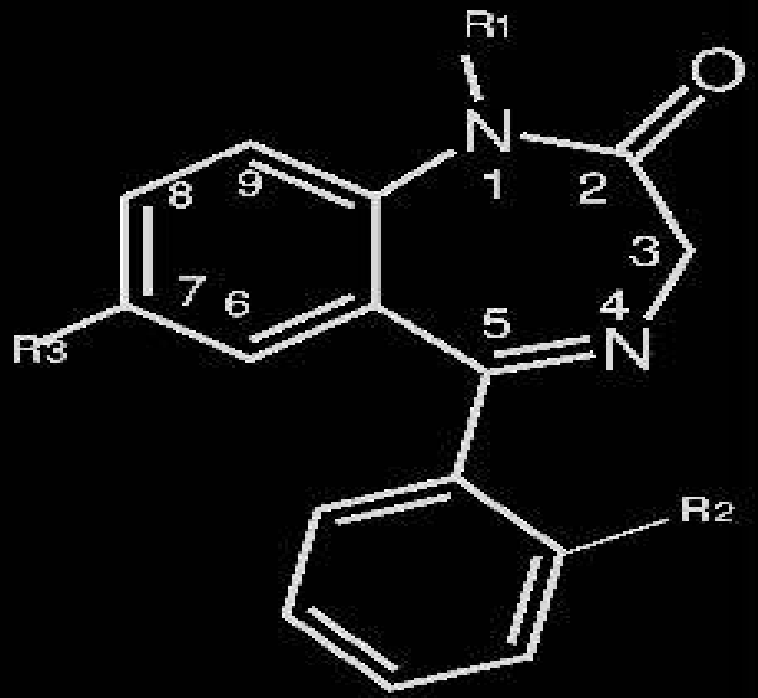
- The electron withdrawing atom or group at position 7 increases the anti-epileptic activity while electron donating substituents at 7, 8 or 9 positions decrease it.
- A phenyl group at position 5 is necessary for activity. But only halogen substituents are allowed in the ortho position.



Benzodiazepines

Contd..

- The electron withdrawing groups at ortho or diortho positions at 5-phenyl increase the activity while any substituents on meta or para position at 5-phenyl decreases the activity.
- Methyl substitution at position 1 confirms high activity.



Benzodiazepines

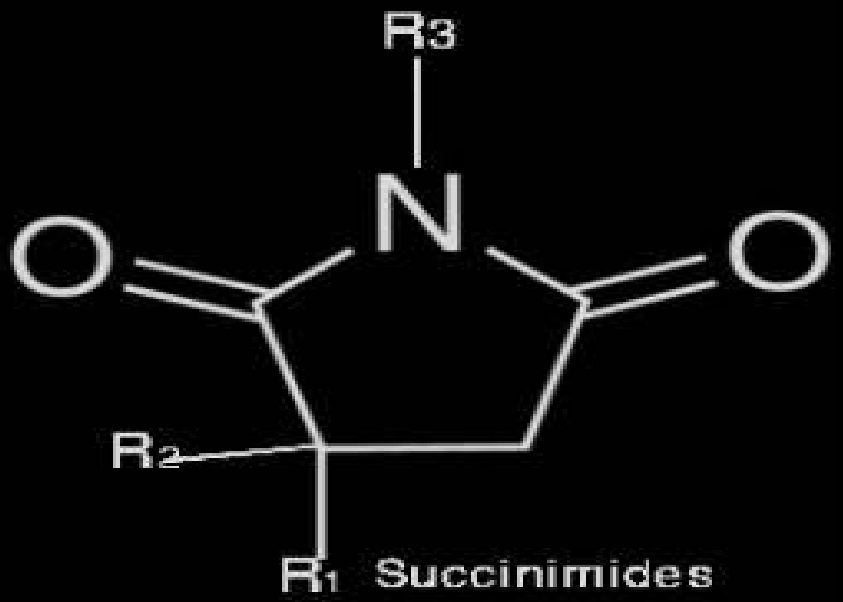
4. Valproic Acid

- Among other relatives of valproic acid, 3, 3, 4-trimethylpentanoic acid is also as active as valproic acid.
- The anticonvulsant activity increases with increased chain length.
- Introduction of a double bond decreases the activity.

Valproic Acid

5. Succinimides

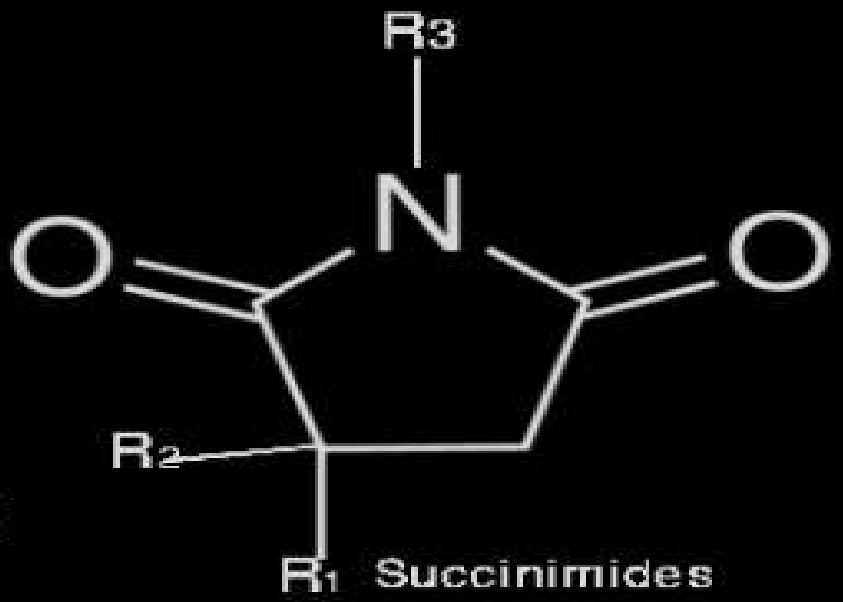
- Phensuximide
  $R_1 = C_6H_5$ $R_2 = H$ $R_3 = CH_3$
- Methsuximide
  $R_1 = C_6H_5$ $R_2 = R_3 = CH_3$
- Ethosuximide
  $R = C_2H_5$ $R_2 = CH_3$ $R_3 = H$



Succinimides

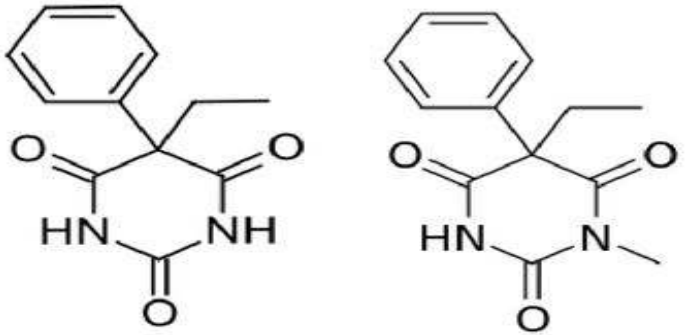
Contd..

- Methsuximide and phensuximide have phenyl substituents which makes them active against electrically induced convulsion.
- N-Methylation decreases activity against electroshock seizures and impart more activity against chemically induced convulsion.



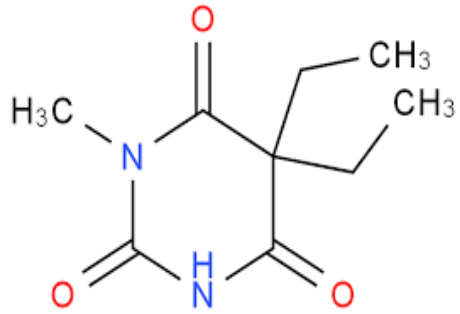
Succinimides

Barbiturates

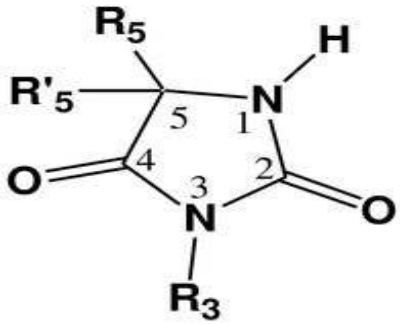


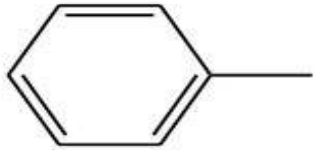
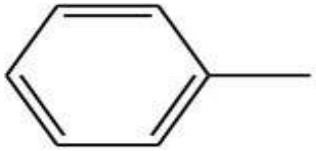
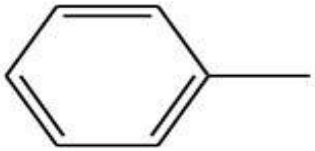
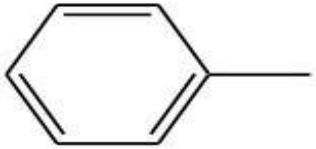
- **Phenobarbital** and **mephobarbital** display enough anticonvulsant selectivity for use as antiepileptics.
- The metabolism of phenobarbital involves p-hydroxylation, followed by conjugation.
- **Mephobarbital** is extensively N-demethylated in vivo and is thought to owe most of its activity to the metabolite phenobarbital.
- In keeping with their structures, both agents are effective against generalized tonic-clonic and partial seizures.

- Metharbital binds at a distinct binding site associated with a Cl^- ionopore at the $GABA_A$ receptor, increasing the duration of time for which the Cl^- ionopore is open.
- The post-synaptic inhibitory effect of GABA in the thalamus is prolonged.
- The net result of barbiturate action is acute potentiation of inhibitory GABAergic tone.
- **Barbiturates also act through potent and direct inhibition of excitatory AMPA-type glutamate receptors, resulting in a profound suppression of glutamatergic neurotransmission.**



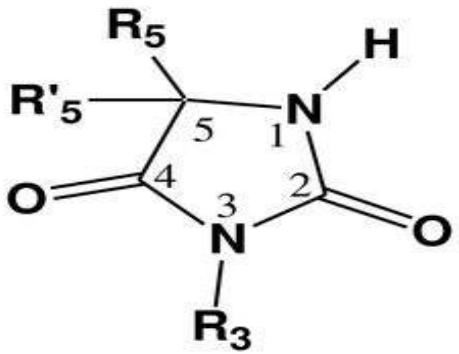
Hydantoins

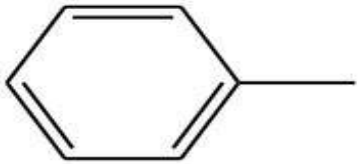
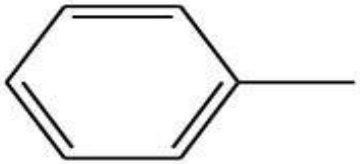
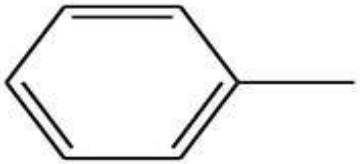
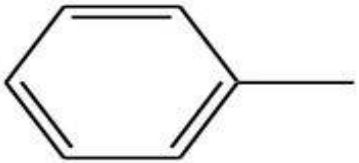


R_5	R'_5	R_3	
		H	Phenytoin
	$H_3C-\underset{H_2}{C}-$	H_3C-	Mephenytoin
	H	$H_3C-\underset{H_2}{C}-$	Ethotoin

- The hydantoins are close structural relatives of the barbiturates, differing in lacking the 6-oxo group. They are cyclic monoacylureas rather than cyclic diacylureas. As a consequence of losing a carbonyl group, they are weaker organic acids than the barbiturates, thus, aqueous solutions of sodium salts, such as of phenytoin sodium, generate strongly alkaline solutions.

- The compounds have antigeneralized tonic-clonic activity. Hydantoins with lower alkyl substituents reportedly have antiabsence activity.

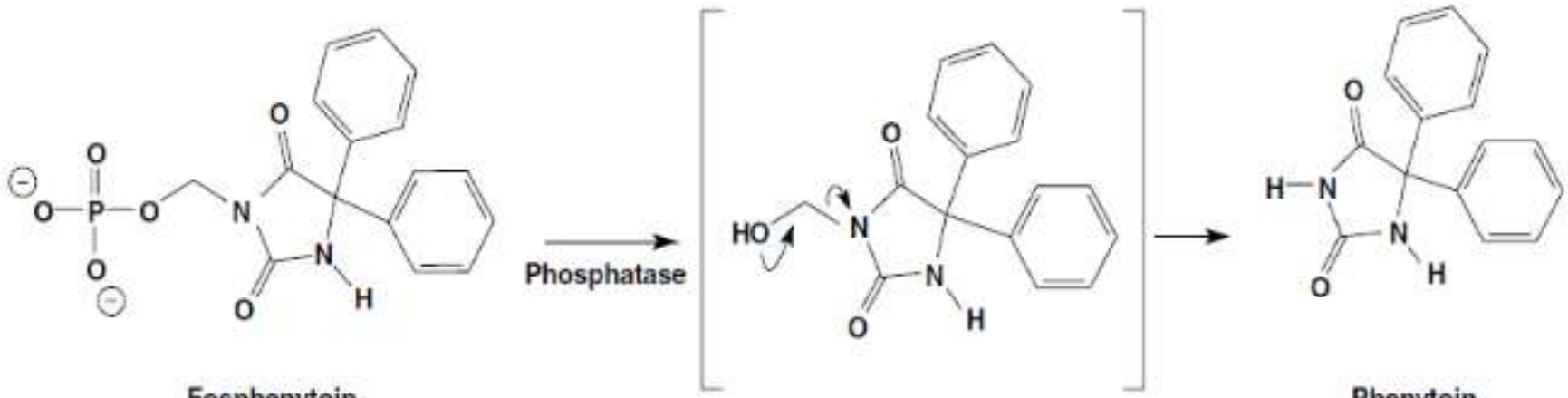


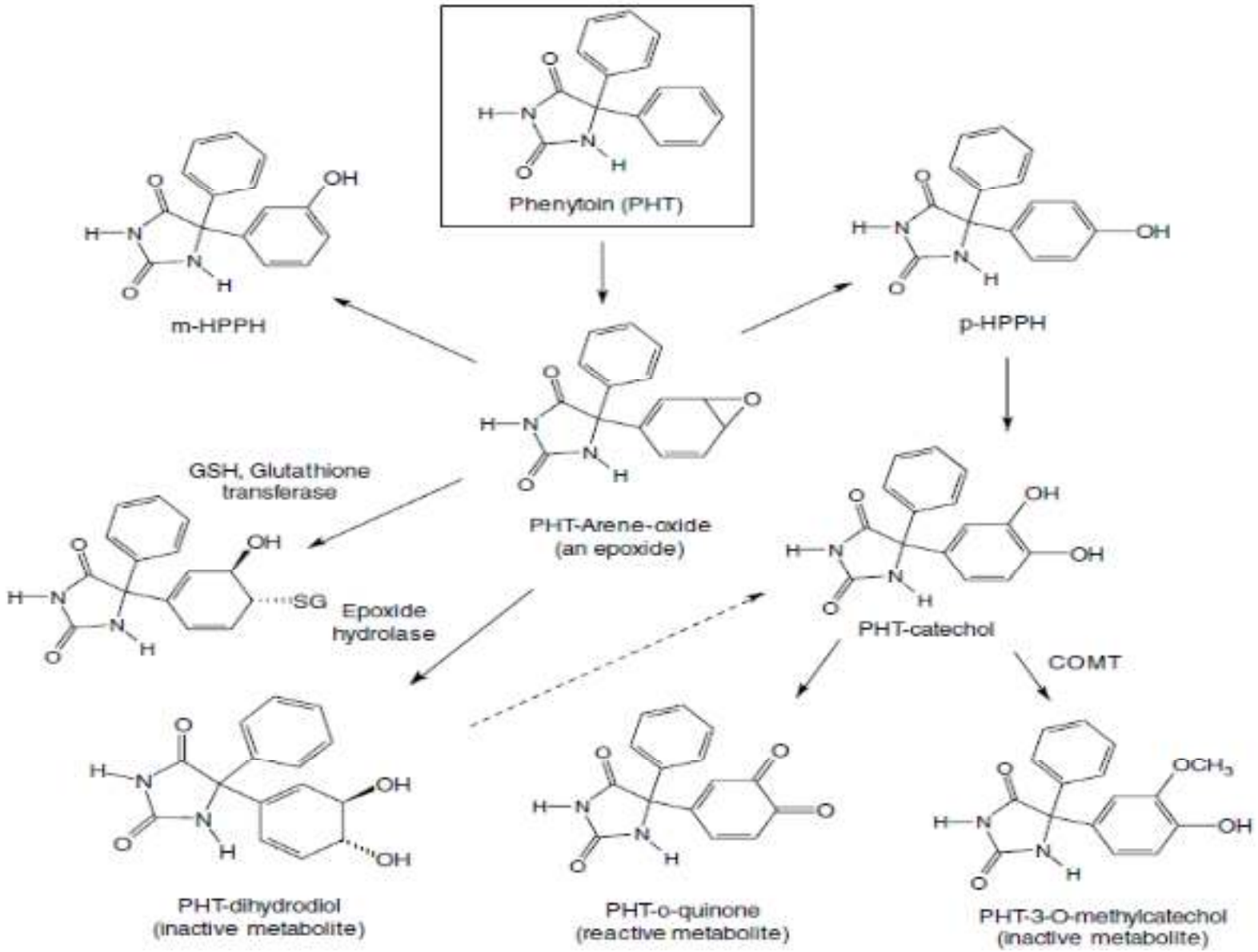
R_5	R'_5	R_3	
		H	Phenytoin
	$H_3C-\underset{H_2}{C}-$	H_3C-	Mephenytoin
	H	$H_3C-\underset{H_2}{C}-$	Ethotoin

Phenytoin and Phenytoin Sodium

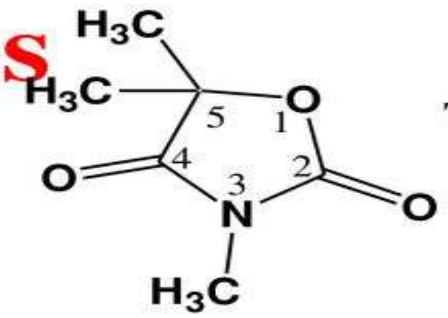
- Is the first anticonvulsant in which it was clearly demonstrated that anticonvulsant activity could definitely be separated from sedative-hypnotic activity.
- Acting as a sodium channel blocker.
- The drug is useful against all seizure types except absence.
- Is incompletely or erratically absorbed from sites of administration due to its very low water solubility.
- Metabolism proceeds by p-hydroxylation of an aromatic ring, followed by conjugation.

- **Bioactivation of Fosphenytoin:**
- Phenytoin isabsorbed incompletely or erratically from sites of administration because of its very low water solubility.
- For this reason, fosphenytoin, a prodrug of phenytoin, was developed to avoid complications such as vein irritation, tissue damage, and muscle necrosis associated with parenteral phenytoin administration.




Phenytoin (PHT)
m-HPPH
p-HPPH
PHT-Arene-oxide
(an epoxide)
GSH, Glutathione
transferase
Epoxide
hydrolase
PHT-catechol
COMT
PHT-dihydrodiol
(inactive metabolite)
PHT-o-quinone
(reactive metabolite)
PHT-3-O-methylcatechol
(inactive metabolite)

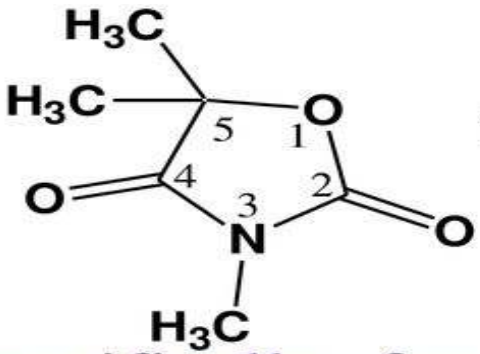
Oxazolidinediones



Trimethadione

- Replacement of the **N-H** group at position 1 of the hydantoin system with an **oxygen** atom yields the oxazolidine-2,4dione system.
- The oxazolidinedione system has antiabsence activity, although these compounds is substituted with lower alkyls.
- Aryl substituted oxazolidine-2,4-diones have shown activity against generalized tonic-clonic seizures.
- Dermatological and hematological toxicities associated with the group may be the problem.

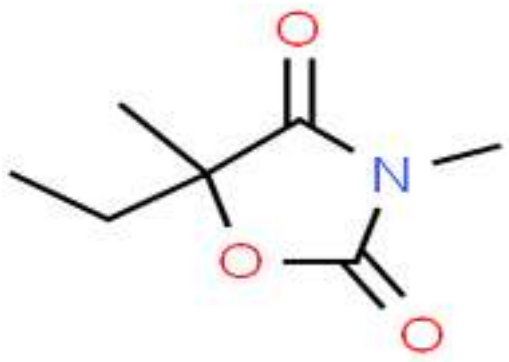
Trimethadione



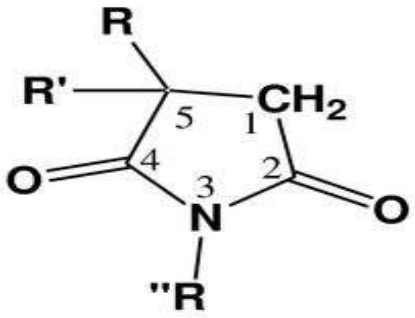
Trimethadione

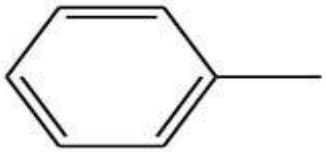
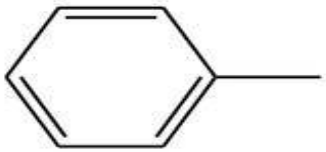
- Was the first drug introduced specifically for treating absence seizures.
- It is important as a prototype structure for antiabsence compounds.
- Dermatological and hematological toxicities limit its clinical use.
- The drug is metabolized by **N-demethylation** to the active metabolite **dimethadione**.
- Dimethadione is a calcium T channel blocker.
- Dimethadione is a water soluble and less lipophilic and thus is excreted unchanged.

- Paramethadione is an anticonvulsant in the oxazolidinedione class.
- It is associated with fetal trimethadione syndrome, which is also known as paramethadione syndrome.
- It is an oxazolidinedione anticonvulsant similar to trimethadione that acts on the CNS to reduce the number of absence seizures.
- Paramethadione acts on thalamic neurons in the thalamic reticular nucleus.



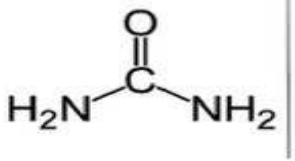
Succinimides



R	R'	R''	
	H	CH_3	Phensuximide
	CH_3	CH_3	Methsuximide
$H_3C-\underset{H_2}{C}-$	CH_3	H	Ethosuximide

- Succinimides (CH_2 replaces O) have activity against generalized tonic-clonic, partial seizures absence, and complex partial seizures . Three are now in clinical use.

Ureas and Monoacylureas

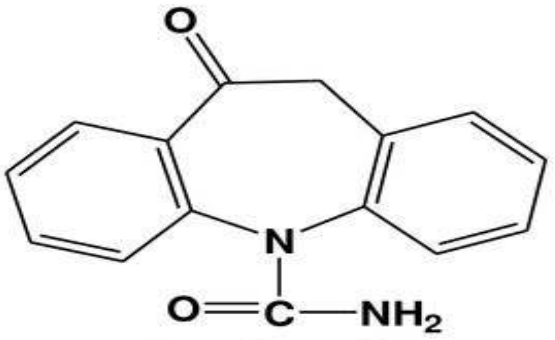


- Ureas and monoacylureas, have a long history of producing compounds with anticonvulsant activity.
- The numerical yield of clinically useful compounds has not been great, however, most of the simpler compounds have gone by the way.
- For convenience of grouping, **carbamazepine** and **oxcarbazepine** can be considered **N,N-diacylureas**.

Carbamazepine

- SAR can be viewed either as an ethylene-bridged 1,1diphenylurea or an amido substituted tricyclic system.
- The two phenyls substituted on the urea nitrogen fit the pattern of antigeneralized tonic activity.
- Mode of action: sodium channel block.
- Carbamazepine is useful in generalized tonic-clonic and partial seizures.

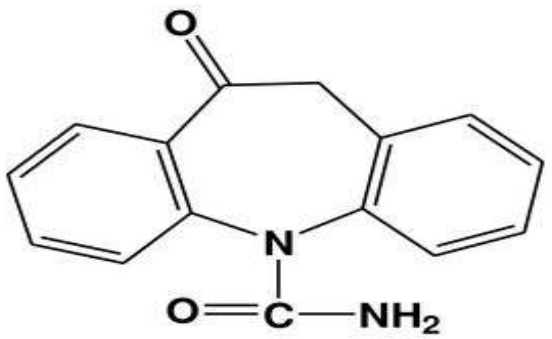
Carbamazepine



Oxcarbazepine

- The drug has the potential for serious hematological toxicity, and it is used with caution.
- Metabolism proceeds largely through the **epoxide** formed at the (Z) cis-stilbene double bond. In humans, the epoxide reportedly is converted largely to the 10,11-trans-diol. The epoxide is a suspect in the idiosyncratic reactions carbamazepine may produce (**aplastic anemia**).
- With this in mind, compounds designed to avoid the epoxide such as oxcarbazepine were developed.

Carbamazepine

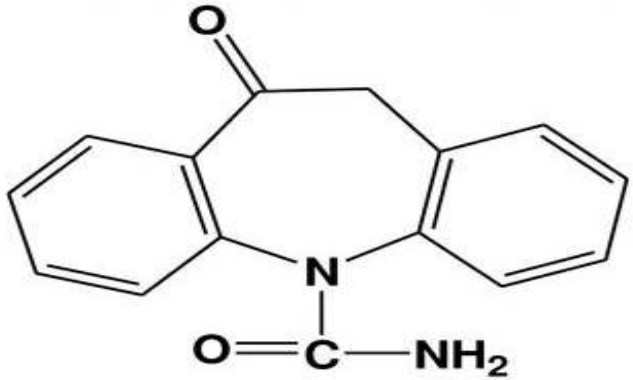


Oxcarbazepine

Oxcarbazepine

- Oxcarbazepine is reduced to the monohydroxy compound.
- The monohydroxy compound is considered the major active metabolite.
- The drug is used against partial seizures.
- The major mechanism of action is sodium channel block.

Carbamazepine



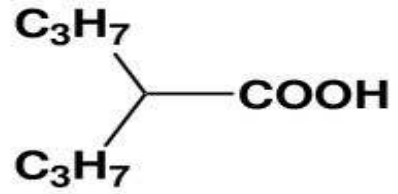
Oxcarbazepine

Miscellaneous Agents

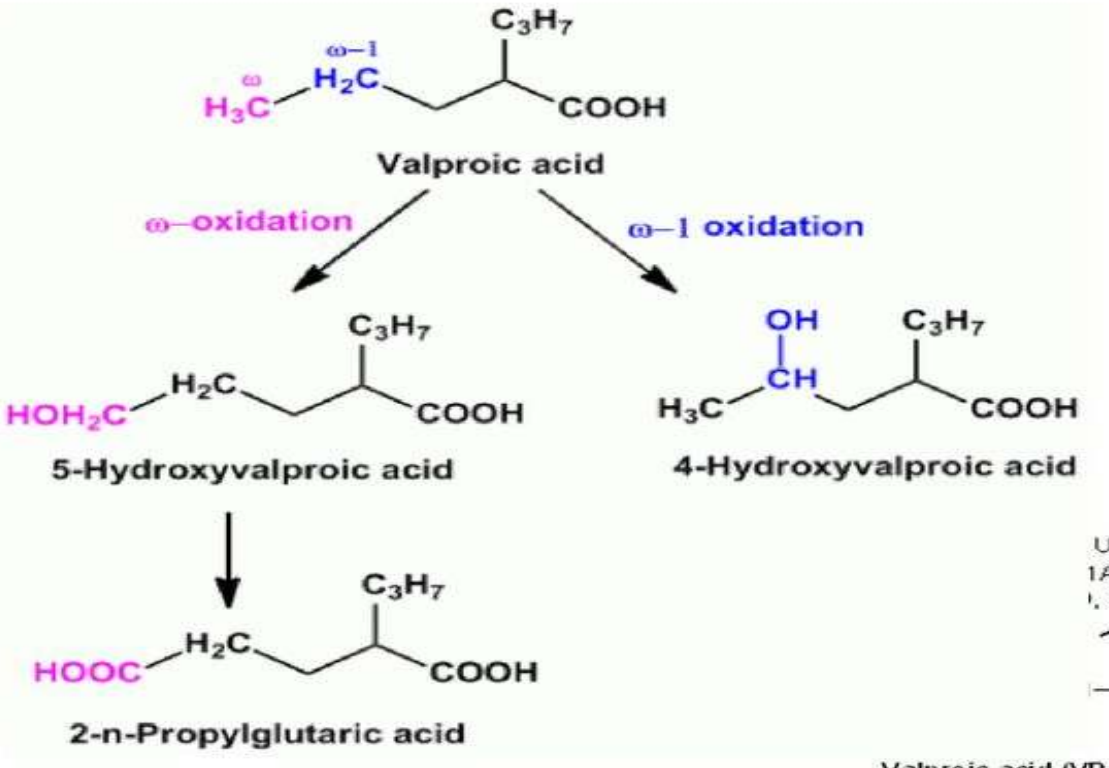
- Many carboxylic acids have anticonvulsant activity, although often of low potency, possibly in part because extensive dissociation at physiological pH produces poor partitioning across the blood brain barrier.

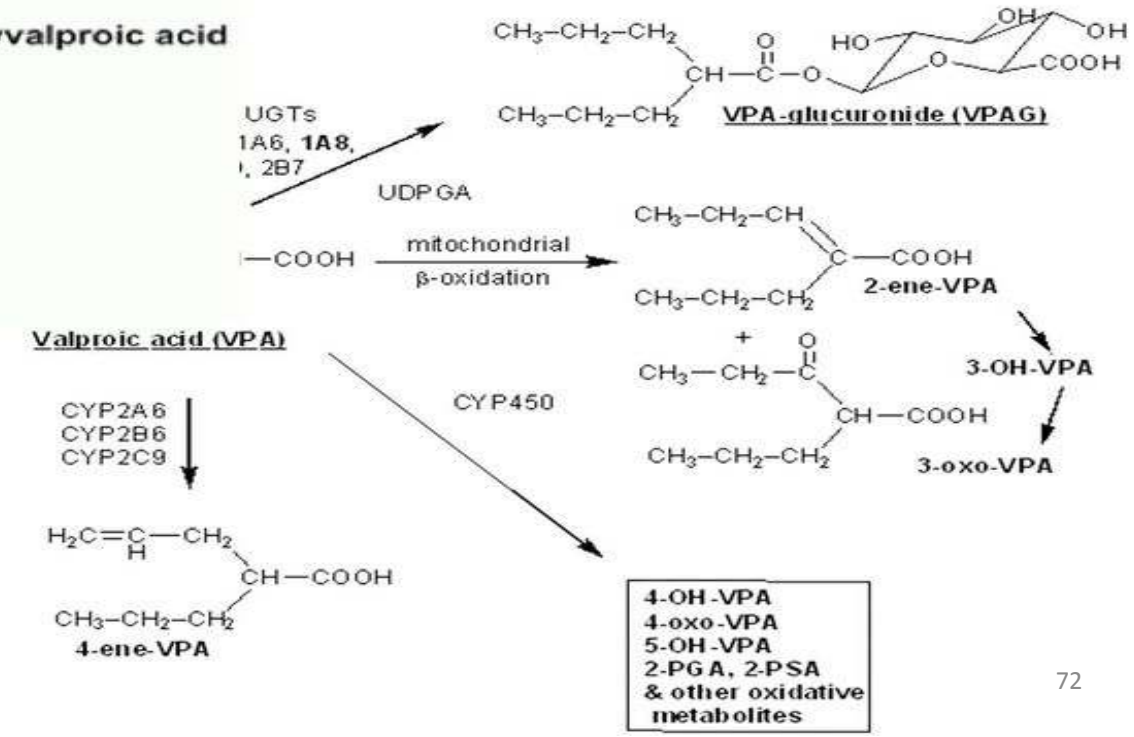
Valproic acid

- 2-propylpentanoic acid (Depakene) has good potency and is used against typical and atypical absence seizures and absence seizure with generalized tonic-clonic seizure.
- Mechanistically, the drug is a sodium channel blocker.
- Metabolism is by conjugation of the carboxylic acid group and oxidation of one of the hydrocarbon chains.
- Many of the side effects are mild. Rare, but potentially fatal, fulminant hepatitis has caused concern.



Valproic Acid

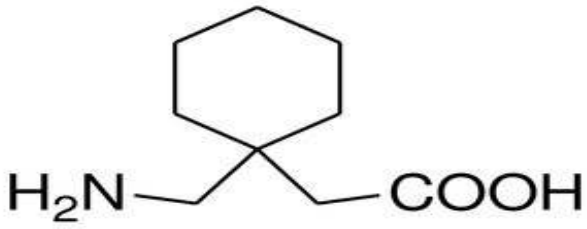

Valproic acid
ω–oxidation
ω–1 oxidation
5-Hydroxyvalproic acid
4-Hydroxyvalproic acid
2-n-Propylglutaric acid


VPA-glucuronide (VPAG)
UGTs
UDPGA
mitochondrial
β-oxidation
2-ene-VPA
3-OH-VPA
3-oxo-VPA
Valproic acid (VPA)
CYP2A6
CYP2B6
CYP2C9
CYP450
4-ene-VPA
4-OH-VPA
4-oxo-VPA
5-OH-VPA
2-PGA, 2-PSA
& other oxidative
metabolites

Gabapentin

- Despite the fact that gabapentin is a relative of GABA with increased hydrophobic character; a binding site on calcium channels has been identified.
- The drug is said to have a good pharmacokinetic profile and to cross the blood-brain barrier well.
- It was introduced for adjunctive therapy of refractory partial seizures and, secondarily, generalized tonic-clonic seizures.

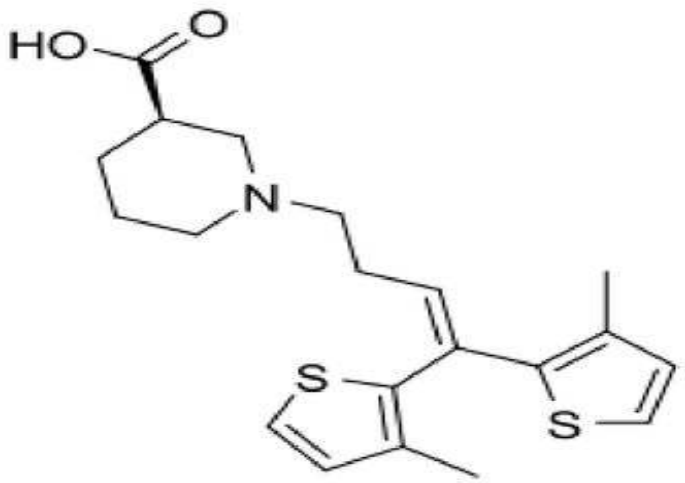
GABA



Gabapentin

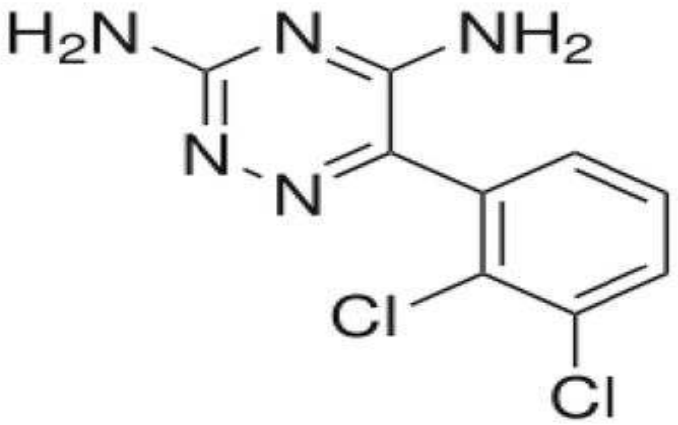
Tiagabine (Gabitril)

- It blocks GABA reuptake.
- Its use is against partial seizures.

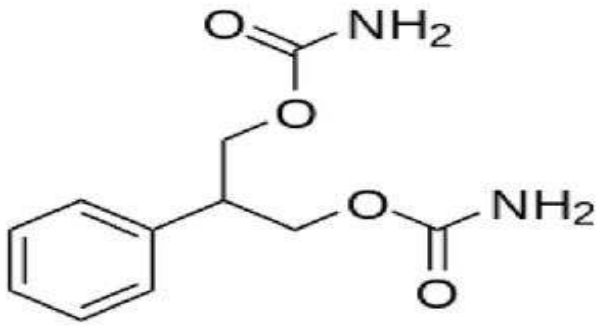


Lamotrigine (Lamictal)

- Lamotrigine has been found effective against refractory partial seizures.
- It is act by blocking sodium channels and preventing glutamate release.



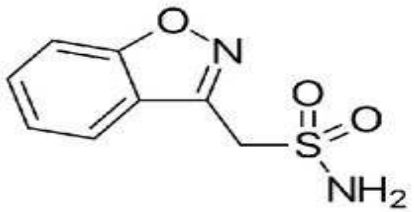
Felbamate

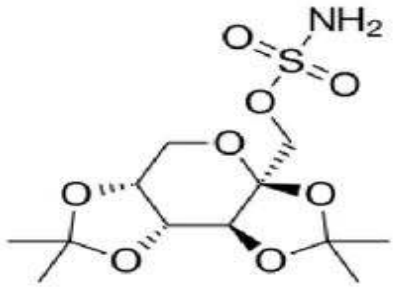


- It is a sodium channel blocker.
- Felbamate has been used successfully in refractory patients with generalized tonic-clonic seizures and complex partial seizures.
- The drug is associated with a serious risk aplastic anemia.
- It is used with extreme caution after other anticonvulsants have been tried and a careful risk-to-benefit has been made.

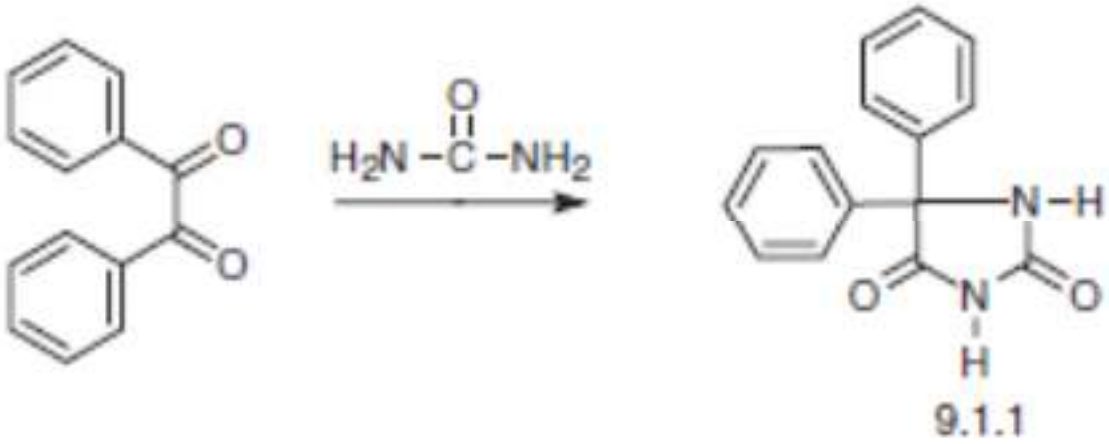
Zonisamide (Zonegran) Topiramate (Topamax)

- Zonisamide and Topiramate have, respectively, the sulfonamide and sulfate amido (sulfamate) as the small polar group and an extensive hydrophobic group as the large end.
- Both are sodium channel blockers. Zonisamide also blocks calcium-T channels and Topiramate increases the effect of GABA and antagonizes glutamate receptor. Each of the drugs is employed adjunctively against partial seizures.



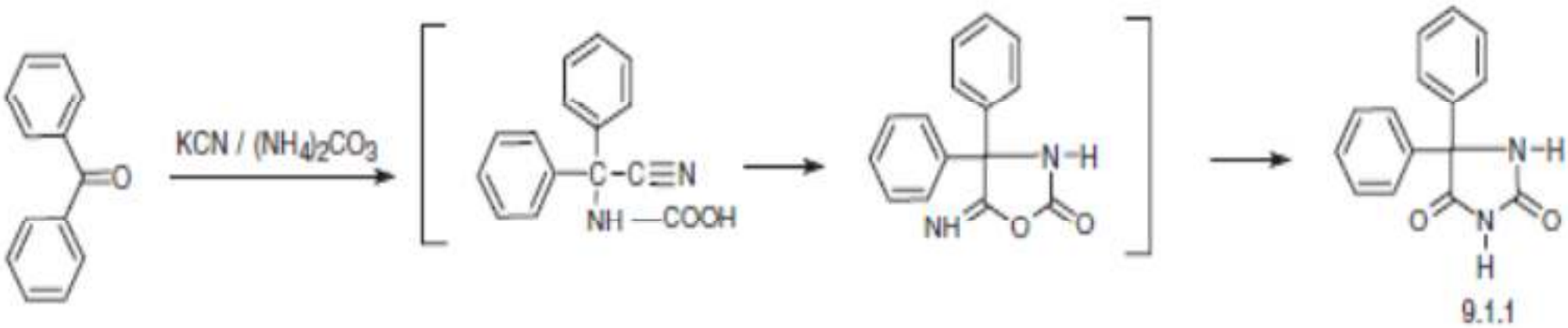


- **Synthesis of Phenytoin:**
- Phenytoin, 5,5-diphenylimidazolidinedione (9.1.1) is synthesized in two different ways.
- The first involves a rearrangement on the reaction of benzil with urea to form the desired product (9.1.1) [1].



9.1.1

- The second method involves the reaction of benzophenone with sodium cyanide in the presence of ammonium carbonate, followed by the simultaneous cyclization of the resulting product (carboxyaminonitrile) and its rearrangement under the reaction conditions to form phenytoin.

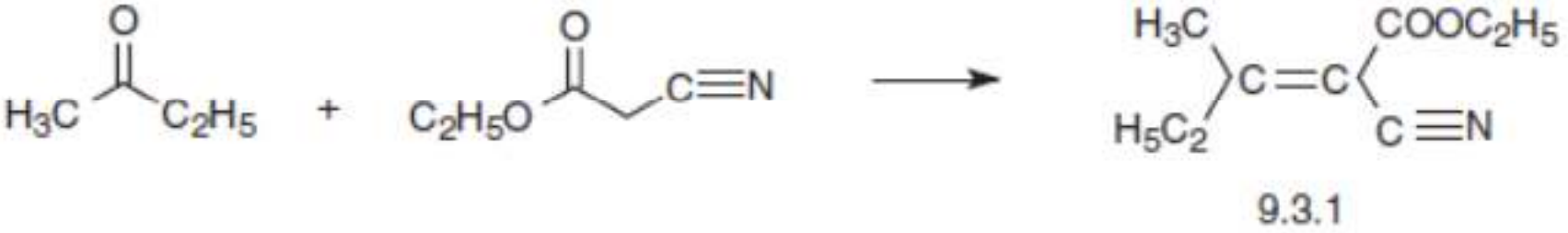


9.1.1

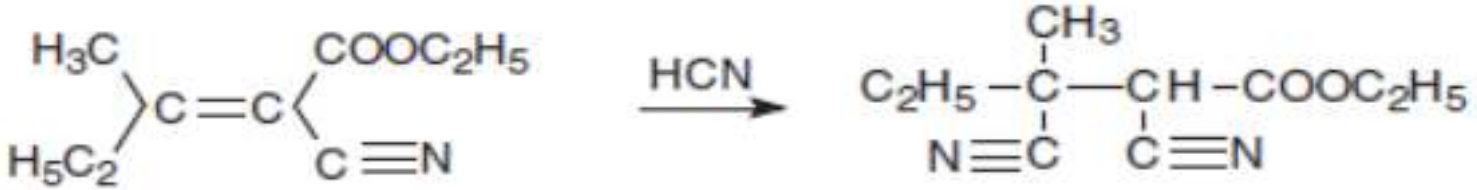
- ***Synthesis of Ethosuximide***

- Ethosuximide, 3-ethyl-3-methypyrrolidine-2,5-dione (9.3.4) is synthesized from methylethylketone and cyanoacetic ester, which are condensed in Knoevanagel reaction conditions.

- Then hydrogen cyanide is added to the resulting product (9.3.1).

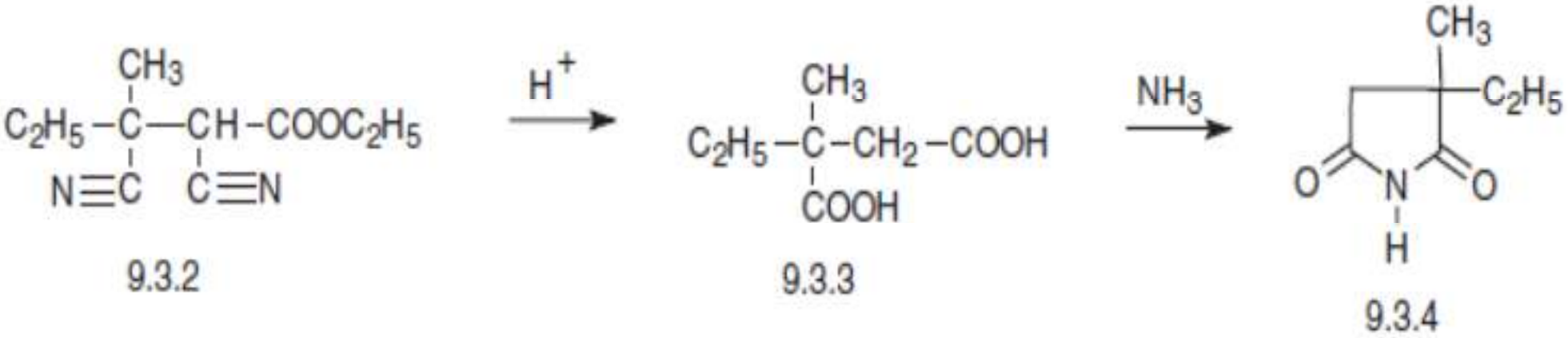


9.3.1



9.3.1 9.3.2

- After acidic hydrolysis and decarboxylation of synthesized dinitrile (9.3.2), 2-methyl-2-ethylsuccinic acid (9.3.3) is formed.
- Reacting this product with ammonia gives the diammonium salt, and heterocyclization into the ethosuximide (9.3.4) takes place during subsequent heating.

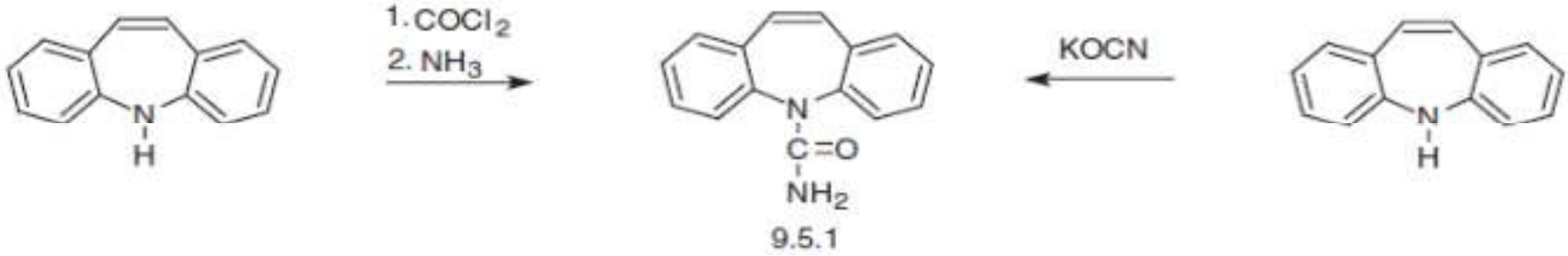


9.3.2 9.3.3 9.3.4

- ***Synthesis of Carbamazepine***

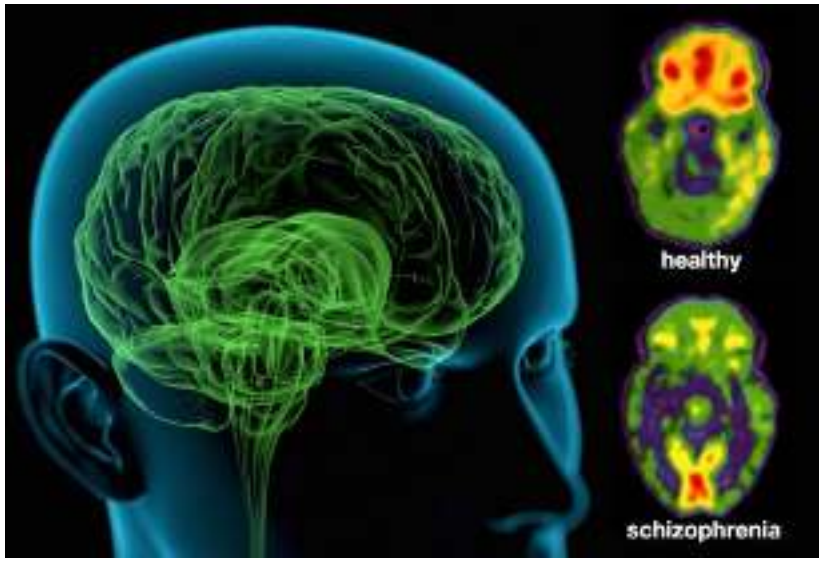
- Carbamazepine, 5*H*-dibenz-[b,f]-azepine-5-carboxamide (9.5.2), is synthesized by reacting 5*H*-dibenz-[b,f]-azepine and phosgene, which forms 5-chlorcarboxy- 5*H*-dibenz-[b,f]-azepine (9.5.1), and its subsequent reaction with ammonia to give the desired carbamazepine (9.5.2) [16].

- An alternative method of synthesis is the direct reaction of 5*H*-dibenz[b,f]azepine with potassium cyanate



9.5.1

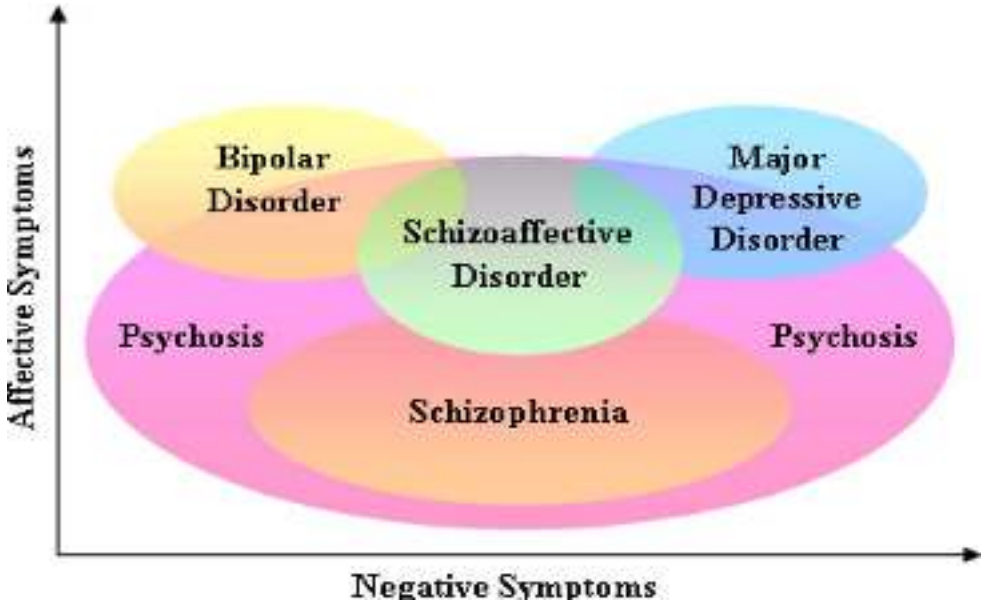
ANTIPSYCHOTICS



https://www.webmd.com/schizophrenia/ss/slideshow-schizophrenia-overview

https://www.webmd.com/schizophrenia/guide/schizophrenia-treatment-care

- **PSYCHOSIS:**
- It is a psychogenic mental disorder involving a loss of contact with reality.
- The psychotic disorders include-



- ➢ Schizophrenia,
- ➢ Acute idiopathic psychotic illness,
- ➢ Manic phase of bipolar (Manic–depressive) illness,
- ➢ Other conditions marked by severe agitation.

- Psychosis is a condition that affects the way brain processes information.
- It causes loss of touch with reality.
- The affected person might see, hear, or believe things that aren’t real.
- Psychosis is a symptom, not an illness.
- A mental or physical illness, substance abuse, or extreme stress or trauma can cause it.

- The most common is **schizophrenia**, in which-

- ➢ Perception,
- ➢ Thinking,
- ➢ Communication,
- ➢ Social functioning, and
- ➢ Attention are **altered**.

- Symptoms are called *positive* (e.g., delusions, hallucinations) or *negative* (e.g., flat affect, apathy); cognitive dysfunction may occur.
- A defect in the brain's informational gating mechanism.
- Basically, brain has difficulty discriminating between relevant and irrelevant stimuli.
- The etiology of psychosis remains unknown, although genetic, neurodevelopmental and environmental causative factors have all been proposed.

- Psychoses can be-

➢ organic and related to a specific toxic chemical

(e.g., delirium produced by central anticholinergic agents),

➢ drug induced like *N*-methyl D-aspartate (NMDA) receptor antagonist

(e.g., phencyclidine [PCP]),

➢ a definite disease process (e.g., dementia), or

➢ they can be idiopathic.

- The basic defect appears to involve over activity of dopaminergic neurons in the mesolimbic system.
- **DA hypothesis** is the basis for drug therapy because-

➢ (a) drugs that increase dopaminergic neurotransmission, such as levodopa (a DA precursor), amphetamines (a DA releaser), and apomorphine (a DA agonist), induce or exacerbate schizophrenia.

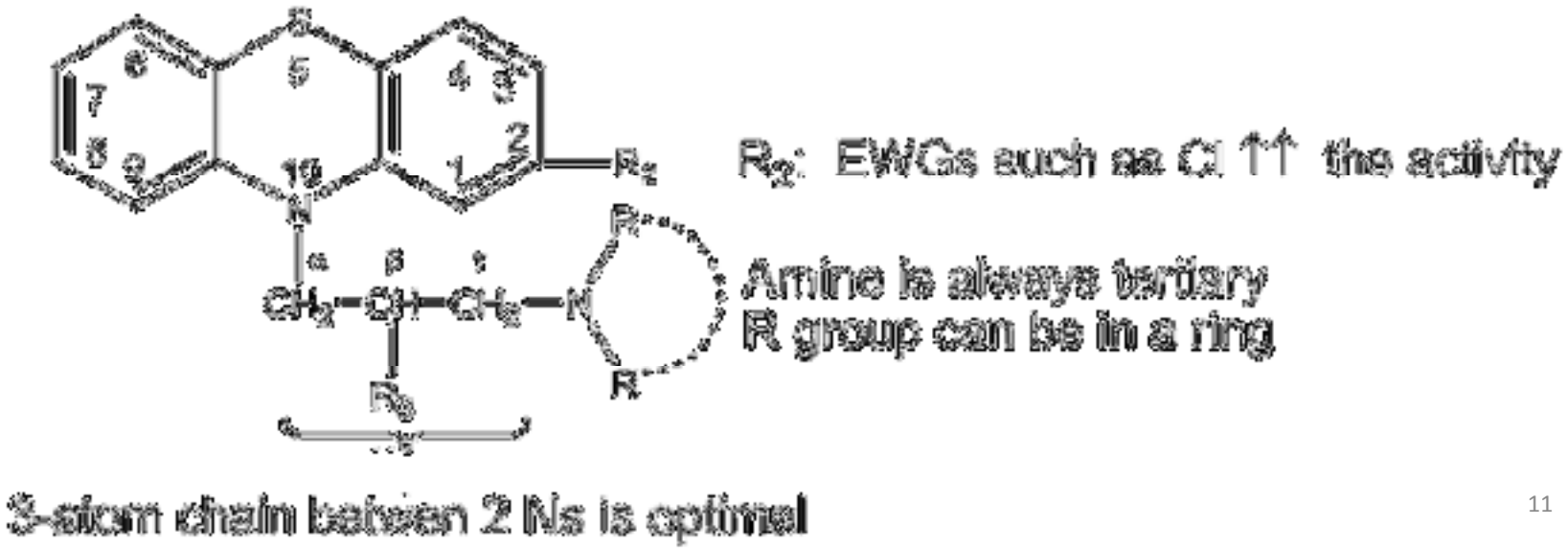
- (b) DA receptor density is increased in certain brain regions of untreated schizophrenics;
- (c) many antipsychotic drugs strongly block postsynaptic D2 receptors in CNS;
- (d) successful treatment of schizophrenic patients has been reported to change the amount of homovanillic acid (HVA), a DA metabolite, in the cerebrospinal fluid, plasma, and urine.

- The antipsychotic action is now thought to be produced by their ability to block DA receptors in the mesolimbic and mesofrontal systems.
- Moreover, extrapyramidal side effects of antipsychotic drugs correlate with their D2 antagonism effect.
- The hyperprolactinemia that follows treatment with antipsychotics is caused by blockade of DA's tonic inhibitory effect on prolactin release from the pituitary.
- It is now appreciated that schizophrenia is far more complex than originally supposed.

- **Classification of Antipsychotics:**
- Several classes of drugs are effective for symptomatic treatment.
- EPS=Extra Pyramidal Sideffects (involuntary or uncontrollable movements, tremors and muscle contractions).

Drug Groups	Structure Features	Examples	Comments
Phenothiazines	Aliphatic side chain Piperidine side chain Piperazine side chain	Chlorpromazine Thioridazine Fluphenazine	Least potent Least potent and ↓ EPS More potent and more EPS
Thioxanthenes	Double bond on C10	Thiothixene	Less potent than other phenothiazines
Butyrophenones	Aromatic butylpiperidines and diphenylbutylpiperidines	Haloperidol	More potent Fewer autonomic SEs Greater EPS
Newer drugs	Miscellaneous	Risperidone Clozapine Olanzapine	Less EPS Also good for negative symptoms

- **Phenothiazines**
- Several phenothiazine antipsychotic drugs are chemically related agents used worldwide.
- Other phenothiazines are marketed primarily for their antiemetic, antihistaminic, or anticholinergic effect.



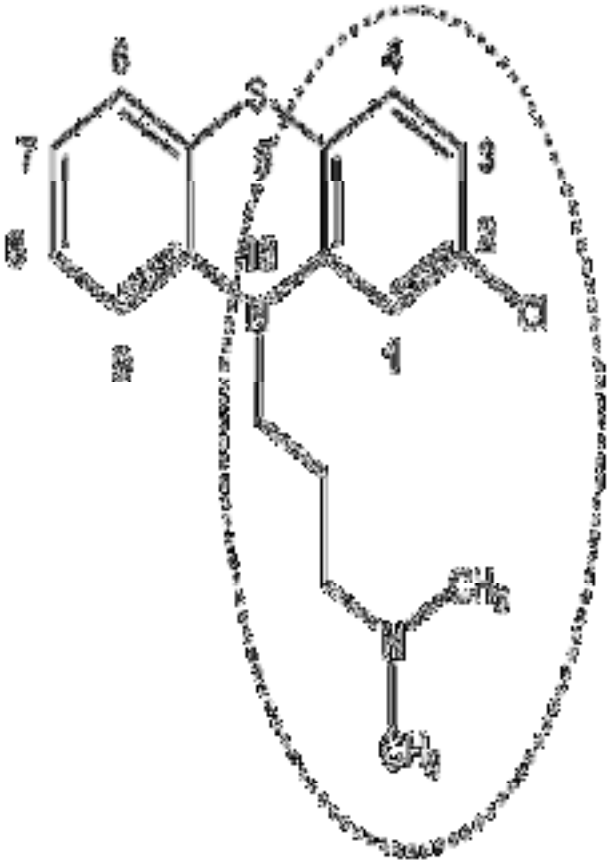
- Phenothiazines have a tricyclic structure (6-6-6 system) in which two benzene rings are linked by a sulfur and a nitrogen atom.
- The best position for substitution is the 2-position.
- Activity increases (with some exceptions) as electron-withdrawing ability of the 2-substituent increases (e.g., chlorpromazine vs. promazine).
- The presence of an unshared electron pair on an atom or atoms of the 2-substituent increases potency.

- Substitution at the 3-position can improve activity over non-substituted compounds but not as significantly as substitution at the 2-position.
- Substitution at position 1 and 4 (to a lesser extent) reduce antipsychotic activity.
- **The significance of these substituent effects could be that the hydrogen atom of the protonated amino group of the side chain H-bonds with an electron pair of an atom of the 2-substituent to develop a DA-like arrangement.**

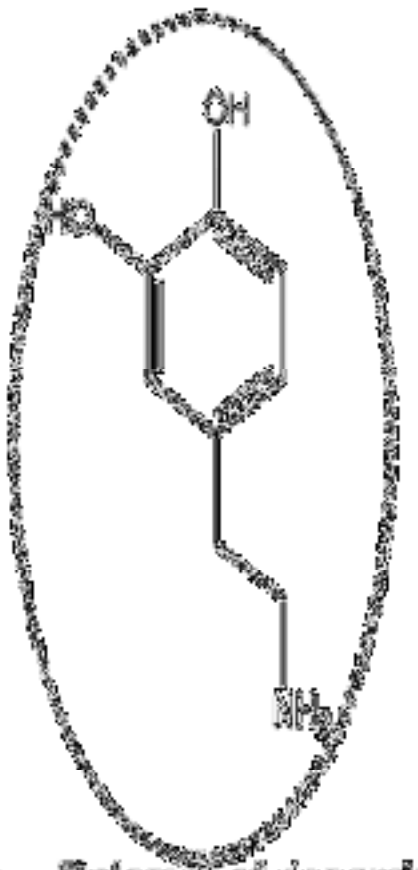
- The **X-ray crystallography model** proposed that-

  - the chlorine-substituted ring of chlorpromazine could be superimposed on the aromatic ring of DA.
  - the sulfur atom aligned with the *p*-hydroxyl group of DA.
  - the aliphatic amino groups of the two compounds also aligned.

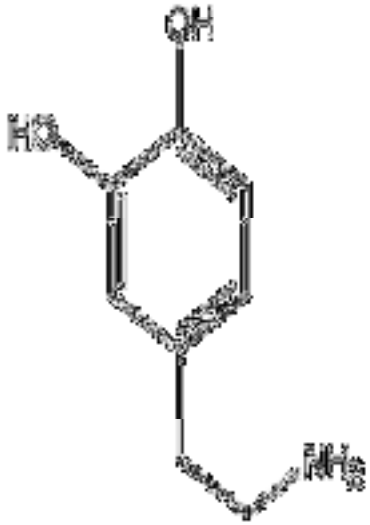
- The X-ray crystallography model involves the protonated species rather than the free base.



Promethazine



trans-o-Polomer of dopamine (active)



cis-o-Polomer of dopamine

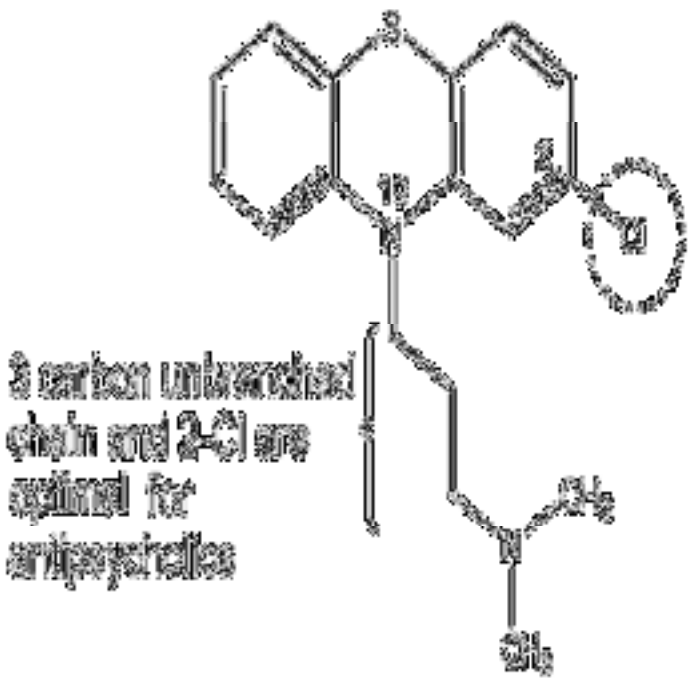
- The substituent at the 1-position may interfere with the side chain's ability to bring the protonated amino group in proximity with the 2-substituent.
- The sulfur atom at position 5 is in a position analogous to the *p*-hydroxyl group of DA, and is esponsible for receptor binding.
- A substituent at position 4 might interfere with receptor binding by the sulfur atom.

- The three-carbon chain between position 10 and the aliphatic amino nitrogen is critical for neuroleptic activity.
- Shortening or lengthening the chain at this position drastically decreases the activity.
- The three-atom chain length may be necessary to bring the protonated amino nitrogen in proximity with the 2-substituent.
- Shortening the chain to two carbons has the effect of amplifying the antihistaminic and anticholinergic activities.

For example, promethazine is effective antihistamine, whereas the amino ethyl derivatives diethazine (anticholinergic) and ethopropazine (antimuscarinic) have proved useful in the treatment of Parkinson disease.

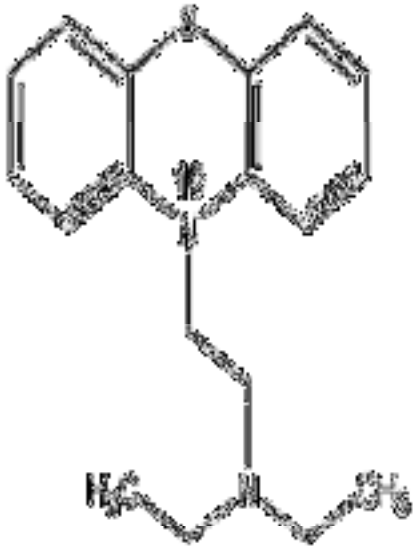
- The amine is always tertiary.
- *N*-dealkylation of the side chain or increasing the size of amino *N*-alkyl substituents reduces antidopaminergic and antipsychotic activity.

- Branching with large groups (e.g., phenyl) decreases activity, as does branching with polar groups.
- Methyl branching on the β-position has a variable effect on activity.
- More importantly, the antipsychotic potency of *levo* (the more active) and *dextro* isomers differs greatly.
- Decreases in size from a dimethylamino group (e.g., going to a monomethylamino) greatly decrease activity.

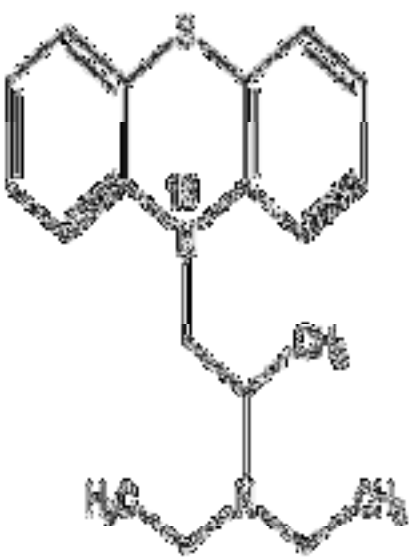


Chlorpromazine (antipsychotic)
Log P = 5.53, Log D = 5.19
pKa = 9.43

Promethazine (antihistamine)
Also antidopaminergic



Diphenhydramine (antihistamine)



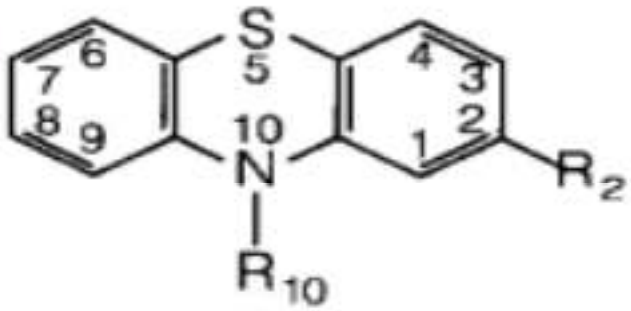
Ethopropazine (antihistamine)

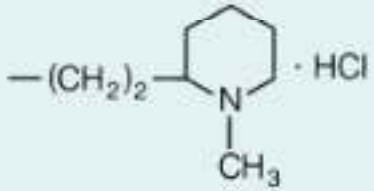
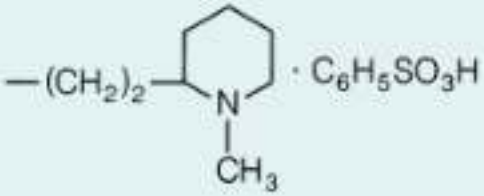
- **Structure and Pharmacokinetics:**
- Several piperazine phenothiazines are esterified at a free hydroxyl with long-chain fatty acids to produce highly lipophilic and long-acting prodrugs.
- They tend to have large volumes of distribution and have very high affinity for selected NT receptors in the CNS.
- They generally have a much longer clinical duration of action.

- Because of the high lipophilicity of most antipsychotic drugs, they are highly membrane and protein bound (92%–99%) mostly to albumin.
- They accumulate in the brain, lung, and other tissues with a rich blood supply and also enter the fetal circulation and breast milk.
- Most phenothiazines undergo significant first-pass metabolism.
- Thus, oral doses of chlorpromazine and thioridazine have systemic availability of 25% to 35%, whereas parenteral (intramuscular) administration increases the bioavailability of active drug 4 to 10 fold.

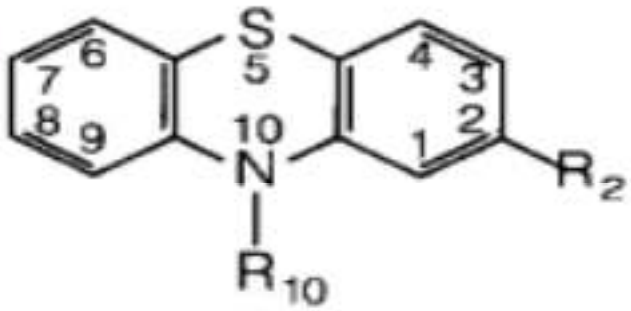
- In contrast, haloperidol, which is less likely to be metabolized, has an average systemic availability of about 65%.
- Metabolism of the phenothiazines is complex.
- A major route is 7-hydroxylation of the tricyclic system.
- Because electron-withdrawing 2-Cl substituent blocks the hydroxylation on chlorophenyl ring, the hydroxylation occurs at 7-position rather than 2-position.

Phenothiazine Derivatives



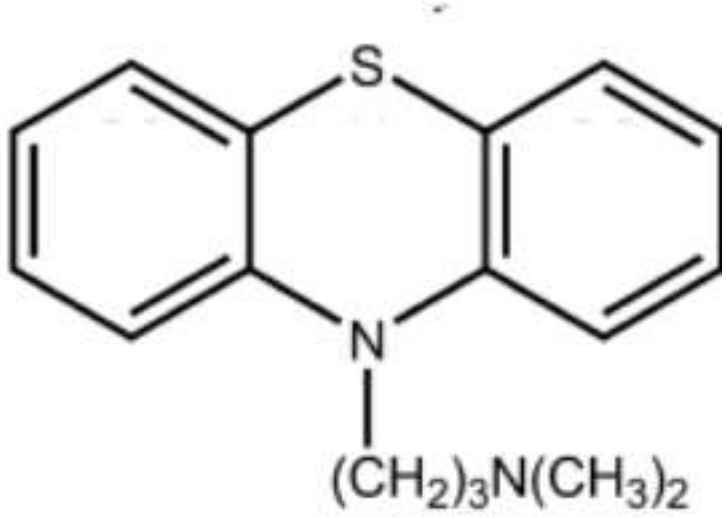
Generic Name *Proprietary Name*	R_{10}	R_2
Propyl Dialkylamino Side Chain		
Promazine hydrochloride, *USP* *Sparine*	$-(CH_2)_3N(CH_3)_2 \cdot HCl$	H
Chlorpromazine hydrochloride, *USP* *Thorazine*	$-(CH_2)_3N(CH_3)_2 \cdot HCl$	Cl
Trifluprazine hydrochloride, *USP* *Vesprin*	$-(CH_2)_3N(CH_3)_2 \cdot HCl$	CF_3
Akyl Piperidyl Side Chain		
Thioridazine hydrochloride, *USP* *Mellaril*		SCH_3
Mesoridazine besylate, *USP* *Serentil*		O ↑ SCH_3

Phenothiazine Derivatives

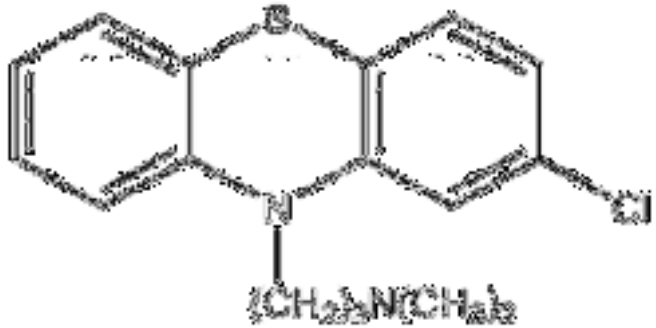


Generic Name *Proprietary Name*	R_{10}	R_2
Propyl Piperazine Side Chain		
Prochlorperazine maleate, *USP* *Compazine*	$-(CH_2)_3-N\langle\rangle N-CH_3 \cdot 2C_4H_4O_4$	Cl
Trifluoperazine hydrochloride, *USP* *Stelazine*	$-(CH_2)_3-N\langle\rangle N-CH_3 \cdot 2HCl$	CF_3
Perphenazine, *USP* *Trilafon*	$-(CH_2)_3-N\langle\rangle N-CH_2-CH_2-OH$	Cl
Fluphenazine hydrochloride, *USP* *Permitil, Prolixin*	$-(CH_2)_3-N\langle\rangle N-CH_2-CH_2-OH \cdot 2HCl$	CF_3

- ***Promazine.***
- IUPAC: 10-[3-(dimethylamino) propylphenothiazine.
- It was introduced into antipsychotic therapy after its 2-chloro-substituted relative.
- The 2H-substituent vis-à-vis the 2Cl substituent gives a milligram potency decrease as an antipsychotic.
- Tendency to EPS is also lessened.



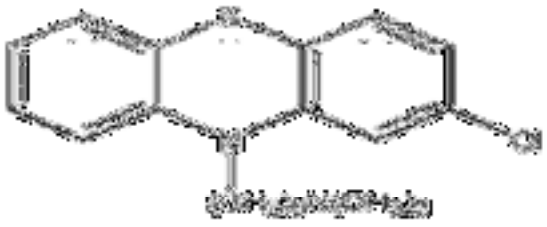
- ***Chlorpromazine Hydrochloride*.**
- IUPAC: 2-chloro-10-[3-(dimethylamino)propyl]phenothiazine.
- It was the first phenothiazine compound introduced into therapy.
- It is still useful as an antipsychotic.



- Other uses are in nausea, vomiting, and hiccough.
- It also possess sedative and hypnotic activity.

- The sedative and hypotensive properties are possibly due to central histaminergic and peripheral α1- anticholinergic activity, respectively.
- Effects of peripheral anticholinergic activity are common.
- As with the other phenothiazines, the effects of other CNS-depressant drugs, such as sedatives and anesthetics, can be potentiated.

CPZ-Pr-acid



Chlorpromazine (CPZ): Log D at pH 7 = 3.01

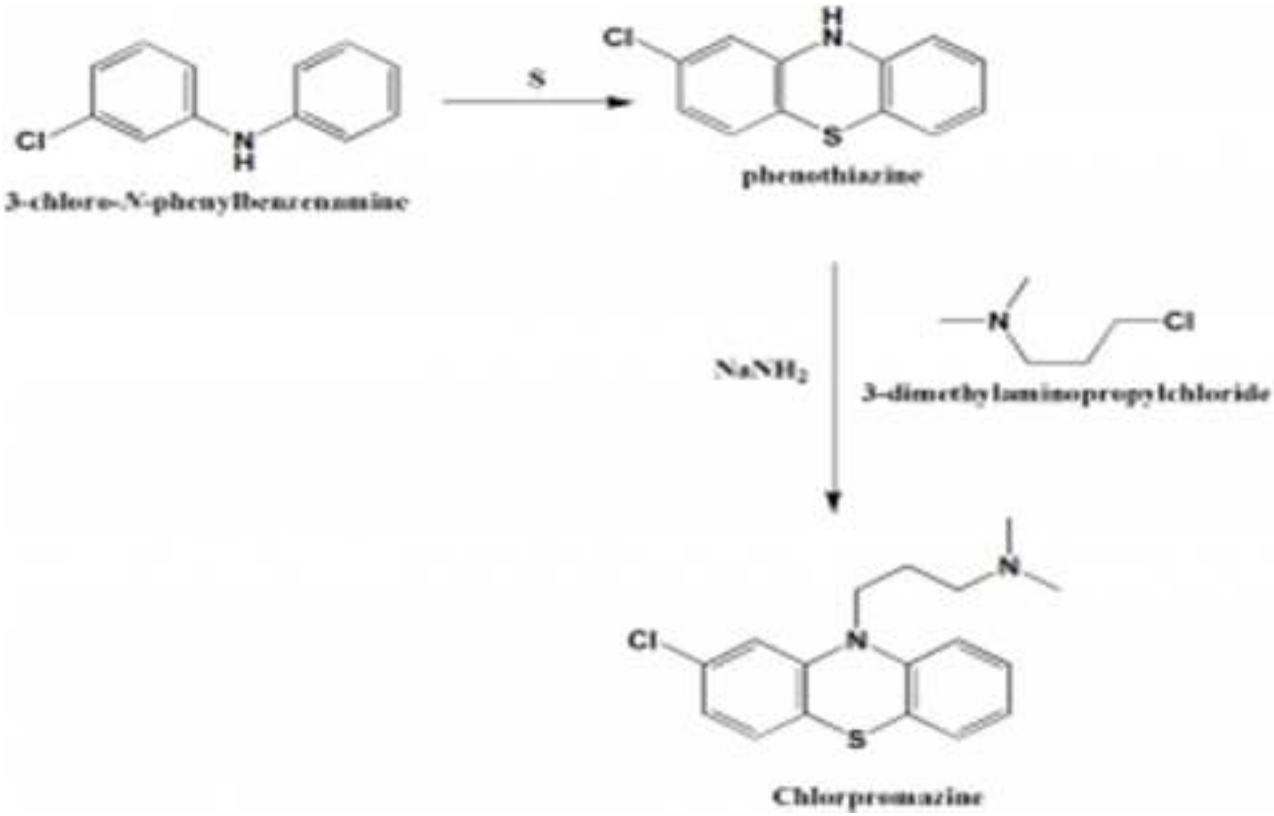
Major pathway

7-OMe-CPZ

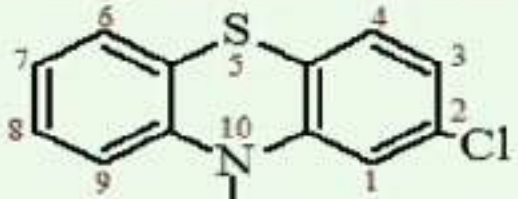
7-OH-CPZ (active)

7-O-glucuronide-CPZ (excreted)

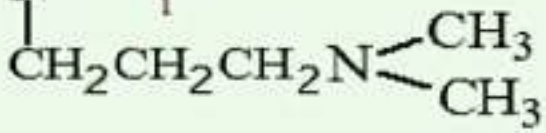
- **Synthesis of Chlorpromazine:**
- **i.3-chloro-N-phenylbenzenamine reacts with sulfur to give 2-chloro-10H-phenothiazine.**
- **ii. Chlorpromazine can be synthesized from 2-chloro-10H-phenothiazine by alkylation with 3-dimethylaminopropylchloride in the presence of sodium amide.**



Chlorpromazine Hydrochloride



· HCl

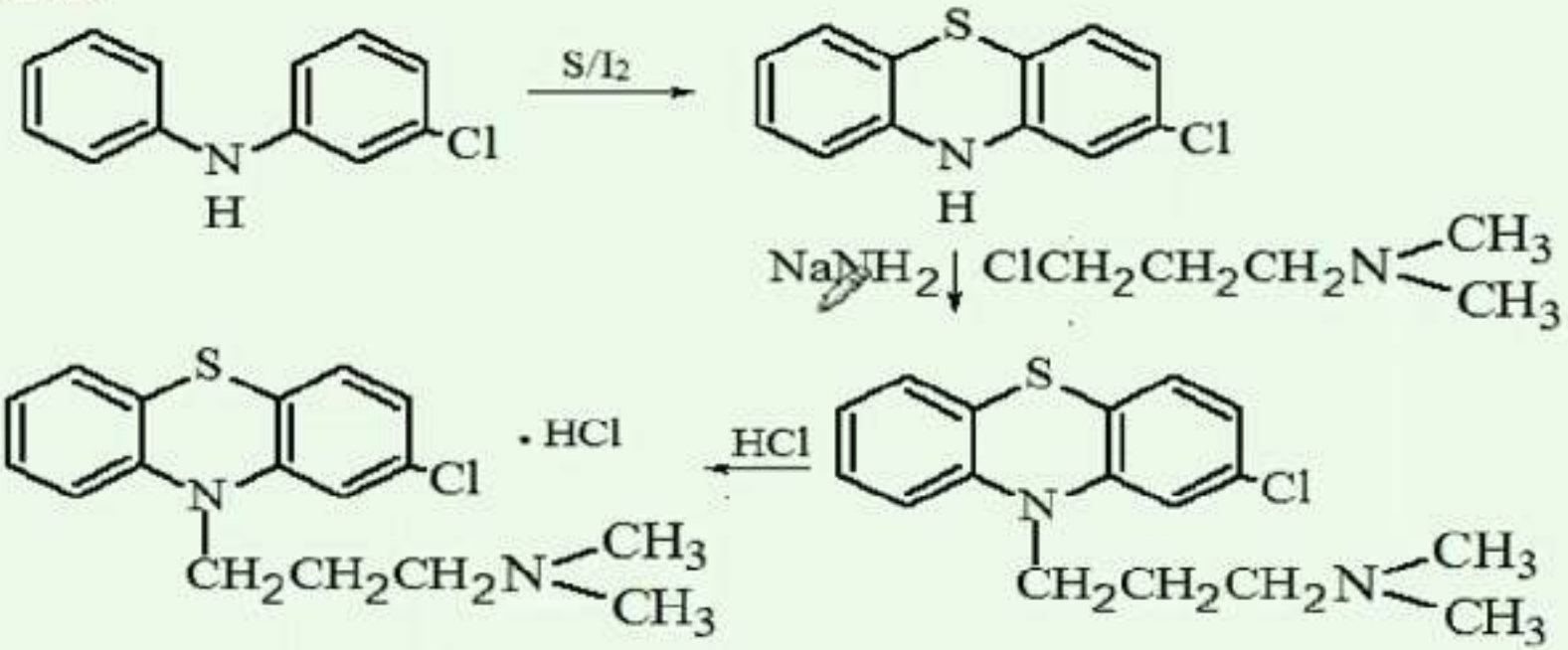


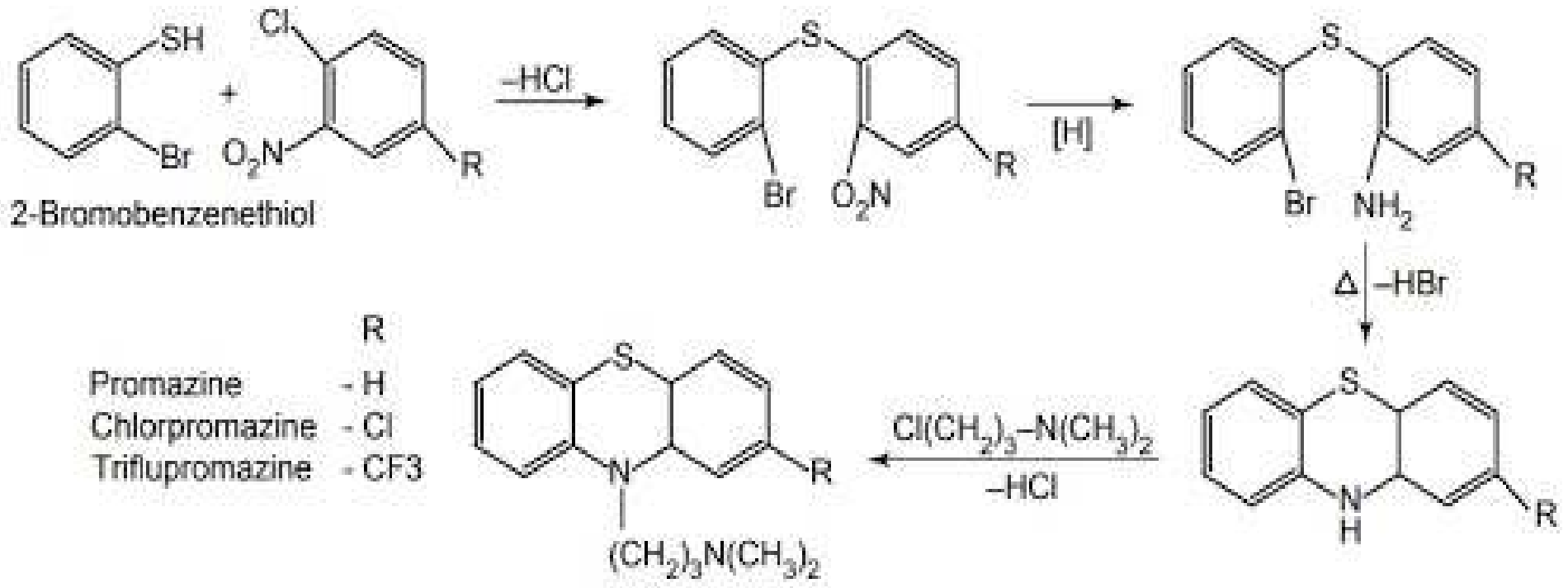
Uses: Used as Antipsychotic & Antiemetic drug

Mechanism of action : Block the Dopamine (D_2), Histamine (H_1) and Muscarinic (M_1) Receptors

IUPAC Name: 3-(2-Chloro-10H-Phenothiazin-10-yl)-N,N-Dimethyl-propan-1-amine hydrochloride

Synthesis:

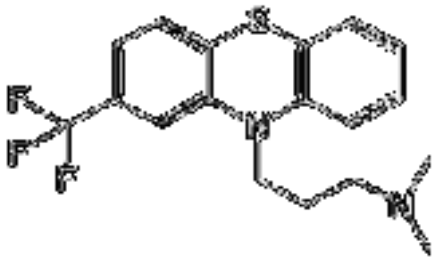



SH
Cl
Br
O_2N
R
2-Bromobenzenethiol
–HCl
S
Br
O_2N
R
[H]
S
Br
NH_2
R
Δ –HBr
S
N
H
R
$Cl(CH_2)_3–N(CH_3)_2$
–HCl
S
N
R
$(CH_2)_3N(CH_3)_2$
R
Promazine - H
Chlorpromazine - Cl
Triflupromazine - CF3

- https://gpatindia.com/chlorpromazine-hydrochloride-synthesis-sar-mcqstructurechemical-properties-and-therapeutic-uses/
- **The correct order for the synthesis of drug Chlorpromazine hydrochloride from 3-chloro-N-phenylbenzenamine can be?**
- **I. Reaction with Iodine**
- **II. Reaction with sulfur**
- **III. Alkylation with 3-dimethylaminopropylchloride**
- **IV. Alkylation with 2-methylaminopropylchloride**
- a) I – III
- b) I – IV
- c) II – III
- d) II – IV

- **Which amongst the following statements is/are INCORRECT related to the SAR of chlorpromazine hydrochloride?**
- **I. Optimal neuroleptic activity occurs when the ring A substituent is in the 3rd-position.**
- **II. A trifluoromethyl substituent pro, vides a greater number of favorable Van der Waal's contacts with the side chain than the chlorine substituent. Thus, phenothiazne with trifluoromethyl substituents are more potent than those with chlorine substituent.**
- **III. A piperazine side chain provides more Van der Waal's contacts with 2-substituent than the alkylamino side chain. Thus, piperizine phenothiazine are less potent in antischizophrenic effects than alkylamino phenothiazines.**
- **IV. Hydroxyethylpiperazine side chain phenothiazines displays more favorable Van der Waal's interactions with ring A than simple piperazines.**
- a) I, III, IV b) I, II c) III, IV d) I, III

- ***Triflupromazine*.**
- IUPAC:10-[3-(dimethylamino)propyl]-2-(trifluoromethyl) phenothiazine.
- It has a greater milligram potency as an antipsychotic, higher EPS, but lower sedative and hypotensive effects than chlorpromazine.
- The 2-CF3 versus the 2-Cl is associated with these changes.
- Overall, the drug has uses analogous to those of chlorpromazine.

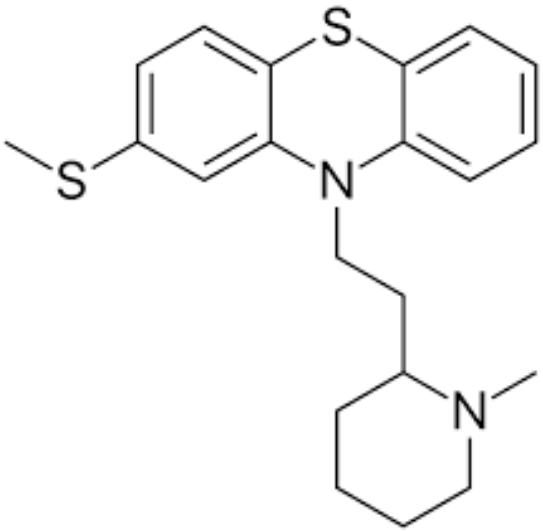


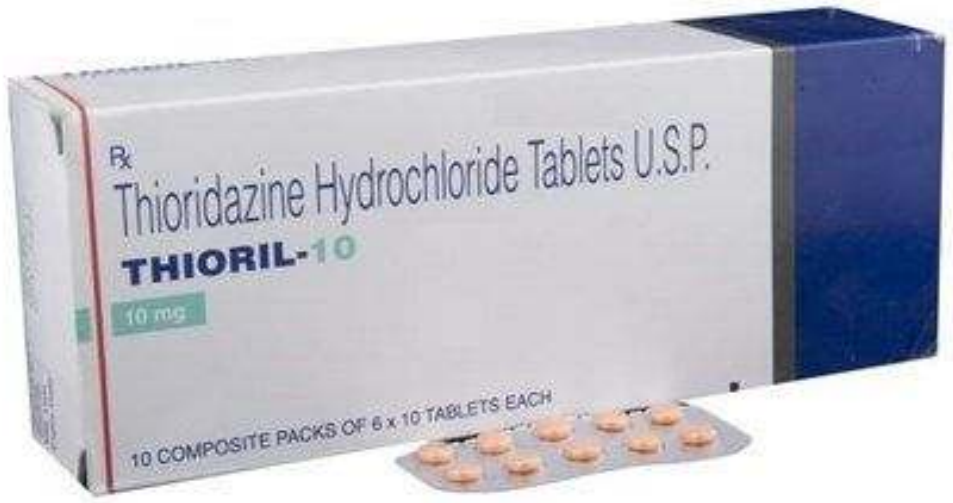
- ***Thioridazine*.**

- IUPAC: 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio) phenothiazine.

- It is a member of the piperidine subgroup of the phenothiazines.

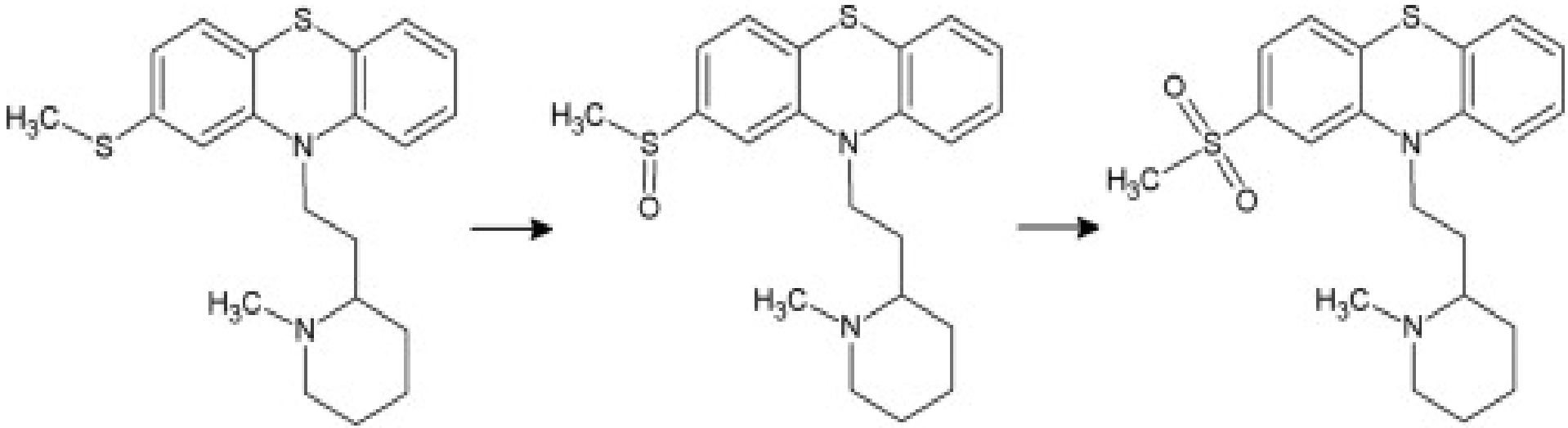
- The drug has a relatively low tendency to produce EPS.



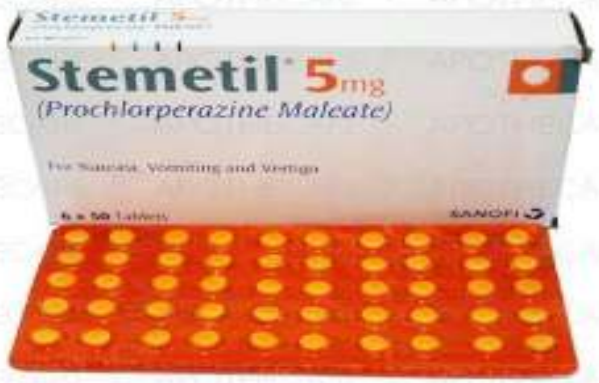


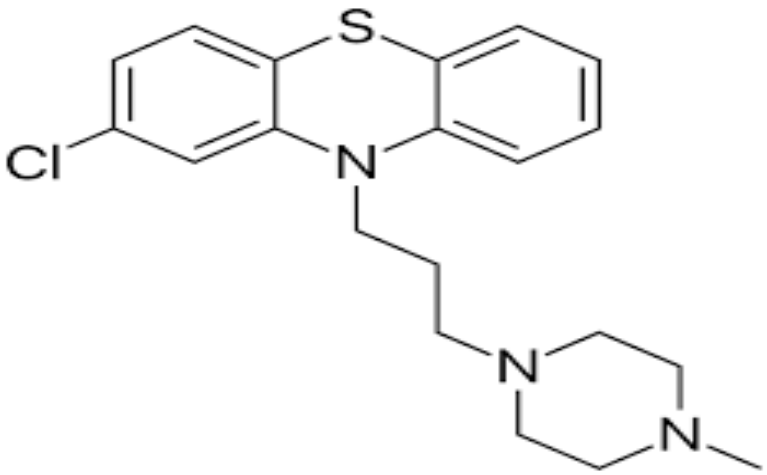
- The drug has high anticholinergic activity, and this activity may be responsible for the low EPS.
- It also has been suggested that there may be increased DA receptor selectivity, which may be responsible.
- The drug has sedative and hypotensive activity in common with chlorpromazine and less antiemetic activity.
- At high doses, pigmentary retinopathy has been observed.

- Its major metabolites include *N*-demethylated, ringhydroxylated, and *S*-oxidized products.
- Thioridazine is prominently converted to the active metabolite mesoridazine, which probably contributes to the antipsychotic activity of thioridazine.



- ***Prochlorperazine*.**
- IUPAC: 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]phenothiazine.
- It is in the piperazine subgroup of the phenothiazines.
- It is characterized by high-milligram antipsychotic potency.
- A high prevalence of EPS.
- Low sedative and autonomic effects.

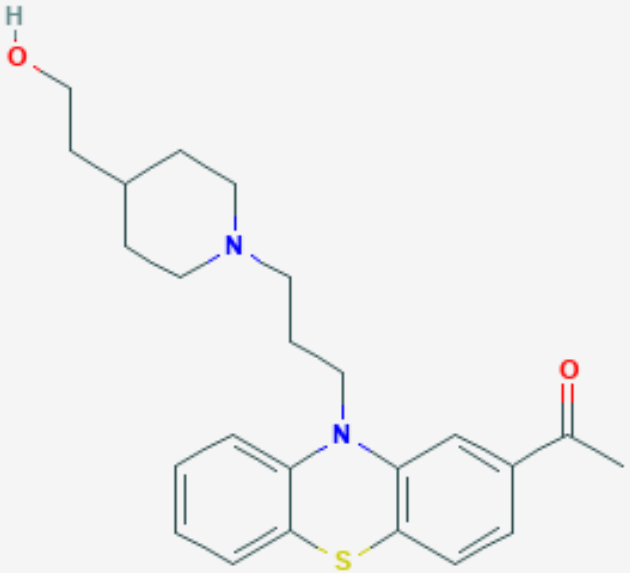




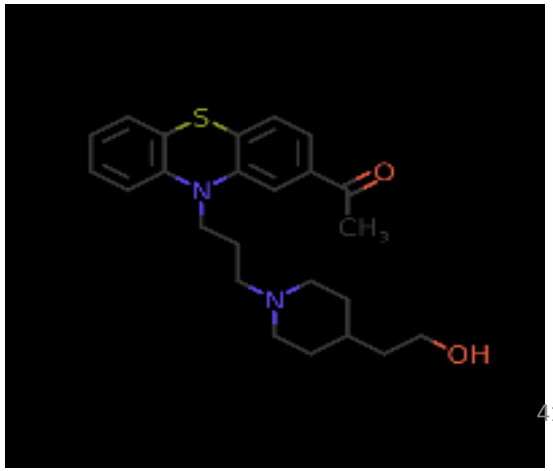
- Prochlorperazine is more potent on a milligram basis than its alkylamino counterpart, chlorpromazine.
- Because of the high prevalence of EPS, however, it is used mainly for its antiemetic effect, not for its antipsychotic effect.

- **Piperacetazine.**
- 1-[10-[3-[4-(2-hydroxyethyl)-1-piperidinyl]propyl]

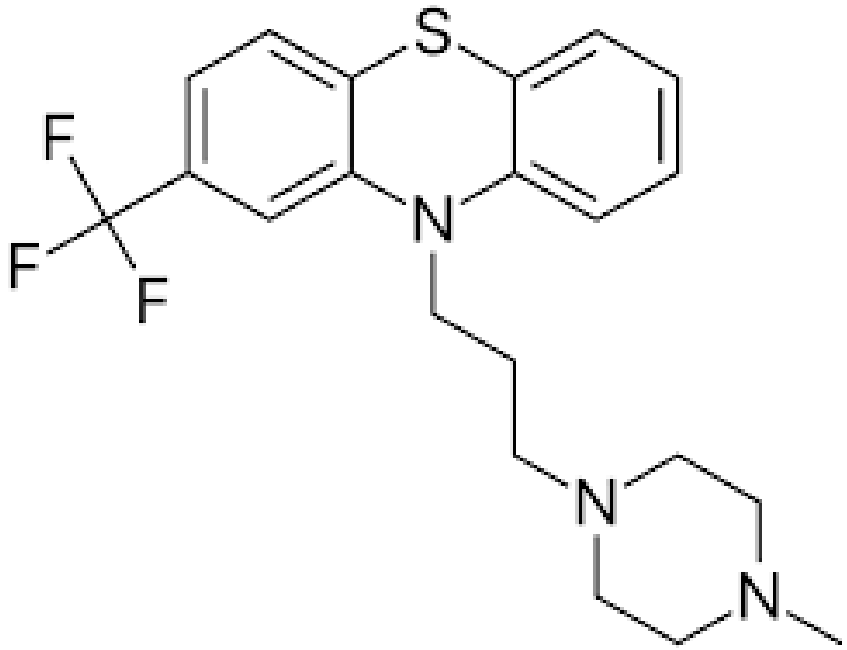
-2-phenothiazinyl]ethanone.



- First generation ‘typical’ antipsychotic agent.
- It is used primarily to treat positive symptoms including the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions).
- It may cause side effects like dyskinesias such as repetitive, involuntary, and purposeless body or facial movements, Parkinsonism (cogwheel muscle rigidity, pill-rolling tremor and reduced or slowed movements), akathisia (motor restlessness, especially in the legs, and resembling agitation) and dystonias such as muscle contractions causing unusual twisting of parts of the body, most often in the neck.
- These effects are caused by the dopamine receptor antagonist action of these drugs.
- https://library.neura.edu.au/schizophrenia/treatments/physical/pharmaceutical/first-generation-antipsychotics/piperacetazine/



- **Trifluoperazine.**
- 10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)phenothiazine.
- Trifluoperazine is a phenothiazine derivative and a dopamine antagonist with antipsychotic and antiemetic activities.
- Trifluoperazine exerts its antipsychotic effect by blocking central dopamine receptors, thereby preventing effects such as delusions and hallucinations caused by an excess of dopamine.



SEDATIVES AND HYPNOTICS-2

BARBITURATE SPEED

Ultra-Short Acting

Surgery

Short to Intermediate Acting

Sleep

Long Acting

Pain/Migraine Relief

Physicochemical and Pharmacokinetic properties

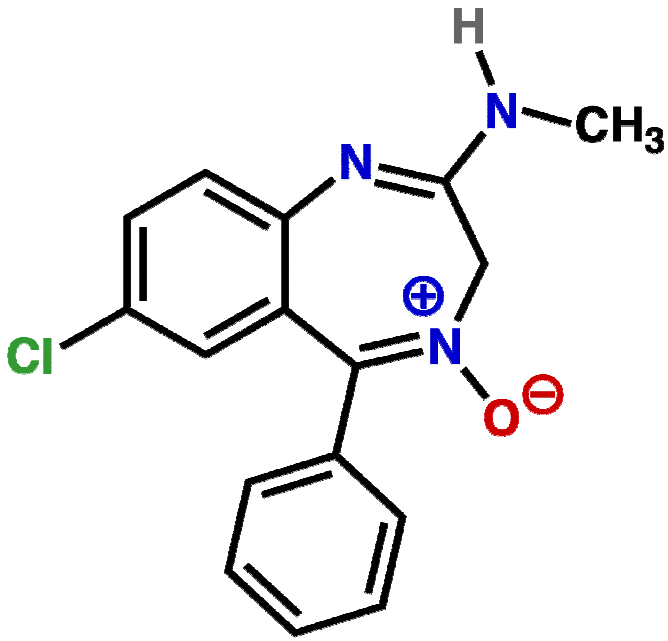
- The physicochemical and pharmacokinetic properties of the benzodiazepines greatly affect their clinical utility.
- Most benzodiazepines are lipophilic and exist in the nonionized form.
- They are well absorbed from the GI tract.
- Some are more polar compounds (e.g., those with a 3-hydroxyl group) and tend to be absorbed more slowly than the more lipophilic compounds.

- These drugs tend to be highly bound to plasma proteins; in general, the more lipophilic the drug, the greater the binding.
- However, they do not compete with other protein bound drugs.
- They are also very effectively distributed to the brain.
- Generally, the more lipophilic the compound, the greater is the distribution to the brain, at least initially.

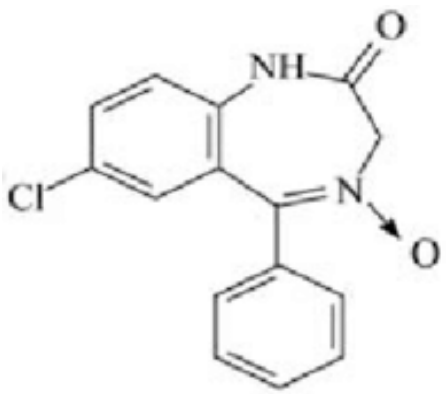
- When diazepam is used as an anesthetic, it initially distributes to the brain and then redistributes to sites outside the brain.
- The benzodiazepines are extensively metabolized.
- Metabolites of some benzodiazepines are not only active but also have long half-lives, thus these drugs are long acting.
- Many benzodiazepines are metabolized by cytochrome P450 (CYP) 3A4 and CYP2C19.

- CYP3A4 inhibitors (erythromycin, clarithromycin, ritonavir, itraconazole, ketoconazole, nefazodone, and grapefruit juice) can affect their metabolism.
- However, they do not induce the metabolism of other drugs.
- Therefore, the drugs have fewer drug interactions than barbiturates.
- In addition, they have lower abuse potential and a much greater margin of safety than the barbiturates.

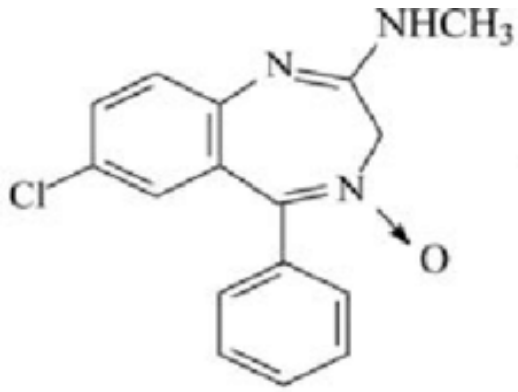
- ***CHLORDIAZEPOXIDE***
- IUPAC: 7- chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide.
- It is well absorbed after oral administration.
- Peak plasma levels are reached in 2 to 4 hours.
- The half-life is 6 to 30 hours.
- *N*-demethylation and hydrolysis of the condensed amidino group are rapid and extensive, producing demoxepam as a major metabolite.



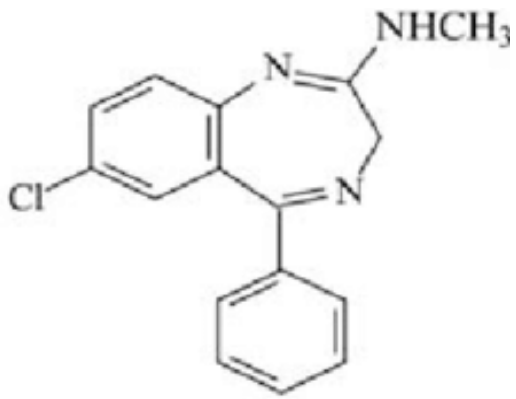
- Demoxepam is converted principally to its active metabolite nordazepam, which is also a major active metabolite of diazepam, clorazepate, and prazepam.
- Nordazepam is converted principally to active oxazepam (marketed separately).
- Because of the long half-life of parent drug and its active metabolites, this drug is long acting and self-tapering.
- As with diazepam, repeated administration of chlordiazepoxide can result in accumulation of parent drug and its active metabolites.



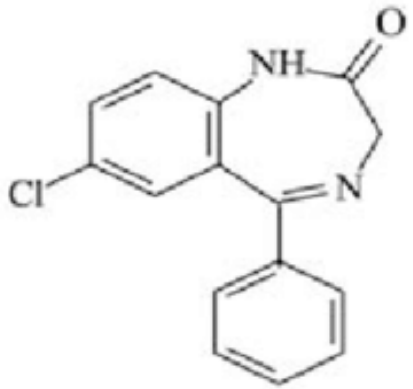
Demoxepam



Chlordiazepoxide



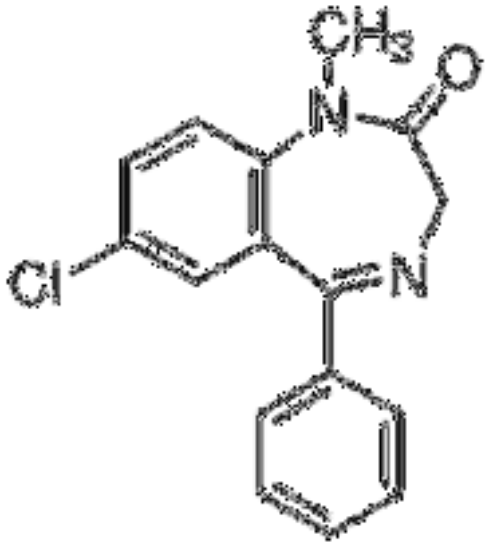
Desoxychlordiazepoxide



Nordiazepam

•*DIAZEPAM*

- IUPAC:7-chloro-1,3-dihydro-1- methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-one.
- It is prototypical and was the first member of the benzodiazepine- 2-one group.
- It is very lipophilic and is thus rapidly and completely absorbed after oral administration.
- Maximum peak blood concentration occurs in 2 hours.
- Elimination is slow, with a half-life of about 46 hours.

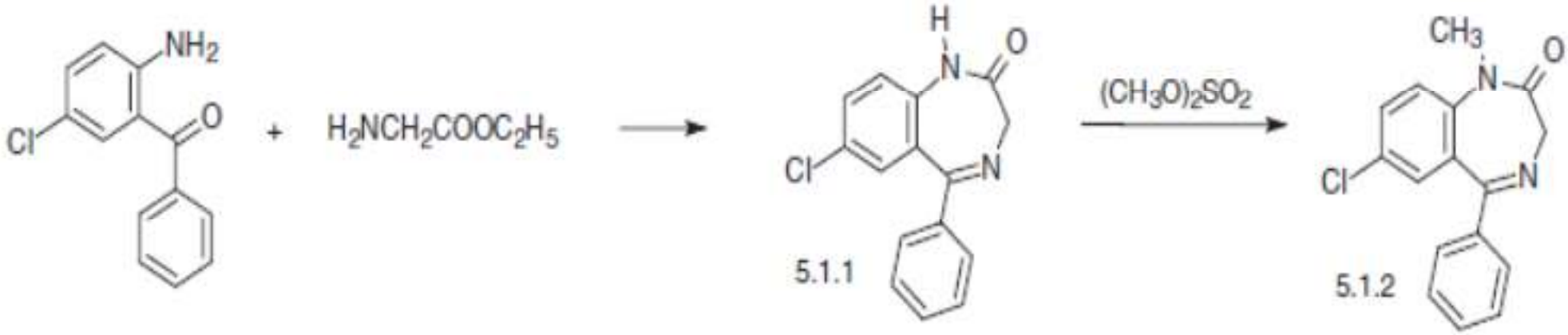


- As with chlordiazepoxide, diazepam is metabolized by *N*-demethylation to active nordazepam, which is 3-hydroxylated to active oxazepam.
- Like chlordiazepoxide, repeated administration of diazepam leads to accumulation of an active nordazepam.
- Diazepam is metabolized to nordazepam by CYP2C19 and CYP3A4.
- Cimetidine, by inhibiting CYP3A4, decreases the metabolism and clearance of diazepam.

- Because diazepam clearance is decreased in the elderly and in patients with hepatic insufficiency, a dosage reduction may be warranted.
- It is widely used for several anxiety states and has an additional wide range of uses (e.g., as an anticonvulsant, a premedication in anesthesiology, and in various spastic disorders).

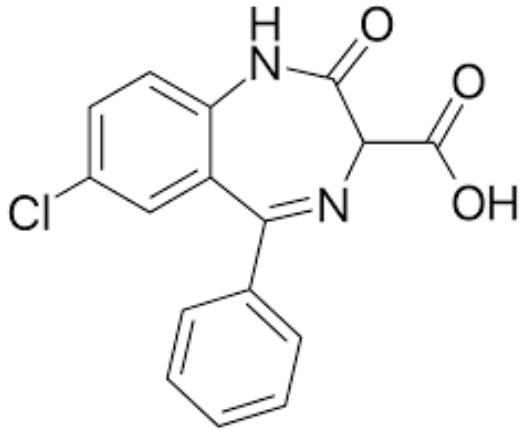
Synthesis of Diazepam

- The direct cyclocondensation of 2-amino-5-chlorobenzophenone with ethyl ester of glycine hydrochloride gives 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (5.1.1).
- The amide nitrogen atom of the obtained (5.1.1), is methylated by dimethylsulfate, which leads to the formation of diazepam (5.1.2).

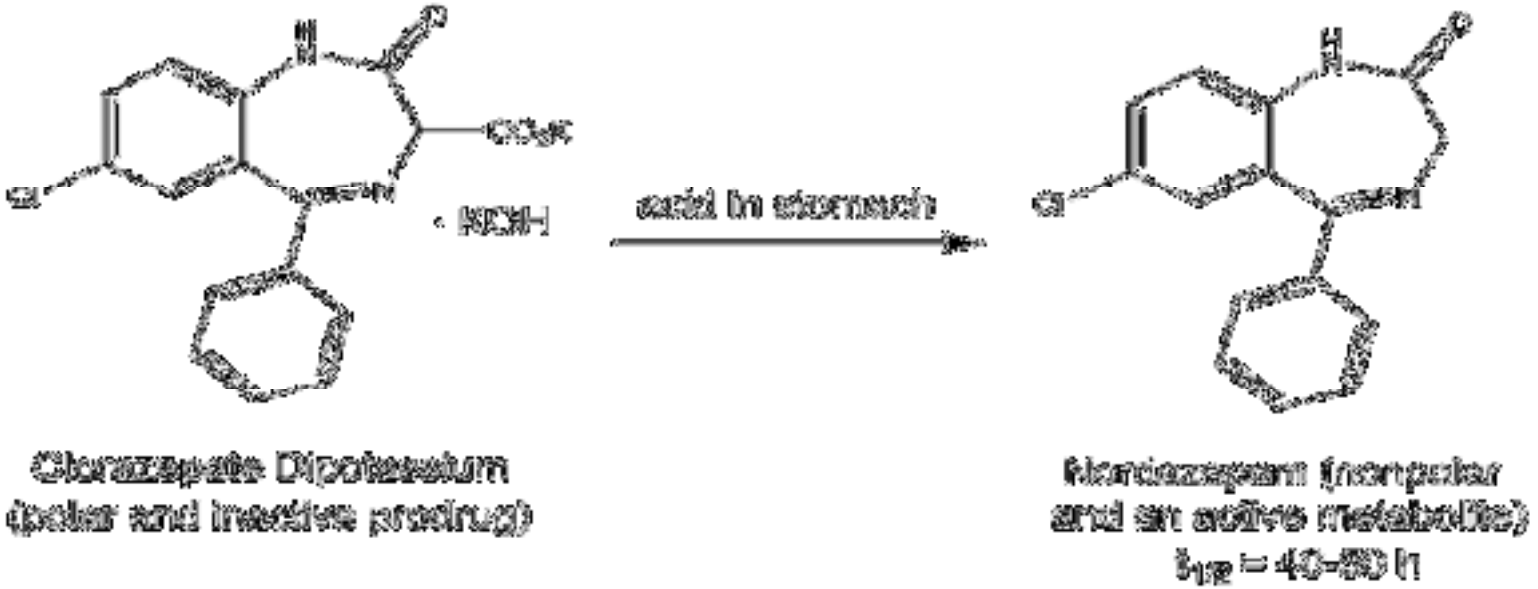


• *CLORAZEPATE*

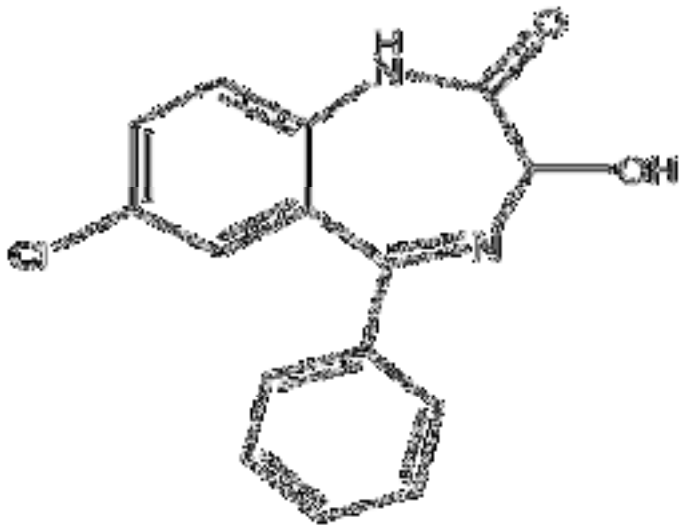
- IUPAC: 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine- 3-carboxylic acid.
- It can be considered as a prodrug.
- Inactive itself, it undergoes rapid decarboxylation by the acidity of the stomach to nordazepam.



- Nordazepam has a long half-life and undergoes hepatic conversion to active oxazepam.
- It has a quick onset, overall long half-life, and shares similar clinical and pharmacokinetic properties to chlordiazepoxide and diazepam.



- ***OXAZEPAM***
- IUPAC: 7-chloro-1,3-dihydro-3- hydroxy-5-phenyl-2*H*-1,4-benzodiazpin-2-one.
- It is an active metabolite of both chlordiazepoxide and diazepam.
- It can be considered as a prototype for the 3-hydroxy benzodiazepines.



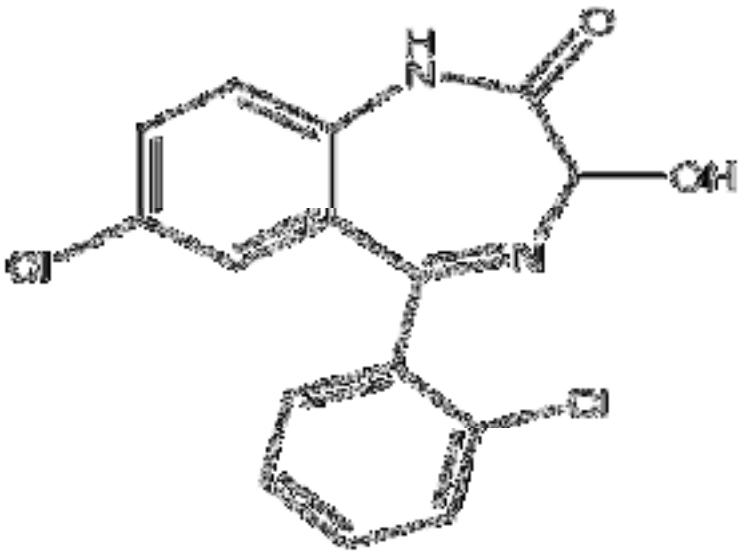
Oxazepam, Log P = 2.31

rapid glucuronidation
and excretion → $t_{1/2}$ = 4-8 h

- It is much more polar than diazepam.
- Oxazepam is rapidly inactivated to glucuronidated metabolites that are excreted in the urine.
- Thus, the half-life of oxazepam is about 4 to 8 hours, and it is marketed as a short-acting anxiolytic.
- As a result, its cumulative effects with chronic therapy are much less than with long-acting benzodiazepine such as chlordiazepoxide and diazepam.

IS OXAZEPAM ASYMMETRIC?

- ***LORAZEPAM***
- IUPAC: 7-chloro-5-(2-chlorophenyl)- 3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepine-2-one.
- It is the 2-chloro derivative of oxazepam.



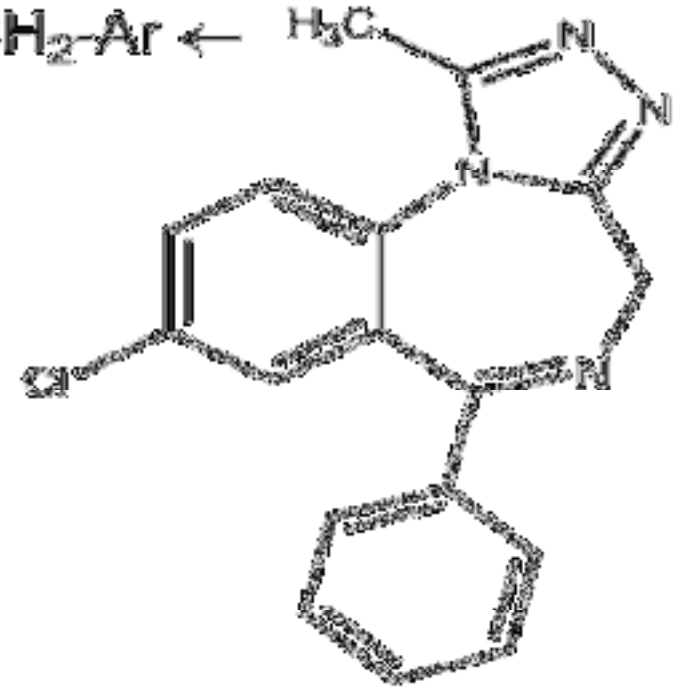
Lorazepam

rapid glucuronidation and excretion → $t_{1/2}$ = 2-5 h

- In keeping with overall SARs, the 2-chloro substituent increases activity.
- As with oxazepam, metabolism is relatively rapid and uncomplicated because of the 3-hydroxyl group in the compound.
- Thus, it also has short half-life (2–6 hours) and similar pharmacological activity.

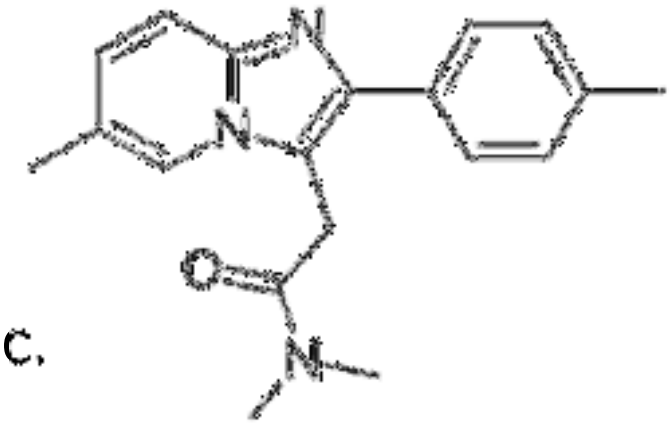
- ***ALPRAZOLAM***
- IUPAC: 8-chloro-1-methyl-6- phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine.
- It is rapidly absorbed from the GI tract.
- Protein binding is lower (70%) than with most benzodiazepines because of its lower lipophilicity.
- α-Hydroxylation of the methyl group to the methyl alcohol (a reaction analogous to benzylic hydroxylation) followed by conjugation is rapid.
- Therefore duration of action is short.
- The drug is a highly potent anxiolytic on a milligram basis.

↓ DOA ← rapid conjugation ← $HOCH_2$-Ar ←



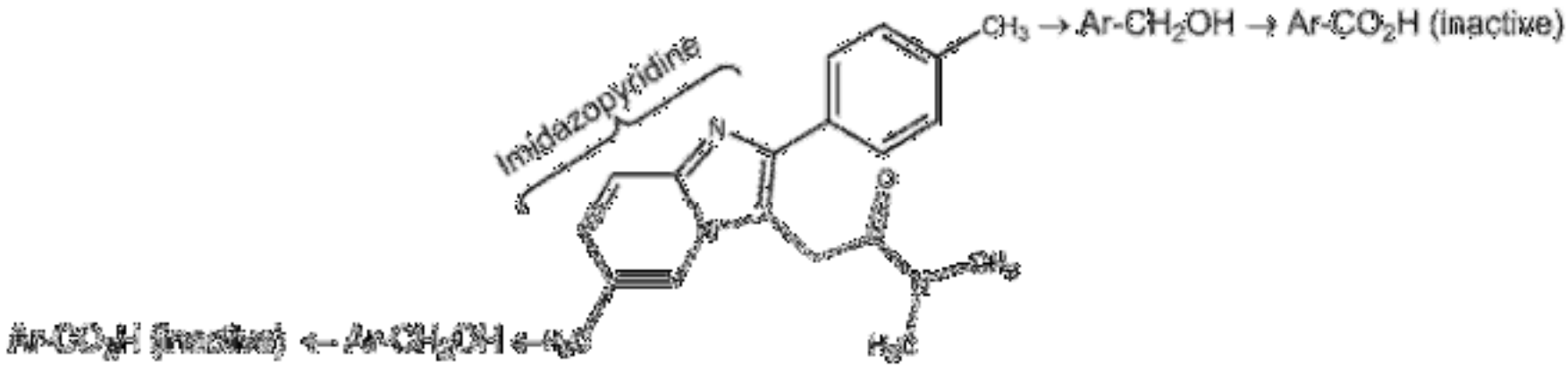
Alprazolam
$t_{1/2}$ = ~12 h
Log P = 2.50
protein binding = ~70%

- ***ZOLPIDEM***



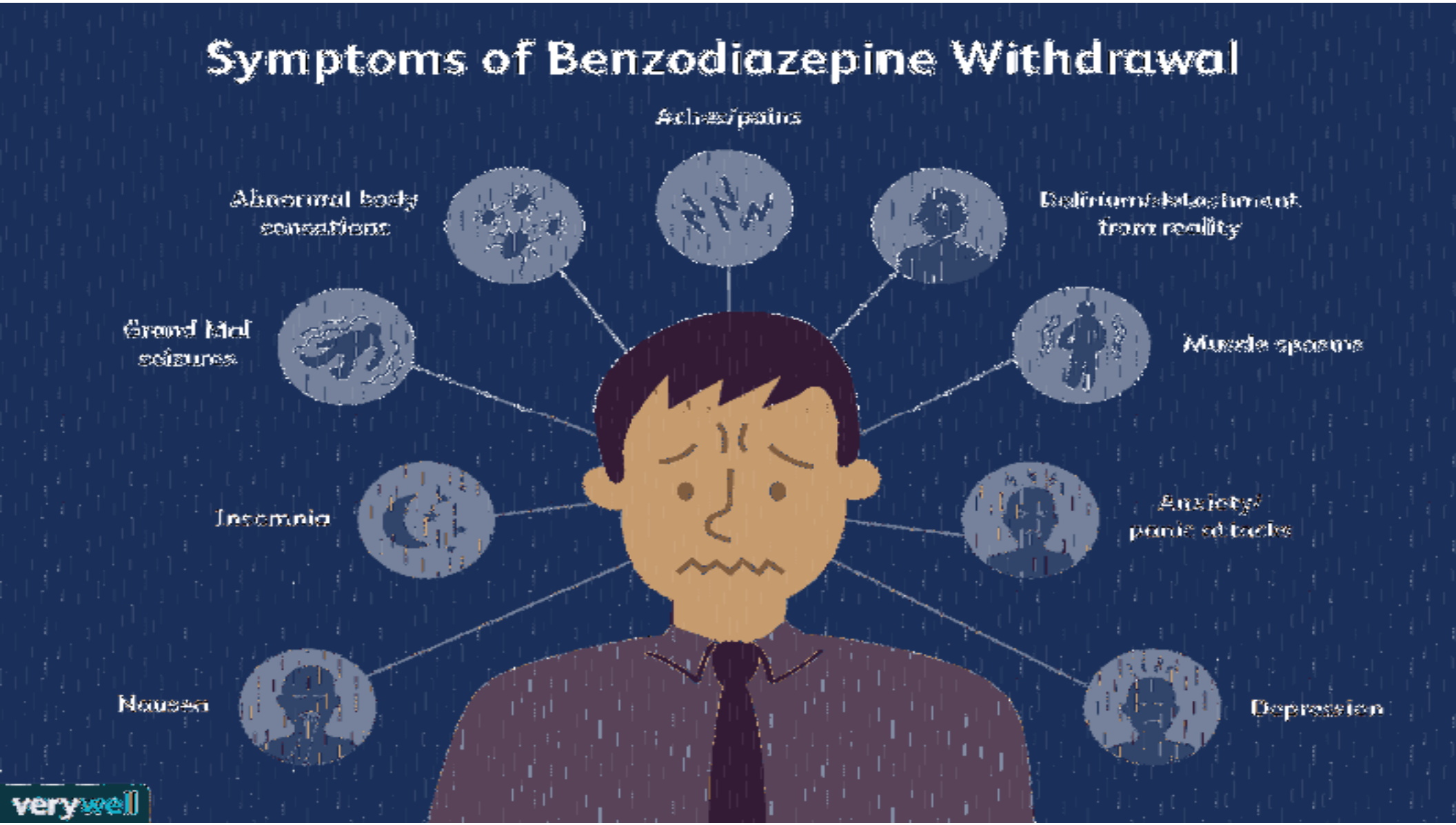
- *It is a derivative of imidazopyridine.*
- *It is* a *nonbenzodiazepine* short acting hypnotic.
- It exhibits a high selectivity for the α1 subunit of benzodiazepine binding site on GABAA receptor complex.
- It is lipophilic and has no ionisable groups at physiological pH.
- It has a rapid onset of action of 1.6 hours and good bioavailability (72%).

- It has short elimination half-life, because its aryl methyl groups is extensively α-hydroxylated to inactive metabolites by CYP3A4 followed by further oxidation by aldehyde dehydrogenase to the ionic carboxylic acid.
- The metabolites are inactive, short-lived, and eliminated in the urine.

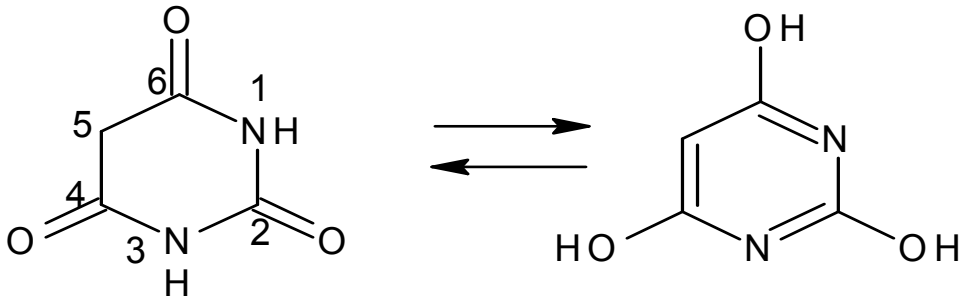


Zolpidem
Log P = 2.61
$t_{1/2}$ = 2.5
short-acting

- Its half-life in the elderly or the patients with liver disease is increased.
- Therefore, dosing should be modified in patients with hepatic insufficiency and the elderly.
- Because it has longer elimination half-life than zaleplon, it may be preferred for sleep maintenance.
- It was the most commonly prescribed drug for insomnia in 2001.


Symptoms of Benzodiazepine Withdrawal
Aches/pains
Abnormal body sensations
Delirium/detachment from reality
Grand Mal seizures
Muscle spasms
Insomnia
Anxiety/ panic attacks
Nausea
Depression
verywell

- **BARBITURATES: (5,5-DISUBSTITUTED BARBITURIC ACIDS)**
- These are derivatives of barbituric acid.
- Barbituric acid is chemically 2,4,6-trioxo hexahydro pyrimidine.
- It exhibits keto-enol tautomerism and exists in both keto and enol form.
- Thermodynamically, keto form is more stable than enol form.
- Presence of two hydrogen atoms at 5^{th} position are responsible for tautomerism in barbituric acid.



Keto form

Enol form

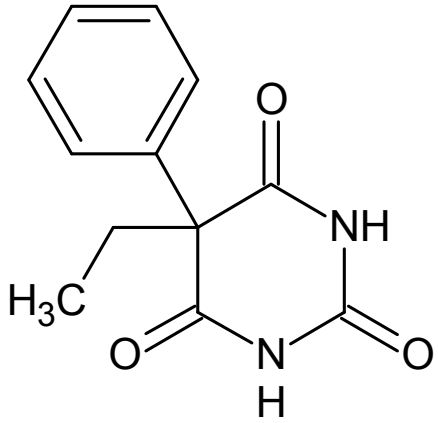
- Unlike benzodiazepines, they bind at different binding sites and appear to increase the *duration* of the GABA-gated chloride channel openings.
- In addition, by binding to the barbiturate modulatory site, barbiturates can also increase chloride ion flux without GABA attaching to its receptor site on GABAA.
- This has been termed a ***GABA mimetic effect***.
- It is thought to be related to the profound CNS depression that barbiturates can produce.

- **Classification of Barbiturates:**

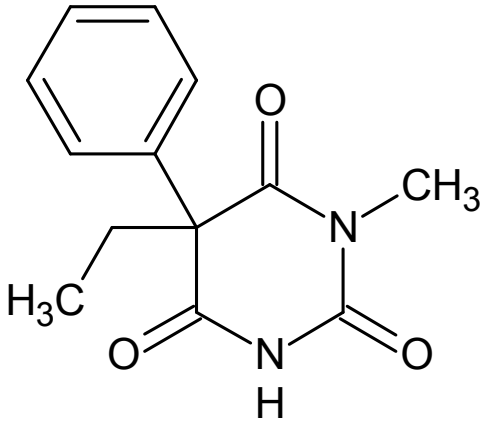
- **Based on the duration of action, barbiturates are divided in to four classes. They are as follows:**

- **Long acting Barbiturates:**

- Phenobarbital and mephobarbital are long acting sedative and hypnotic barbiturates. Their duration of action is in between 6-8 hrs.

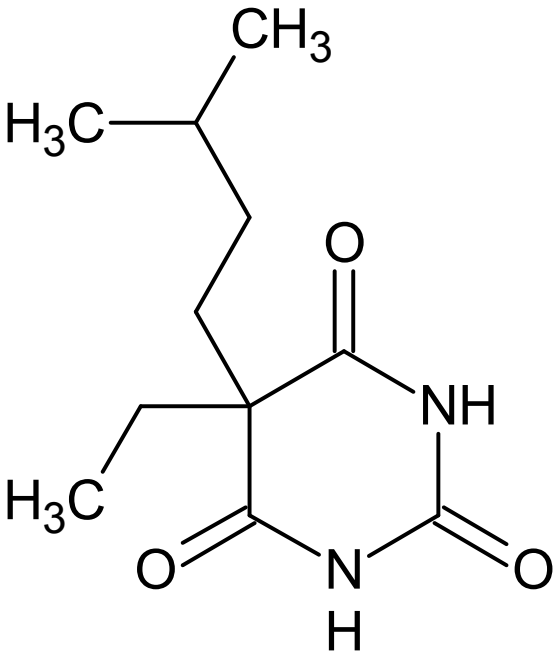


Phenobarbital

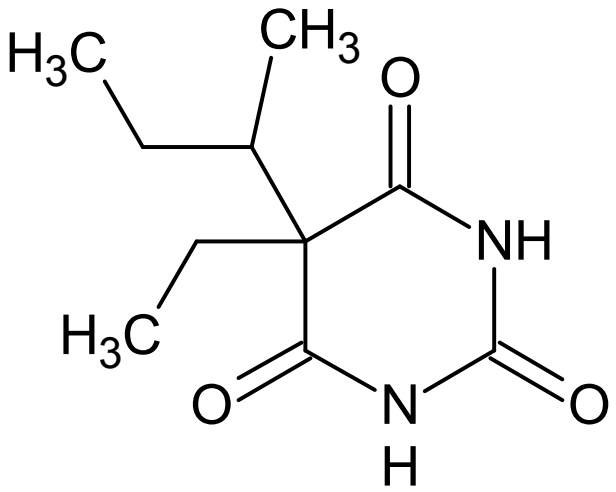


Mephobarbital

- **Intermediate acting Barbiturates:**
- Amobarbital and butabarbital has a duration of action between 3-6 hrs.

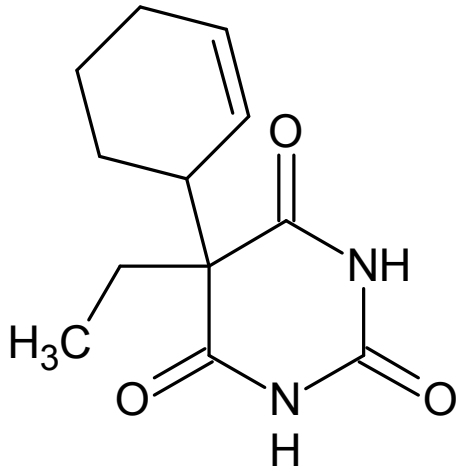


Amobarbital

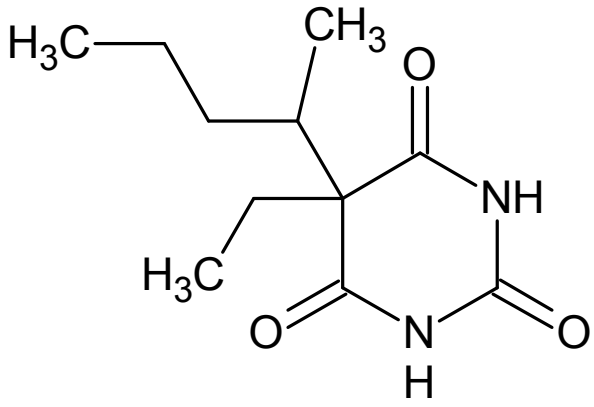


Butabarbital

- **Short acting barbiturates:**
- These barbiturates are short acting CNS depressants with duration of action between 1-3 hrs.
- Examples for this class include cyclobarbital and pentobarbital.

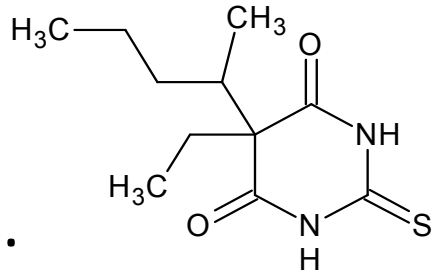


Cyclobarbital



Pentobarbital

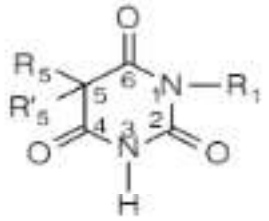
- **Ultra short acting barbiturates:**
- Because of their ultra short action, these barbiturates are not used as sedatives and hypnotics.
- They are clinically used to induce general anesthesia.



Thiopental

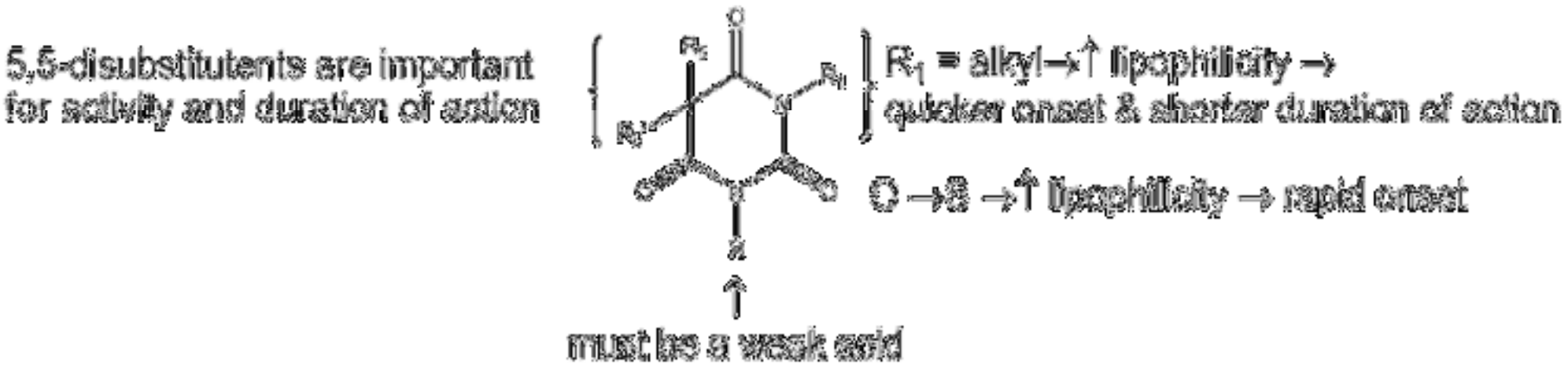
- Thiopental is a classical example for ultra short acting barbiturate.
- Presence of sulfur atom at 2nd position of barbiturate nucleus greatly increases the lipophilicity and reduces duration of action.

General Structure



Generic Name *Proprietary Name*	Substituents			Sedative Dose (mg)	Hypnotic Dose (mg)	Usual Onset of Action (min)
	R_5	R'_5	R_1			
A. Long Duration of Action (more than 6 hours)						
Mephobarbital, *USP* *Mebaral*	C_2H_2		CH_3	30–100[a]	100	30–60
Phenobarbital, *USP* *Luminal*	C_2H_2		H	15–30[a]	100	20–40
B. Intermediate Duration of Action (3–6 hours)						
Amobarbital, *USP* *Amytal*	CH_3CH_2—	$(CH_3)_2CHCH_2CH_2$—	H	20–40	100	20–30
Butabarbital sodium, *USP* *Butisol Sodium*	CH_3CH_2—	$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H$—	H	15–30	100	20–30
C. Short Duration of Action (less than 3 hours)						
Pentobarbital sodium, *USP* *Nembutal Sodium*	CH_3CH_2—	$CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H$—	H	30	100	20–30
Secobarbital, *USP* *Seconal*	$CH_2{=}CHCH_2$—	$CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H$—	H	15–30	100	20–30

- **SAR of Barbiturates:**



- The sum of the carbon atoms of both substituents at 5th position should be between 6 and 10.
- Branched chain isomer has greater lipid solubility and hypnotic activity than unbranched isomer.

- Branching of alkyl groups at 5^{th} position reduces duration of action.
- Cyclic rings at 5^{th} position generally reduce the duration of action.
- Aromatic rings or alicyclic rings at 5^{th} position generally increases potency.
- Alkyl groups on nitrogen atom (1^{st} or 3^{rd} position) reduces onset of action and increases duration of action. This is due to reduced acidity value.
- Replacement of oxygen atom by sulfur at 2^{nd} position greatly reduces onset of action and duration of action.
- This is due to enhanced lipophilicity.

- **Structure and Pharmacokinetics: (Part of SAR)***
- The barbituric acid is 2,4,6-trioxohexahydropyrimidine, which lacks CNS depressant activity.
- However, the replacement of both hydrogens at position 5 with alkyl or aryl groups confers the activity.
- Both hydrogen atoms at the 5^{th} position of barbituric acid must be replaced.
- This may be because if one hydrogen is available at position 5, tautomerization to a highly acidic trihydroxypyrimidine (pKa 4) can occur.

- Consequently, the compound is largely in the anionic form at physiological pH, with little nonionic lipid-soluble compound available to cross the blood-brain barrier.
- In general, increasing lipophilicity increases hypnotic potency and the onset of action and decreases the duration of action.
- Thus, beginning with lower alkyls, there is an increase in onset and a decrease in duration of action with increasing hydrocarbon content up to about seven to nine total carbon atoms substituted on the 5-position.

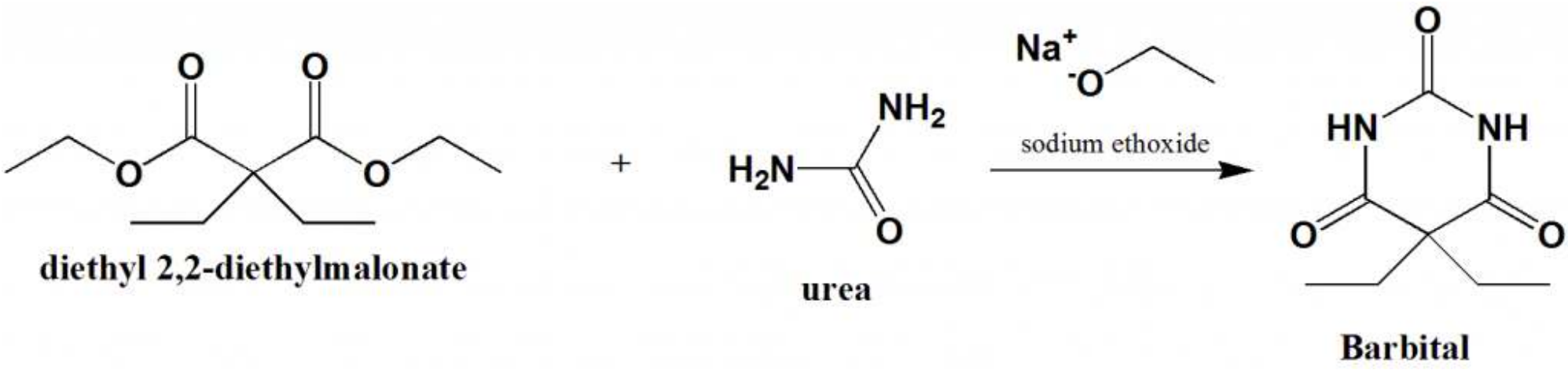
- It is because that lipophilicity and an ability to penetrate the brain in the first case (increase in onset) and an ability to penetrate liver microsomes in the second (decrease in duration) may be involved.
- In addition for more lipophilic compounds, partitioning out of the brain to other sites can be involved in the second instance (decrease in duration).
- There is an inverse correlation between the total number of carbon atoms substituted on the 5^{th} position and the duration of action.
- For example, phenyl substituent, approximately a three- to four-carbon aliphatic chain, branching of alkyls, presence of an isolated double or triple bond.

- Additionally, these groups can influence the ease of oxidative metabolism by effects on bond strengths as well as by influencing partitioning.
- Absorption from the GI tract is good.
- Binding to blood proteins is substantial.
- Compounds with low lipophilicity may be excreted intact in the urine, whereas highly lipophilic compounds are excreted after metabolism to polar metabolites.

- Increasing the lipophilicity generally increases the rate of metabolism, except for compounds with an extremely high lipophilicity (e.g., thiopental), which tend to depotize and are thus relatively unavailable for metabolism.
- **Metabolism** generally follows an ultimate (ω) or penultimate (ω-1) oxidation pattern.
- Ring-opening reactions are usually minor.
- *N*-methylation decreases duration of action, in large part, probably, by increasing the concentration of the lipid-soluble free barbituric acid.
- 2-Thiobarbiturates have a very short duration of action because their lipophilicity is extremely high, promoting depotization.

- **Mechanism of action:**
- Positive allosteric modulation of GABA-A receptors and opening of chloride ion channels.
- **Therapeutic uses:**
- Treatment of insomnia, convulsions, psychiatric disorders and to induce general anesthesia.

- **Synthesis of Barbital:**
- Barbital can be synthesized by the condensation of diethylmalonic ester with urea in presence of sodium ethoxide.

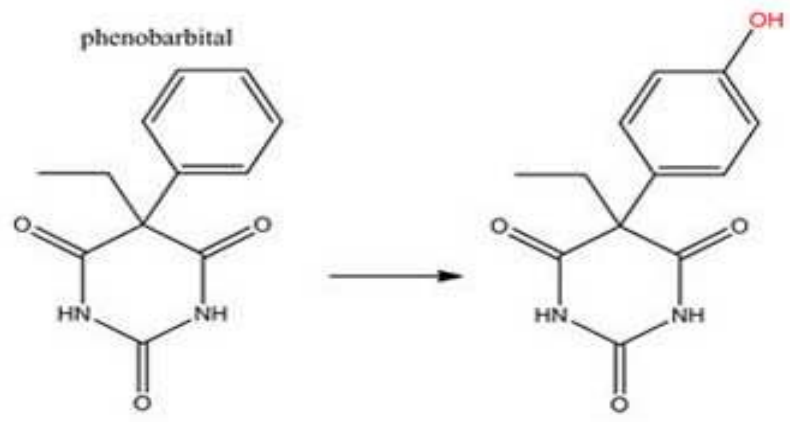


- ***MEPHOBARBITAL*** **IUPAC: 3-methyl-5- ethyl-5-phenylbarbituric acid.**
- Long acting barbiturate.
- Its principal use is as an anticonvulsant.
- It is metabolically *N*-demethylated to phenobarbital, which is responsible for almost all of the activity.

Mephobarbital (Mebaral)
Log P = 1.85

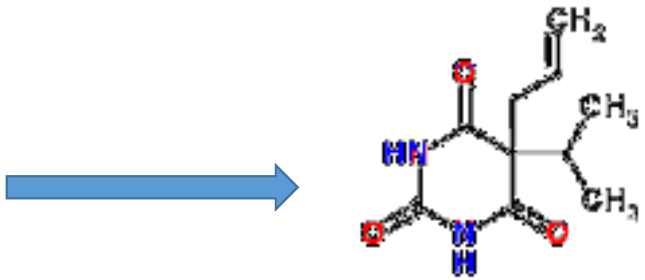
Phenobarbital (Luminal)
Log P = 1.71

- ***PHENOBARBITAL***

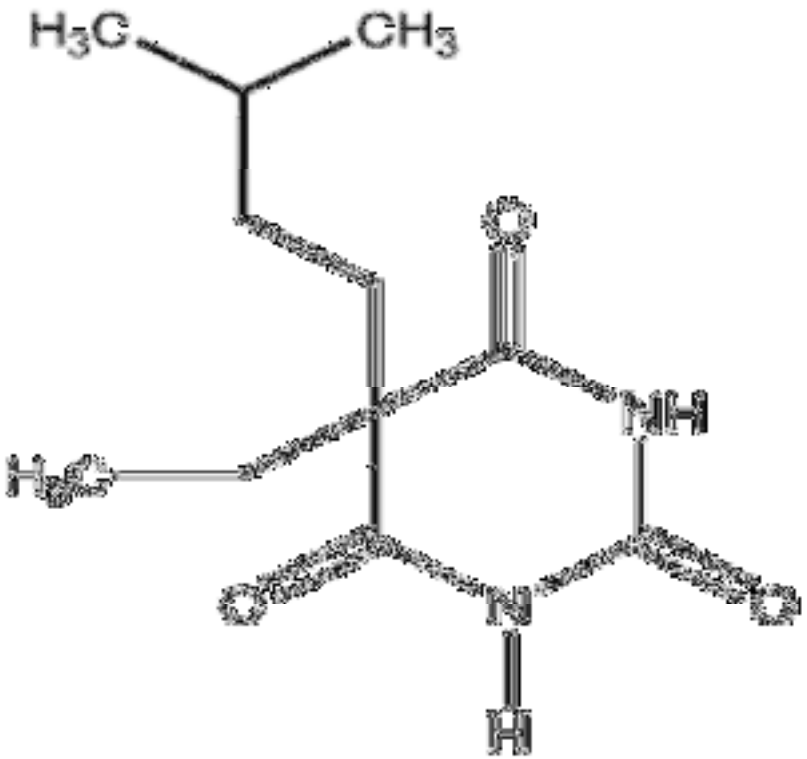


- IUPAC:5-ethyl-5-phenylbarbituric acid.
- It is a long-acting sedative and hypnotic.
- It is also a valuable anticonvulsant, especially in generalized tonic–clonic and partial seizures.
- Metabolism to the *p*-hydroxylphenyl compound followed by glucuronidation accounts for about 90% of a dose.

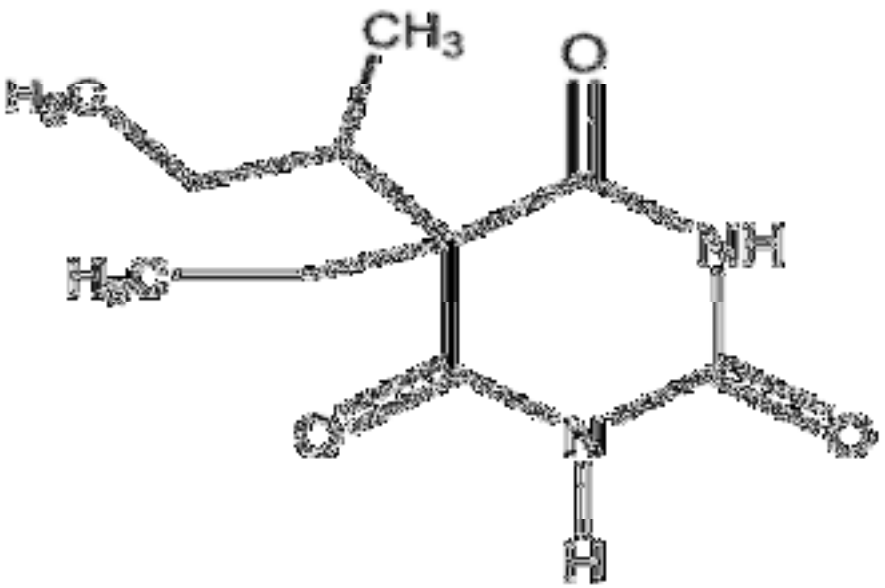
- **AMOBARBITAL and BUTABARBITAL**
- Barbiturates with an intermediate duration of action are used principally as sedative–hypnotics.
- They include-
- **Amobarbital**, 5-ethyl-5-isopentylbarbituric acid and its water-soluble sodium salt, amobarbital sodium.
- **Aprobarbital**, 5-allyl-5-isopropylbarbituric acid.



- **Butabarbital sodium**, the water-soluble sodium salt of 5-*sec*-butyl-5–ethyl barbituric acid.



Amobarbital
Log P = 2.10



Butabarbital
Log P = 1.56

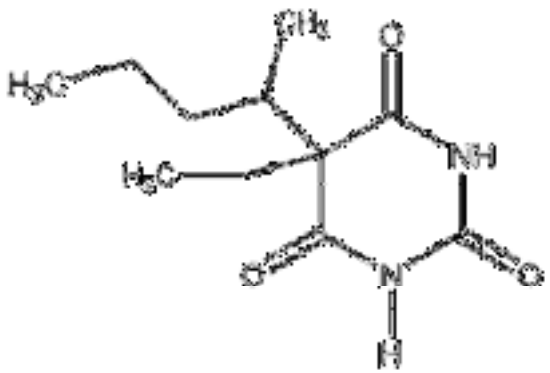
- **PENTOBARBITAL and SECOBARBITAL:**

- Barbiturates that have substituents in the 5-position promoting more rapid metabolism (e.g., by increasing the lipophilicity) than the intermediate group include –

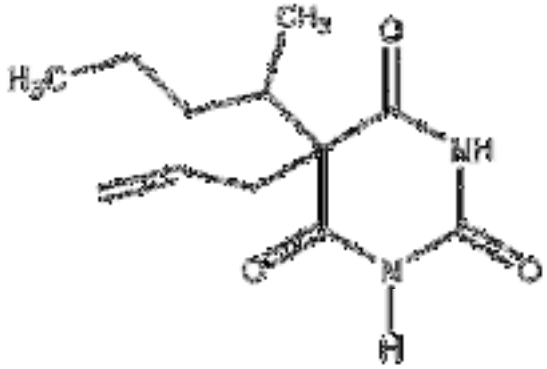
- Pentobarbital sodium, sodium 5-ethyl-5-(1-methylbutyl)barbiturate;

- Secobarbital, 5-allyl-5-(1-methylbutyl) barbituric acid;

- Sodium salt secobarbital.



Pentobarbital
Log P = 2.10

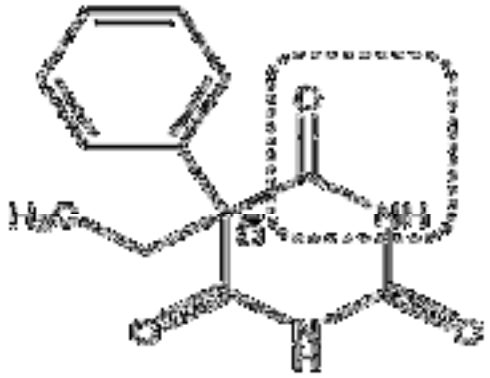


Secobarbital
Log P = 2.33

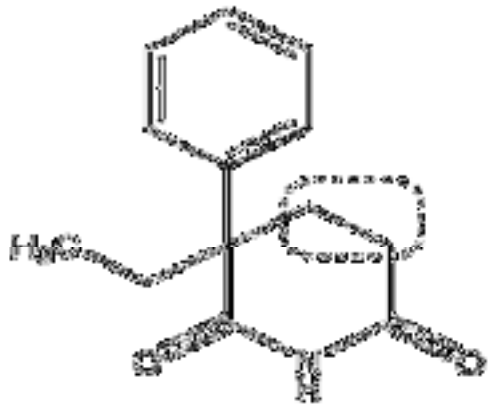
- **Miscellaneous Sedative–Hypnotics**
- A wide range of chemical structures (e.g., imides, amides, alcohols) can produce sedation and hypnosis resembling those produced by the barbiturates.
- Despite this structural diversity, the compounds have generally similar structural characteristics and chemical properties: a nonpolar portion and a semipolar portion that can participate in H-bonding.
- In some cases, modes of action are undetermined.
- Most of these agents act by mechanisms similar to those proposed for barbiturates and alcohols.

• AMIDES AND IMIDES

- ***GLUTETHIMIDE*** **IUPAC: 2-ethyl-2-phenylglutarimide.**
- It is one of the most active nonbarbiturate hypnotics that is structurally similar to the barbiturates, especially phenobarbital.
- Because of glutethimide's low aqueous solubility, its dissolution and absorption from the GI track is somewhat erratic.



Phenobarbital, Log P = 1.71

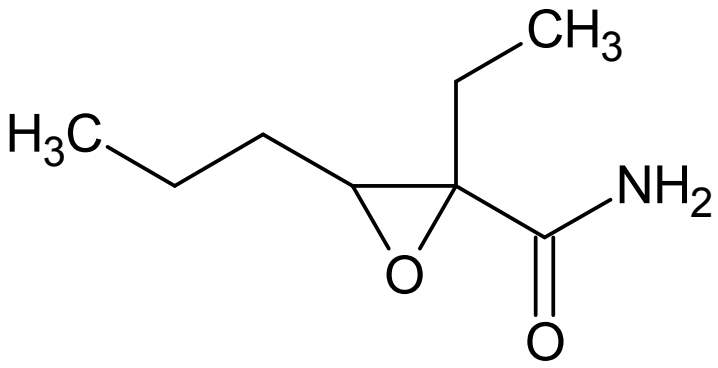


Glutethimide, Log P = 2.70

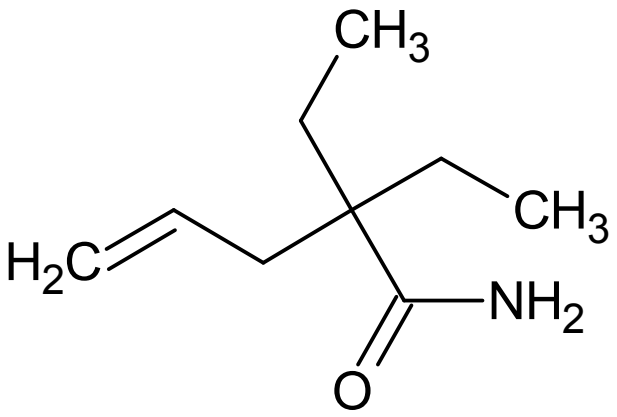
- It undergoes extensive oxidative metabolism in the liver with a half-life of approximately 10 hours.
- Glutethimide is used as a racemic mixture with the (+) enantiomer being primarily metabolized on the glutarimide ring and the (-) enantiomer on the phenyl ring.
- These metabolites are excreted after conjugation with glucuronic acid at the hydroxyl group.

- The drug is an enzyme inducer.
- In the therapeutic dosage range, adverse effects tend to be infrequent.
- Toxic effects in overdose are as severe as, and possibly more troublesome than, those of the barbiturates.
- Most of the amide agents are marketed as tranquillizers and muscle relaxants having good sedative properties.
- **Oxanamide** and **diethylallyl acetamide** are two important drugs in this class.

- **Diethylallyl acetamide is more potent hypnotic from this class**.
- Clinical utility is very limited due to toxicity.



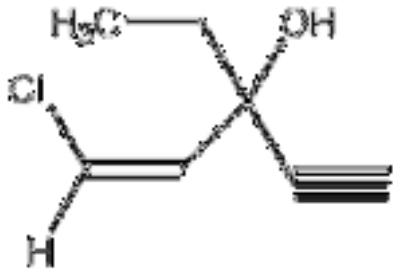
Oxanamide



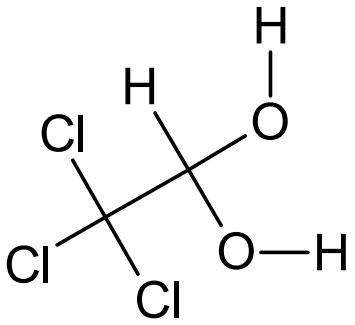
Diethylallyl acetamide

- **Alcohol & their Carbamate derivatives:**
- Alcohols are very good sedatives and hypnotics.
- Almost all alcohols containing 1-8 carbon atoms shows CNS depressant action but very few are used clinically due to rapid metabolic inactivation.
- Branching of alkyl chain in alcohols gives resistance to metabolic inactivation.
- Therefore majority of clinically useful alcohols are either secondary alcohols or tertiary alcohols.

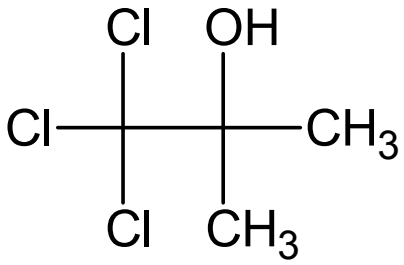
- Halogenation of alcohols greatly reduces the metabolic inactivation and increases lipophilicity.
- Examples are ethchlorvynol, chloral hydrate and chlorobutanol.



Ethchlorvynol



Chloral hydrate

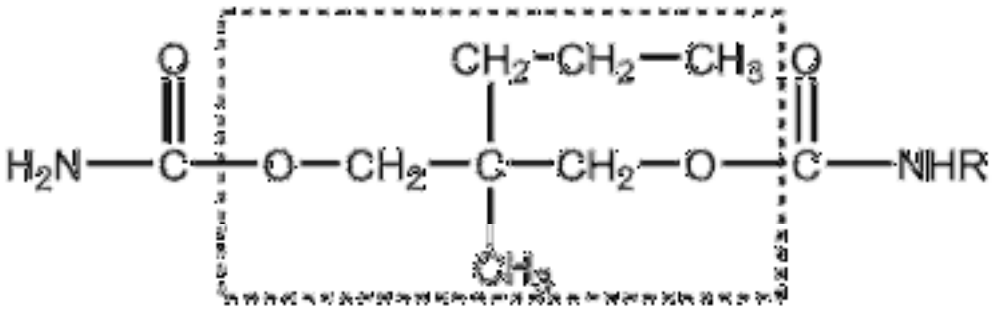


Chlorbutanol

- ***ETHCHLORVYNOL***
- **IUPAC: 1-chloro-3-ethyl-1-penten-4-yn-3-ol.**
- It is a mild sedative–hypnotic with a quick onset and short duration of action (*t*1/2 5.6 hours).
- Because of its highly lipophilic character, it is extensively metabolized to its secondary alcohol (90%) prior to its excretion.
- It reportedly induces microsomal hepatic enzymes.

Ethchlorvynol

- ***MEPROBAMATE*** ***IUPAC:*** **2-methyl-2- propyltrimethylene dicarbamate or 2-methyl-2-propyl-1,3- propanediol dicarbamate.**
- It is officially indicated as an antianxiety agent.
- It is also a sedative–hypnotic agent.
- It is also a centrally acting skeletal muscle relaxant.

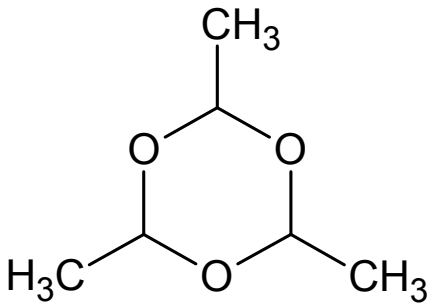


- It has several overall pharmacological properties resembling those of benzodiazepines and barbiturates.
- It is also used in several conditions, such as strains and sprains that may produce acute muscle spasm.
- Its interneuronal blocking properties at the level of the spinal cord is responsible for skeletal muscle relaxation.
- The general CNS depressant property may contribute to, or be responsible for the skeletal muscle relaxant activity.

- **Carisoprodol** is N-isopropyl analog.
- It is indicated in acute skeletomuscular conditions characterized by pain, stiffness, and spasm.
- As expected, a major side effect of the drug is drowsiness.
- Other important carbamate drugs include **Chlorphenesin Carbamate and Methocarbamol.**

- **ALDEHYDES and Their Derivatives:**

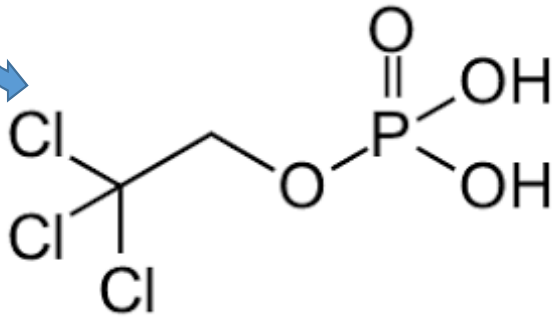
- The first sedative and hypnotic drugs are chemically aldehydes.
- In 1882, **paraldehyde** was introduced in to therapy as a sedative and hypnotic drug.
- It is one of the oldest and safest hypnotic drug.
- Now a days it is not widely used in therapy.

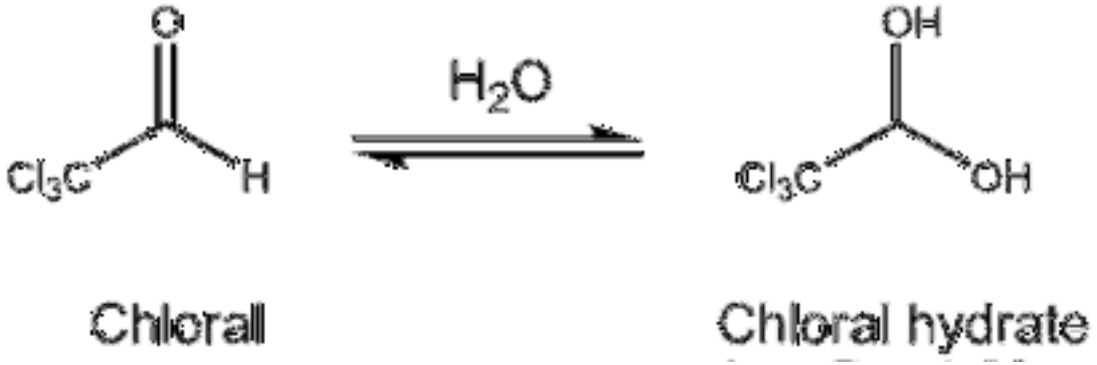


Paraldehyde

- This is because of its unpleasant taste, pungent odour and mucous membrane irritating properties.

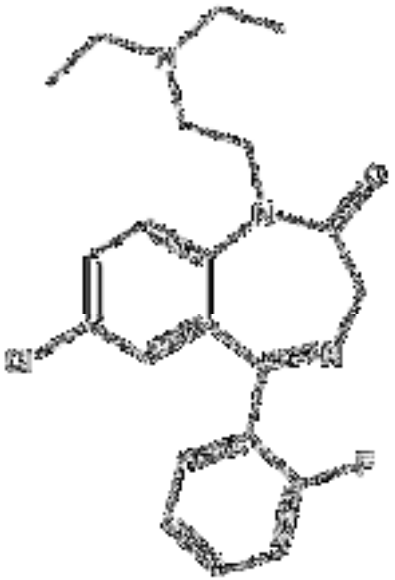
- Paraldehyde, 2,4,6-trimethyl-trioxane, paracetaldehyde, is the cyclic trimer of acetaldehyde.
- It is a liquid with a strong characteristic odor detectable in the expired air and an unpleasant taste.
- **Triclofos** is the monophosphate sodium salt of trichloroethanol (pharmacologically active metabolite of chloral hydrate).



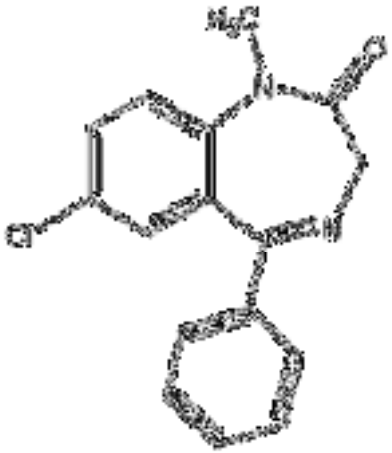


- One gram of triclofos sodium is equivalent to 600 mg of chloral hydrate.
- Triclofos may be a better sedative in view of better palatability and less gastric irritation as compared to chloral hydrate.

- **Which benzodiazepines shown below is/are short acting? Why?**



1



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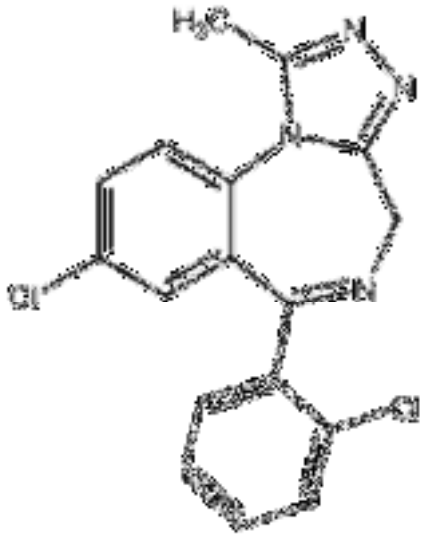

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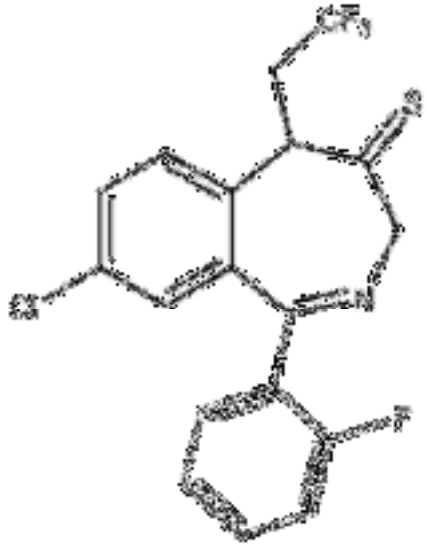
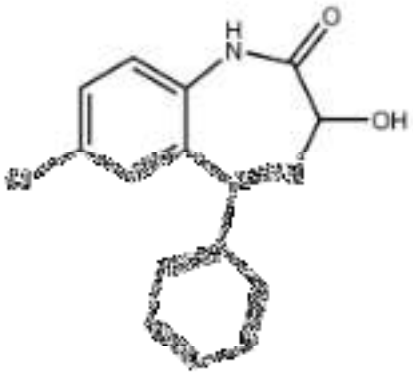
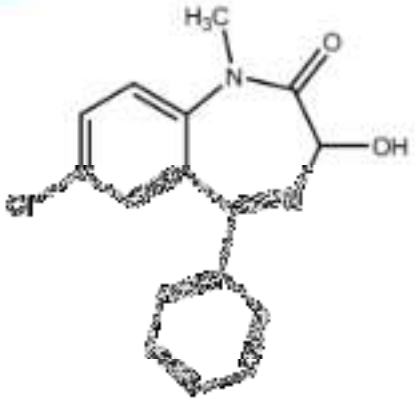


4

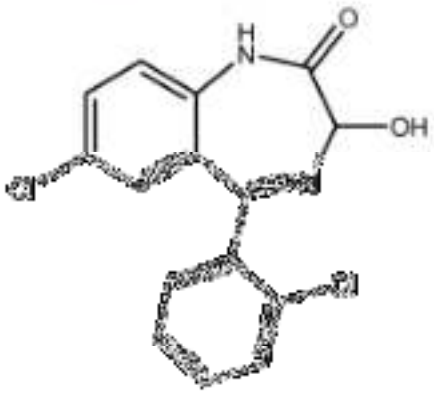
- **Which of the following drugs is/are metabolized to a compound that will continue to have significant sedative and hypnotic effect?**



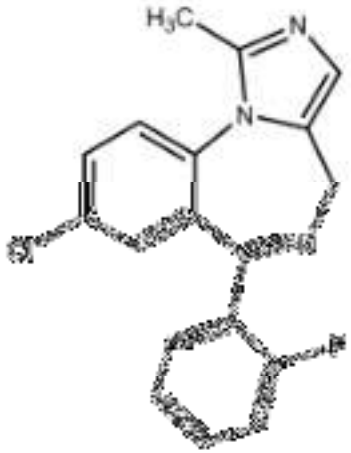
1. Oxazepam



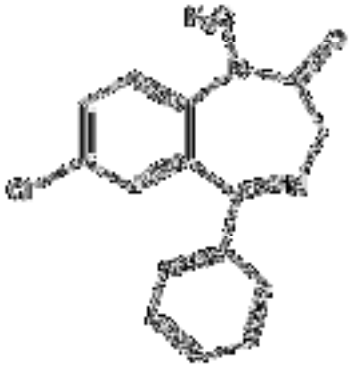
2. Temazepam



3. Lorazepam

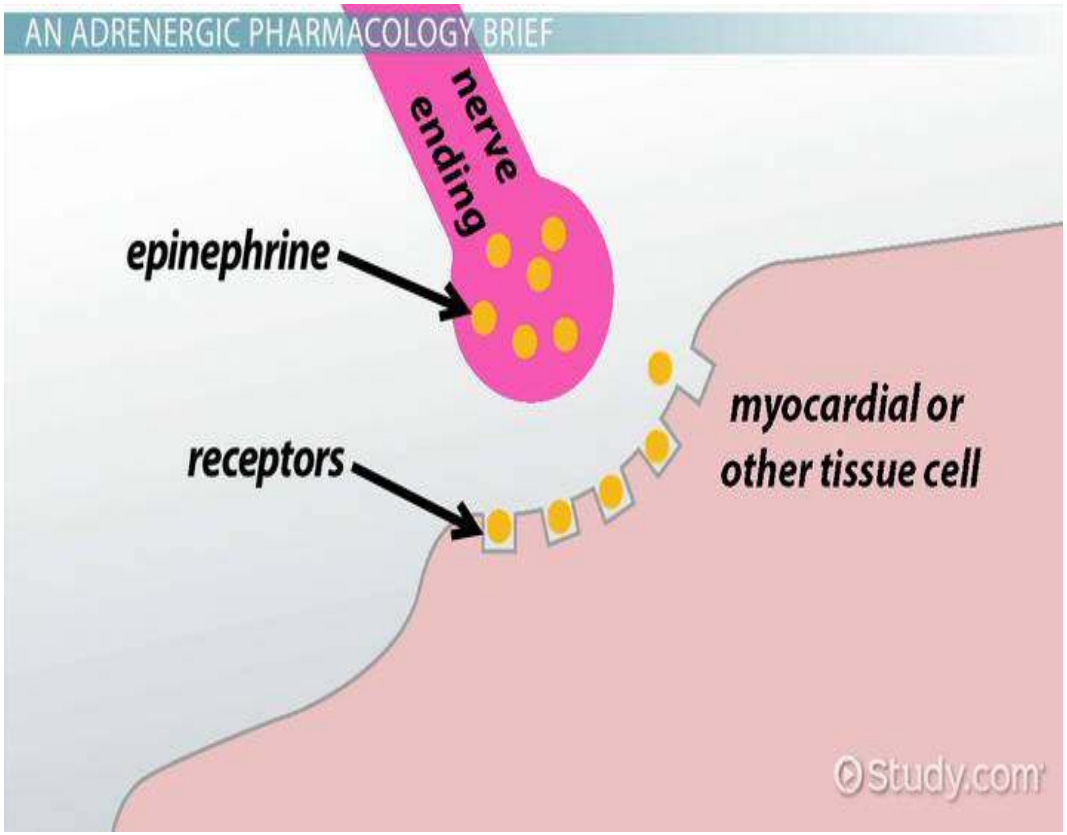


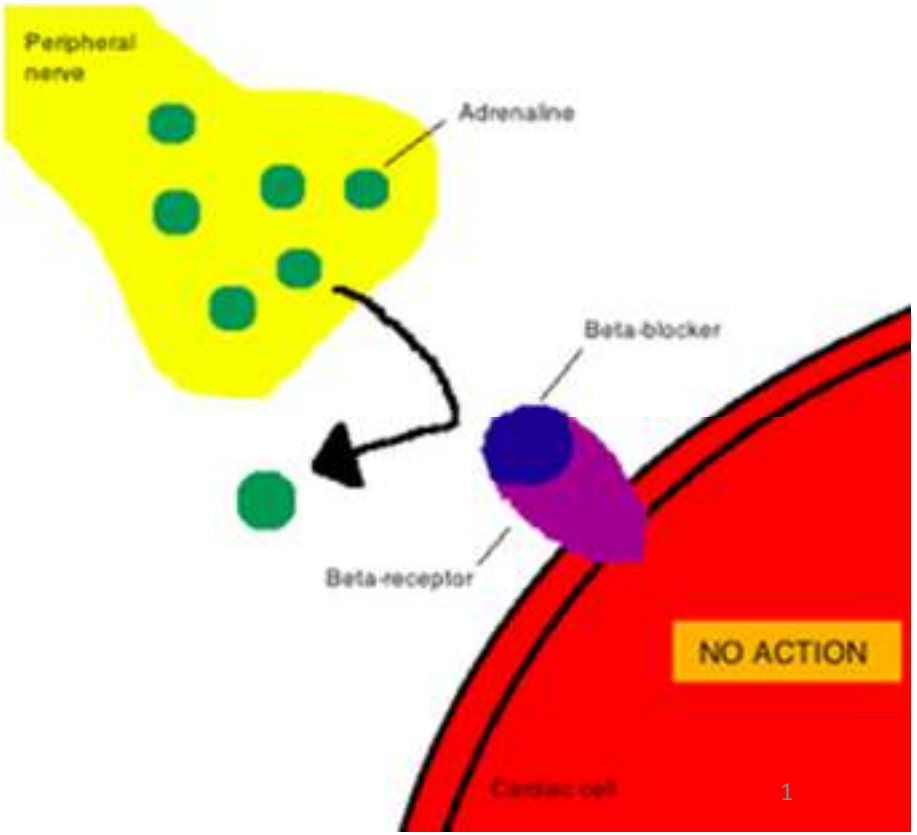
4. Midazolam



5. Diazepam

BETA BLOCKERS

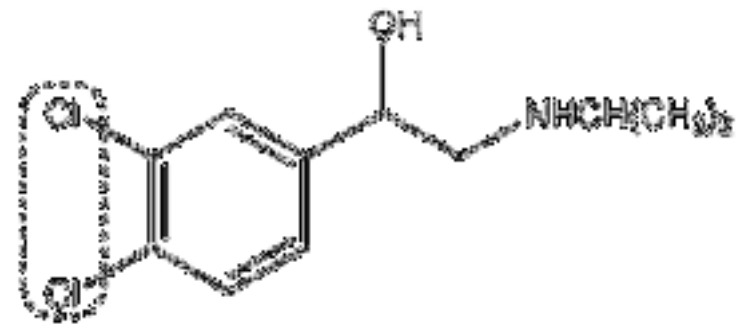




β-BLOCKERS

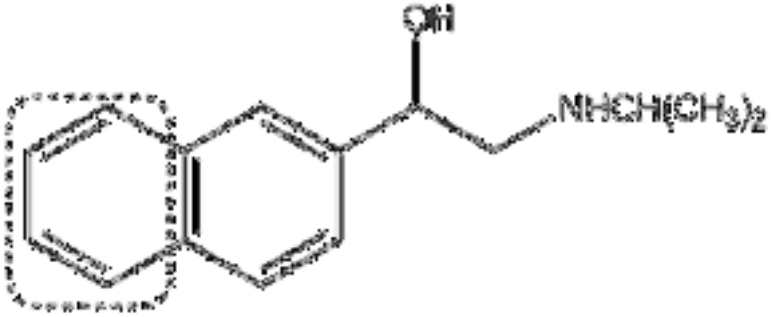
- **STRUCTURE–ACTIVITY RELATIONSHIPS:**
- β -Blockers are among the most widely used **antihypertensives** and are also the first-line drugs for glaucoma.
- Most of β-blockers are in the chemical class of **ARYLOXYPROPANOLAMINES**.
- **Dichloroisoproterenol (DCI)** is the first β –blocker.
- DCI differs structurally from isoproterenol in that the agonist directing 3,4-di-OH groups have been replaced by two chloro groups.

- This simple structural modification, involving the replacement of the aromatic OH groups, has provided the basis to design and synthesize therapeutically useful β-blockers.
- Unfortunately, DCI is not a pure antagonist but a partial agonist.
- The substantial direct sympathomimetic action of DCI stopped its development as a clinically useful drug.

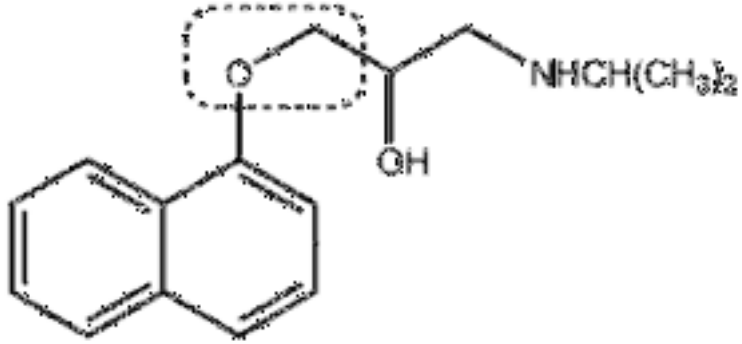


Dichloroisoproterenol (DCI, a partial β agonist)

- **Pronethalol** was the next important β-blocker developed.
- Its sympathomimetic activity (partial agonist) is less than DCI.
- But, it was withdrawn from clinical testing because of tumorogenicity.
- **Propranolol** is a close structural relative of pronethalol.
- Propranolol has become one of the most widely used drugs in the therapy.
- It is the standard against which all other β-blockers are compared.

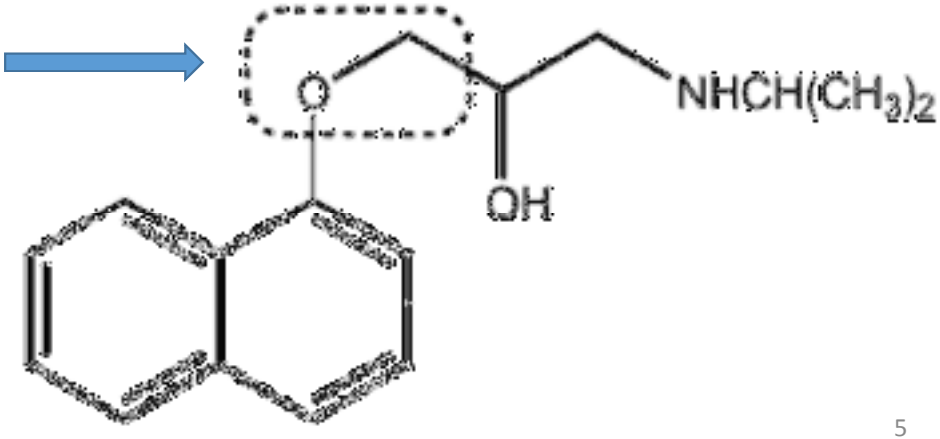


Pronethalol (a β blocker with toxicity)



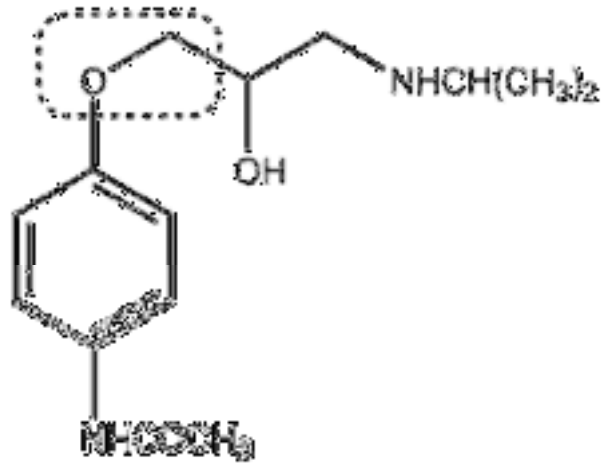
Propranolol (a prototype of β blockers)

- Propranolol belongs to the ***aryloxypropanolamines*** group of β-blockers.
- An **-OCH2-** group is present between the aromatic ring and the propylamino side chain.
- Because this structural feature is frequently found in β-blockers, the assumption is made that the -OCH2- group is responsible for the antagonistic properties of the molecules.
- Propranolol is nonselective.



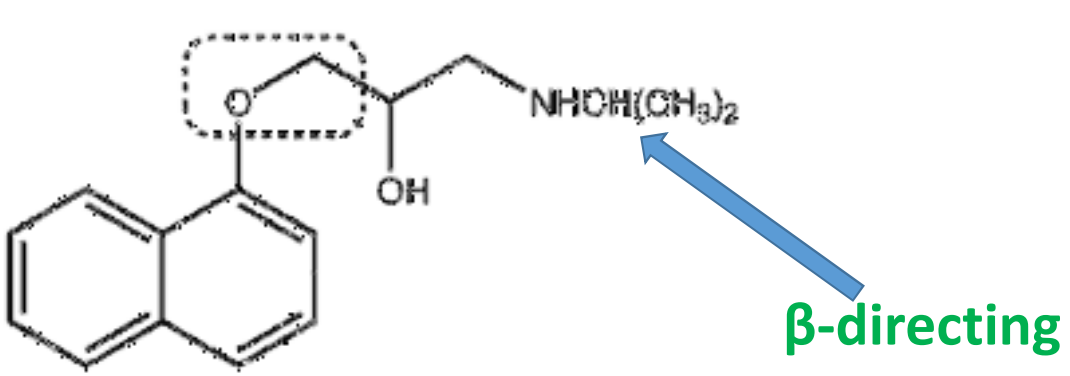
- However, this is not true; in fact, the -OCH2- group is present in several potent β-agonists.
- The nature of the aromatic ring and its substituents are the primary determinants of β –antagonistic activity.
- The aryl group also affects the absorption, excretion, and metabolism of the β-blockers.
- Note that the side chain has been moved from C2 to the C1 position from the naphthyl ring.

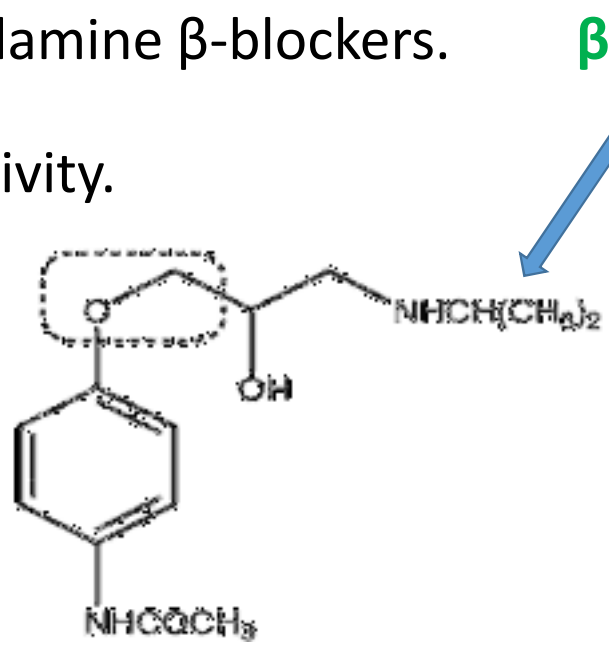
- The nature of the aromatic ring is also determines β1-selectivity.
- One common structural feature of many cardioselective β-blockers is the presence of a *para* substituent of sufficient size on the aromatic ring along with the absence of *meta*-substituents.
- **Practolol** is the prototypical example of a β1-blocker of this structural type.



Practolol (a prototype of β_1 blockers)

- Practolol was the **first cardioselective β1-blocker.**
- Because it produced **several toxic effects**, however, it is no longer in general use in most countries.
- Like β-agonists, **β-directing *tert*-butyl and isopropyl groups**, are normally found on the amino function of the aryloxypropanolamine β-blockers.
- It must be a secondary amine for optimal activity.



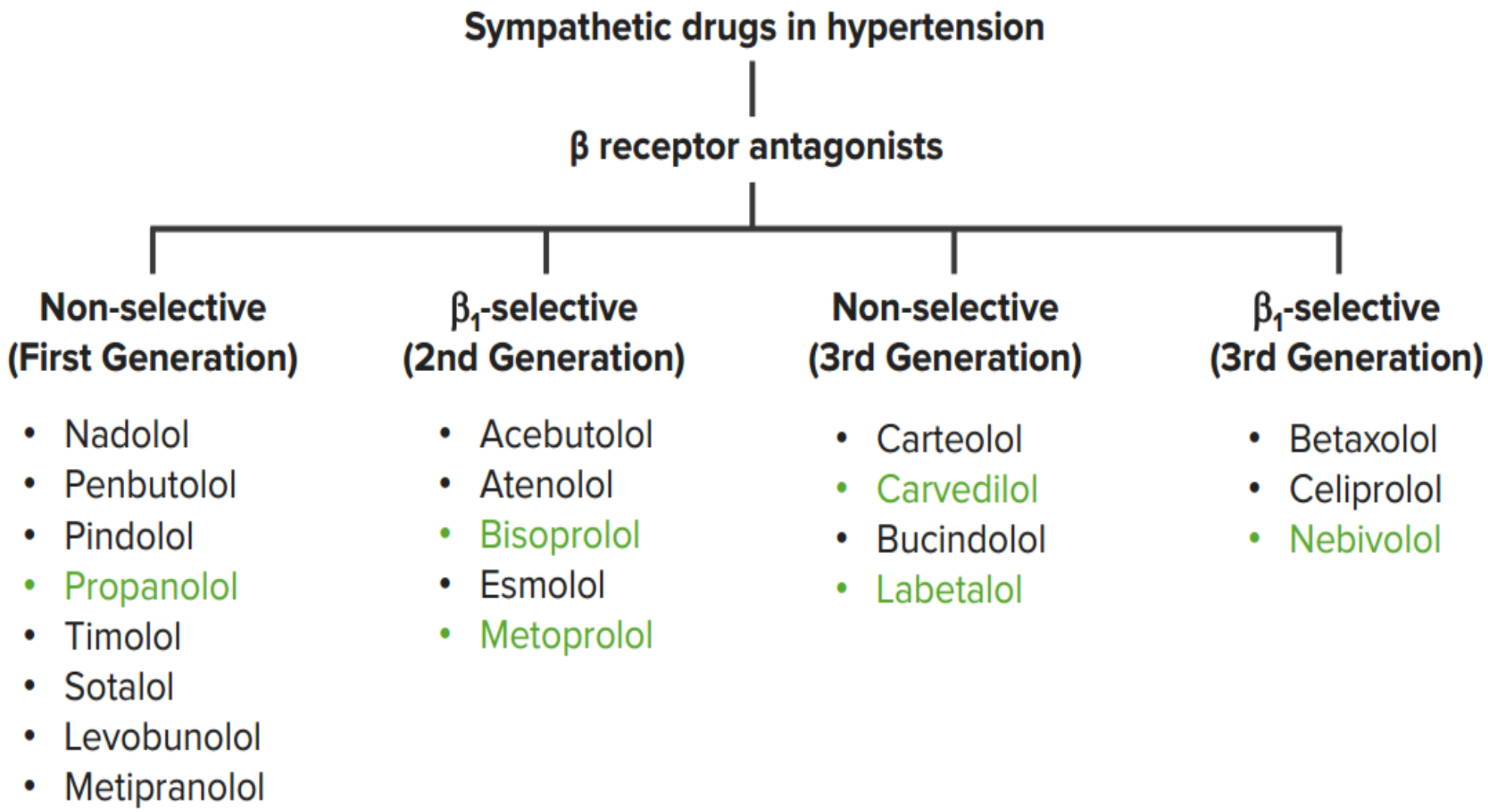


- **Stereochemistry and Activity:**
- For arylethanolamine adrenergic agonists, the β–OH substituted carbon must be in the *R* absolute configuration for maximal direct activity.
- **However, for β-blockers, the β-OH-substituted carbon must be in the *S* absolute configuration for maximal β-blocking activity.**
- Because of the insertion of an oxygen atom in the side chain of the aryloxypropanolamines, the Cahn-Ingold Prelog priority of the substituents around the asymmetric carbon differs from the agonists.

- The pharmacologically more active enantiomer of β-blockers interacts with the receptor recognition site in same manner as that of the agonists.
- In spite of the fact that nearly all of the β-blocking activity resides in one enantiomer, propranolol and most other β-blockers are used clinically as racemic mixtures.
- The only exceptions are levobunolol, timolol, and penbutolol, with which the (S) enantiomer is used.

- **Structure-Physicochemical properties- CNS Side effects:**
- Propranolol (log P 3.10) is the most lipophilic drug.
- It enters the CNS much better than the less lipophilic drug such as atenolol (log P 0.10) or nadolol (log P 1.29).
- The use of **lipophilic β-blockers** such as propranolol produces more **CNS side effects**, such as dizziness, confusion, or depression.

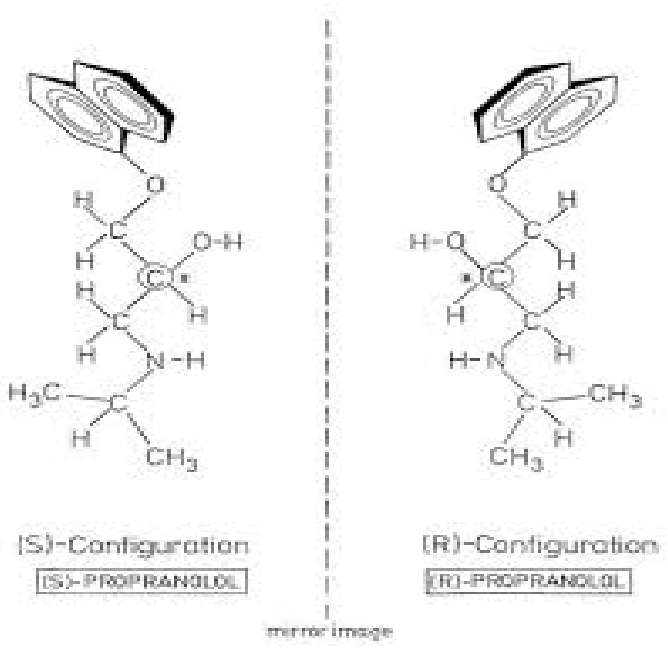
- These side effects can be avoided, however, with the use of hydrophilic drugs, such as atenolol or nadolol.
- The **more lipophilic drugs** are primarily cleared by the liver, and so their **doses need to be adjusted** in patients with **liver disease**.
- In contrast, the **less lipophilic drugs** are cleared by the kidney and so their **doses need to be adjusted** in patients with **impaired renal function**.

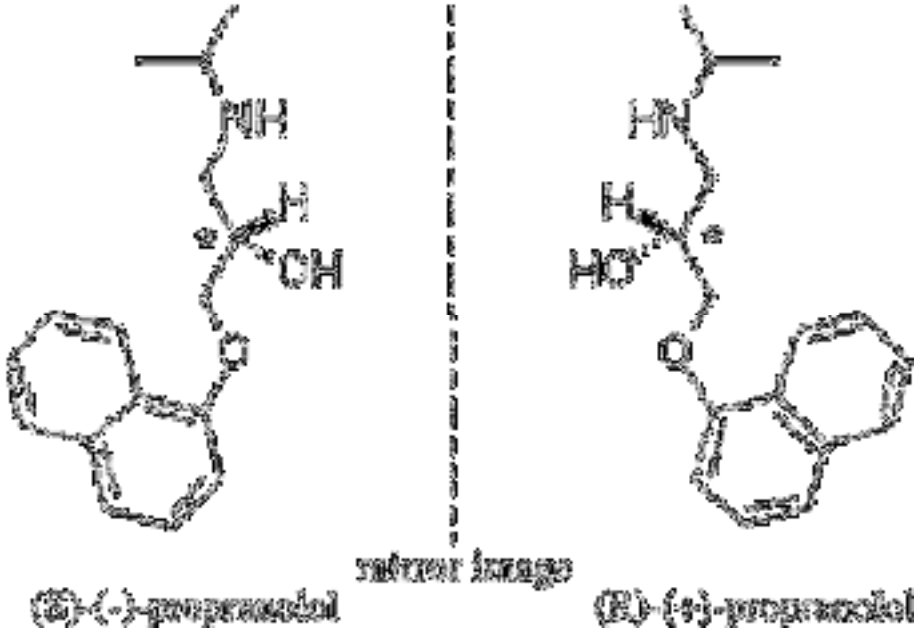

Sympathetic drugs in hypertension
β receptor antagonists
Non-selective (First Generation)
• Nadolol
• Penbutolol
• Pindolol
• Propanolol
• Timolol
• Sotalol
• Levobunolol
• Metipranolol
β1-selective (2nd Generation)
• Acebutolol
• Atenolol
• Bisoprolol
• Esmolol
• Metoprolol
Non-selective (3rd Generation)
• Carteolol
• Carvedilol
• Bucindolol
• Labetalol
β1-selective (3rd Generation)
• Betaxolol
• Celiprolol
• Nebivolol

NONSELECTIVE β-BLOCKERS (FIRST GENERATION)

- ***Propranolol:***
- Prototypical and nonselective β-blocker.
- Blocks the β1- and β2-receptors with equal affinity (Nonselective).
- Lacks Intrinsic Sympathomimetic Activity and does not block α-receptors.
- It is a competitive blocker whose receptor-blocking actions can be reversed with sufficient concentrations of β-agonists.
- It is lipophilic and crosses BBB.

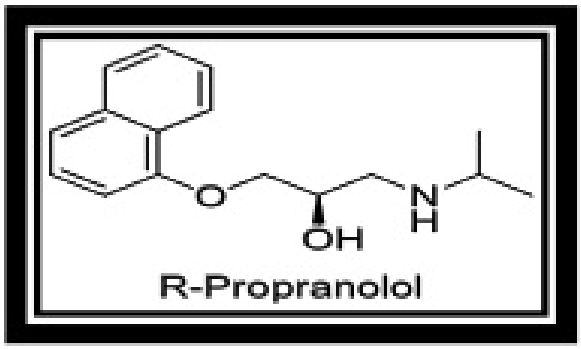
- **Stereochemistry of Propranolol:**
- Propranolol exist in two different enantiomers, (S)-(−)- and (R)-(+)-enantiomers.
- The (S)-isomer is 100-fold more potent than the (R)-isomer and that is the general rule for most β-blockers.



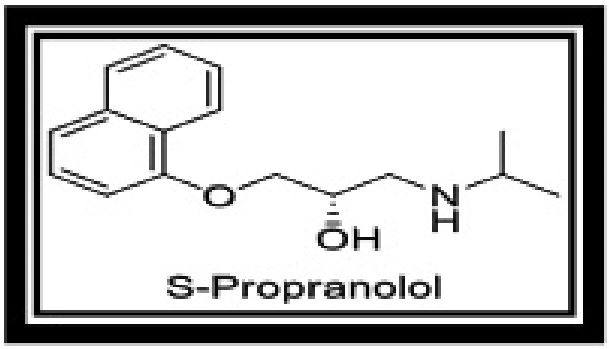


- **Influence of stereochemistry on Protein binding, Metabolism and Potency:**

Ex// the R-propranolol binding to albumin is greater than S-propranolol and the opposite is observed for α_1 -acid glycoprotein.



R-Propranolol



S-Propranolol

*** Highly albumin bound**

*** Less potent**

*** Highly metabolized**

*** Low plasma concentration**

*highly bound to AAG
available as unbound

* 40-100 time more potent

*Less metabolized

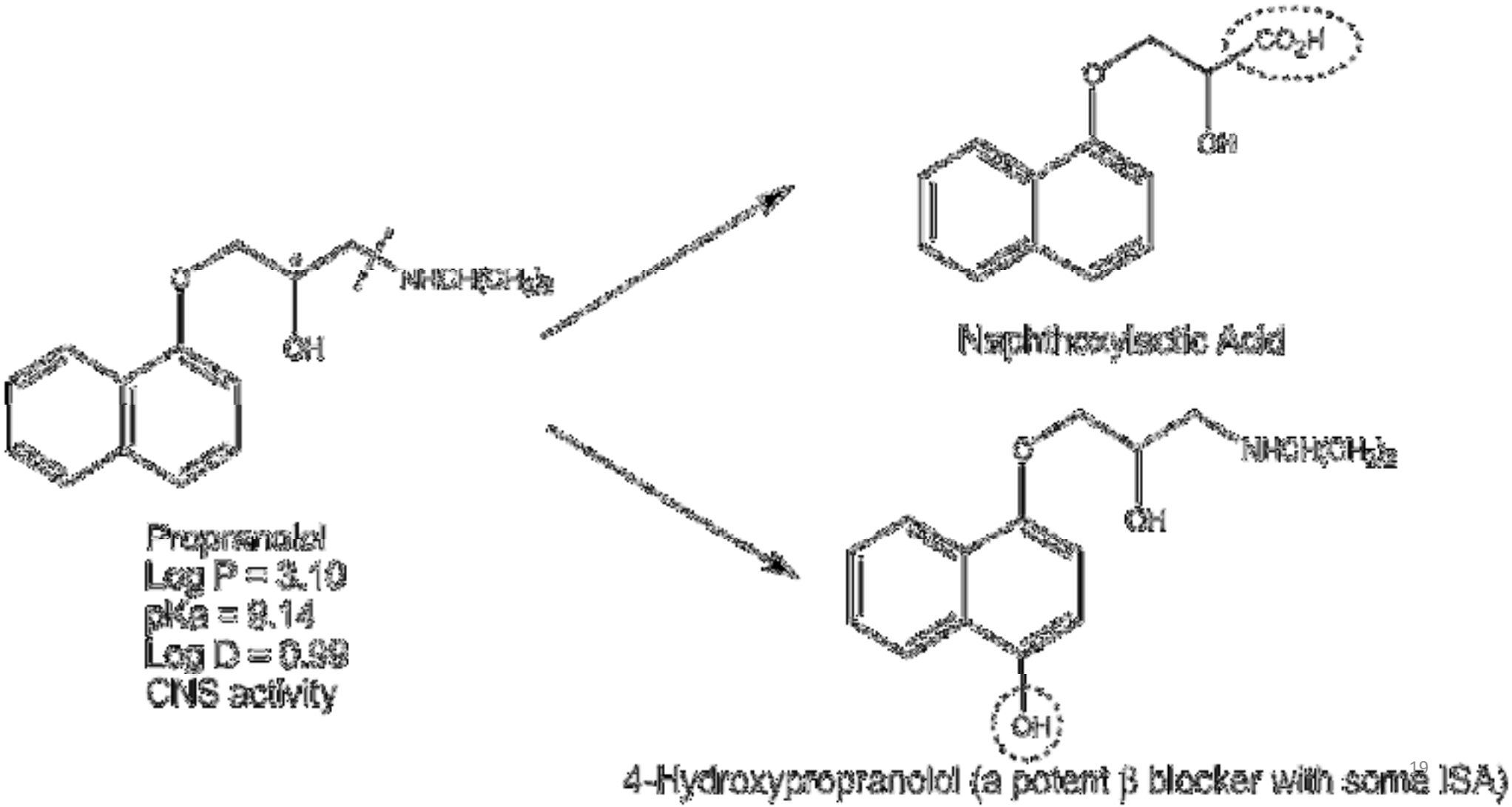
*High plasma concentration

19

- **Pharmacological Actions of Propranolol:**
- Some of the most prominent effects of propranolol are on the cardiovascular system.
- By blocking the β–receptors of the heart, propranolol slows the heart, reduces the force of contraction, and reduces cardiac output.
- Because of reflex sympathetic activity and blockade of vascular β2- receptors, administration may result in increased peripheral resistance.
- The antihypertensive action, at least in part, may be attributed to its ability to reduce cardiac output, as well as to its suppression of renin release from the kidney.
- Because it exhibits no selectivity for β1-receptors, it is contraindicated in the presence of conditions such as asthma and bronchitis.

- **Pharmacokinetics:** **(ADMET data can be predicted using admetSAR)**
- Well absorbed after oral administration.
- Undergoes extensive first-pass metabolism before it reaches the systemic circulation.
- The active enantiomer is cleared more slowly than the inactive enantiomer.
- One of the major metabolites is naphthoxylactic acid.
- It is formed by a series of metabolic reactions involving *N*-dealkylation, deamination, and oxidation of the resultant aldehyde.
- Another metabolite is 4-hydroxypropranolol, which is a potent β-blocker.
- The half-life of propranolol after a single oral dose is 3 to 4 hours, which increases to 4 to 6 hours after long-term therapy.

- **Metabolism of Propranolol:**



- **Therapeutic Uses:**

➢ **Hypertension**

➢ **Cardiac arrhythmias**

➢ **Angina pectoris**

➢ **Postmyocardial infarction**

➢ **Hypertrophic cardiomyopathy**

➢ **Pheochromocytoma**

➢ **Migraine prophylaxis**

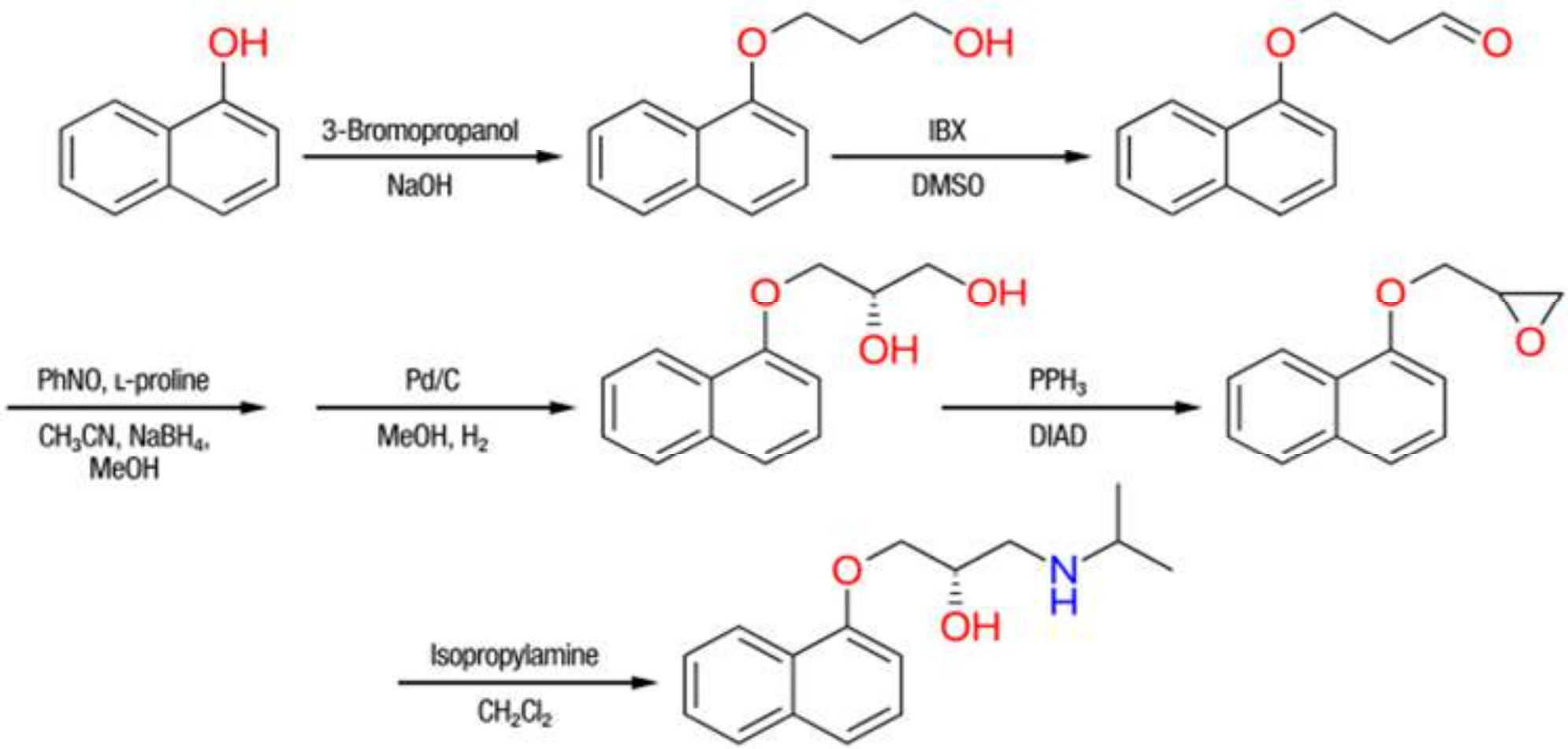
➢ **Essential tremor.**

➢ Due to **high lipophilicity** and ability to penetrate the **CNS**, propranolol has found use in treating-

➢ **anxiety**

➢ and is under investigation for the **treatment of schizophrenia, alcohol withdrawal syndrome, and aggressive behavior.**

- **Synthesis of Propranolol:**



- It is possible to prepare the (S)-propranolol enantiomer from α-naphthol and 3-bromopropanol.
- α-Naphthol and 3-bromopropanol are refluxed for 6 hours to give alcohol.
- The alcohol is oxidized by using 2-Iodoxybenzoic acid (IBX) to give aldehyde.
- The aldehyde is subjected to L-proline catalyzed asymmetric α-aminoxylation and a reduction is made with NaBH4 in methanol.
- A diol is obtained by Pd/C-catalyzed hydrogenolysis.
- Finally the diol is converted to epoxide using the Mitsunobu reaction and stirred with isopropyl amine in CH2Cl2 to give (S)-propranolol.

- ***Other Nonselective β-Blockers.***
- Other nonselective β-blockers include

➢ *Nadolol,*

➢ *Pindolol,*

➢ *Penbutolol,*

➢ *Carteolol,*

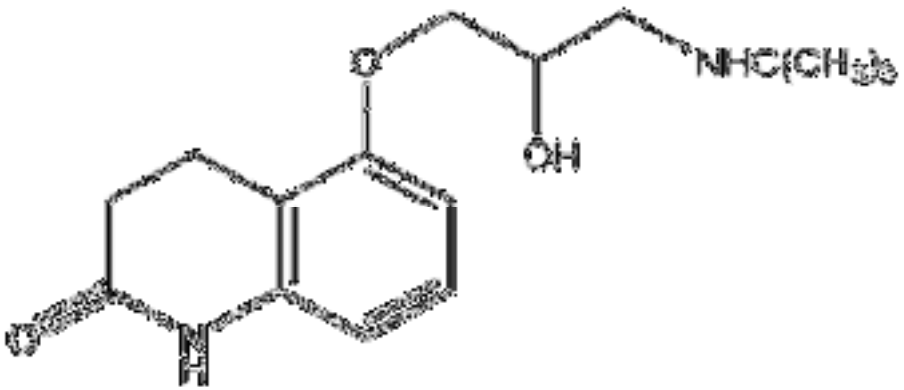
➢ *Timolol*,

➢ *Levobunolol,*

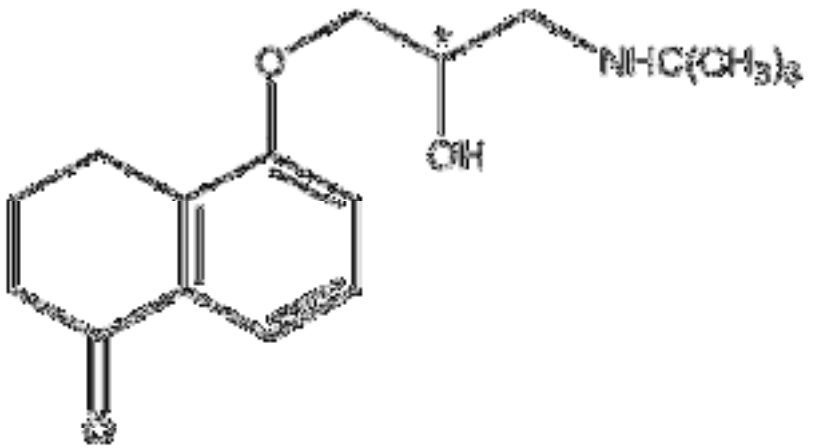
➢ *Sotalol*, and

➢ ***Metipranolol***.

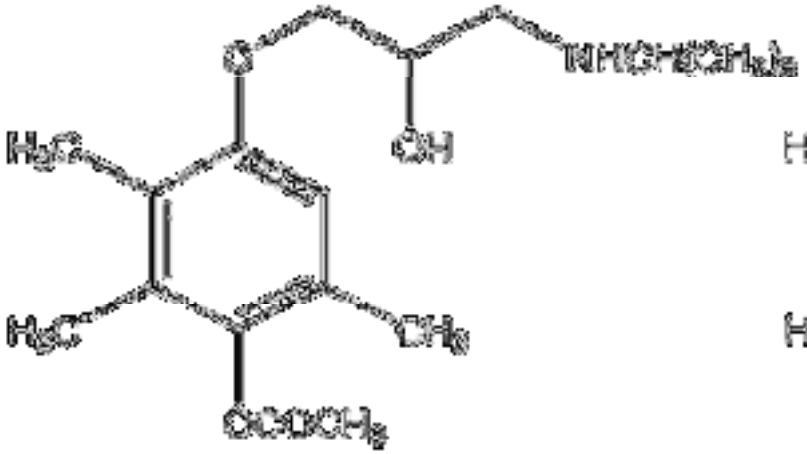
- The first five of these blockers are used to treat hypertension.



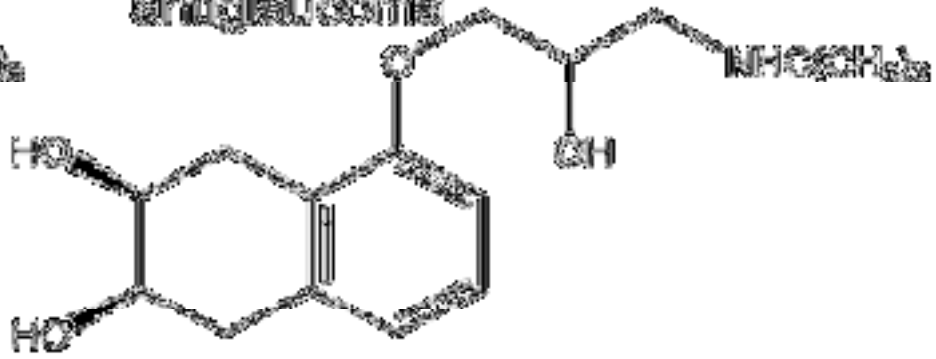
Carteolol: antihypertensive & antiglaucoma



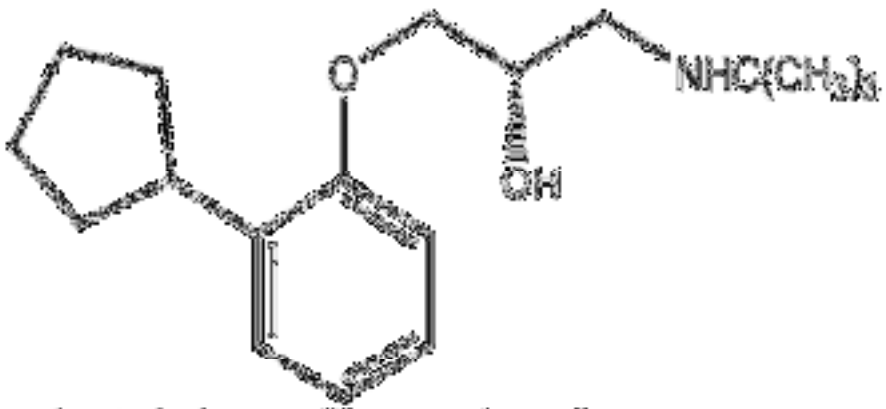
Bunalol
Levobunolol, S(-) isomer of bunolol
antiglaucoma



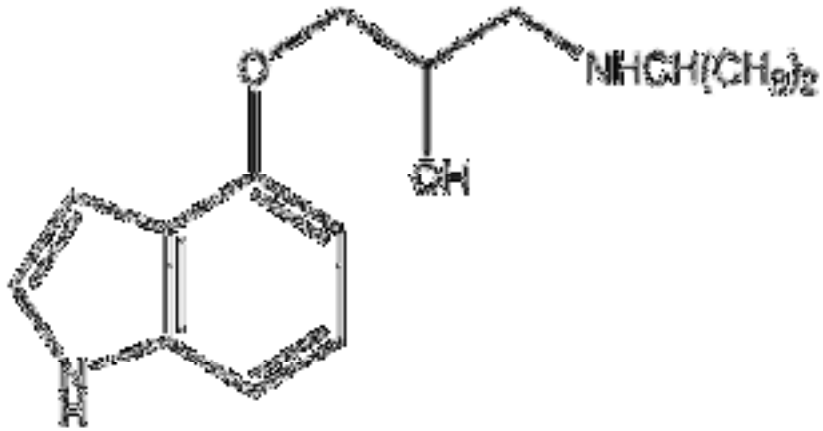
Metipranolol: antiglaucoma



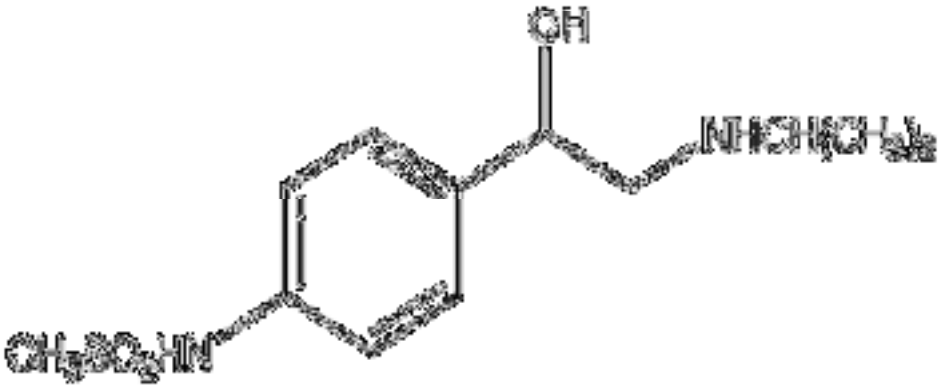
Nadolol: antihypertensive



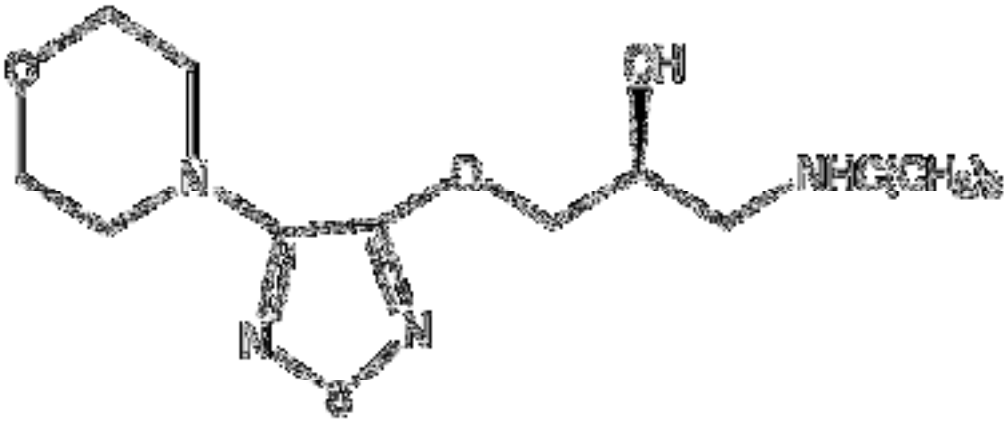
Penbutolol: antihypertensive



Pindolol: antihypertensive

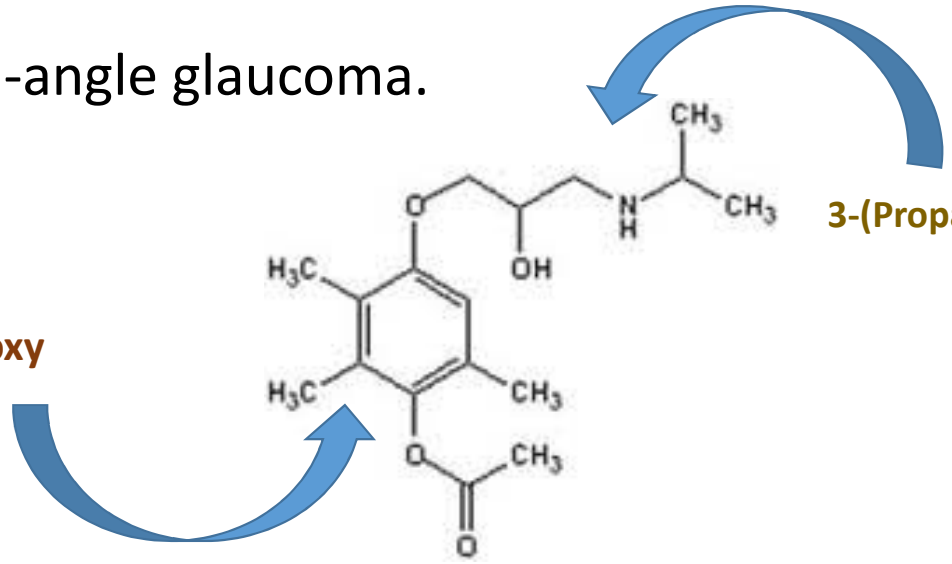


Sotalol: antiarrhythmics & only phenylethylamine



Timolol: antihypertensive & antiglaucoma

- **Metipranolol:**
- Metipranolol is 3-(Propan-2-ylamino)propane-1,2-diol in which the hydrogen of the primary hydroxy group is substituted by a 4-acetoxy-2,3,5-trimethylphenoxy group.
- A non-cardioselective beta-blocker, it is used to lower intra-ocular pressure in the management of open-angle glaucoma.



3-(Propan-2-ylamino)propane-1,2-diol

4-acetoxy-2,3,5-trimethylphenoxy

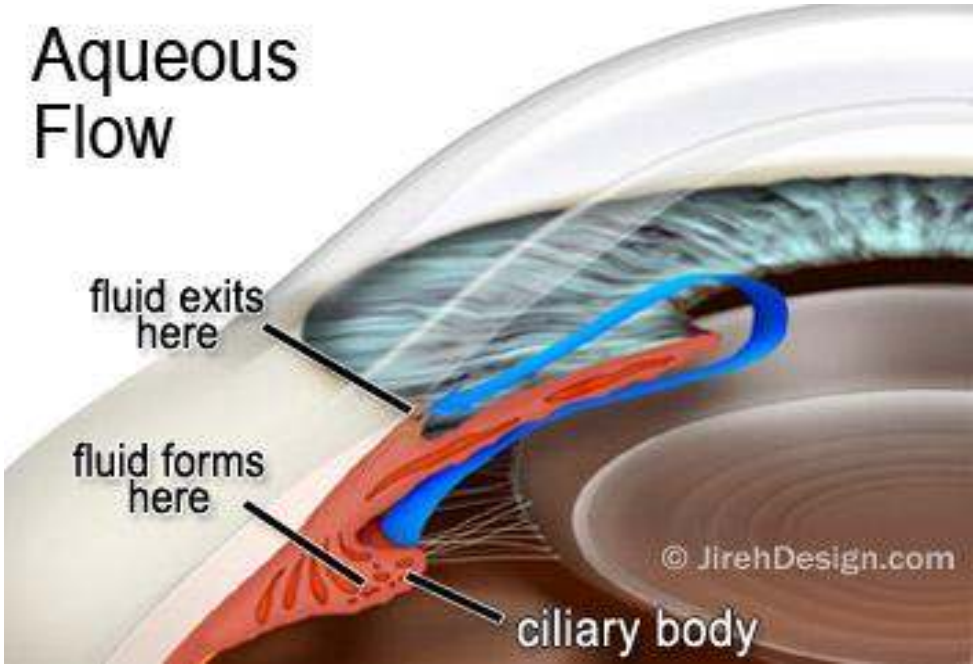
- It has a role as –

➢ a beta-adrenergic antagonist,

➢ an anti-arrhythmic drug,

➢ an antihypertensive agent and

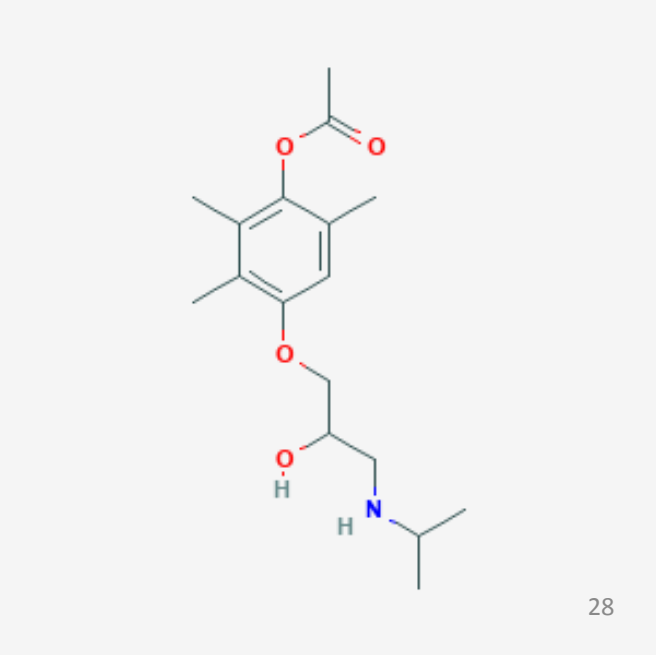
➢ an antiglaucoma drug.



- It is a propanolamine, an acetate ester, an aromatic ether and a secondary amino compound.

- Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss and optic nerve damage.
- Metipranolol reduces intraocular pressure with little or no effect on pupil size or accommodation in contrast to the miosis which cholinergic agents are known to produce.

- **4-{2-hydroxy-3-[(propan-2-yl)amino]propoxy}-2,3,6-trimethylphenyl acetate**
- **SMILES:CC(C)NCC(O)COC1=C(C)C(C)=C(OC(C)=O)C(C)=C1**



•SMILES ☺?

- **For detailed and schematic presentation of Metipranolol's mechanism:**
- **Source:** Human Metabolome Database (HMDB)
- **Record Name:** Metipranolol
- **URL:** http://www.hmdb.ca/metabolites/HMDB0015345
- **Description:** The Human Metabolome Database (HMDB) is a freely available elec tronic database containing detailed information about small molecule metabolit es found in the human body.
- **License Note:** HMDB is offered to the public as a freely available resource. Use and re-distribution of the data, in whole or in part, for commercial purposes requires explicit permission of the authors and explicit acknowledgment of the source material (HMDB) and the original publication (see the HMDB citing page). We ask that users who download significant portions of the database cite the HMDB paper in any resulting publications.
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CID 31477

Metipranolol

FDA Orange Book

2 items

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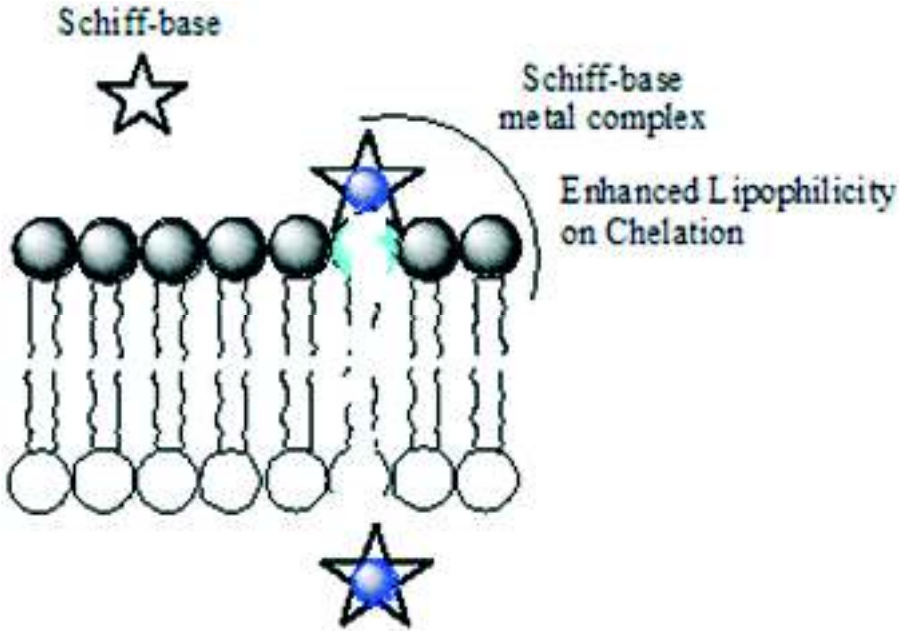
#	Trade Name	Active Ingredient	Marketing Status	Dosage Form/Route	Strength	Application Number	Applicant	Approval Date	US Patent
1	METIPRANOLOL	METIPRANOLOL HYDROCHLORIDE	Discontinued	SOLUTION/DROPS;OPHTHALMIC	0.3%	A075720	SANDOZ INC	Aug 6, 2001	
2	OPTIPRANOLOL	METIPRANOLOL HYDROCHLORIDE	Discontinued	SOLUTION/DROPS;OPHTHALMIC	0.3%	N019907	BAUSCH AND LOMB PHARMACEUTICALS INC	Dec 29, 1989	

FDA Drugs

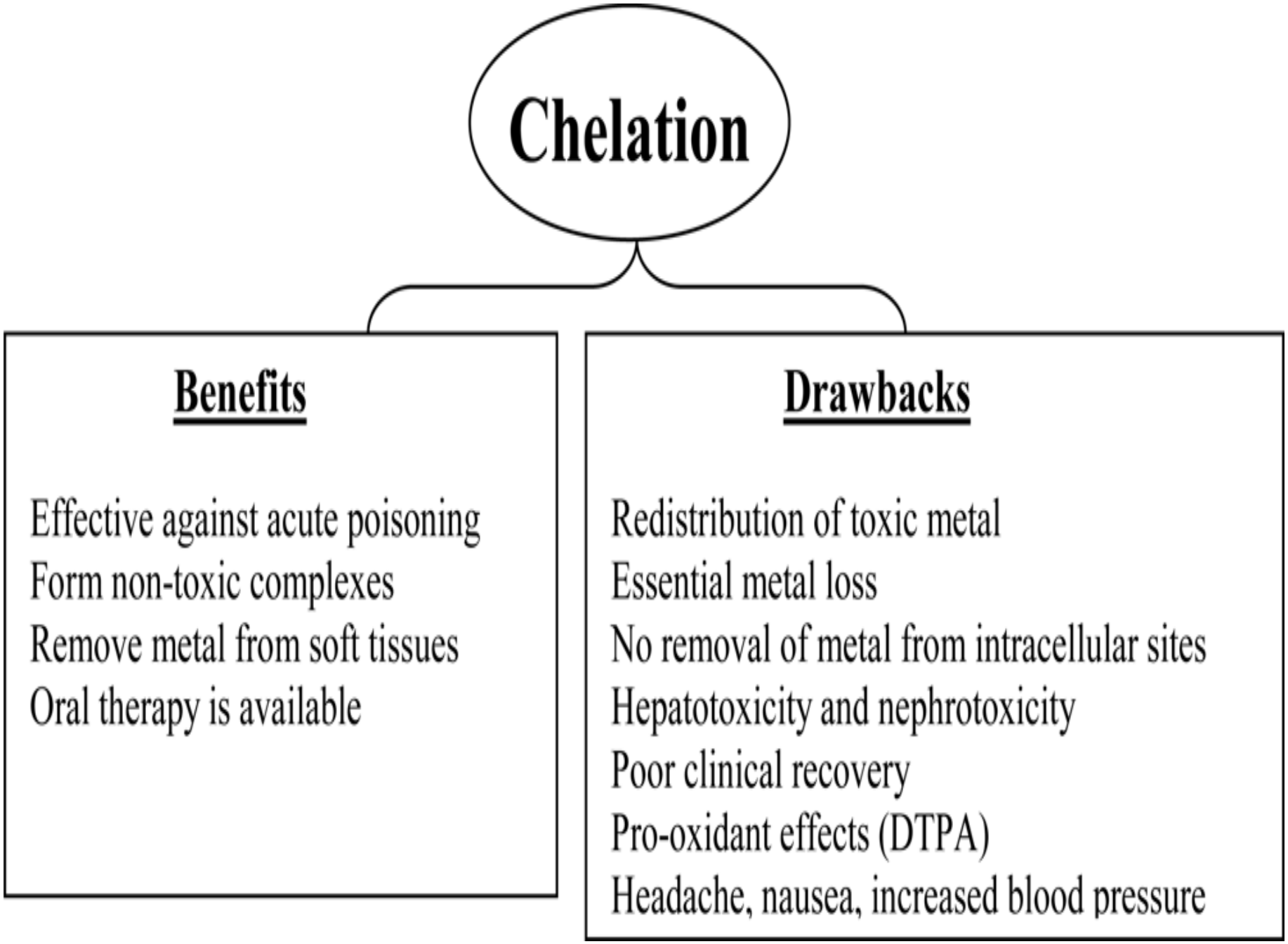
Chelation
Bioisosterism
Optical and Geometrical Isomerism

- **Chelation**
- Metal chelation principles offer new opportunities in the drug design field.
- Synthesizing the appropriate coordination compound, for example, may modify a number of properties including charge, lipophilicity, shape and redox potential.



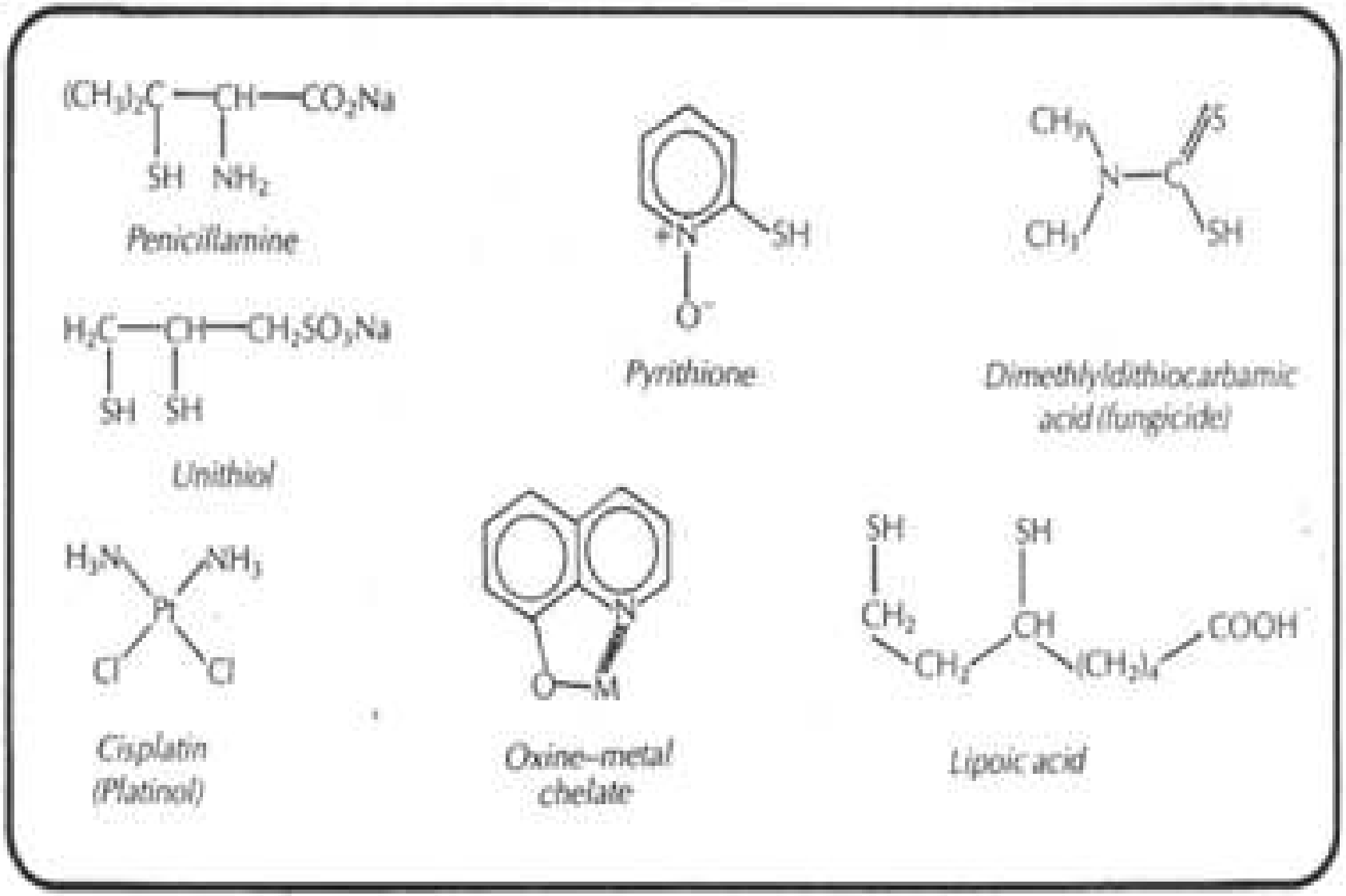
Chelating Agents

- Chemical antidotes - chemically inactivate the poison
- Compete with enzyme systems for the metals
- Reverse the metals toxic effects
- Enhance the excretion of the metal
- The chelate formed is a stable compound
- Chelates are water soluble
- Chelates are excreted by the kidneys


Chelation
Benefits
Effective against acute poisoning
Form non-toxic complexes
Remove metal from soft tissues
Oral therapy is available
Drawbacks
Redistribution of toxic metal
Essential metal loss
No removal of metal from intracellular sites
Hepatotoxicity and nephrotoxicity
Poor clinical recovery
Pro-oxidant effects (DTPA)
Headache, nausea, increased blood pressure

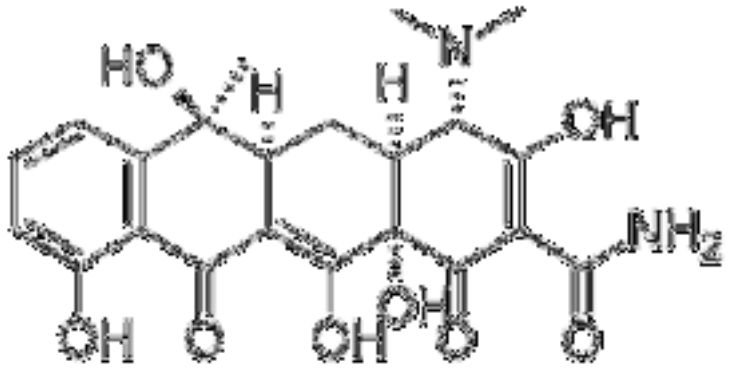
- Chelates are used in medicine:
  - To complex toxic metals.
  - To release traces of essential metals or deprive the cellular components of them.
  - To produce therapeutic interactions with cellular macromolecules.
- Metal ions such as As, Hg, Pb, Au, form chelates with the thiol groups of enzymes and proteins blocking their functions.
- The effect of masses exerted by the chelating agent releases the enzyme from the metal ion, allowing its normal functioning, concentrating the metal chelate in the kidney for urinary excretion.
- The solubilizing chelating agents of the **unithiol or penicillamine** type are the most effective.

- Chemical structure of some ligands of therapeutic interest



- The chelate can act as a carrier to release a bioactive ligand.
- For example, the **transplatin** (isomer of cisplatin) transports the cytotoxic ligand 6-mercaptopurine through the membranes thus exhibiting its antitumor activity against cancer.
- Chelating agents may be potentially useful in the treatment of neurodegenerative diseases.
- Example: **Clioquinol,** a bidentate chelating antimicrobial agent is also useful in treatment of Alzheimer's disease.

- **Tetracyclines and chelation:**
- Stable chelate complexes are formed by the tetracyclines with many metals, including calcium, magnesium, and iron.
- Such chelates are usually very insoluble in water, accounting for the impaired absorption of most tetracyclines in the presence of milk; calcium-, magnesium-, and aluminum-containing antacids; and iron salts.

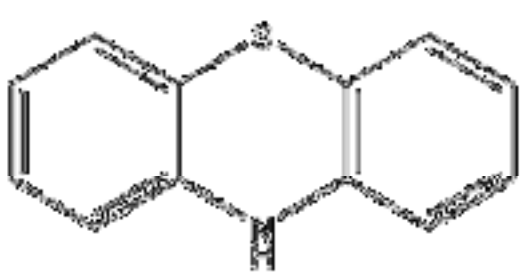


- **Bioisosterism**
- Bioisosterism is one of the important structural modification strategy used in lead optimization, scaffold hopping and drug designing.
- It consists of a complete replacement of the initial molecular structure by another one, isofunctional, but based on a different scaffold.
- Langmuir defined *isosteres* as 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 N2 and CO both possess 14 total electrons and no charge and show similar physical properties.

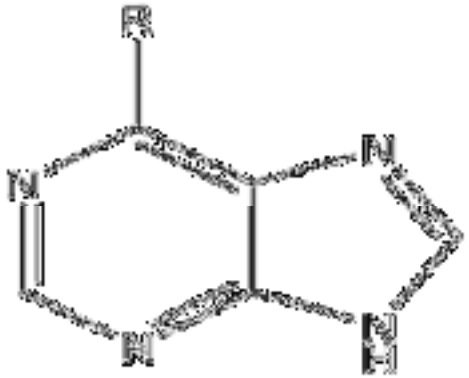
A. Univalent atoms and groups					
(1)	$-CH_3$	$-NH_2$	$-OH$	$-F$	$-Cl$
(2)	$-Cl$	$-SH$			
(3)	$-Br$	$-i-Pr$			
B. Bivalent atoms and groups					
(1)	$-CH_2-$	$-NH-$	$-O-$	$-S-$	
(2)	$-COCH_2R$	$-CONHR$			
(3)	$-CO_2R$	$-COSR$			
C. Trivalent atoms and groups					
(1)	$-CH=$	$-N=$			

- 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*.
- The early recognition that benzene and thiophene were alike in many of their properties led to the term *ring equivalents* for the vinylene group (—CH=CH—) and divalent sulfur (—S—).



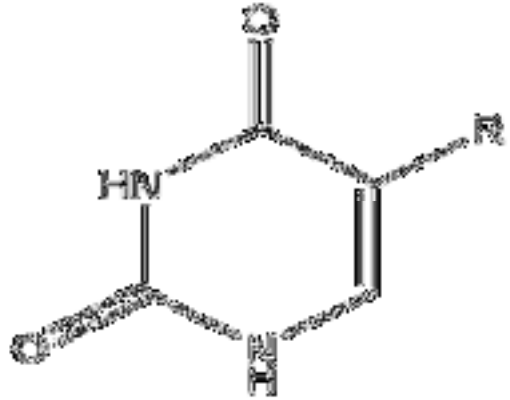
- Examples of isosteric pairs that possess similar steric and electronic configurations are the carboxylate (COO-) and sulfonamide (SO2NR-) ions; ketone (C=O) and sulfone (O=S=O); chloride (Cl) and trifluoromethyl (CF3); hydrogen (-H) and fluorine (-F); hydroxy (-OH) and amine (-NH2); hydroxy (-OH) and thiol (-SH).
- Divalent ether (-O-), sulfide (-S-), amine (-NH-), and methylene (-CH2-) groups, although dissimilar electronically, are sufficiently alike in their steric nature to be frequently interchangeable in designing new drugs.

- Isosteric replacement sometimes produces analogs that act as antagonists.
- The 6-NH2 and 6-OH groups appear to play essential roles in the hydrogen bonding interactions of base pairs during nucleic acid replication in cells.
- Adenine, hypoxanthine and the antineoplastic 6-mercaptopurine illustrate how substitution of the weaker hydrogen bonding isosteric sulfhydryl groups results in a partial blockage of this interaction and a decrease in the rate of cellular synthesis.



Adenine R = NH_2] Metabolites
Hypoxanthine R = OH]

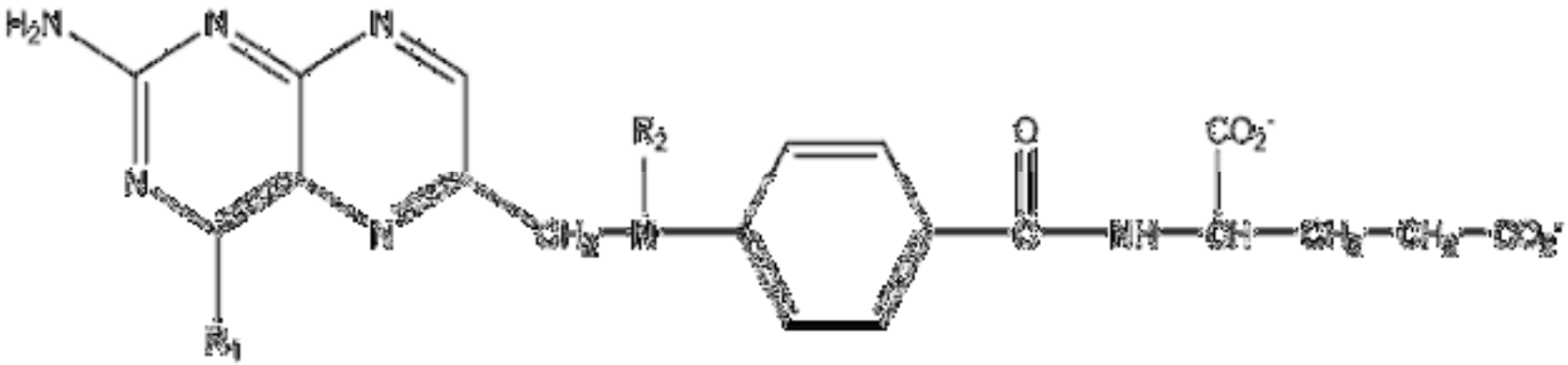
6-Mercaptopurine R = SH Antimetabolite



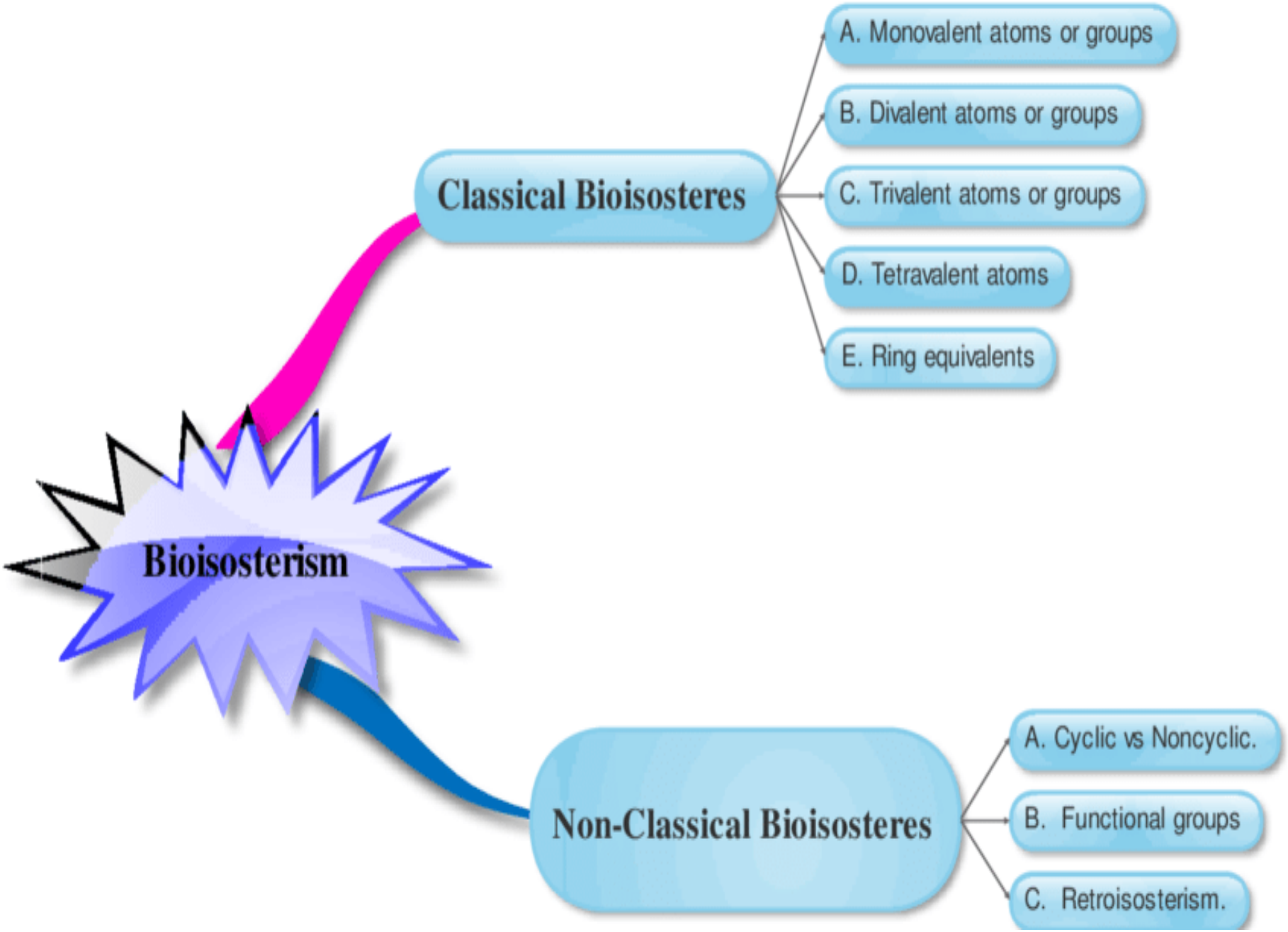
Uracil R = H Metabolites

5-Fluorouracil Antimetabolite

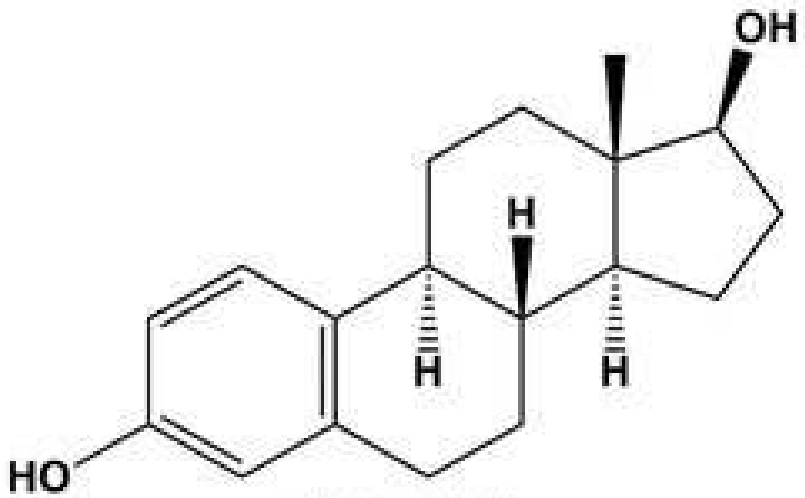
- Similarly, replacement of the hydroxyl group of folic acid by the isosteric amino group and addition of the methyl group to the *p*-aminobenzoate leads to the methotrexate, a folate antimetabolite.
- Replacement of the hydrogen at the 5-position of uracil with the isosteric fluorine producing 5-fluorouracil blocks the methylation step leading to thymine.



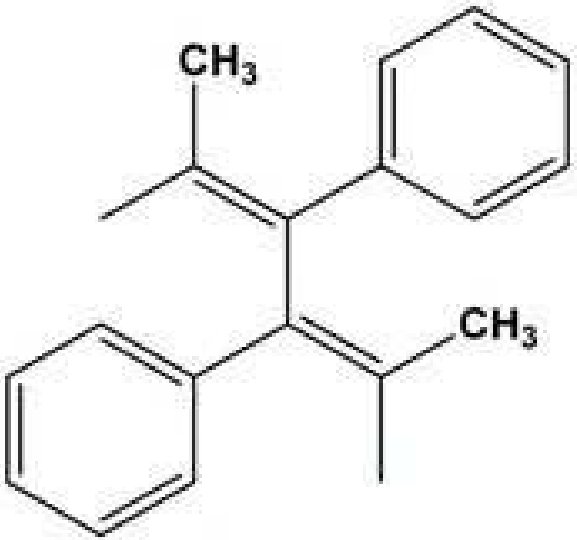
Folic Acid	$R_1 = OH$; $R_2 = H$	Vitamin
Methotrexate	$R_1 = NH_2$; $R_2 = CH_3$	Antimetabolite


Bioisosterism
Classical Bioisosteres
A. Monovalent atoms or groups
B. Divalent atoms or groups
C. Trivalent atoms or groups
D. Tetravalent atoms
E. Ring equivalents
Non-Classical Bioisosteres
A. Cyclic vs Noncyclic.
B. Functional groups
C. Retroisosterism.

1) Cyclic and Noncyclic Isosterism

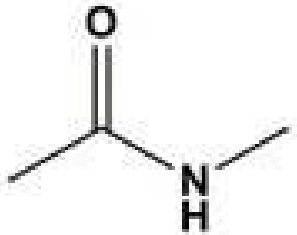


Estradiol

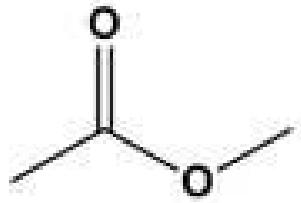


Dienestrol

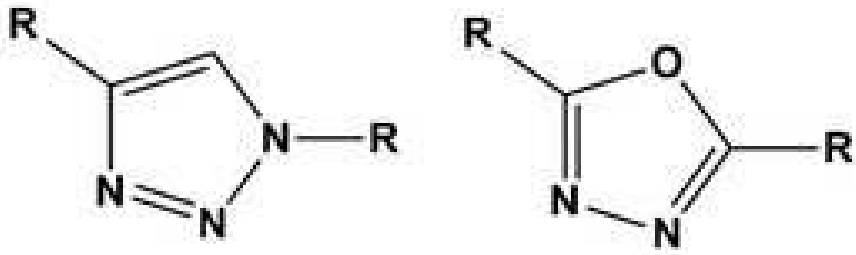
2) Functional Groups



Amide

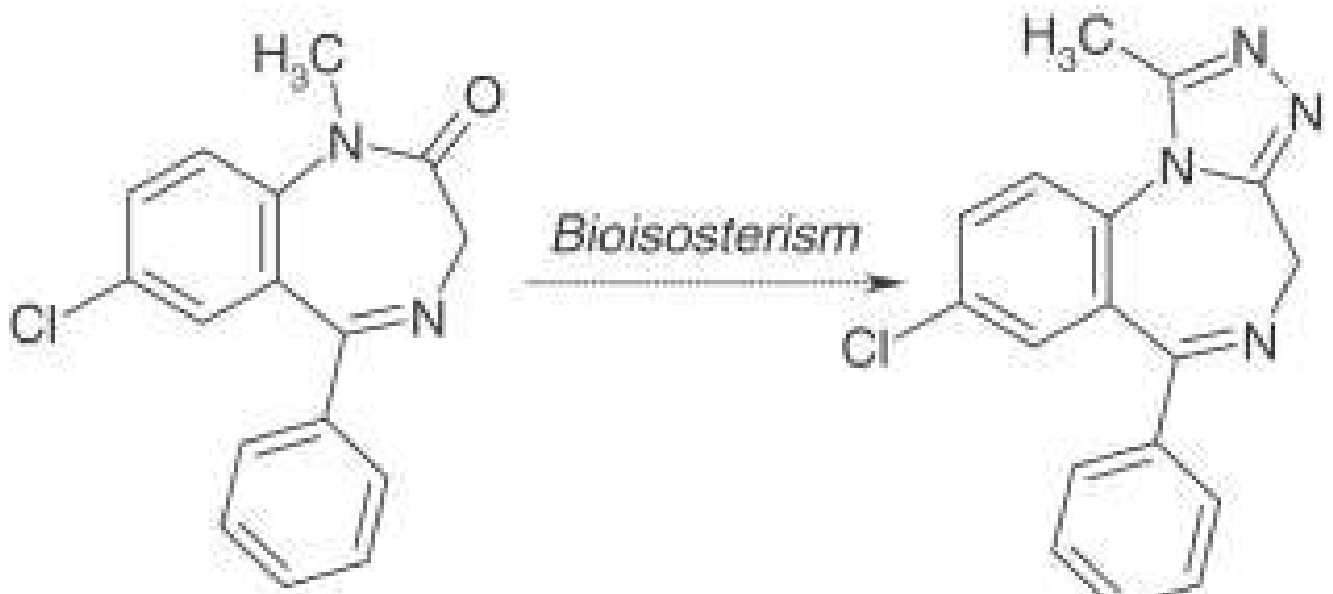


Ester



Tri- and Diazoles

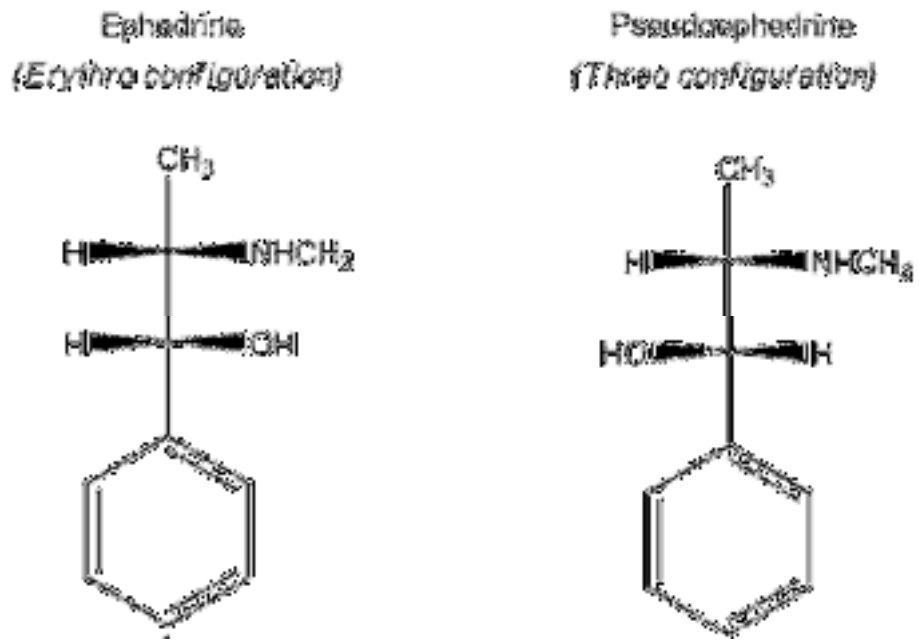
The replacement of methylated carboxamide function of diazepam by its bioequivalent methylated triazole group in alprazolam preserves the high affinity for the central benzodiazepine receptor.



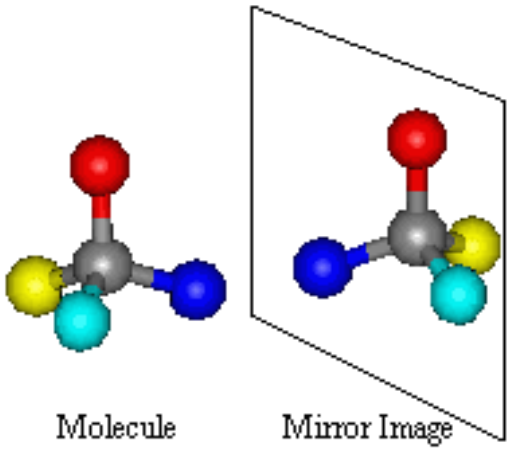
Diazepam

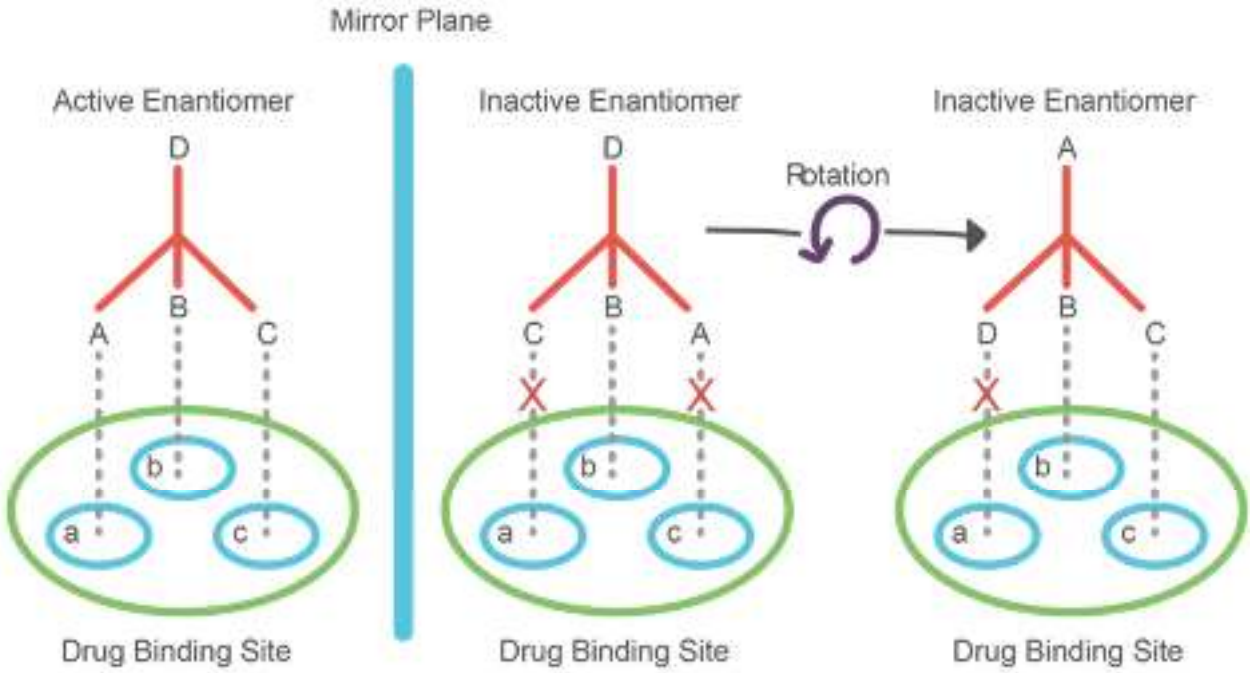
Alprazolam

- **Optical Isomerism**
- Most commercial drugs are asymmetric.
- Although D- and L-isomers have the same physical properties, 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.



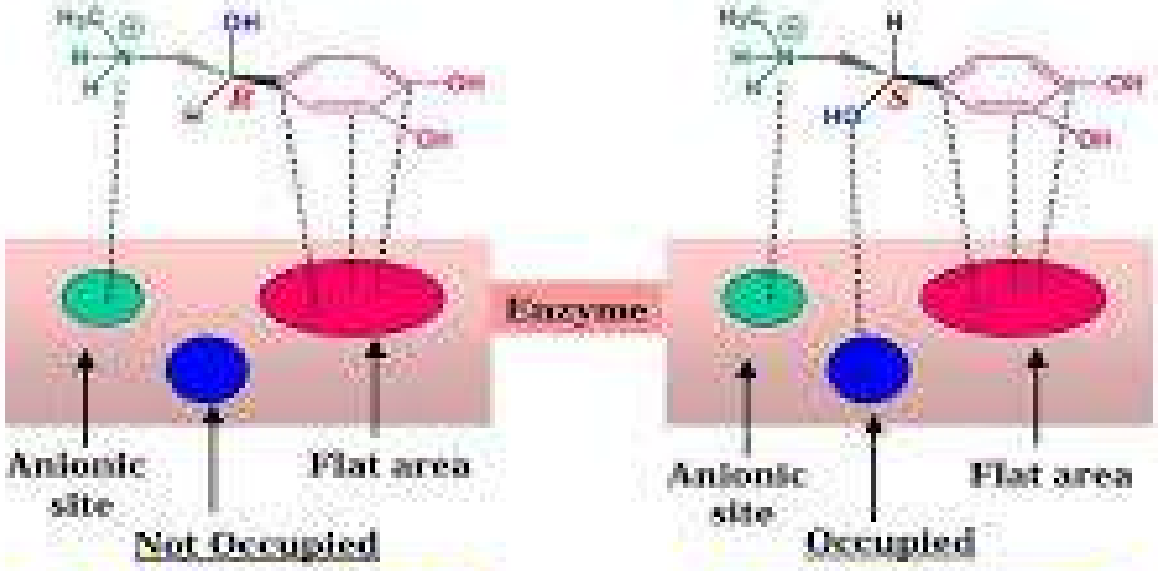
- Ephedrine: MP 79_0 C and water soluble.
- Pseudoephedrine: 118_0C and sparingly soluble in water.





Biological activity of enantiomers

Enantiomers of Epinephrine



(+)-Epinephrine

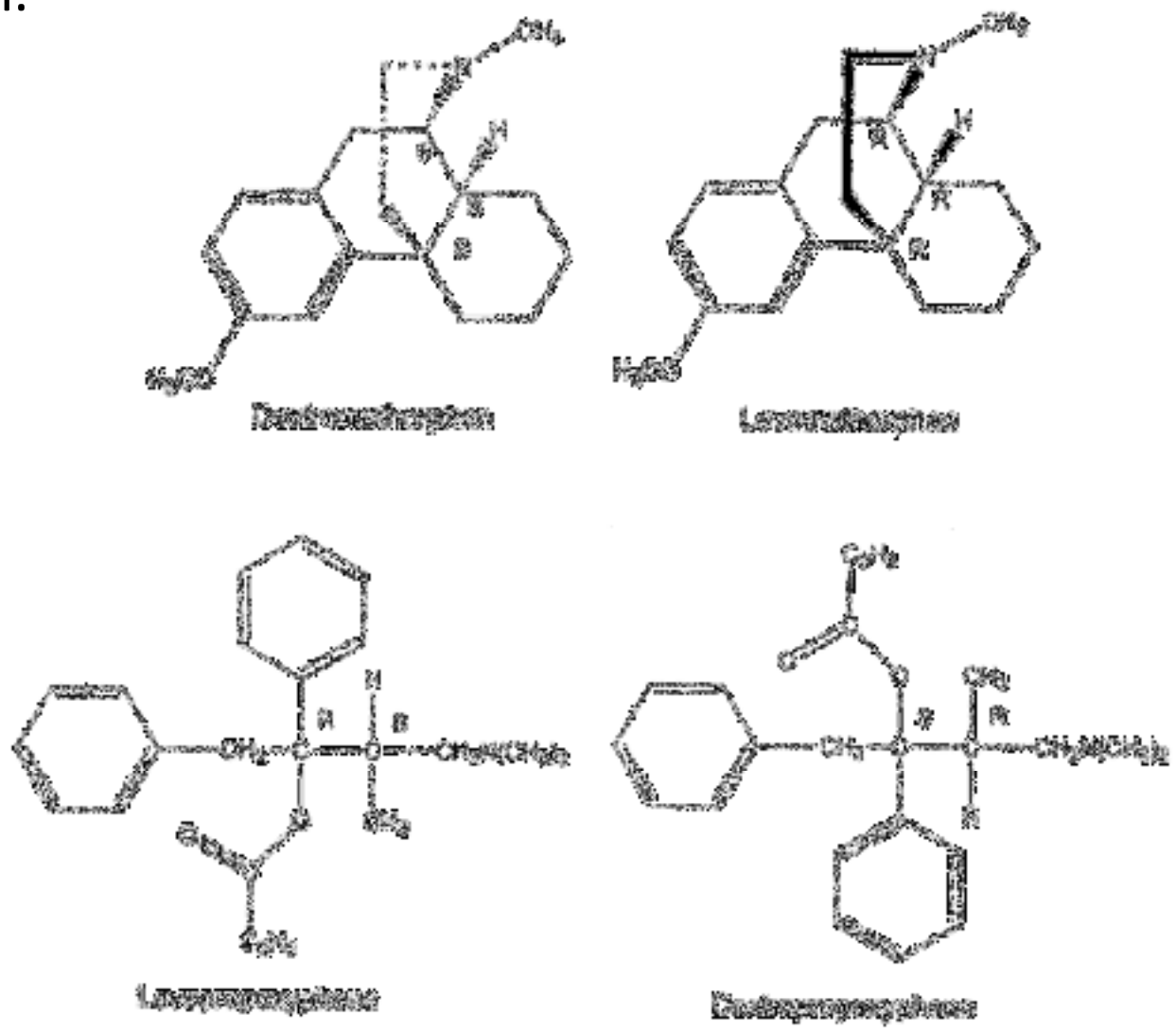
Poorer Fit ⇒ Less Active

(-)-Epinephrine

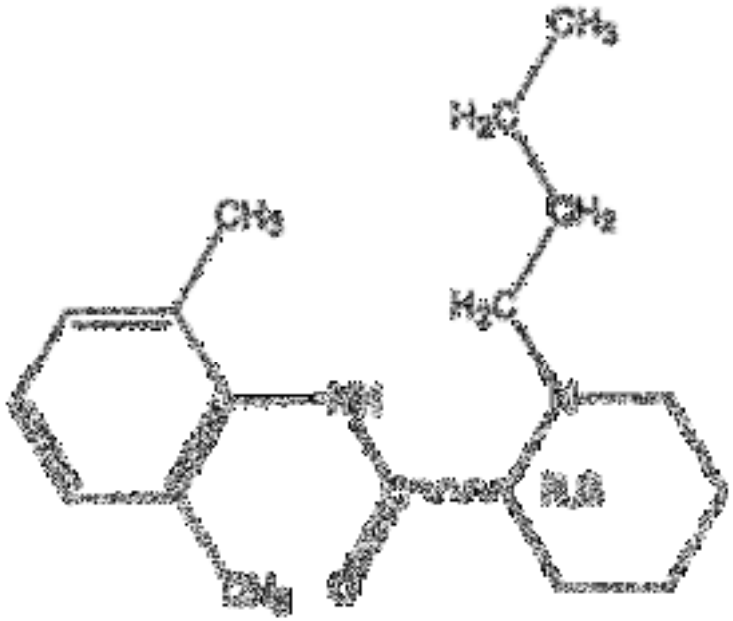
Better Fit ⇒ More Active

- Receptors are chemically proteins and are constructed from L-amino acids.
- Therefore, these receptors are asymmetric.
- This makes optical isomers to differ in biological activities.
- (-)Hyoscyamine exhibits 15 to 20 times more mydriatic activity than (+) hyoscyamine.
- (-) Ephedrine shows three times more pressor activity than (+) ephedrine, five times more pressor activity than (+)-pseudoephedrine, and 36 times more pressor activity than (-)pseudoephedrine.

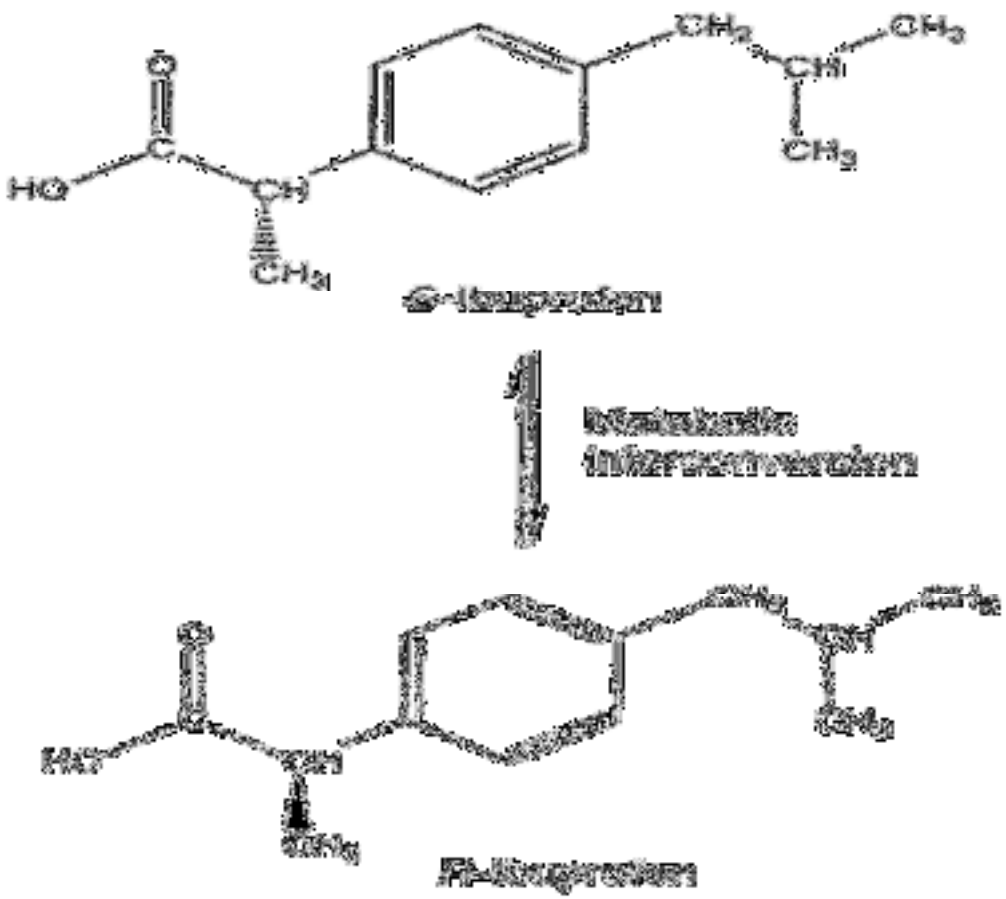
- The dextrorotatory isomers of morphine derivatives are cough suppressants with less risk of addiction, whereas the levorotatory isomers contain the analgesic activity and significant risk of addiction.



- The local anesthetic levobupivacaine 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 good local anesthetic activity.



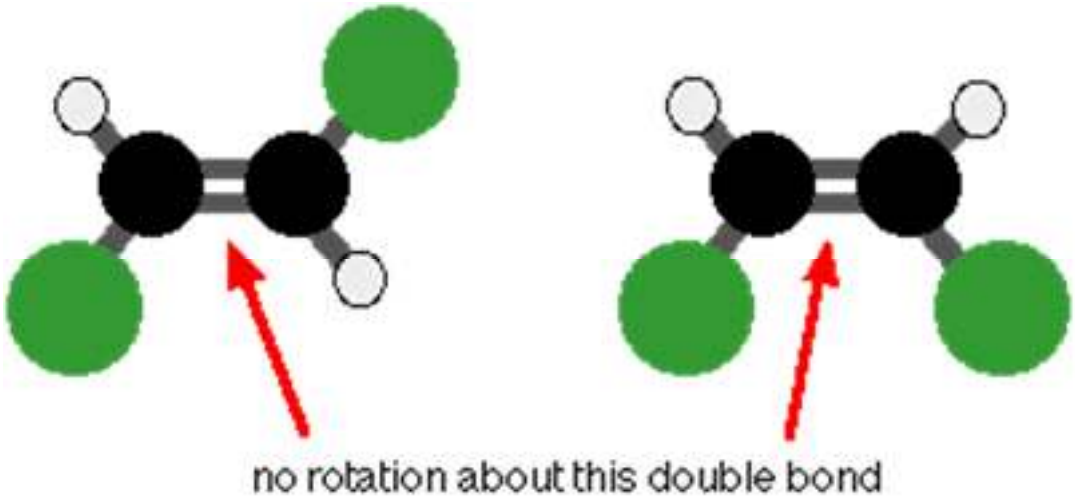
- Sometimes, racemic mixture of drug is approved.
- Ibuprofen is sold as the racemic mixture. The S-enantiomer contains the anti-inflammatory activity by inhibiting cyclooxygenase.
- The *R*-isomer does have centrally acting analgesic activity, but it is converted to the *S* form in vivo.



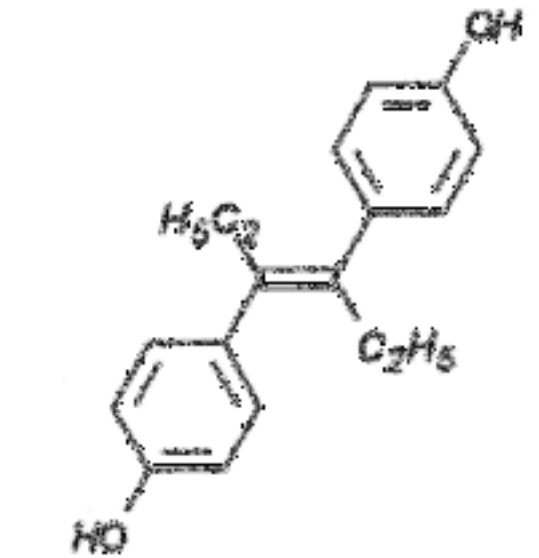
- **Reasons for differences in biological activities of optical isomers:**

- Asymmetric receptors affecting drug affinity.
- Asymmetric metabolizing ezymes affecting biological half lives.
- Asymmetric carrier molecules affecting drug transportation.
- Different physical properties affecting drug distribution

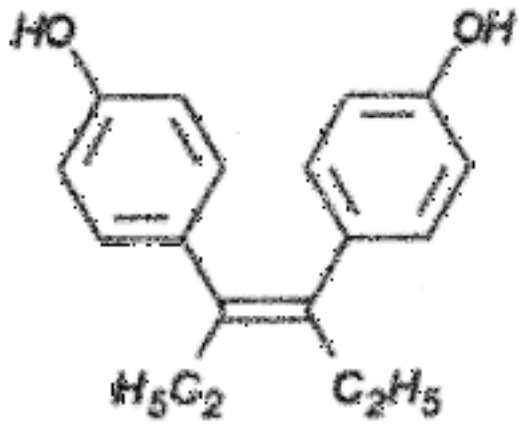
- **Geometrical Isomerism**
- *Geometric isomers*, such as the *cis*- and the *trans*-isomers, hold structural features at different relative positions in space.
- These isomers also have significantly different physical and chemical properties.
- Therefore, their bio-distribution and biological activities are different.



- *trans*-Diethylstilbestrol is estrogenic, whereas the *cis*-isomer is only 7% as active.
- In *trans*-diethylstilbestrol, resonance interactions and minimal steric interference tend to hold the two aromatic rings and connecting ethylene carbon atoms in the same plane.

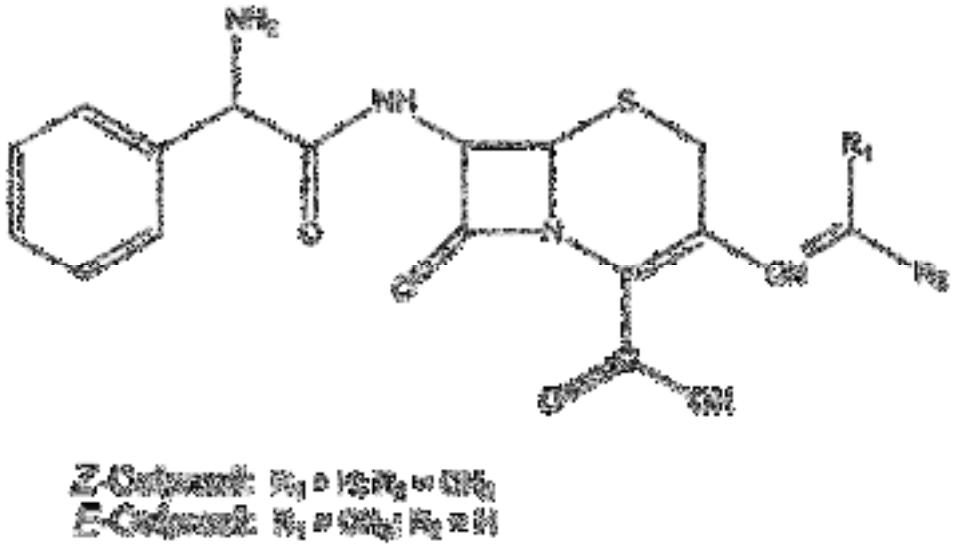


trans-Diethylstilbestrol

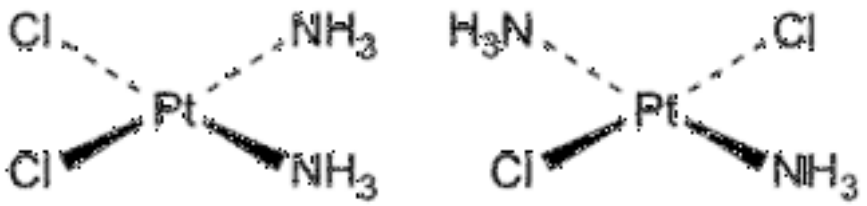


cis-Diethylstilbestrol

- *E*-Cefprozil is more active antibiotic than *Z*-cefprozil.

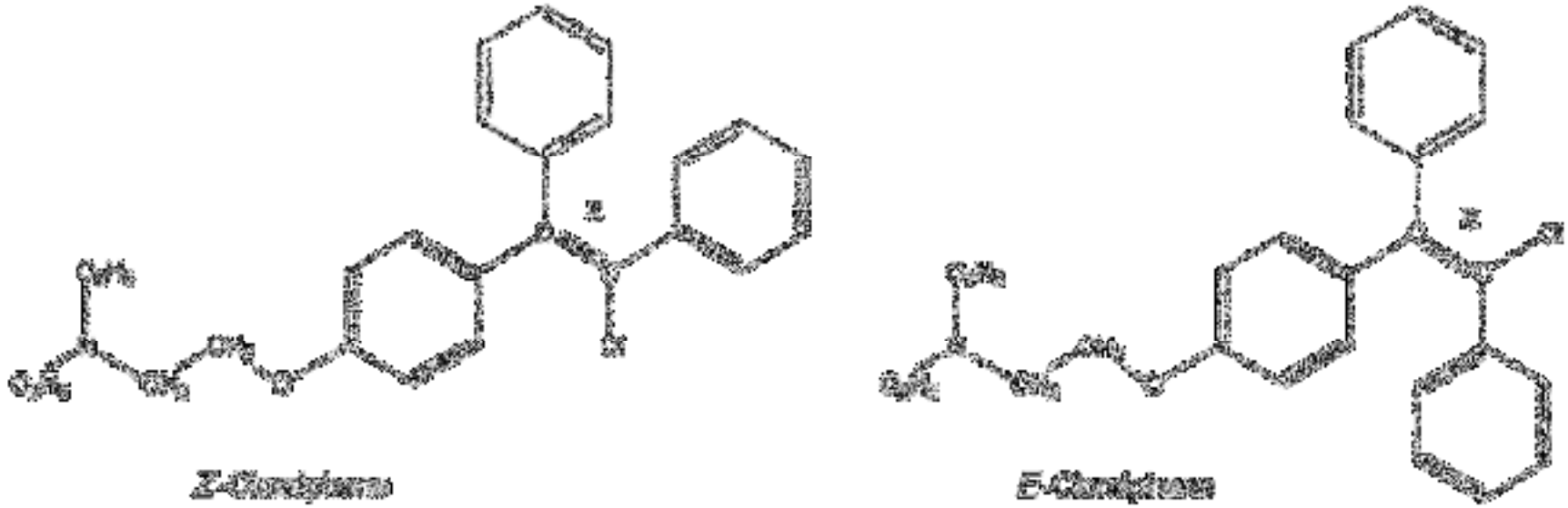


- Cisplatin is more active than transplatin as an anticancer agent.

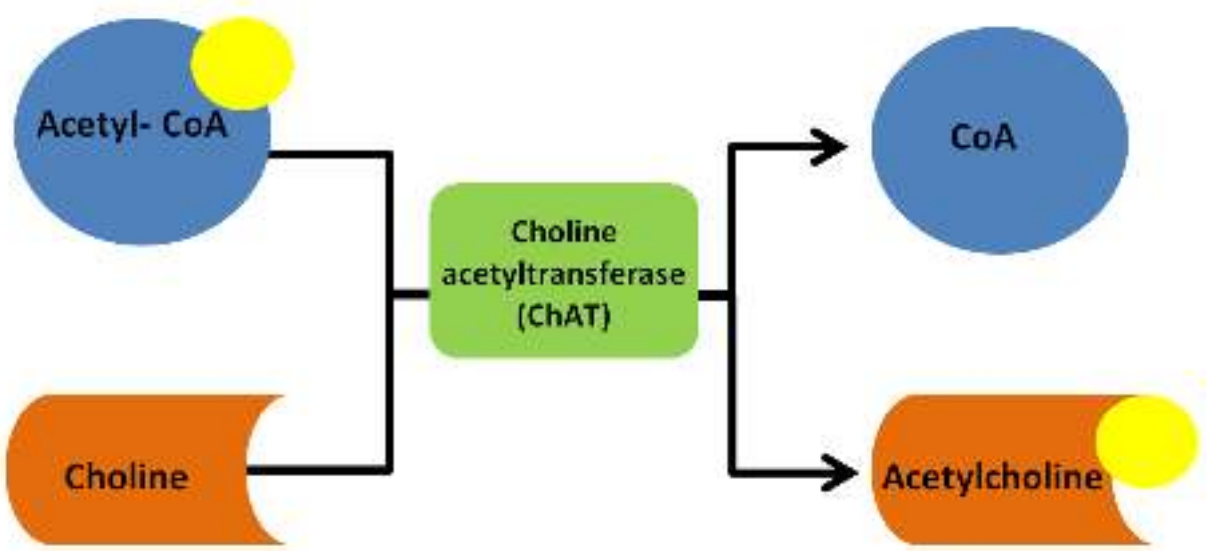


Cisplatin Transplatin

- Clomiphene is chemically a mixture of two geometric isomers, zuclomiphene, the *cis*-isomer, and enclomiphene, the *trans*-isomer.
- These isomers have different estrogenic actions in different tissues.
- Zuclomiphene have weak agonist actions on all tissues.
- Enclomiphene has antagonist actions on uterine tissue, but agonist action on bone tissue.

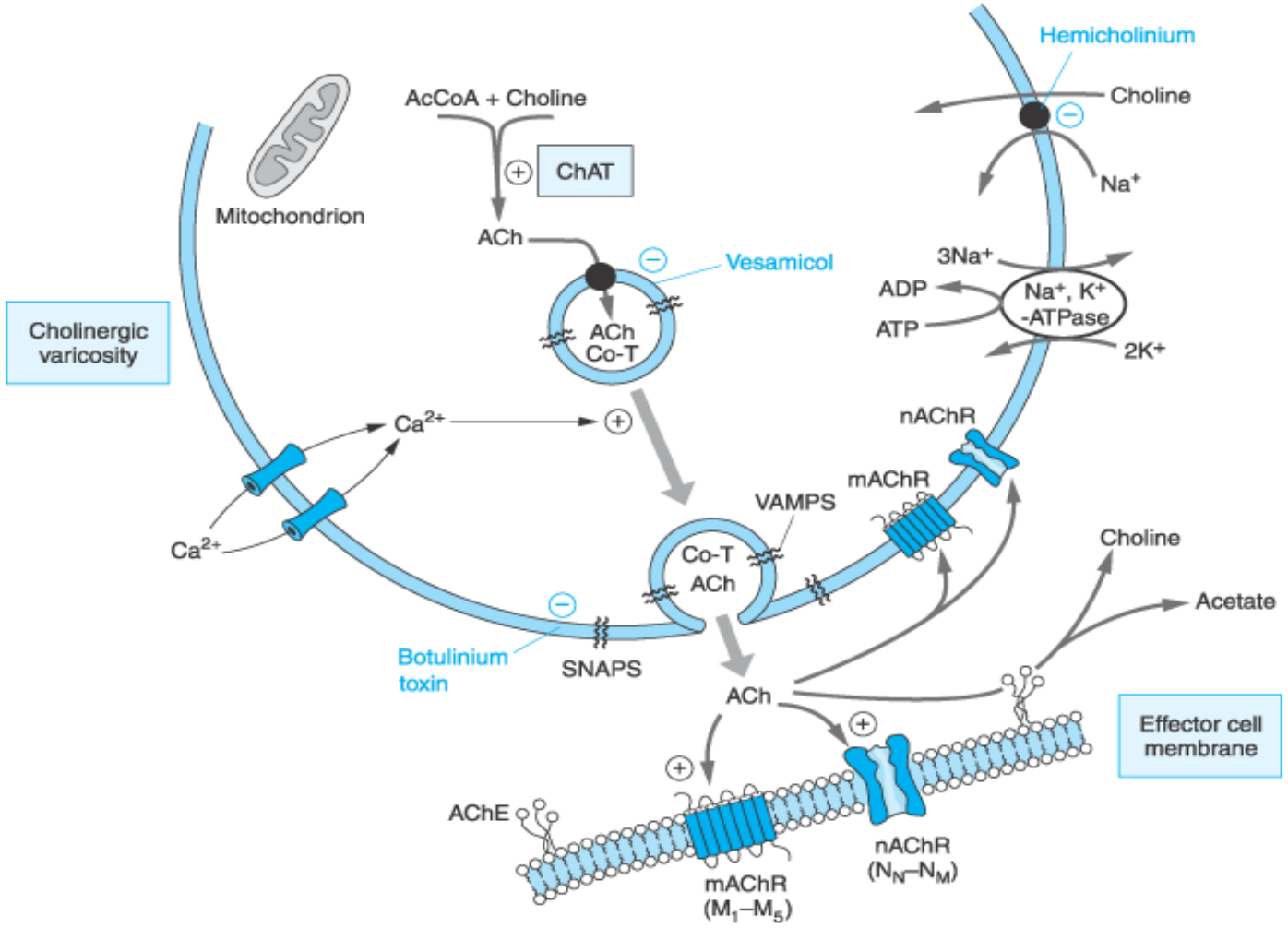


CHOLINERGIC NEUROTRANSMITTERS & PARASYMPATHOMIMETICS



- The synthesis, storage, and release of ACh follow a similar life cycle in all cholinergic synapses, including those at skeletal neuromuscular junctions, preganglionic sympathetic and parasympathetic terminals, postganglionic parasympathetic nerves, postganglionic sympathetic nerves innervating sweat glands in the skin, and in the CNS.

- **The neurochemical events that underlie cholinergic neurotransmission:**



NICOTINIC RECEPTORS

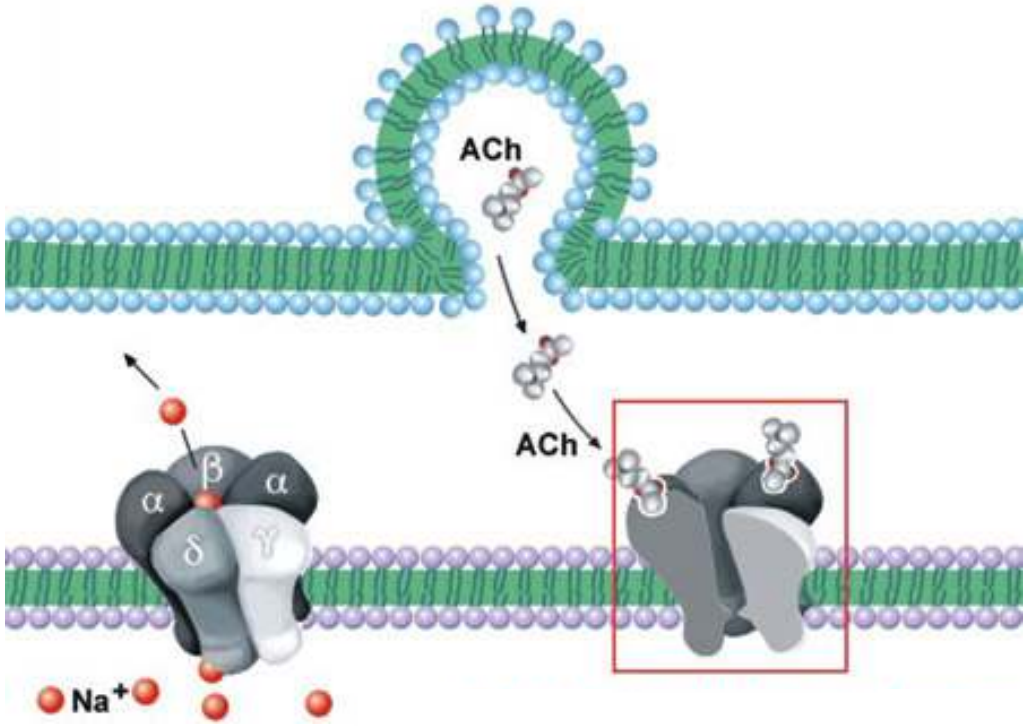
- **Location:**
- These receptors are found at-

➢Skeletal Neuromuscular junction

➢Adrenal Medulla

➢ CNS

➢Autonomic Ganglia

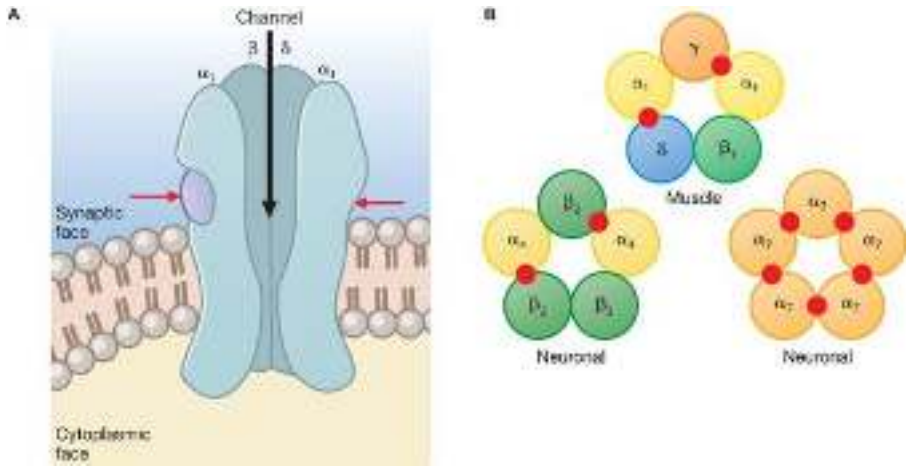


- They play important role in Myasthenia gravis(an autoimmune disease).

- **Types:**

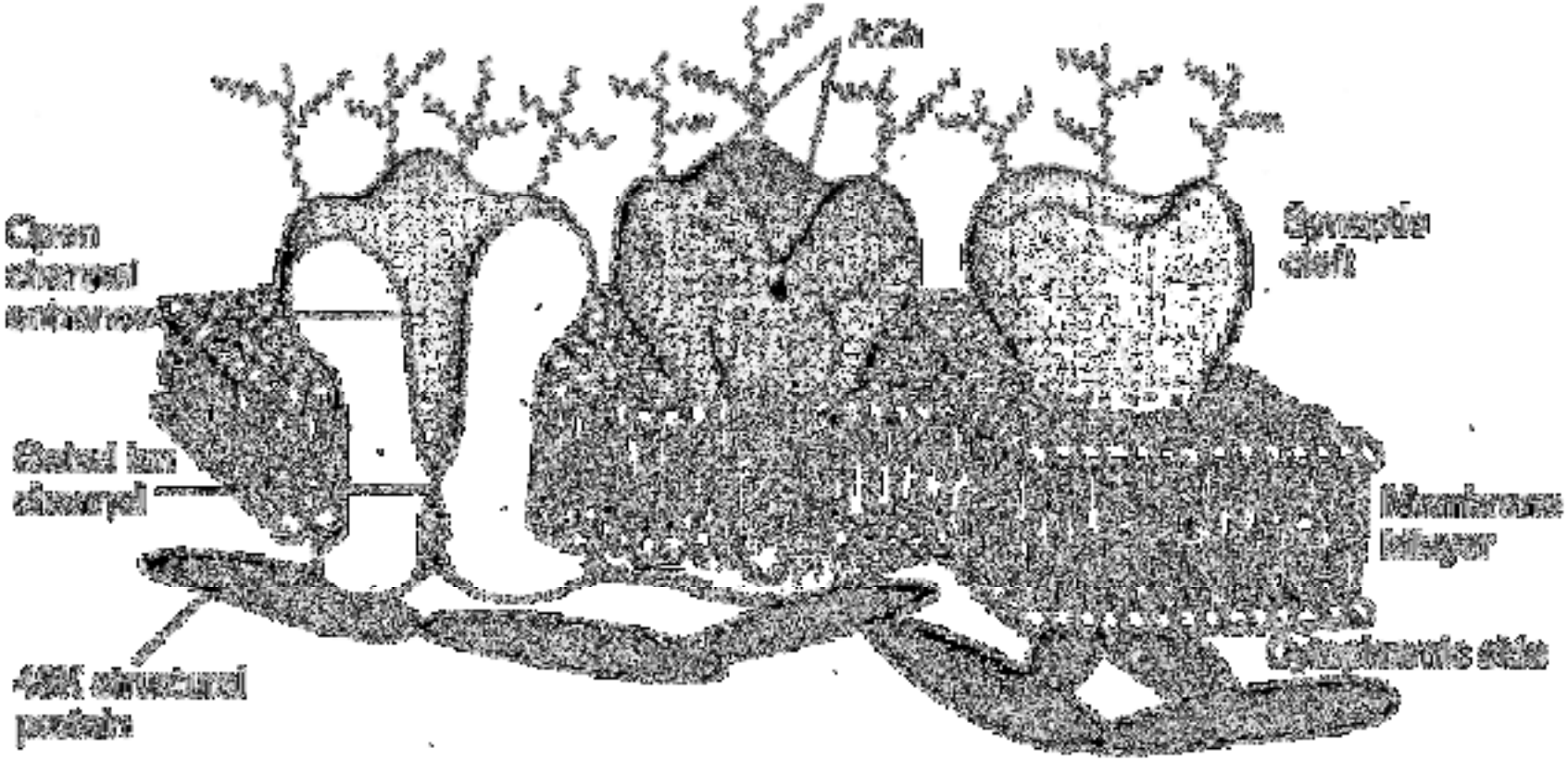
➢Neuronal nicotinic receptors

➢ Muscular nicotinic receptors



- **Neuronal nicotinic receptors** exist as a heteromeric pentamer composed of α and β subunits. Each of these subunits have large number of subtypes.
- **Muscular nicotinic receptor** is a transmembrane glycopeptide made up of four types of subunits α,β,γ and δ.
- **Acetylcholine is the natural ligand** for these receptors and after binding it modulate the passage of ions , principally , K^+ &Na^+ ions.

- **Model of the nicotinic receptor consisting of five protein subunits embedded in a cell membrane, based on electron microscopy and neutron scattering data.**
- ***Jagged lines* represent oligosaccharide chains on the upper part of the receptor.**
- **A 43K protein is bound to the receptor on the cytosolic side of the cell membrane.**
- **The ACh-binding sites are shown on the two-subunit proteins.**



MUSCARINIC RECEPTORS

- Majority of clinically effective cholinergic drugs are either muscarinic agonists or antagonists.
- Muscarinic receptors are found in-

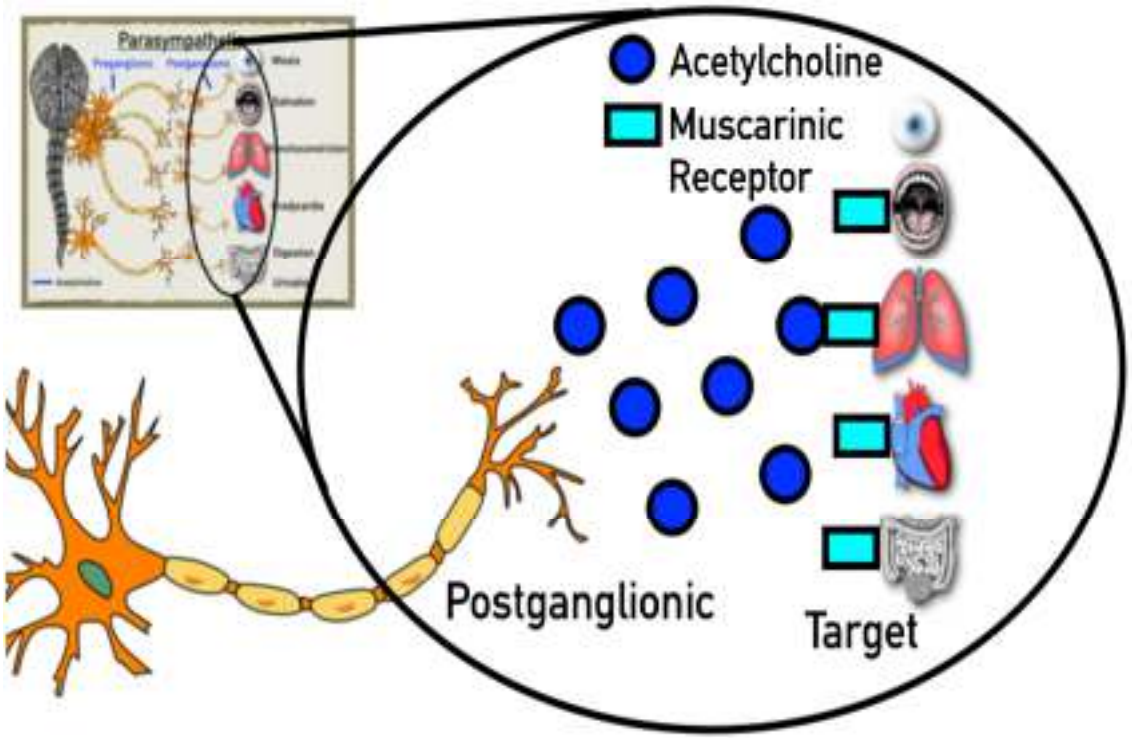
➢ Autonomic ganglia

➢CNS

➢Heart

➢Gastric & Salivary glands

➢Smooth muscles

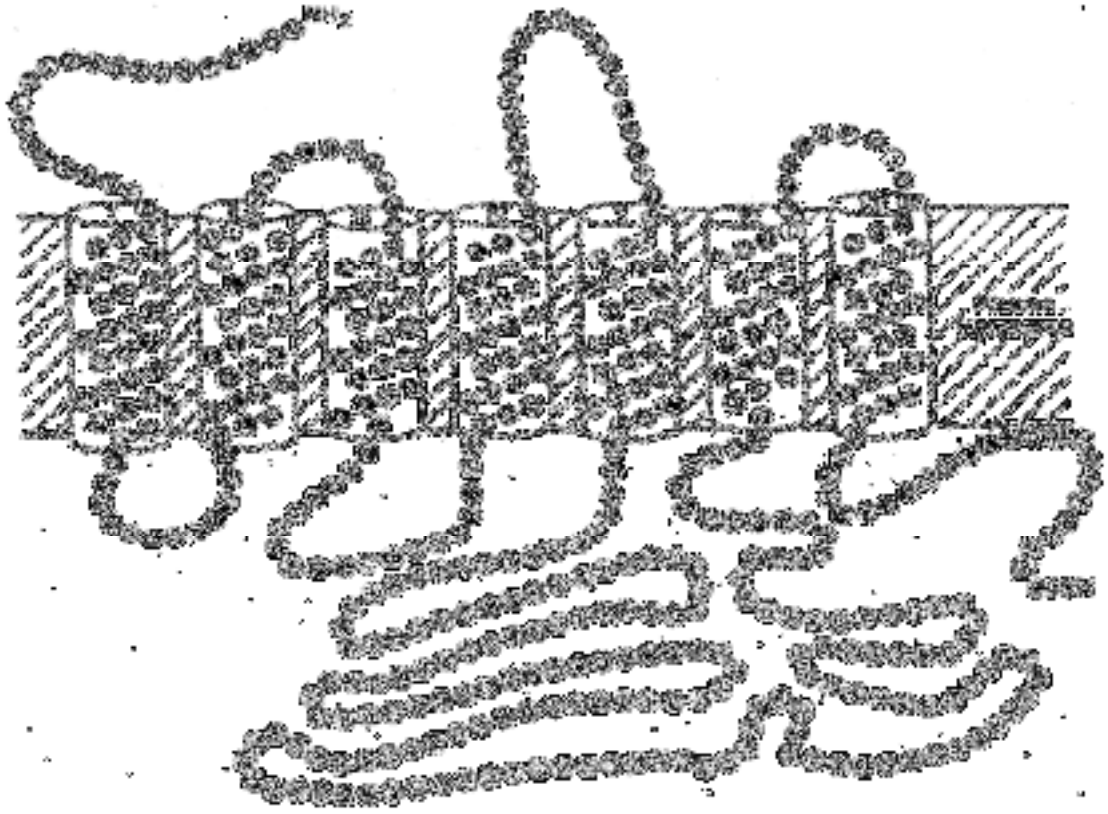


- **Types:**

- There are 5 subtypes of muscarinic receptors present in CNS and other tissues.
- They are M1,M2,M3,M4&M5 and acetylcholine is the natural ligand for all these subtypes.
- Binding of acetylcholine to M1,M3 & M5 results in activation of phospholipase C , A2 & D.
- Activation of phospholipase C stimulates the production of second messengers diacylglycerol and inositol triphosphate (IP3).

- IP3 activation leads to the release of intracellular calcium ions.
- Diacylglycerol , along with calcium, activates protein kinase C which phosphorylates proteins.
- Activation of phospholipase A2 results in release of arachidonic acid and synthesis of eicosanoids.
- Binding of acetyl choline to M2 & M4 results in inhibition of adenyl cyclase.
- This results in a decrease of cAMP, inhibition of calcium channels and activation of potassium channels.
- The result is hyperpolarisation and inhibition of these excitable membranes.

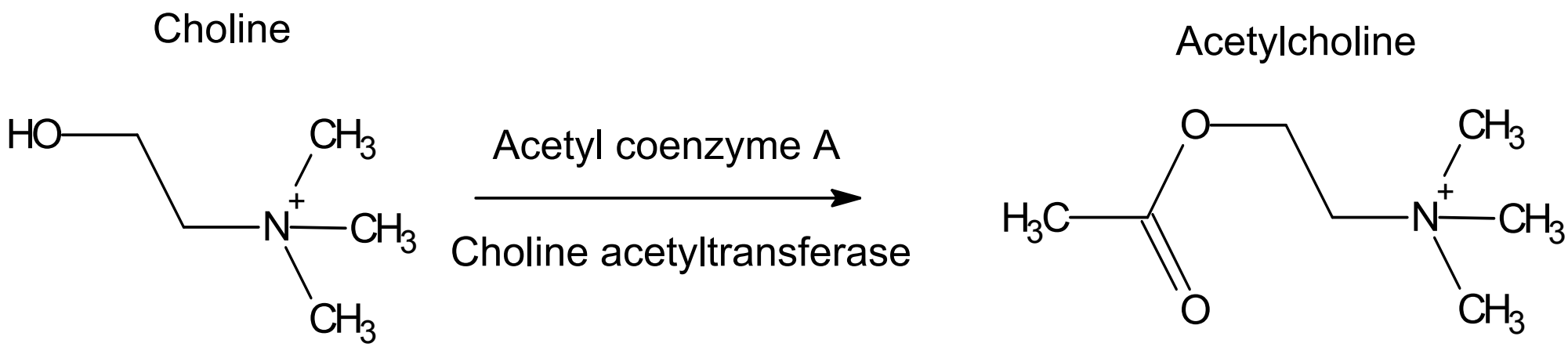
- **Hypothetical model of a muscarinic receptor showing the location of the transmembrane helical protein domains and the extracellular and intracellular domains connecting the 7 α-helical proteins in the membrane.**



- **ACETYLCHOLINE & ITS ANALOGUES (PARASYMPATHOMIMETICS)**

- Acetylcholine is biosynthesized in cholinergic neurons by transfer of acetyl group from acetyl coenzyme A to choline.

- This reaction is catalyzed by choline acetyltransferase.



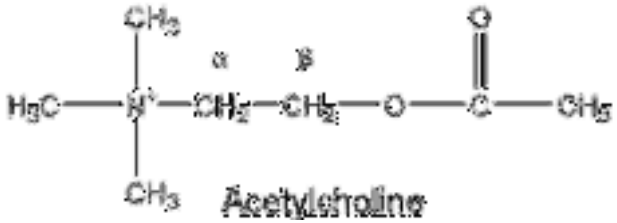
- Most newly biosynthesized acetylcholine is stored in storage vesicles, where it is maintained with ATP along with calcium and magnesium ions.
- Action potential initiates the release of acetylcholine from its storage vesicles.
- Increase in intracellular calcium helps in acetylcholine release.
- Acetylcholine binds with cholinergic receptors present on postsynaptic or presynaptic nerve membranes and produce a response.
- Free acetylcholine that is not bound to receptor is hydrolyzed by acetylcholine esterase enzyme.

MUSCARINIC AGONISTS

- Interaction of cholinergic agonists with muscarinic receptors leads to following responses:

- Contraction of smooth muscle
- Vasodilation
- Increased secretion from exocrine glands
- Decreased heart rate & force of contraction

- **ACETYLCHOLINE:**



- Cholinergic neurotransmitter that acts on both muscarinic and nicotinic receptors.
- It is a poor therapeutic agent due to two reasons:

➢ (i) Lack of receptor specificity ie acts on both receptors.

➢(ii) Poor physiochemical properties associated with ester and quaternary ammonium functional groups.

- **Disadvantages of Acetylcholine :**

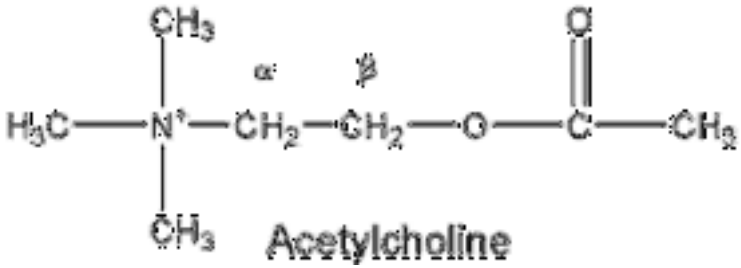
- It is stable in solid crystalline form but undergoes **rapid HYDROLYSIS in aqueous solution**.

- Presence of **ACID/BASE increases the hydrolysis**.

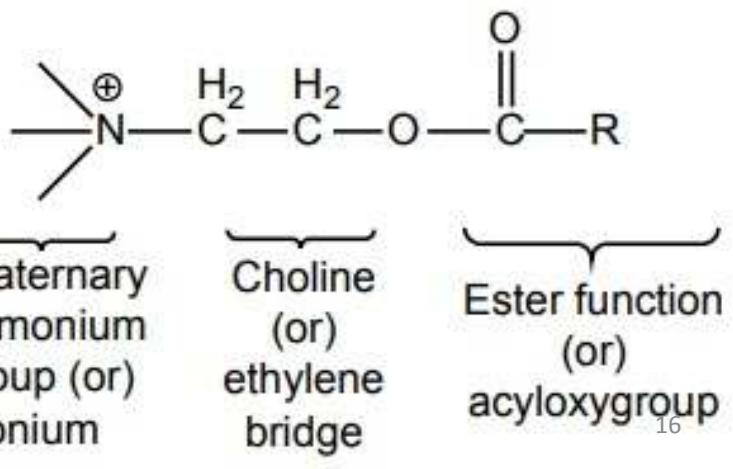
- It is **ORALLY INACTIVE** due to rapid hydrolysis in **acidic stomach**.

- It is **PARENTERALLY INACTIVE** due to **hydrolysis by serum BUTYLCHOLINESTERASE (PSEUDOCHOLINESTERASE)**.

- **Quaternary ammonium group** increases acetylcholine **HYDROPHILICITY**(increased water solubility).
- It is **unable to cross the lipid membranes** due to **hydrophilicity and ionic character**.
- It is **TOPICALLY INACTIVE** because it is **NOT LIPOPHILIC** enough to penetrate cornea(ocular surgery).



Acetylcholine



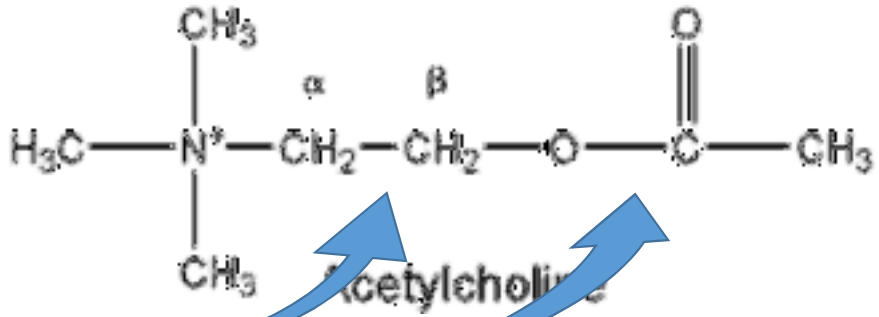
DESIGN OF ACETYLCHOLINE ANALOGUES-SAR

- It is necessary to design compounds that would serve as therapeutic alternatives to acetylcholine.
- To design analogues, acetylcholine structure can be divided into three parts for structural modifications:

➢ Modification of Quaternary ammonium group

➢ Modification of Ethylene bridge

➢ Modification of Acyloxy group



- **Modification of Quaternary Ammonium group:**

1. Analogues in which quaternary nitrogen atom was replaced by sulfur or phosphorus exhibited less activity indicating the importance of positive charge on nitrogen.

2. Compounds in which all the three methyl groups on nitrogen are replaced by large alkyl groups are inactive as muscarinic agonists.

3. When the methyl groups are replaced by three ethyl groups, the resulting group is a cholinergic antagonist.

4. Replacement of only one methyl group by an ethyl or propyl group gives a compound that is less active than acetylchoine.

5. Replacement of quaternary nitrogen atom by tertiary , secondary or primary amine resulted in inactive compounds.

Summary:

- The **trimethylammonium group is the optimal functional moiety for activity**, although some significant exceptions are known (e.g., pilocarpine, arecoline, nicotine, and oxotremorine).
- Phosphonium, sulfonium, arsenonium isosteres, or substituents larger than methyl on the nitrogen increase the size of the onium moiety, produce diffusion of the positive charge, and interfere sterically with proper drug–receptor interaction, resulting in decreased activity.

- The onium group contributes to the **receptor affinity** of the molecule.
- Molecular modeling data show the **binding site to be a negatively charged aspartic acid residue** in the third of the seven transmembrane helixes of the muscarinic receptor.
- Hydrophobic pockets are located in helices 4, 5, 6, and 7 of the muscarinic receptor.

- **Modification of Ethylene Bridge:**

1. There should be no more than 5 atoms present between quaternary nitrogen and terminal hydrogen atom of acyloxy group for therapeutic muscarinic activity.

2. Muscarinic receptors can not accommodate molecules larger than acetylcholine.

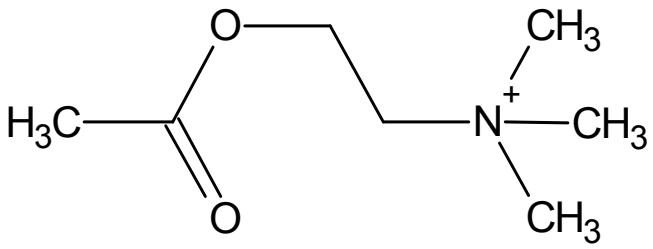
Although larger molecules bind to the receptor, they lack agonist or antagonist properties.

3. Replacement of hydrogen atoms of the ethylene bridge by alkyl groups larger than methyl resulted much less active compounds.

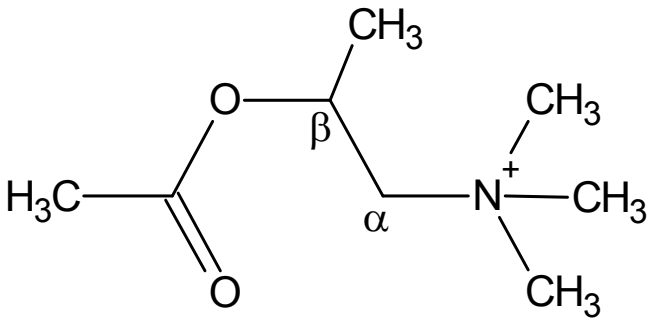
4. Introduction of methyl group on the carbon β to the quaternary nitrogen resulted in **METHACHOLINE** which has much greater muscarinic than nicotinic selectivity. Its potency is equal to acetylcholine.

5. A methyl group on carbon α to the quaternary nitrogen afforded acetyl-α-methylcholine which is less active than acetylcholine.

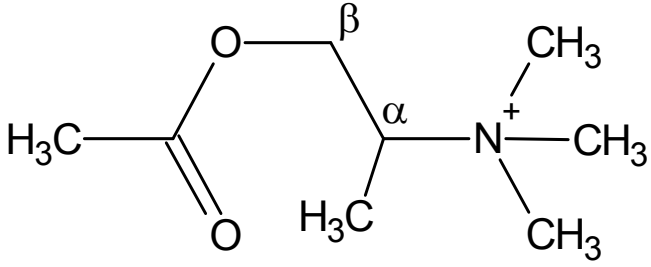
Acetylcholine



Methacholine
(Acetyl - β – methylcholine)



Acetyl - α -methylcholine

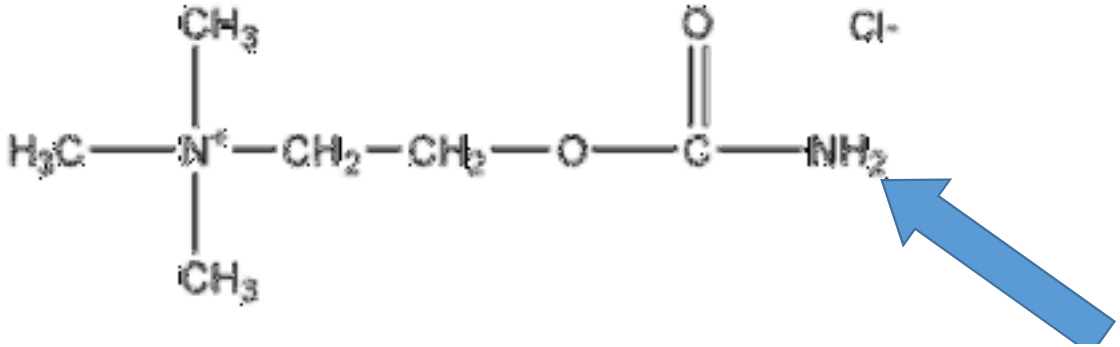


- **Modification of Acyloxy group:**

1. Replacement of acetyl group by higher groups like propionyl or butyryl resulted in less potent compounds.

2. Choline esters of aromatic or higher molecular weight acids possess cholinergic antagonist activity.

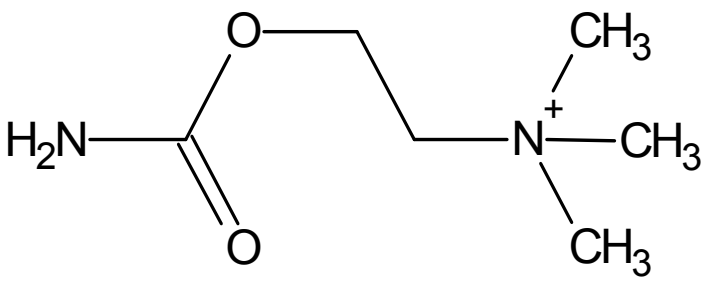
3. Analogues with greater resistance to hydrolysis were developed by synthesis of the carbamic acid ester of choline **(CARBACHOL)**.



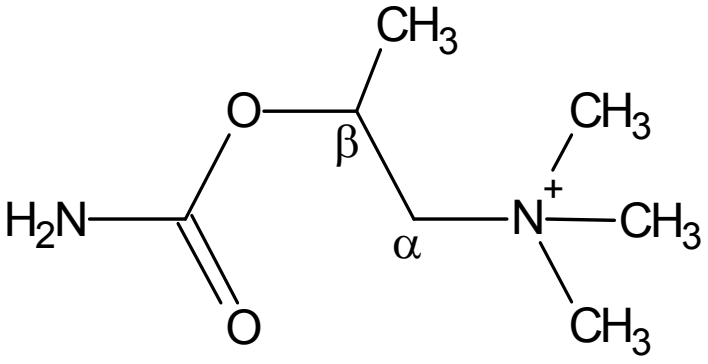
- Carbachol is a potent cholinergic agonist possessing both muscarinic and nicotinic activity.
- It is orally active and less readily hydrolysed by gastric acid, acetylcholinesterase and butyrylcholinesterase.

4. This structural modification was carried on methacholine , which produced **BETHANECHOL**. It is an orally effective potent muscarinic agonist with almost no nicotinic activity at therapeutic doses.

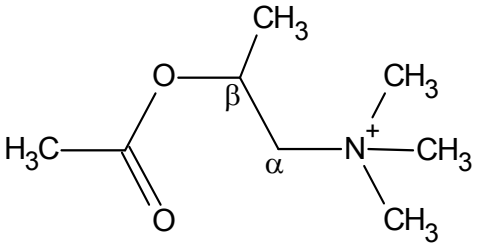
Carbachol



Bethanechol



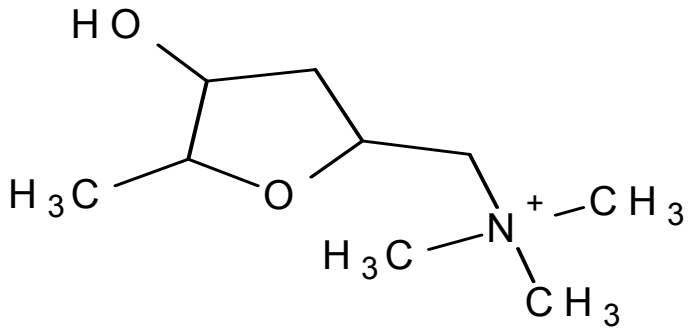
Methacholine



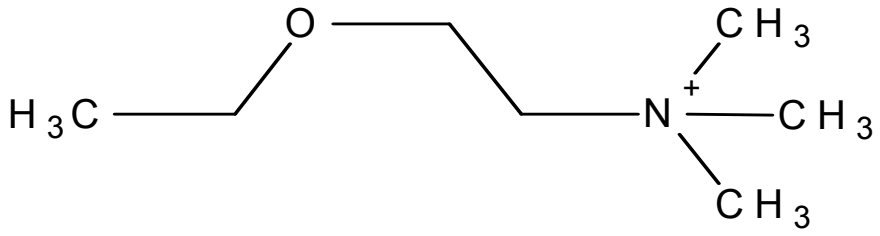
5. **Muscarine** is a natural alkaloid obtained from red mushroom *Amanita muscaria.*

- It is a potent cholinergic agonist.
- Chemically it is a furan(cyclic ether) derivative and this lead to the design of ETHERS of choline.
- The activity of ethers indicate that ester group of acetyl group is not required for muscarinic agonist activity.

Muscarine



Choline ethyl ether



DIRECT-ACTING CHOLINOMIMETICS

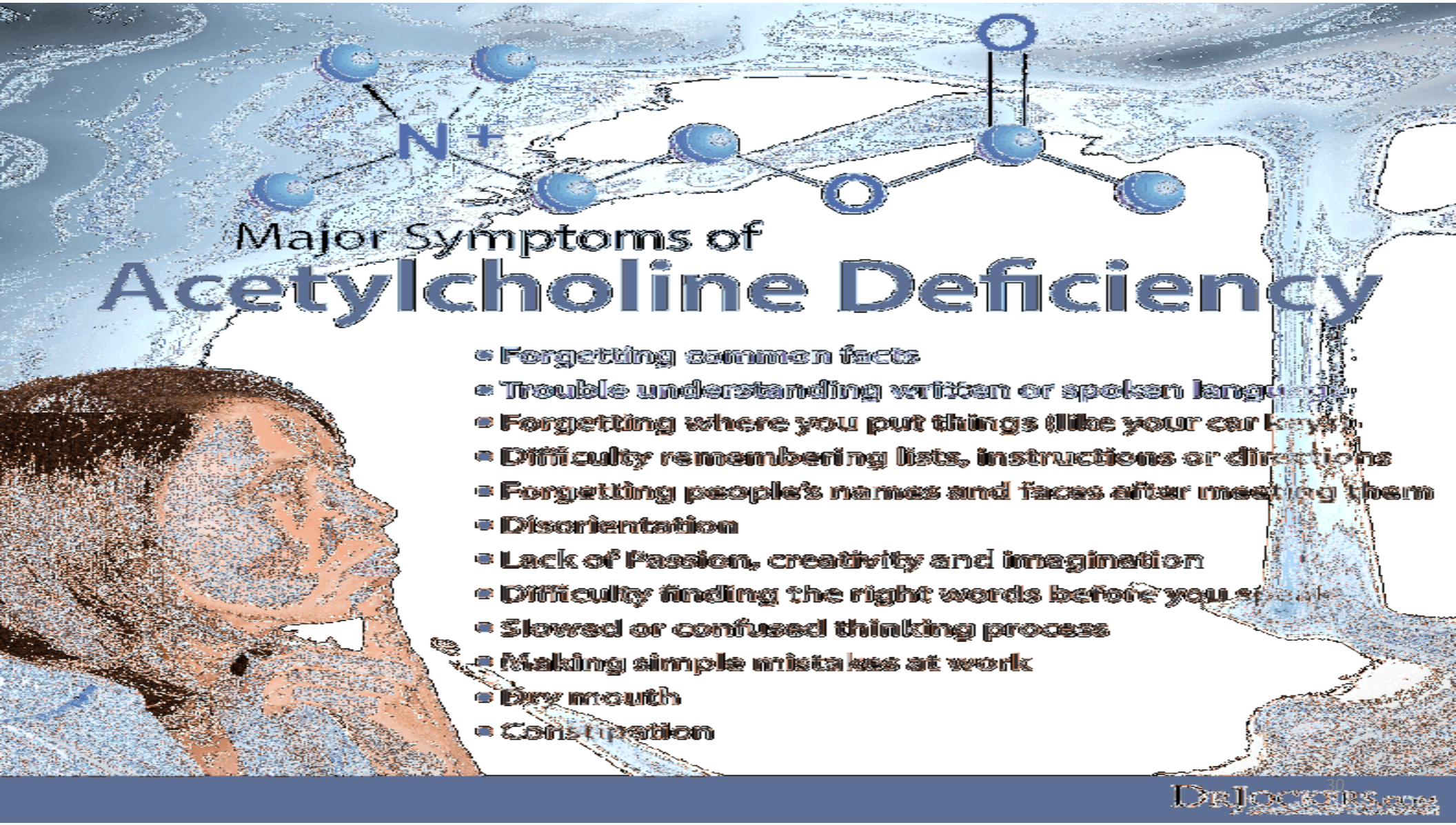
- Direct-acting cholinomimetics are drugs that act directly by stimulating cholinergic receptors.
- These drugs are divided into drugs that stimulate muscarinic or nicotinic receptors.
- Drugs whose efficacy is primarily connected to stimulation of muscarinic receptors, including choline esters, i.e. acetylcholine and its structural analogues, which are methacholine, carbachol, betanechol, and natural alkaloids muscarine and pilocarpine.
- Drugs whose action is based on stimulation of nicotinic receptors include the alkaloids nicotine and lobeline.

- ***Acetylcholine Chloride:***

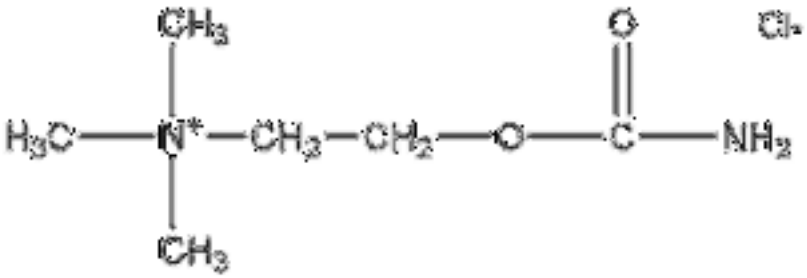
- It exerts a powerful stimulant effect on the parasympathetic nervous system.
- It is a cardiac depressant and an effective vasodilator.
- Stimulation of the vagus and the parasympathetic nervous system produces a tonic action on smooth muscle and induces a flow from the salivary and lacrimal glands.

- Its cardiac-depressant effect results from (a) a negative chronotropic effect that causes a decrease in heart rate and (b) a negative inotropic action on heart muscle that produces a decrease in the force of myocardial contractions.
- The vasodilatory action of ACh is primarily on the arteries and the arterioles, with distinct effect on the peripheral vascular system.
- Bronchial constriction is a characteristic side effect when the drug is given systemically.
- It is a short-acting miotic when introduced into the anterior chamber of the eye and is especially useful after cataract surgery during the placement of sutures.

- When applied topically to the eye, it has little therapeutic value because of poor corneal penetration and rapid hydrolysis by AChE.
- One of the most effective antagonists to the action of ACh is **atropine**, a nonselective muscarinic antagonist.
- Atropine blocks the depressant effect of ACh on cardiac muscle and its production of peripheral vasodilation (i.e., muscarinic effects) but does not affect the skeletal muscle contraction (i.e., nicotinic effect) produced.
- ACh chloride is a hygroscopic powder that is available in an admixture with mannitol to be dissolved in sterile water for injection shortly before use.

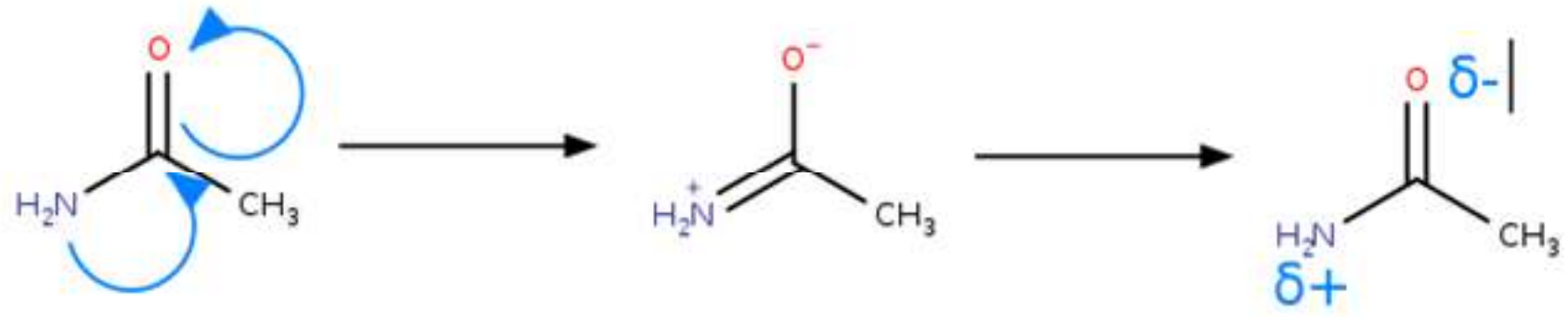

Major Symptoms of
Acetylcholine Deficiency
• Forgetting common facts
• Trouble understanding written or spoken lang
• Forgetting where you put things (like your car k
• Difficulty remembering lists, instructions or dir
• Forgetting people's names and faces after meeting them
• Disorientation
• Lack of Passion, creativity and imagination
• Difficulty finding the right words before you s
• Slowed or confused thinking process
• Making simple mistakes at work
• Dry mouth
• Constipation
DrJockers.com

- ***CARBACHOL:***
- *IUPAC*- 2-carbamoyloxy-*N*,*N*,*N*-trimethylethyl ammonium chloride
- It is nonspecific in its action on muscarinic receptor subtypes.
- Its pharmacological activity is similar to that of ACh.
- It is an ester of choline and thus possesses both muscarinic and nicotinic properties.
- It can also act indirectly by promoting release of ACh and by its weak anticholinesterase activity.



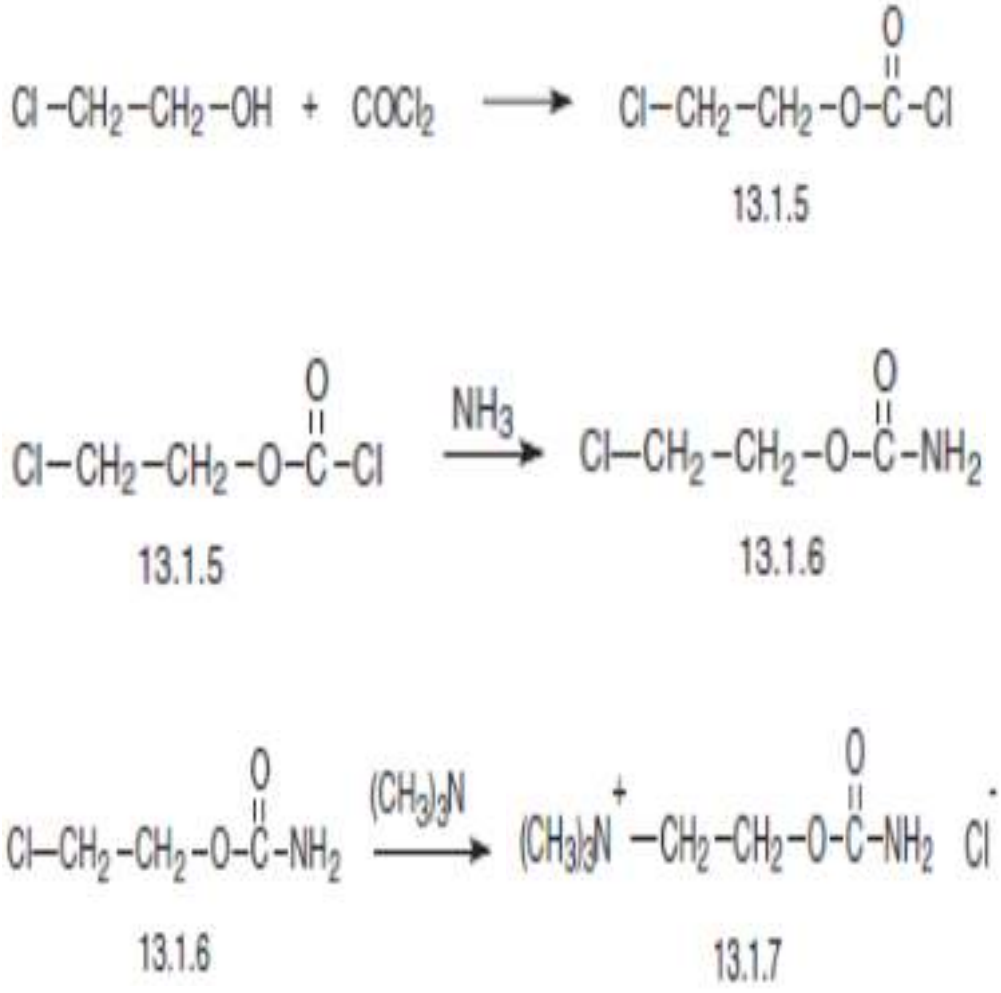
- Carbachol forms a carbamyl ester in the active site of AChE (inactivating enzyme), which is hydrolysed more slowly than an acetyl ester.
- It also exhibits weak anticholinesterase activity.
- Therefore its duration of action is prolonged.
- It is used in the treatment of GLAUCOMA and induction of miosis in ocular surgery.

- Carbachol differs chemically from ACh in its stability to hydrolysis.
- The carbamyl group of carbachol decreases the electrophilicity of the carbonyl and, thus, can form resonance structures more easily than ACh can.
- The result is that carbachol is less susceptible to hydrolysis and, therefore, more stable in aqueous solutions.



Synthesis of Carbachol

- Carbachol (13.1.7), is made by reacting 2-chloroethanol with phosgene, which forms 2-chloroethyl chloroformate (13.1.5).
- Upon reaction with ammonia, it turns into the corresponding amide (13.1.6), which is further reacted with an equimolar quantity of trimethylamine, giving carbachol (13.1.7).



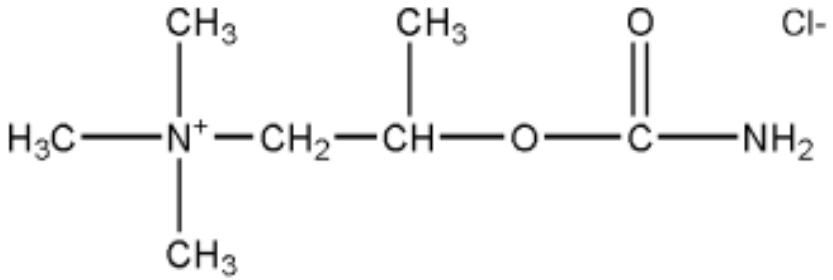
- ***BETHANECHOL CHLORIDE:***

- IUPAC- (2-hydroxypropyl) trimethylammonium chloride carbamate.

- It is nonspecific in its action on muscarinic receptor subtypes but appears to be more effective at M3 receptors.

- It has pharmacological properties similar to those of methacholine.

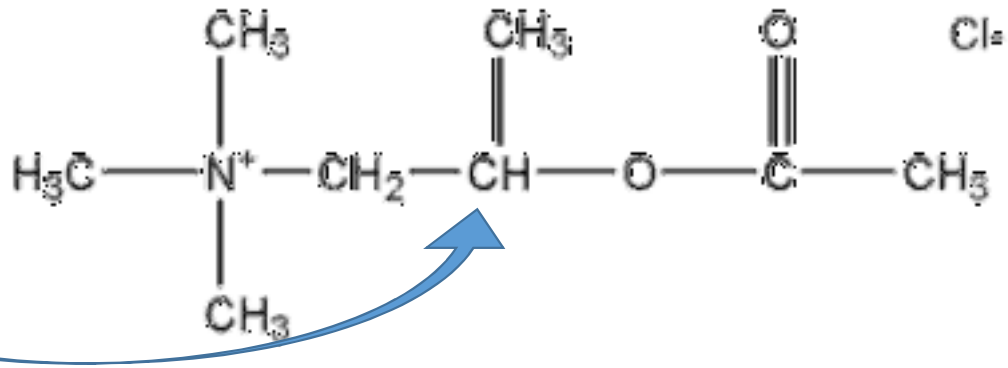
- Both are esters of β-methylcholine and have very weak nicotinic activity.



- Bethanechol is inactivated more slowly by AChE in vivo than is methacholine.
- It is a carbamyl ester and is expected to have stability in aqueous solutions similar to that of carbachol.
- The main use of bethanechol chloride is in the relief of urinary retention and abdominal distention after surgery.
- The drug is used orally and by subcutaneous injection.

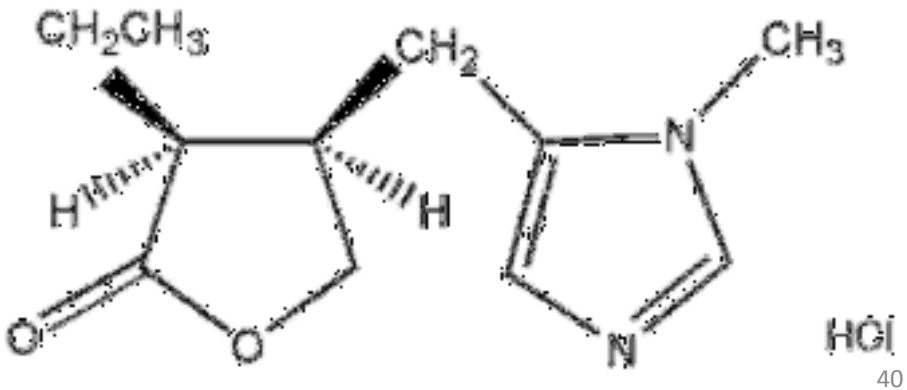
- It must never be administered by intramuscular or intravenous injection because of the danger from cholinergic over stimulation and loss of selective action.
- Proper administration of the drug is associated with low toxicity and no serious side effects.
- Bethanechol chloride should be used with caution in asthmatic patients.
- When used for glaucoma, it produces frontal headaches from the constriction of the sphincter muscle in the eye and from ciliary muscle spasms.
- Its duration of action is 1 hour.

- ***METHACHOLINE CHLORIDE:***
- ***IUPAC-*** (2-hydroxypropyl)trimethylammonium chloride acetate
- Acetyl β-methylcholine chloride or, acetyl ester of β-methylcholine.
- Unlike ACh, methacholine has sufficient stability in the body to give sustained parasympathetic stimulation.
- This action is accompanied by little (1/1,000 that of ACh) or no nicotinic effect.
- **Asymmetric center**

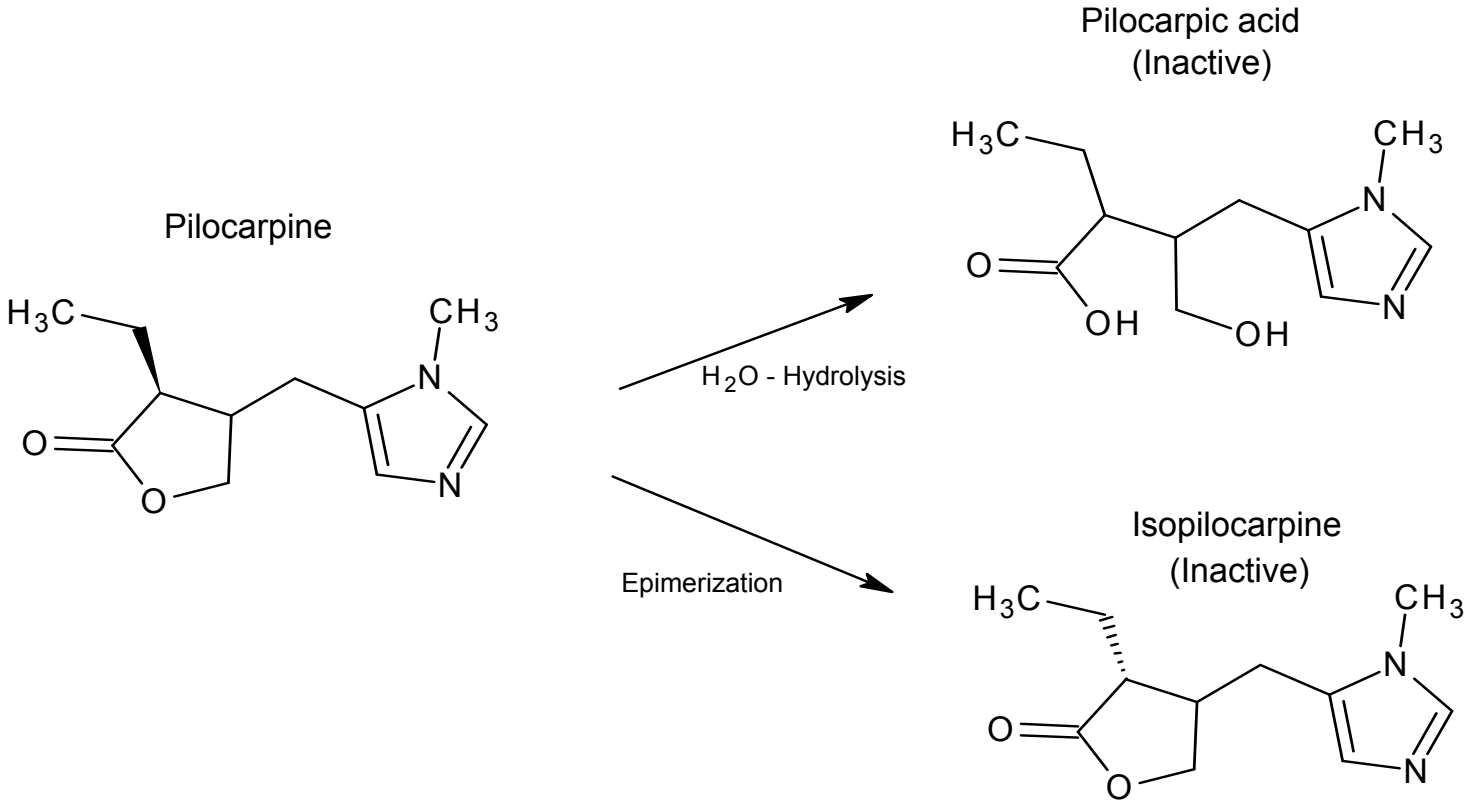


- Methacholine can exist as S(*+*) and R(-) enantiomers.
- Its muscarinic activity resides principally in the S(*+*)-isomer.
- The (*S*)/(*R*) ratio of muscarinic potency for these enantiomers is 240:1.
- But the chemical is used as the racemic mixture.
- S(*+*) enantiomer is hydrolyzed by AChE, whereas the (*R*)(-)-isomer is not.
- It is used via inhalation for the diagnosis of asthma.

- **PILOCARPINE HYDROCHLORIDE:**
- Pilocarpine is an alkaloid obtained from the dried leaflets of *Pilocarpus jaborandi* or *P. microphyllus.*
- It is a nonselective agonist on the muscarinic receptors.
- It is the drug of choice for open-angle glaucoma.
- It is also used in the treatment of Xerostomia(dryness of mouth) caused by radiation therapy of head and neck.

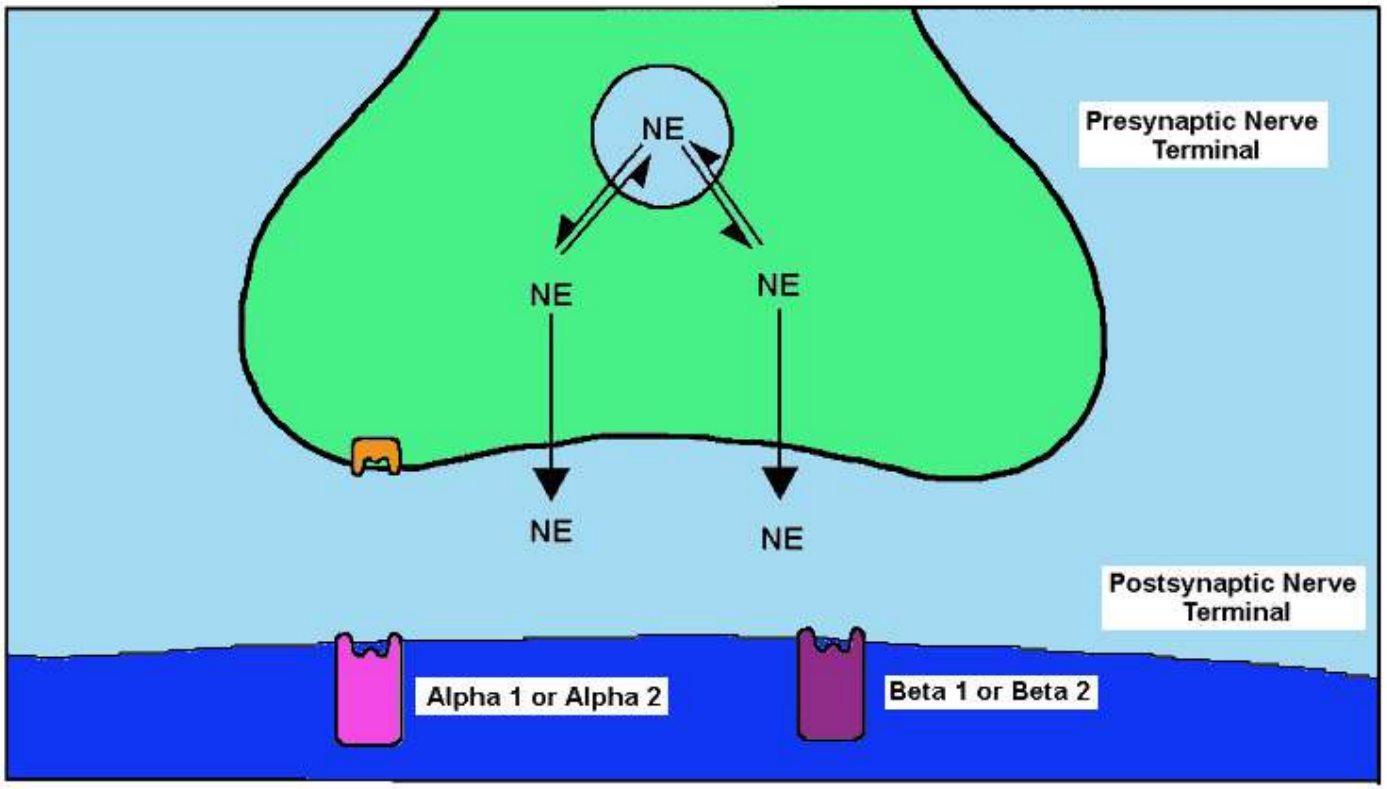


- Because of its lactone structure , it undergoes hydrolysis in aqueous solution to give pilocarpic acid that is inactive .
- It also undergoes epimerization to give isopilocarpine (inactive).



- It acts on M3 receptors in smooth muscle to cause contractions in the gut, trachea, and eye.
- In the eye, it produces pupillary constriction (miosis) and a spasm of accommodation.
- These effects are valuable in the treatment of glaucoma.
- The pupil constriction and spasm of the ciliary muscle reduce intraocular tension by establishing better drainage of ocular fluid.
- Pilocarpine is used as a 0.5% to 0.6% solution (i.e., of the salts) in treating glaucoma.
- Systemic effects include copious sweating, salivation, and gastric secretion.

Direct Acting Sympathomimetics

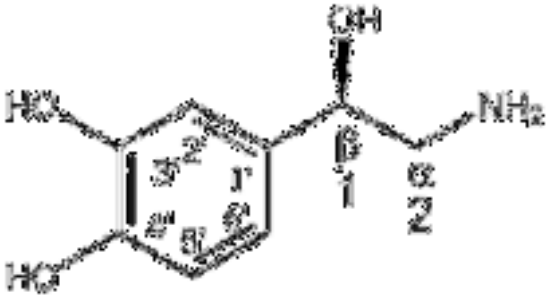


- Direct acting sympathomimetics: Nor-epinephrine, Epinephrine, **Phenylephrine***, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, **Salbutamol***, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.

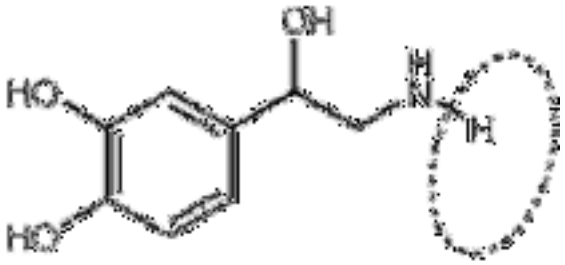
- *** Synthesis**

NOREPINEPHRINE

- It differs from dopamine only by addition of a 1-OH substituent and from epinephrine only by lacking the *N*-methyl group.
- It is polar and rapidly metabolized by both COMT and MAO.
- This results in poor oral bioavailability and short duration of action (1 or 2 minutes even when given intravenously).



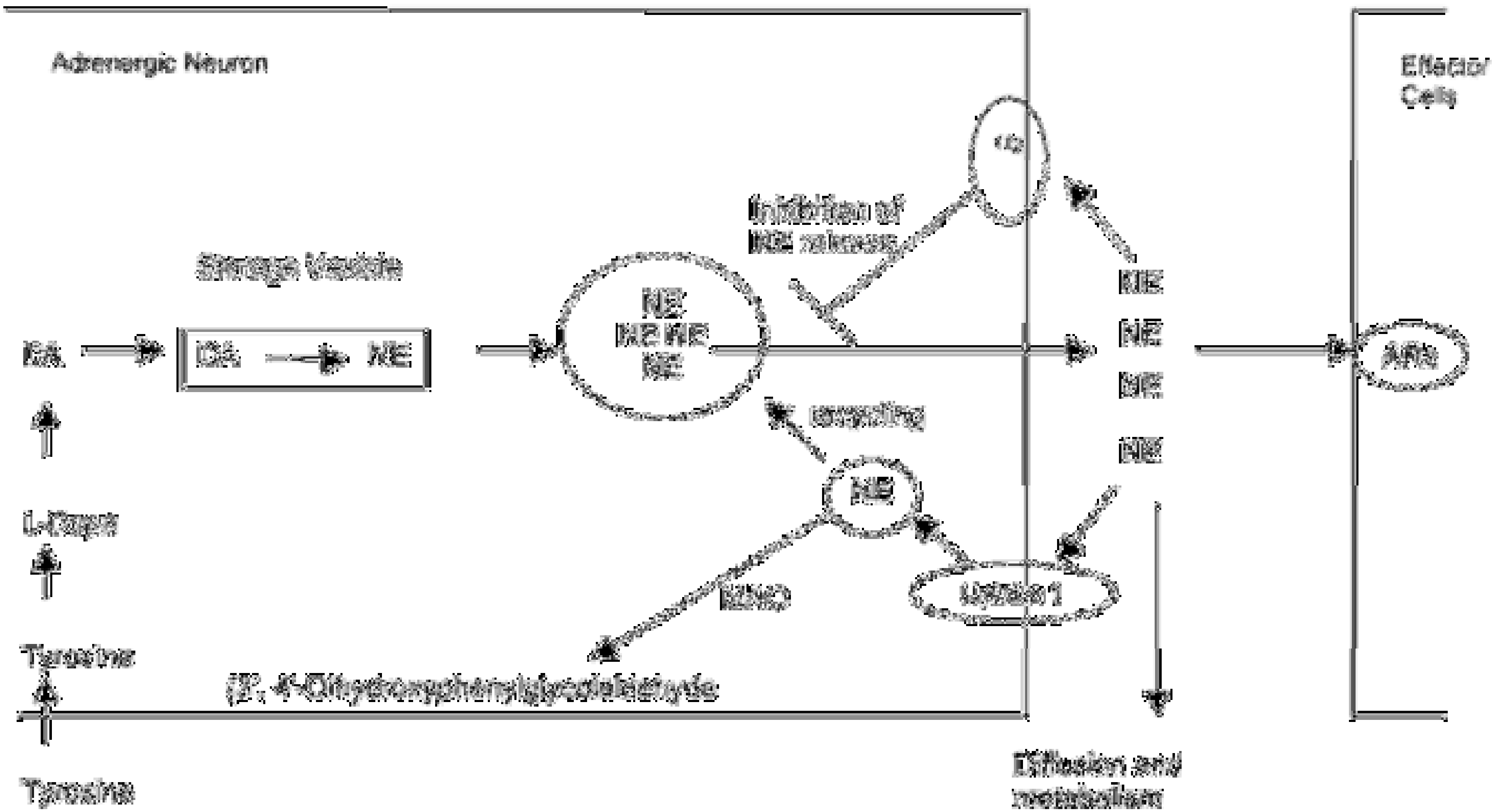
Norepinephrine (NE)



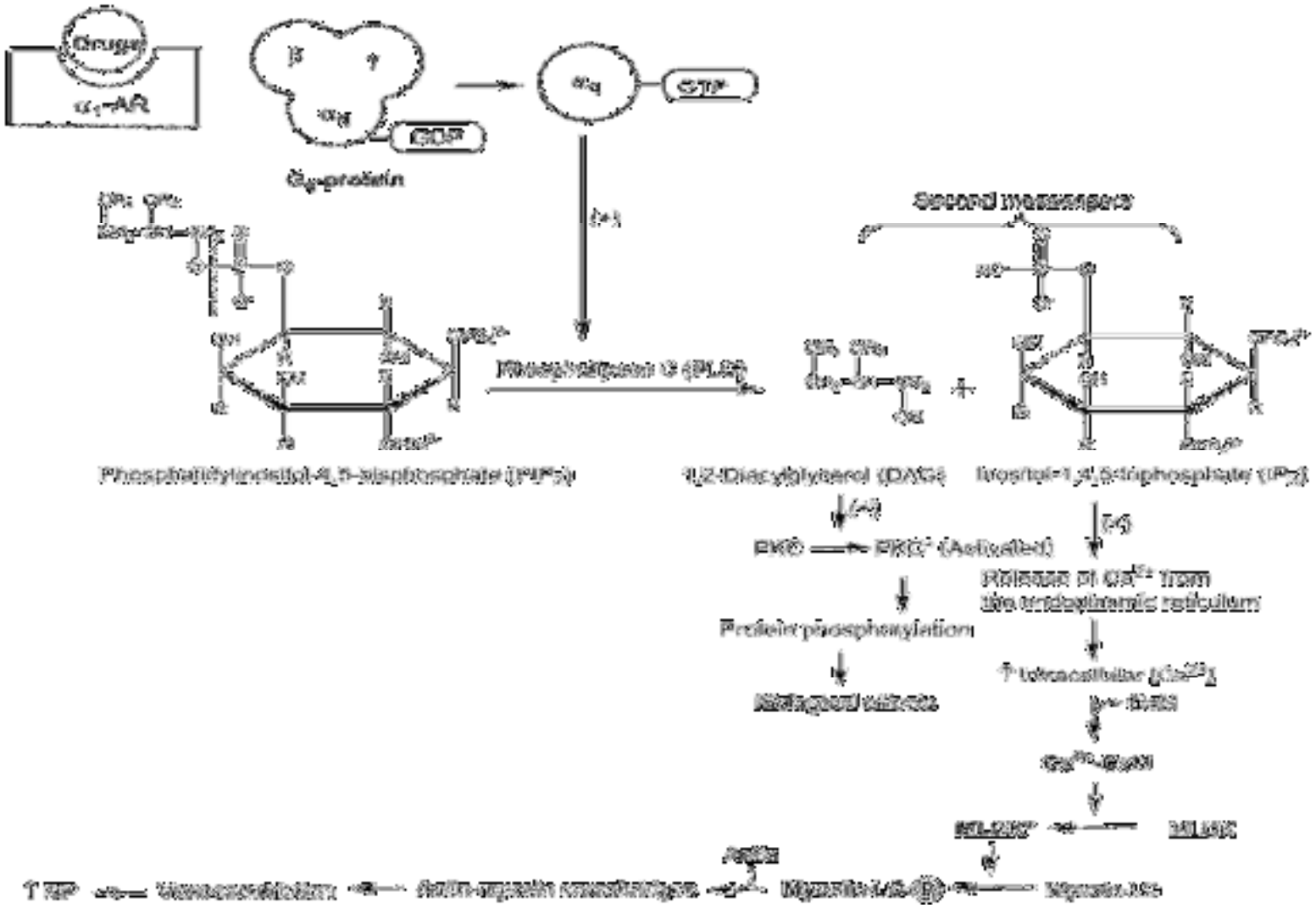
Norepinephrine (NE)
α > β agonist
α agonist

- It is a stimulant of α1-, α2-, and β1-adrenoceptors (notice that lacking the *N*-methyl group results in lacking β2- and β3-activity).
- It is used to **counteract various hypotensive crises**, because **its α-activity raises blood pressure.**
- It is used as an **adjunct treatment in cardiac arrest** because **its β-activity stimulates the heart**.
- It has **limited clinical application** caused by the **nonselective nature of its activities**.

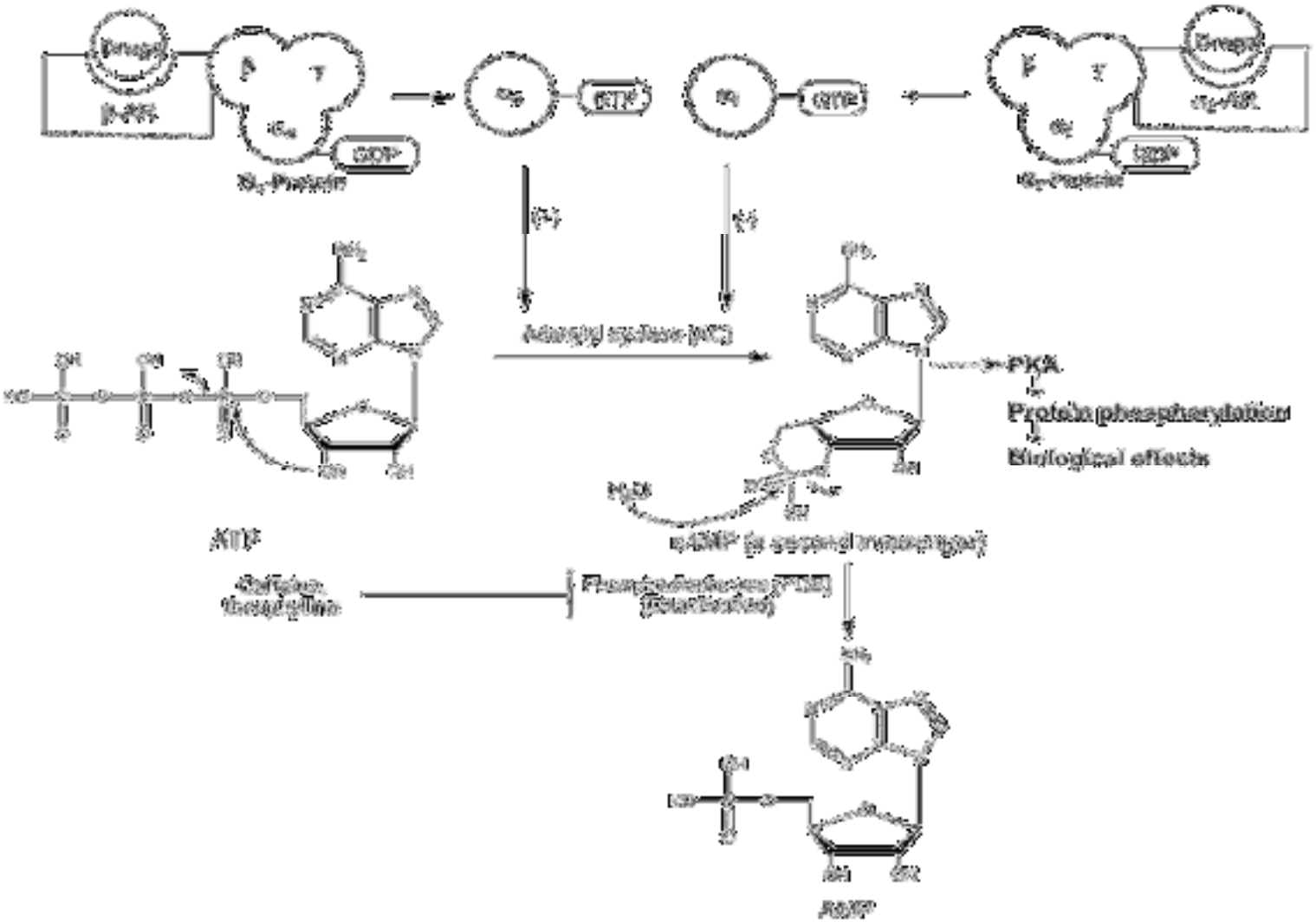
• **Life cycle of Norepinephrine:**



- **Mechanism of α1-receptor mediated signal transduction:**

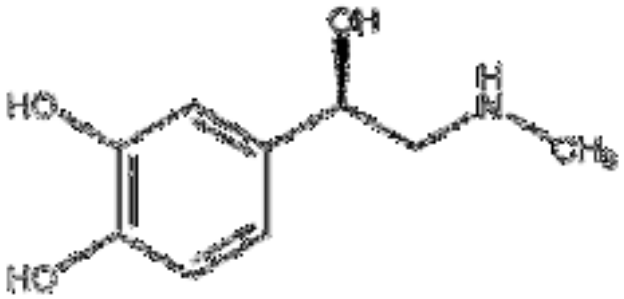


- **Mechanism of β1-receptor mediated signal transduction:**

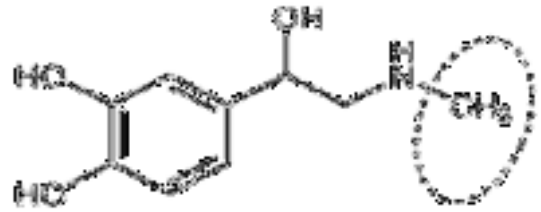


EPINEPHRINE

- It differs from norepinephrine only by the addition of an *N*-methyl group.
- Like norepinephrine, it lacks oral activity and has short duration of action.
- However, it is much more widely used clinically than norepinephrine.
- It is a potent stimulant of all α1-, α2-, β1-, β2-, and β3- adrenoceptors leading to a whole range of desired and side effects.



Epinephrine (E)



Epinephrine (E)
α_1, β_1 and β_2 agonist
nonselective α and β agonist

- **Therapeutic applications:**
- It is a very potent vasoconstrictor and cardiac stimulant.
- **In CVS disorders-**

➢ It has greater β-activity than norepinephrine due to an additional *N*-methyl group.

➢ Therefore, it is used to stimulate the heart in cardiac arrest.

➢ Its use in the treatment of heart block or circulatory collapse is **limited** because of its tendency to **induce cardiac arrhythmias**.

- **In Bronchial Asthma and other disorders**-

➢It is used by injection and by inhalation to relax bronchial smooth muscle in asthma and in anaphylactic reactions.

➢Several OTC preparations containing epinephrine are used for treating bronchial asthma.

- **It is also used in inhibiting uterine contraction**.
- Because of its α-activity, epinephrine is used-

➢ **to treat hypotensive crises and nasal congestion**,

➢ **to enhance the activity of local anesthetics**,

➢and as **a constrictor in hemorrhage**.

Drug	Preparation
Lidocaine 2%	1:50,000 epinephrine 1:100,000 epinephrine
Mepivacaine 3%	Plain (no vasoconstrictor)
Mepivacaine 2%	1:20,000 levonordefrin
Prilocaine 4%	Plain 1:200,000 epinephrine
Articaine 4%	1:100,000 epinephrine 1:200,000 epinephrine
Bupivacaine 0.5%	1:200,000 epinephrine

- **On Eye-**

- In addition, epinephrine is used in the treatment of **open-angle glaucoma**, where it reduces intraocular pressure by increasing the rate of outflow of aqueous humor from the anterior chamber of the eye.

- The irritation often experienced on instillation of epinephrine into the eye has led to the development of other preparations of the drug that potentially are not as irritating. One such example is **dipivefrin**.

Epinephrine (E)
adrenergic: usually oxidized
less lipophilic than dipivefrin
poor absorption and poor penetration of the eye
irritating to eyes when used in treatment of glaucoma

Dipivefrin: Ester and prodrug of E
Metabolized: less easily oxidized
more lipophilic than E
better absorption and penetration of the eye
less irritating to the eye than E

- **Photo-oxidation (Adrenochrome formation) and stabilization:**
- It is light sensitive and easily oxidized on exposure to air because of the catechol ring system.
- The development of a pink-to-brown color indicates oxidative breakdown.
- To minimize oxidation, solutions of the drug are stabilized by the addition of reducing agents such as **sodium bisulfite**.
- **Chemical degradation and salts:**
- It is also destroyed readily in alkaline solutions and by metals (e.g., Cu, Fe, Zn) and weak oxidizing agents.
- It is used in aqueous solution for inhalation as the free amine.
- Like other amines, it forms salts with acids, hydrochloride, and the bitartrate being the most common.

Selective α1-agonists

- All selective α1-agonists have therapeutic activity as **vasoconstrictors**.
- Structurally, they include-
- (a)**Phenylethanolamines:**

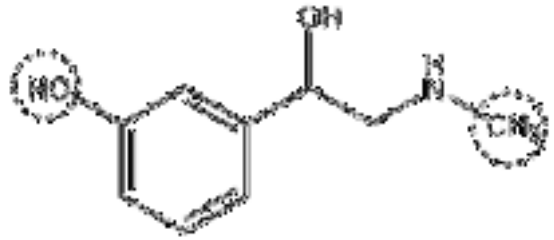
  Phenylephrine, **Methoxamine and Metaraminol (less selective-mixed action)**.

- (b) **2-Arylimidazolines:**

  Xylometazoline, Oxymetazoline, Naphazoline, and **Tetrahydrozoline**.

PHENYLEPHRINE

- It is a prototypical **selective direct-acting α1-agonist** that differs from epinephrine only in lacking a *p*-OH group.
- It is **orally active**, and its **duration of action is about twice** that of epinephrine because it lacks the catechol moiety and thus is **not metabolized by COMT**.
- However, its oral bioavailability is less than 10% because of its hydrophilic properties (log P 0.3), intestinal 3-*O*-glucuronidation/ sulfation and metabolism by MAO.
- **IUPAC- 1-(3-hydroxyphenyl)-2-methylaminoethanol**

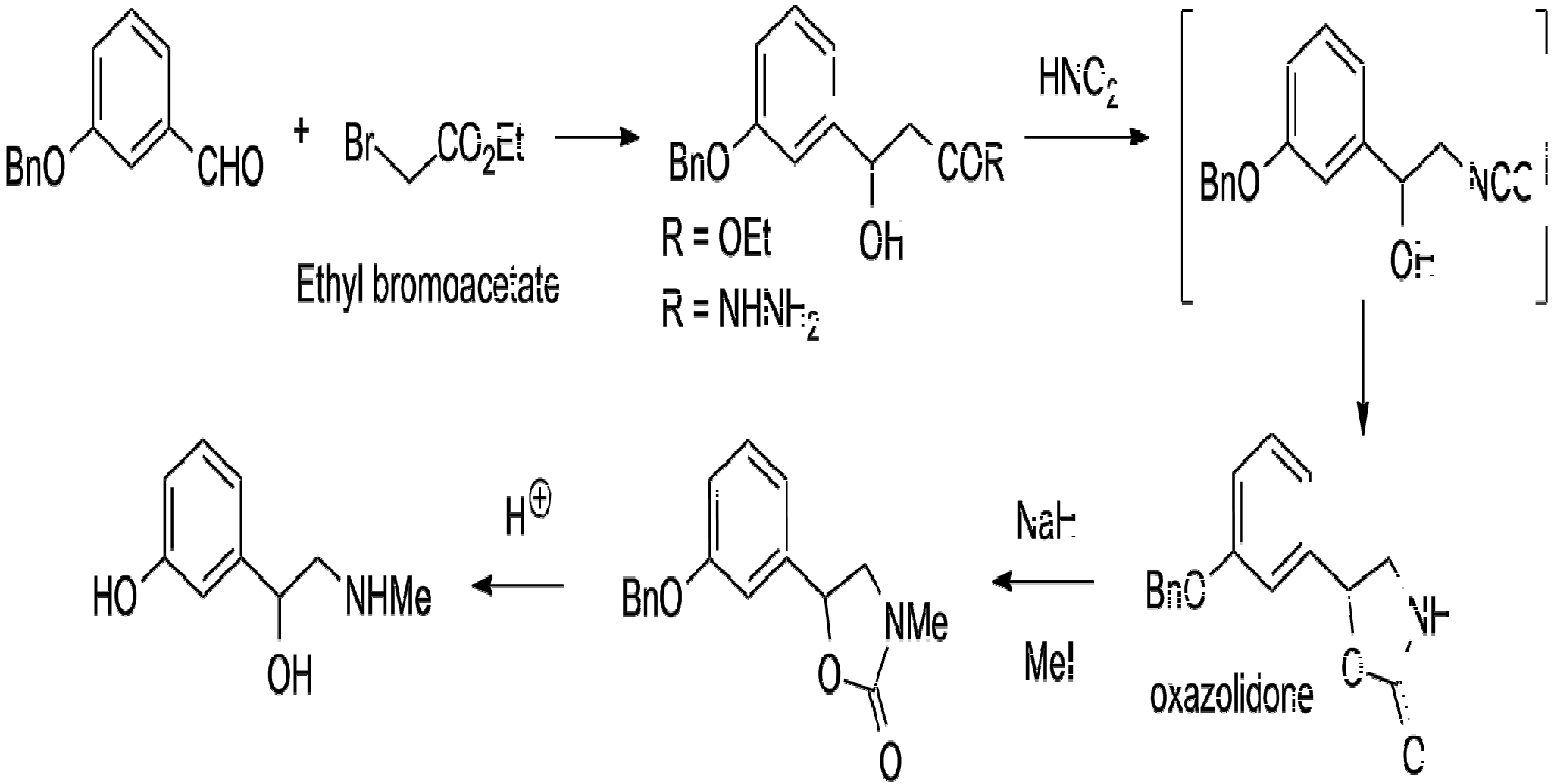


Phenylephrine

- **Therapeutic applications:**
- It is less potent than epinephrine and norepinephrine due to lack of the *p*-OH group.
- But it is a selective α1-agonist and thus a potent vasoconstrictor.
- It is used similarly to metaraminol and methoxamine for hypotension.
- Another use is in the treatment of severe hypotension resulting from either shock or drug administration.

- It also has widespread use as a nonprescription nasal decongestant in both oral and topical preparations.
- When applied to mucous membranes, it reduces congestion and swelling by constricting the blood vessels of the membranes.
- In the eye, it is used to dilate the pupil and to treat open-angle glaucoma.
- In addition, it is used in spinal anesthesia to prolong the anesthesia and to prevent a drop in blood pressure during the procedure.
- It is relatively nontoxic and produces little CNS stimulation.

- **Synthesis of Phenylephrine:**
- i. 3-(benzyloxy)benzaldehyde reacts with ethylbromoacetate to give ethyl3-(3-(benzyloxy)phenyl)-3-hydroxypropanoate.
- ii. The latter compound undergoes nitration to give an intermediate compound which gives oxazolidone later.
- iii. The compound is then reacted with sodium hydride in presence of methyliodide to give 5-(3-(benzyloxy)phenyl)-3-methyloxazolidin-2-one which on reduction gives phenylephrine.
- This method of synthesis illustrates functional group interconversion (FGI) involving functional group protection (FGP).


BnO
CHO
+
Br
CO2Et
Ethyl bromoacetate
BnO
COR
OH
R = OEt
R = NHNH2
HNC
BnO
NCC
OH
BnO
NH
O
C
oxazolidone
NaH
MeI
BnO
NMe
O
O
H⊕
HO
NHMe
OH

EXERCISE GPAT/NIPER model questions-Find the right answer

The correct order for the synthesis of the drug Phenylephrine is?

- **I. Reduction**
- **II. Reaction with sodium hydride**
- **III. Nitration**
- **IV. 3-(benzyloxy)benzaldehyde reacts with ethylbromoacetate**
- a) IV – III – II – I
- b) II – IV – I – III
- c) IV – II – I – III
- d) IV – III – I – II

- **Predict the incorrect statements from the following with respect to the classification of the drug.**
- **I. Phenylephrine is a selective α1-adrenergic agonist**
- **II. Epinephrine is a nonselective adrenergic agonist**
- **III. Norepinephrine is a nonselective adrenergic agonist**
- a) I, II & III
- b) I & II
- c) II only
- d) All statements related to classification are correct

- **The correct sequence of True and False for the given statements with respect to the drug Phenylephrine is-**
- **I. Phenylephrine is a selective ß-adrenergic agonist.**
- **II. It can be synthesized from 3-(benzyloxy)benzaldehyde**
- **III. 3 chiral centers are present in its structure**
- **IV. It is used as a decongestant.**
- a) FTTF
- b) TFTF
- c) FTFT
- d) TFFT

- **Which amongst the following drugs is having highest number of ring system in its structure-**
- a) Phenylephrine
- b) Norepinephrine
- c) Morphine
- d) Penicillin G

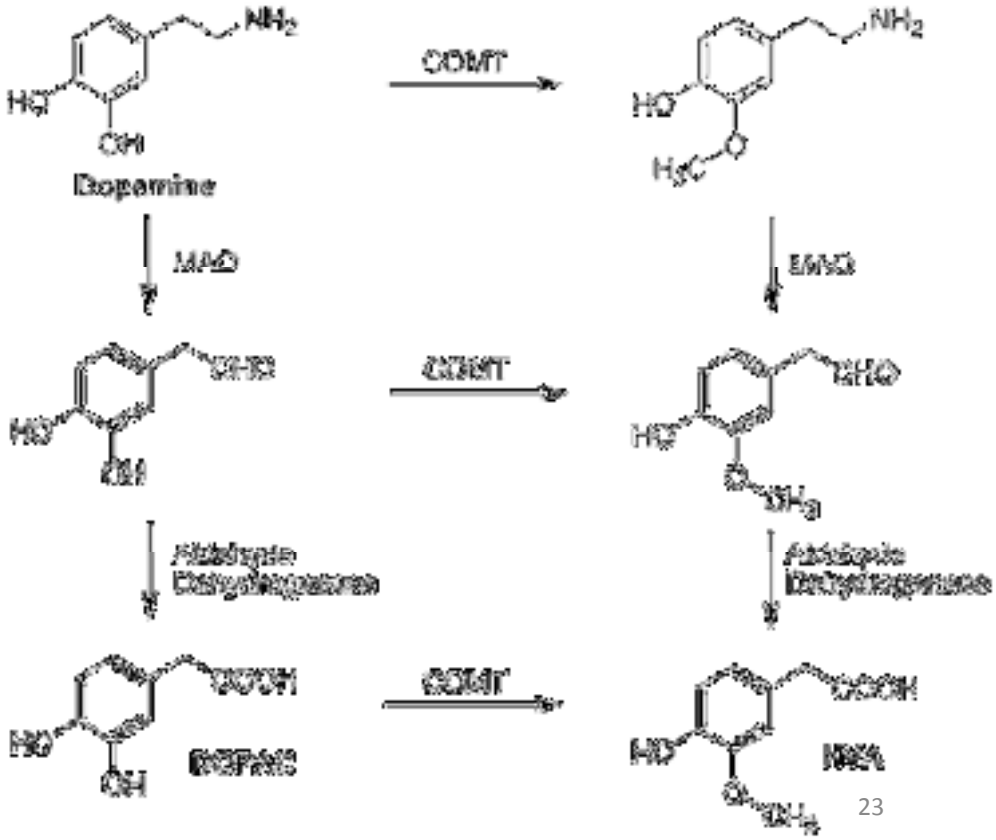
* Morphine has 5 rings

  Penicillin G has 3 rings

  Therefore, option C is the right answer.

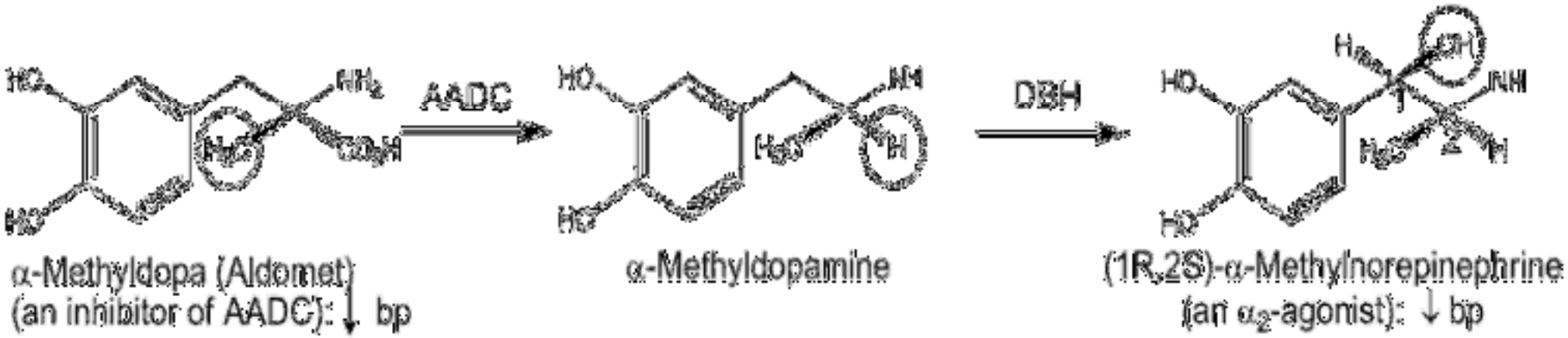
Dopamine

- It acts primarily on α1- and β1-adrenergic receptors, increasing systemic vascular resistance and exerting a positive inotropic effect on the heart.
- It must be administered by an intravenous route, because oral administration results in rapid metabolism by MAO and/or catechol-*O*-methyltransferase (COMT).



Methyldopa (L-α-methyldopa)

- It differs structurally from L-DOPA only in the presence of a α - methyl group.
- It decreases the concentration of DA, NE, E, and serotonin in the CNS and periphery.
- It is metabolised in the CNS to its active metabolite (α-methylnorepinephrine).

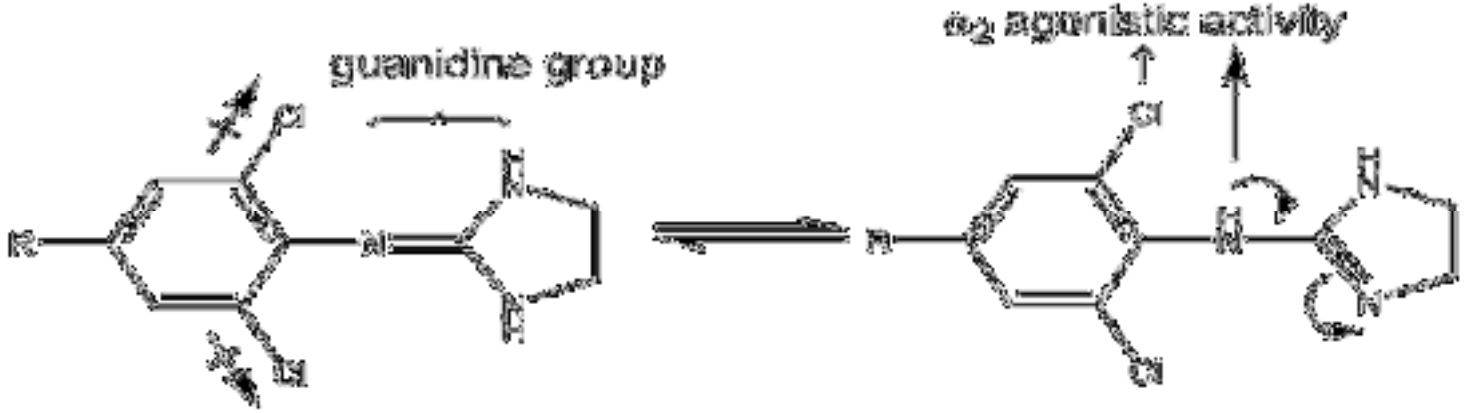


- α -Methylnorepinephrine acts on α2-receptors in the CNS in the same manner as clonidine, to decrease sympathetic outflow and lower blood pressure.
- Methyldopa is transported actively into CNS via an aromatic amino acid transporter, where it is decarboxylated by AADC in the brain to (1*R*,2*S*)- α -methyldopamine.
- This intermediate, in turn, is stereospecifically β-hydroxylated by DBH(dopamine beta hydroxylase) to give the (1*R*,2*S*)- α -methylnorepinephrine.
- This active metabolite is a selective α2-agonist because it has correct (1*R*,2*S*) configuration.

- Absorption can range from 8% to 62% and appears to involve an amino acid transporter.
- Absorption is thus affected by food, and about 40% of that absorbed is converted to methyldopa-*O*-sulfate by the intestinal mucosal cells.
- Methyldopa is used only by oral administration because its zwitterionic character limits its solubility.
- The ester hydrochloride salt of methyldopa, methyldopate, was developed as a highly water-soluble derivative that could be used to make parenteral preparations.
- It is converted to methyldopa in the body through the action of esterases.

Clonidine

- It differs from 2-arylimidazoline α1-agonists mainly by the presence of *o*-chlorine groups and a NH bridge.
- The *o*-chlorine groups afford better activity than *o*-methyl groups at α2 sites.
- Importantly, clonidine contains a NH bridge (aminoimidazolines) instead of CH2 bridge in 2-arylimidazoline.
- The uncharged form of clonidine exists as a pair of tautomers.



Clonidine (pKa = 8.0) : R = H some passage into the CNS

4-Hydroxyclonidine : R = OH no passage into the CNS

Apraclonidine (pKa = 9.22) : R = NH_2 no passage into the CNS

- Clonidine is an example of a imidazolidine derivative that possesses central α2-selectivity.
- The α1: α2 ratio is 300:1.
- Under certain conditions, such as intravenous infusion, clonidine can briefly exhibit vasoconstrictive activity as a result of stimulation of peripheral α-receptors.
- However, this hypertensive effect, if it occurs, is followed by a much longer-lasting hypotensive effect as a result of the ability of clonidine to enter into the CNS and stimulate α 2-receptors located in regions of the brain.

- Stimulation of these α2-receptors brings about a decrease in sympathetic outflow from the CNS, which in turn leads to decreases in peripheral vascular resistance and blood pressure.
- Bradycardia is also produced by clonidine as a result of a centrally induced facilitation of the vagus nerve and stimulation of cardiac prejunctional α2-receptors.
- These pharmacological actions have made clonidine quite useful in the treatment of hypertension.

- The ability of clonidine and its analogs to exert an antihypertensive effect depends on-

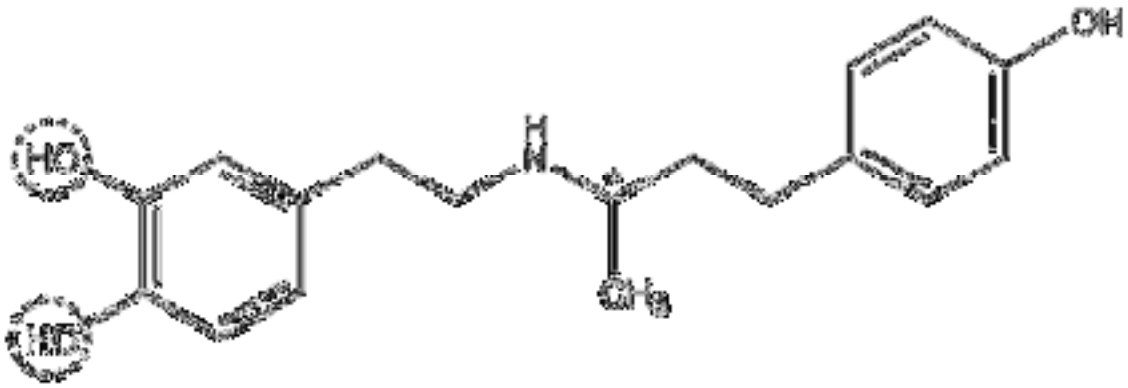
➢ the ability of these compounds to interact with the central α2-receptor.

➢ the ability to gain entry into the CNS.

- The basicity of the guanidine group (pKa 13.6) is decreased to 8.0 (the pKa of clonidine) because of the inductive and resonance effects of the dichlorophenyl ring.
- Thus, at physiological pH, clonidine will exist to a significant extent in the nonionized form required for passage into the CNS.
- It has an oral bioavailability of more than 90%.

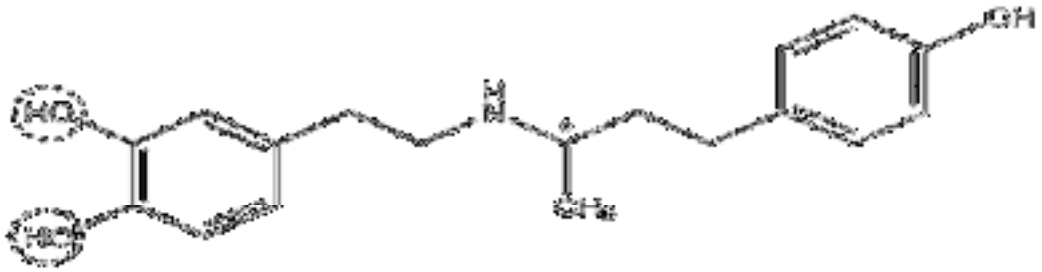
Dobutamine

- It comes under sympathomimetics with DUAL α - AND β -AGONISTS/ANTAGONISTS activity.
- It is a positive inotropic agent administered intravenously for congestive heart failure.
- It resembles DA structurally but possesses a bulky 1-(methyl)- 3-(4-hydroxyphenyl)propyl group on the amino nitrogen.
- It possesses a center of asymmetry, and both enantiomeric forms are present in the racemic mixture used clinically.



- The (-) isomer of dobutamine is a potent α1-agonist, which is capable of causing marked pressor responses.
- In contrast, (+)-dobutamine is a potent α1-antagonist, which can block the effects of (-)-dobutamine.
- Importantly, the effects of these two isomers are mediated via β1-receptors.
- Both isomers appear to be full agonists, but the (+) isomer is a more potent β1-agonist than the (-) isomer (approximately tenfold).

- Dobutamine contains a catechol group and is orally inactive and thus is given by intravenous infusion.
- Solutions of the drug can exhibit a slight pink color because of oxidation of the catechol function.
- It has a plasma half-life of about 2 minutes because it is metabolized by COMT and by conjugation, although not by MAO (**Why?**).

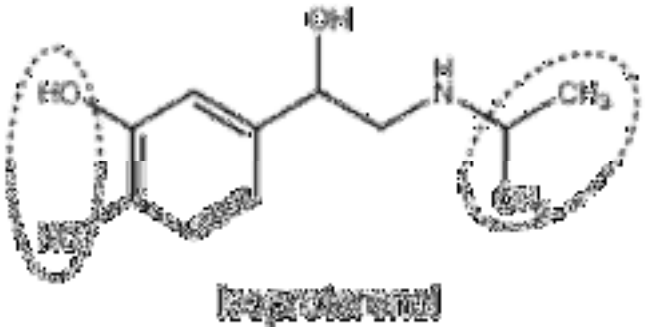


Dobutamine
reduced slightly by air
COMT metabolism and conjugation →
orally inactive and short DOA

Isoproterenol

- It is a nonselective and prototypical β-agonist (β2/β1 = 1).
- It's oral absorption is rather erratic and undependable.
- The principal reason for its poor absorption characteristics and relatively short DOA is its metabolism by sulfate and glucuronide conjugation of the phenolic OH groups and *o*-methylation by COMT.

Di-OH groups result in:
sensitive to air and light
metabolized by COMT, sulfate
and glucuronide conjugation =>
poor absorption and short DOA



Isoproterenol

Isopropyl group results in:
↑ β activity, virtually no α activity
resistant to MAO →

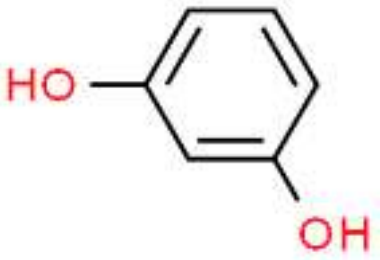
- It is sensitive to light and air.
- Aqueous solutions become pink on standing.
- Unlike epinephrine and norepinephrine, it does not undergo oxidative deamination by MAO.
- The drug has DOA of 1 to 3 hours after inhalation.
- It increases cardiac output by stimulating cardiac β1-receptors.
- It produces bronchodilation through stimulation of β2-receptors in the respiratory tract.

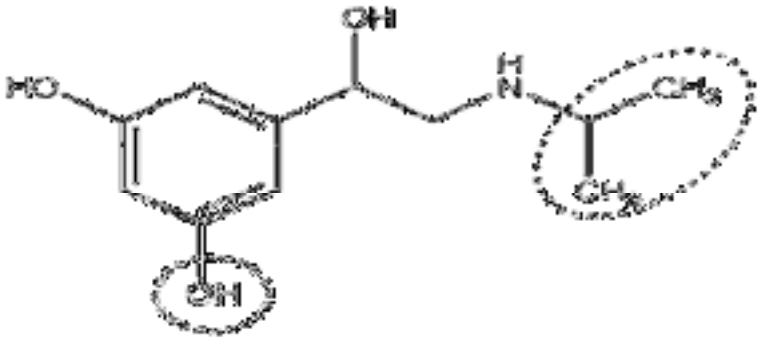
- It is one of the most potent bronchodilators available and is used by inhalation and injection.
- Cardiac stimulation is an occasionally dangerous adverse effect.
- The **cardiac stimulation caused by its β1-activity** and **its lack of oral activity** have led to its **diminished use** in favor of more selective β-agonists.
- The problems have been overcome by the design and development of several **noncatechol selective β2-agonists**.

Terbutaline

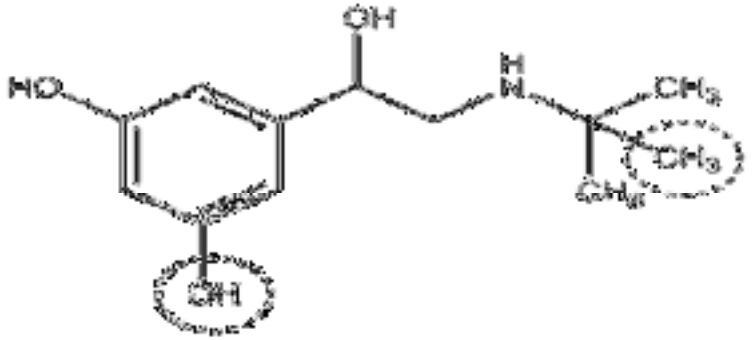
- It belong to the structural class of resorcinol bronchodilators that have 3’,5’-diOH groups of the phenyl ring (rather than 3’,4’-diOH groups as in catechols).
- 3’,5’-diOH groups confer β2-receptor selectivity on compounds with large amino substituents.

RESORCINOL





Metaproterenol
3, 5, DI-OH group result in:
↑ β_2 activity:
not metabolized by COMT
orally active and longer DOA



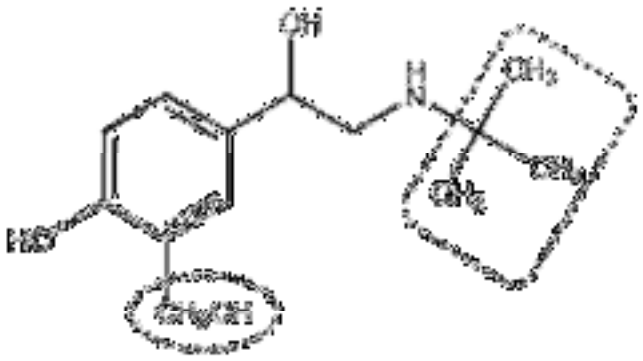
Terbutaline
Bulk N-R group results in:
↑ β_2 activity & virtually no α activity
not metabolized by MAO
orally active and longer DOA

- For example, metaproterenol (a resorcinol analog of isoproterenol), terbutaline (an *N*-*t*-butyl analog of metaproterenol), and other similar compounds are resorcinol β2-selective agonists.
- They relax the bronchial musculature in patients with asthma but cause less direct cardiac stimulation than do the nonselective β-agonists.
- Metaproterenol causes cardiac stimulation due to a β-directing *N*-isopropyl group. Further, it is less β2 selective than either terbutaline or albuterol/salbutamol (both have β2-directing *t*-butyl groups), and hence is not preferred.

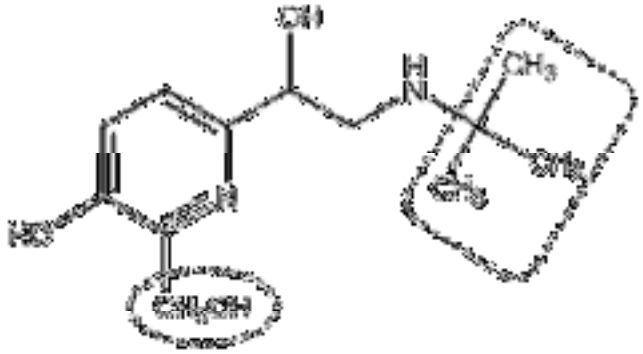
- Although these agents are more selective for β2-receptors, they have a lower affinity for β2-receptors than isoproterenol.
- However, they are much more effective when given orally, and they have a longer DOA.
- This is because they are resistant to the metabolism by either COMT or MAO.
- Instead, their metabolism primarily involves glucuronide conjugation.
- Although both metaproterenol and terbutaline exhibit significant β2-receptor selectivity, the common cardiovascular effects associated with other adrenergic agents can also be seen with these drugs when high doses are used.

Salbutamol (Albuterol)

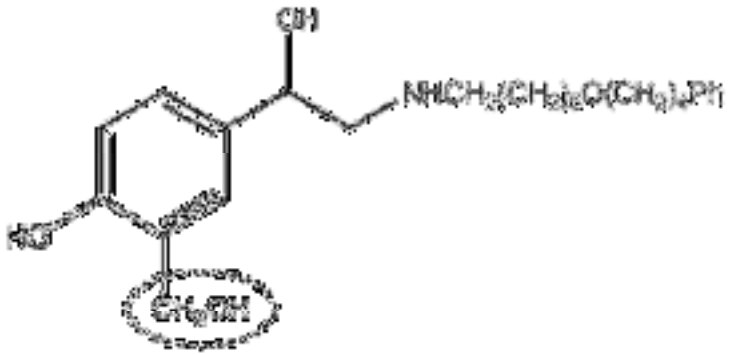
- **It is a selective β2- agonist and widely used as a bronchodilator.**
- **Other examples include pirbuterol and salmeterol.**
- **Their selectivity results from replacement of the *meta*-OH group of the aromatic ring with a hydroxyl methyl (CH2OH) moiety.**
- **Pirbuterol(pyridine ring) is closely related structurally to albuterol (benzene).**
- **Both pirbuterol and albuterol are BIOISOSTERIC DRUGS.**



Albuterol



Pirbuterol

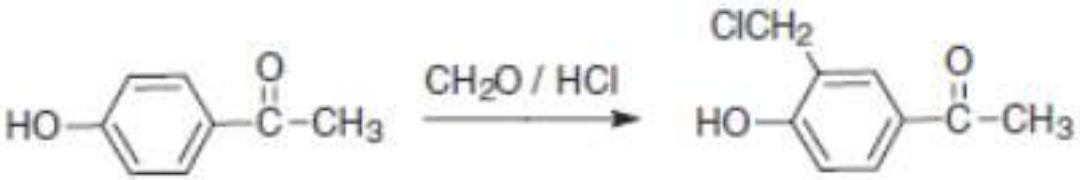


Salmeterol

- These drugs are not metabolized by either COMT or MAO.
- They are conjugated with sulfate.
- They are orally active, and exhibit a longer DOA than isoproterenol.
- The DOA of terbutaline, albuterol, and pirbuterol is in the range of 3 to 6 hours.
- *S(+)*-Albuterol enhances bronchial muscle contraction, and this undesirable effect is completely avoided by using the pure *R(-)*-albuterol.
- Therefore, the efficacy is achieved at $1/4^{th}$ dose of racemic albuterol with markedly reduced adverse effects.

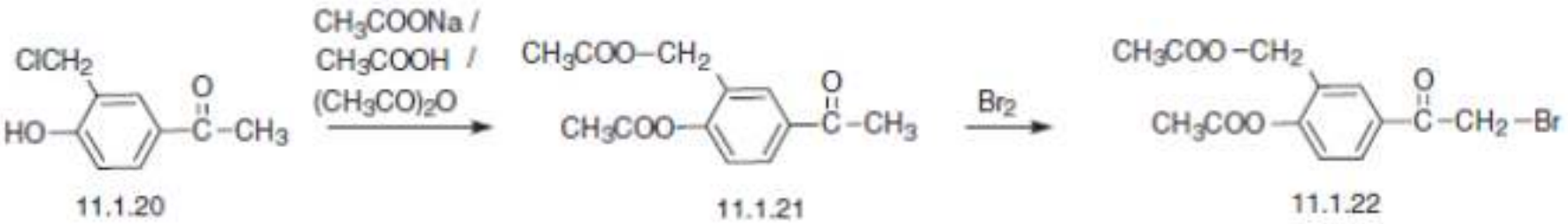
Synthesis of Salbutamol

- It is synthesized in two ways.
- 1st Method
- Step-1 involves **chloromethylation** of 4-hydroxyacetophenone, which gives 4-hydroxy-3-hydroxymethylacetophenone (11.1.20).



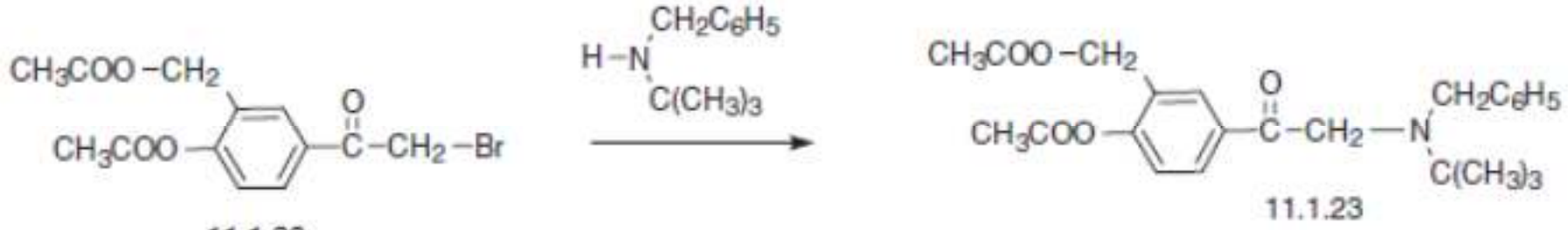
11.1.20

In step-2, (11.1.20) is **acetylated** into a diacetyl derivative (11.1.21), which is further **brominated** into the corresponding bromoacetophenone (11.1.22).



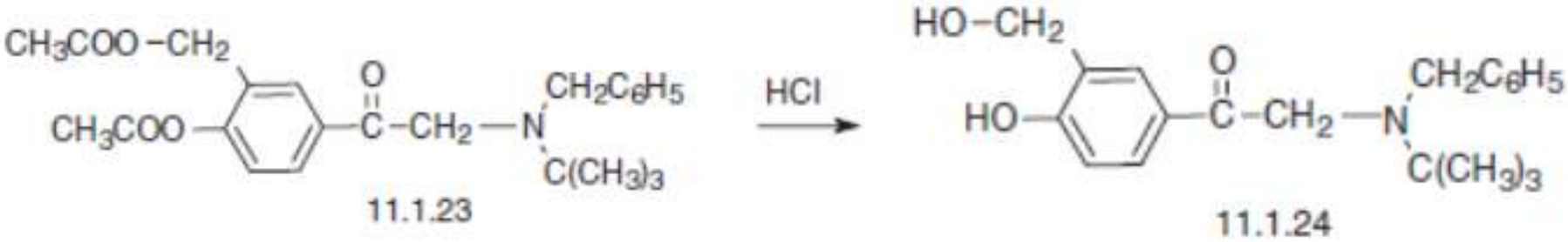
11.1.20 11.1.21 11.1.22

In step-3, (11.1.22) is reacted with N-benzyl- N-*tert*-butylamine to get a derivative of **aminoacetophenone** (11.1.23)



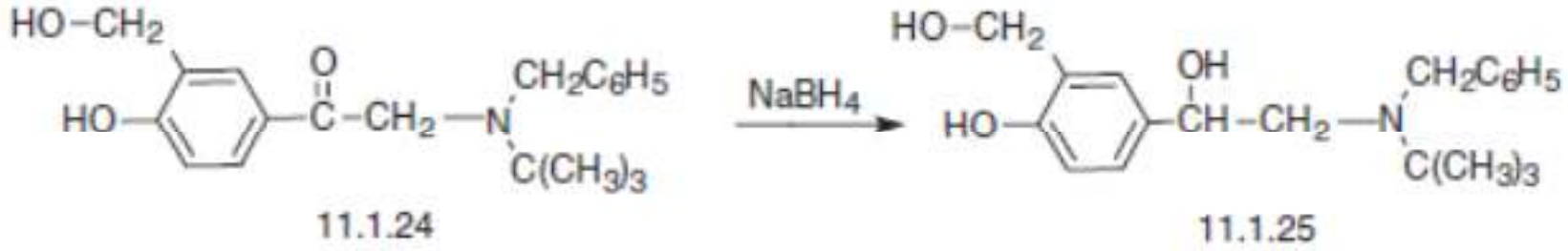
11.1.22 11.1.23

In step-4, the acetyl group of (11.1.23) is **hydrolyzed** by hydrochloric acid to get phenolic product(11.1.24).



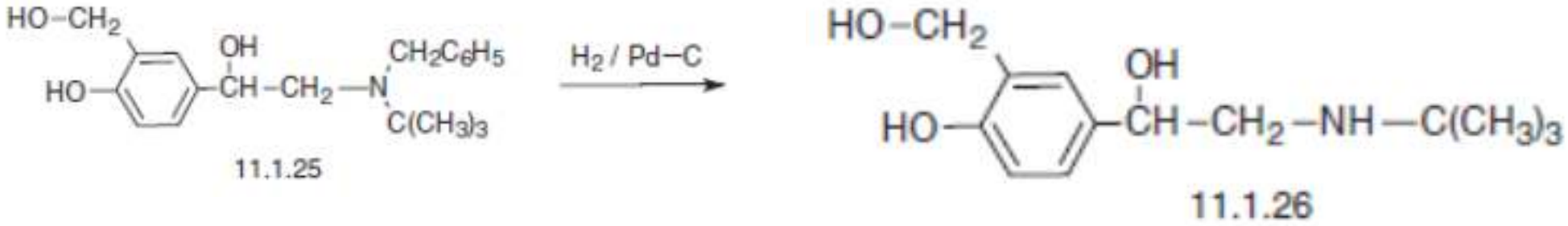
11.1.23 11.1.24

In step-5, phenolic product (11.1.24) undergoes a **reduction** by sodium borohydride for transforming the keto group into a hydroxyl group to give 11.1.25.



11.1.24 11.1.25

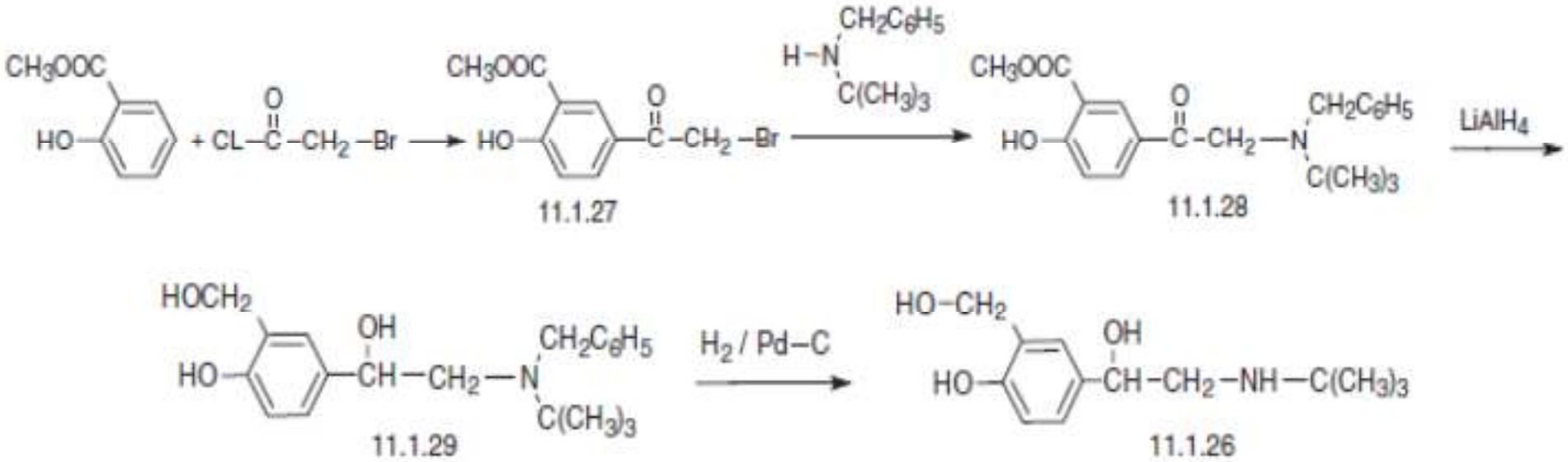
In step-6, **catalytic hydrogenation** of (11.1.25) over a palladium catalyst for removing the benzyl-protecting group, gives **Salbutamol (albuterol).**



11.1.25

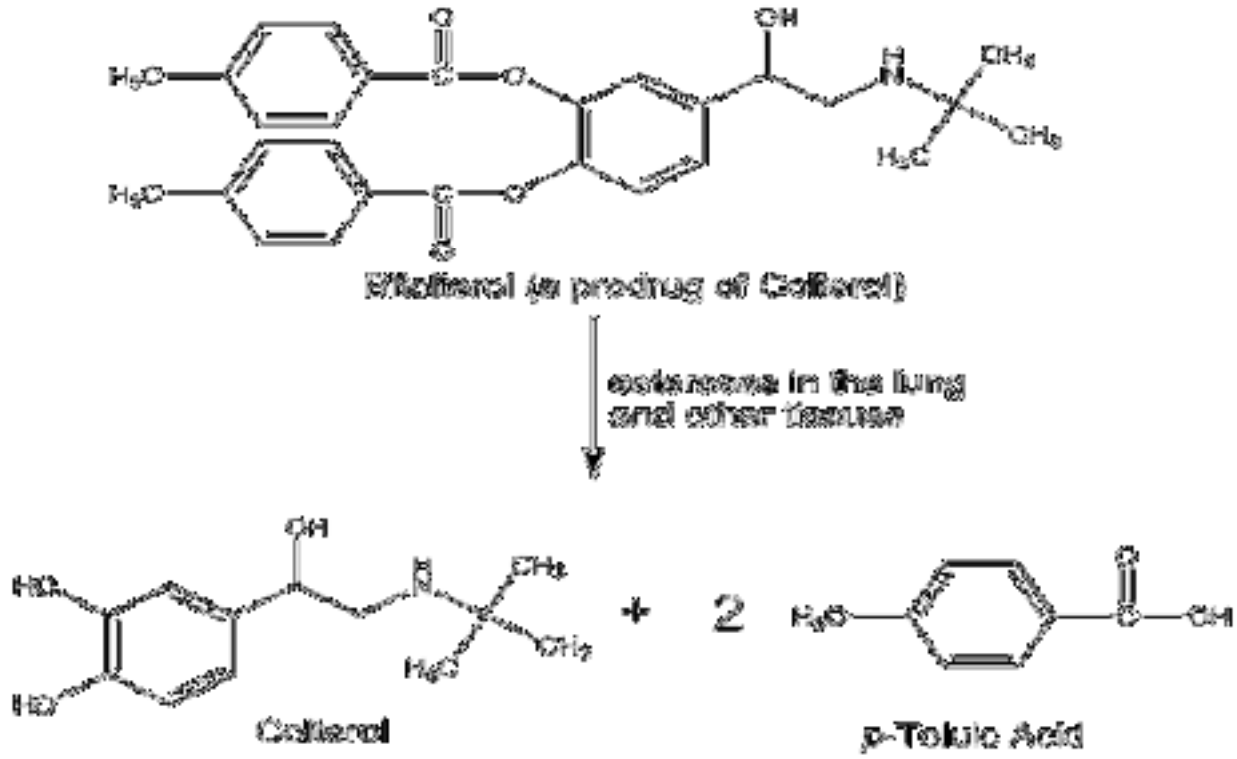
11.1.26

- The second method differs little from the previous, and consists of the initial formation of 4-hydroxy-3-acetoxybromoacetophenone (11.1.27) by acylation of methyl ester salicylic acid using bromoacetyl chloride.
- This is also reacted with *N*-benzyl-*tert*-butylamine, and the resulting product (11.1.28) is completely hydrolyzed by lithium aluminum hydride into the *N*-benzyl substituted albuterol (11.1.29), the benzyl group of which is removed by hydrogen over a palladium catalyst to give the desired albuterol (11.1.26)



BITOLTEROL and COLTEROL

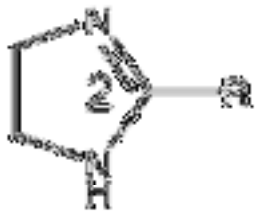
- Bitolterol is a prodrug of colterol (a β2-selective agonist) in which the catechol OH groups have been converted to di-*p*-toluate esters.
- These two lipophilic di-*p*-toluate esters increase lipid solubility of bitolterol.
- Colterol differs from isoproterenol by replacing the β-directing *N*-isopropyl to β2-directing*N*-*tert*-butyl group, which results in the increased β2-selectivity.



- The presence of the bulky di-ester and bulky *N-tert*-butyl groups also prolong the DOA (8 hours) because it is resistant to COMT and MAO metabolism.
- This permit less frequent administration and greater convenience to the patient.
- Bitolterol is administered by inhalation for bronchial asthma and reversible bronchospasm.
- After absorption, it is hydrolyzed by esterases slowly enough in the lung and other tissues to produce the active agent (colterol) affording sustained bronchodilation.
- Colterol is then metabolized after pharmacological action by COMT and conjugation.

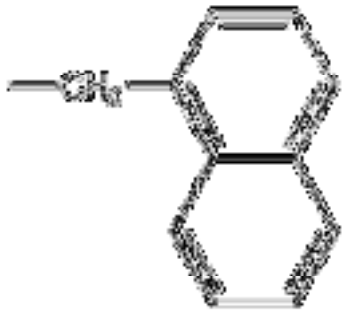
NAPHAZOLINE, TETRAHYDROZOLINE, XYLOMETAZOLINE AND OXYMETAZOLINE

- All are 2-aralkylimidazoline derivatives and α1-agonists.
- These agents are used for their vasoconstrictive effects as nasal and ophthalmic decongestants.
- Although nearly all β-agonists are phenylethanolamine derivatives, α-receptors accommodate more diverse chemical structures.
- All 2-aralkylimidazoline α1-agonists contain a one-carbon bridge between C-2 of the imidazoline ring and a phenyl ring, and thus a phenylethylamine structure feature is there.

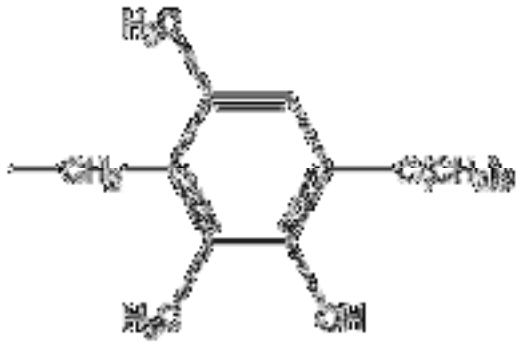


Imidazoline moiety
pKa 9-10
Limited access to the CNS

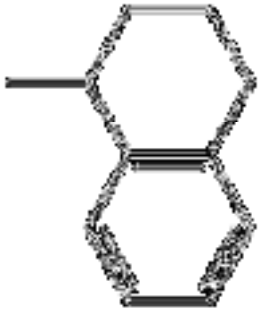
Naphazoline R =



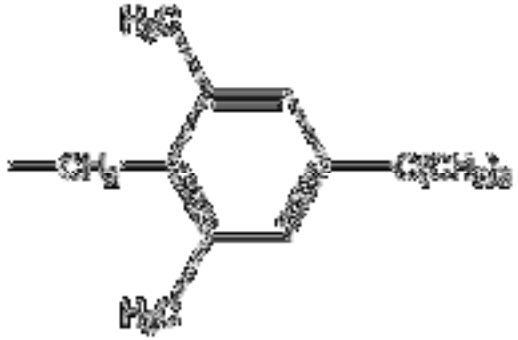
Oxymetazoline R =



Tetrahydrozoline R =

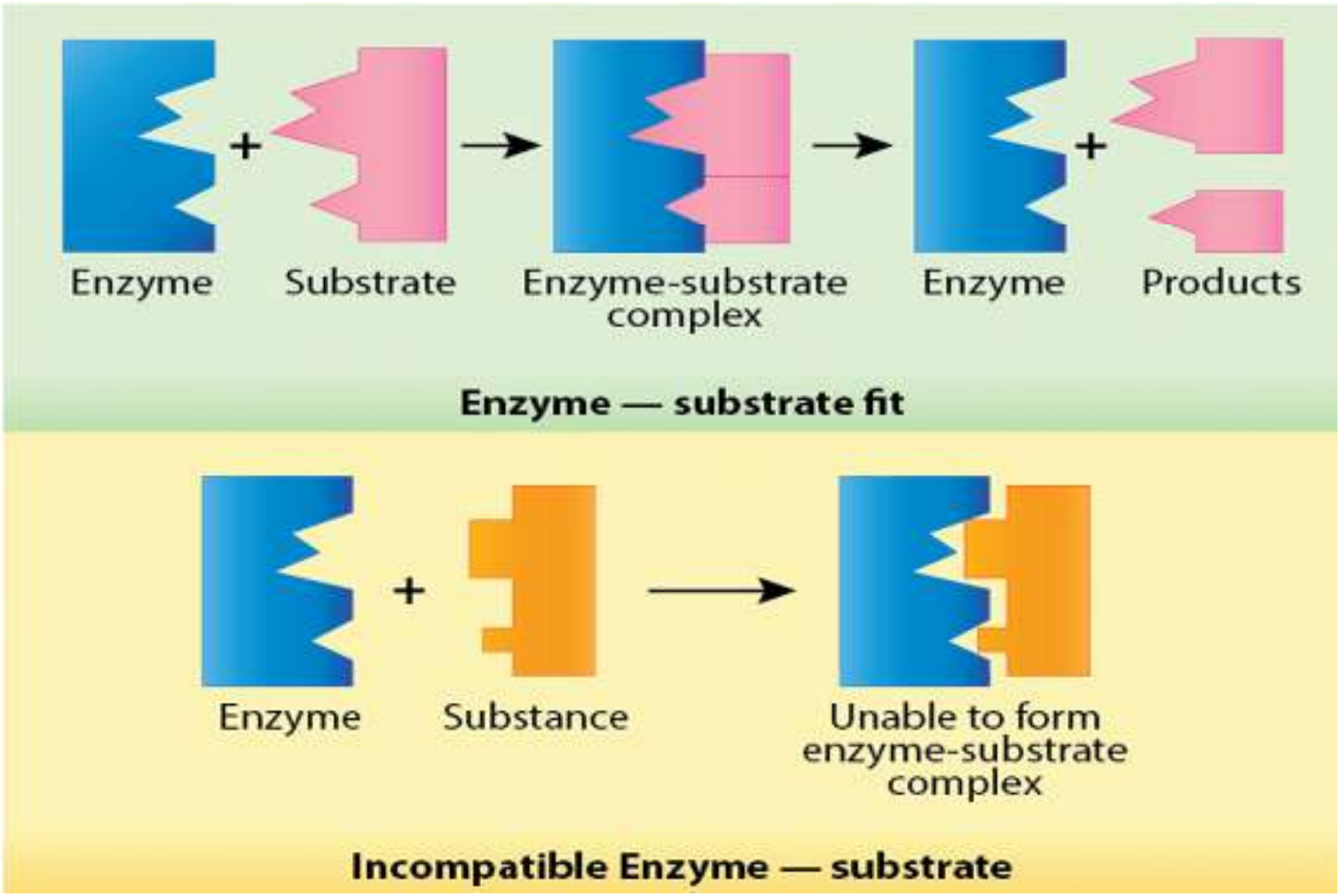


Xylometazoline R =



- *Ortho*-lipophilic groups on the phenyl ring are important for α-activity.
- However, *meta* or *para*-bulky lipophilic substituents on the phenyl ring may be important for the α1-selectivity.
- They have limited access to the CNS, because they exist in an ionized form at physiological pH caused by the very basic nature of the imidazoline ring (pKa 10–11).
- Xylometazoline and oxymetazoline have been used as topical nasal decongestants because of their ability to promote constriction of the nasal mucosa.
- When taken in large doses, oxymetazoline may cause hypotension, presumably because of a central clonidine-like effect.
- Oxymetazoline also has significant affinity for α2A-receptors.

DRUG METABOLISM
PHASE 1 continued

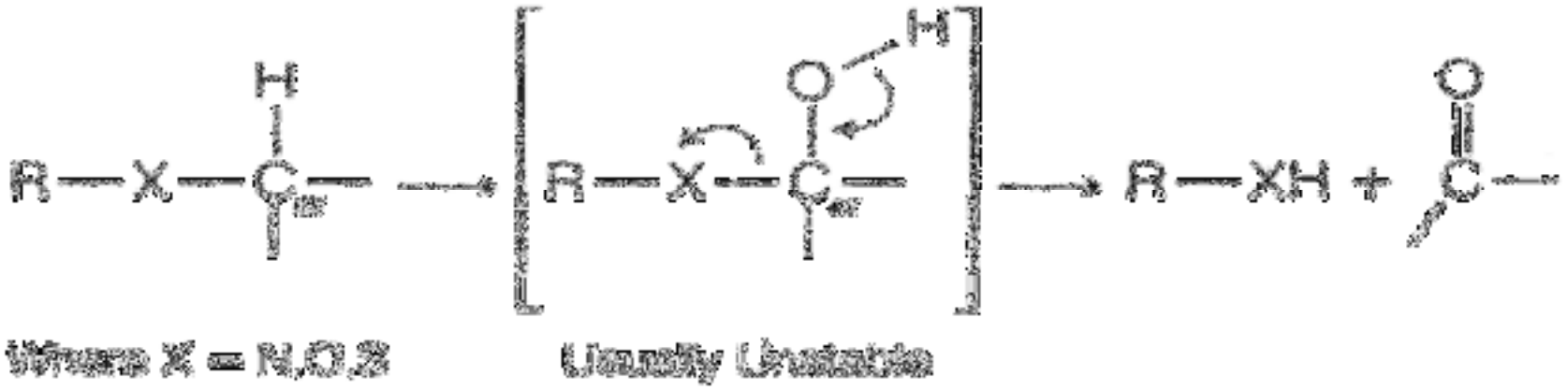


- **Oxidation Involving Carbon–Heteroatom Systems**
- Nitrogen and oxygen functionalities are commonly found in most drugs; sulfur functionalities occur only occasionally.
- Metabolic oxidation of C-N, C-O and C-S systems mainly involves two basic types of biotransformation processes:

➢ 1. Hydroxylation of the α-carbon atom attached directly tothe heteroatom (*N*, *O*, *S*).

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

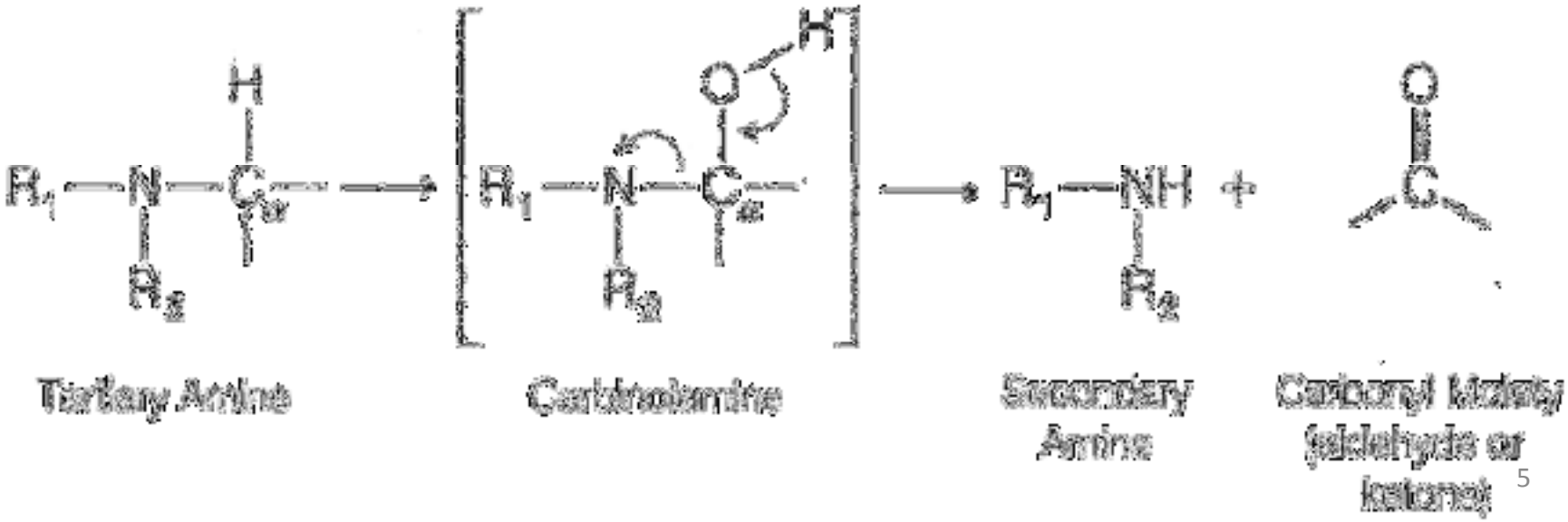
- 1. Hydroxylation of the α-carbon atom attached directly to the heteroatom (*N*, *O*, *S*).
- The resulting intermediate is unstable and decomposes with the cleavage of the carbon–heteroatom bond:



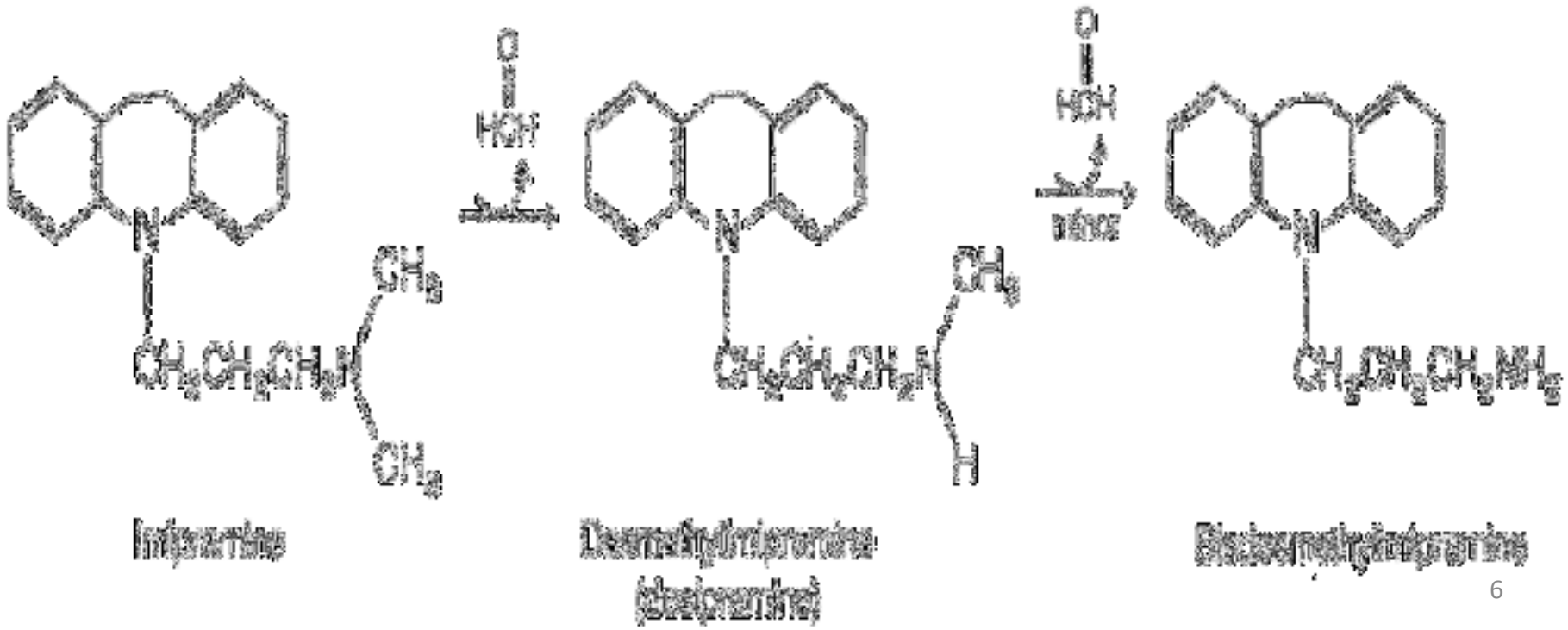
- Oxidative *N*-, *O*-, and *S*-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.

- **Oxidation involving C–N systems:**
- 1. Aliphatic (primary, secondary, and tertiary) and alicyclic (secondary and tertiary) amines
- 2. Aromatic and heterocyclic nitrogen compounds
- 3. Amides
- Enzymes involved:
- CYP mixed-function oxidases **(α-carbon hydroxylation)**.
- *Amine oxidases/N-oxidases* **(N-hydroxylation or *N*-oxidation).**

- ***Tertiary Aliphatic and Alicyclic Amines:***
- The oxidative removal of alkyl groups (particularly methyl groups) from tertiary aliphatic and alicyclic amines is carried out by hepatic CYP mixed-function oxidase enzymes.
- This reaction is commonly referred to as ***oxidative N-dealkylation***.

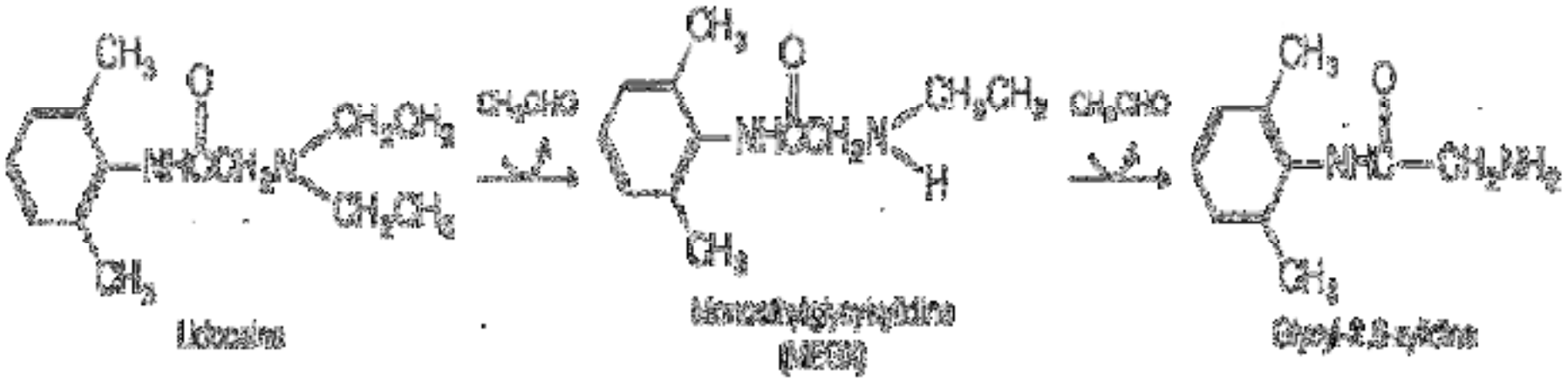


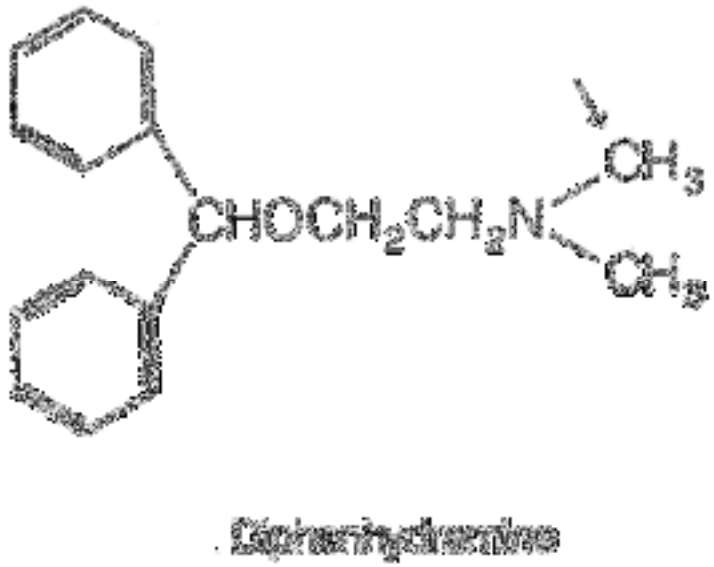
- The initial step involves α-carbon hydroxylation to form a carbinolamine intermediate.
- Carbinolamine is unstable and undergoes spontaneous heterolytic cleavage of the C–N bond to give a secondary amine and a carbonyl moiety (aldehyde or ketone).

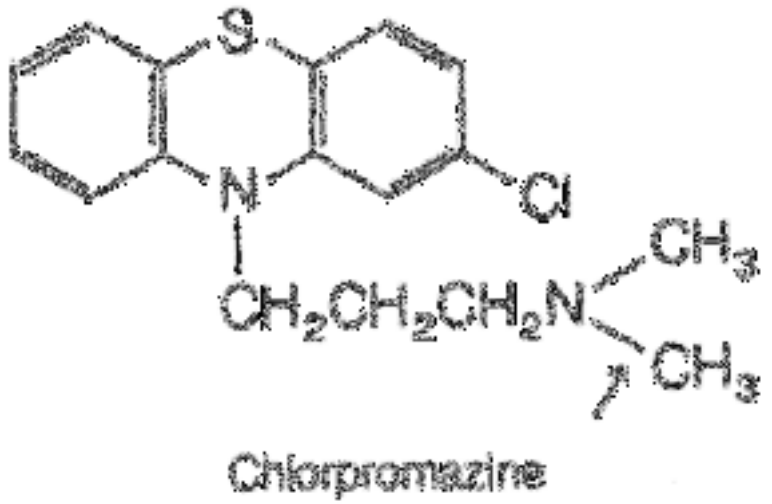


- In general, small alkyl groups, such as methyl, ethyl, and isopropyl, are removed rapidly.
- *N*-dealkylation of the *t*-butyl group is not possible by the carbinolamine pathway because α-carbon hydroxylation cannot occur.
- The first alkyl group from a tertiary amine is removed more rapidly than the second alkyl group.
- In some drugs, bis-dealkylation of the tertiary aliphatic amine to the corresponding primary aliphatic amine occurs very slowly.
- Example: Imipramine.

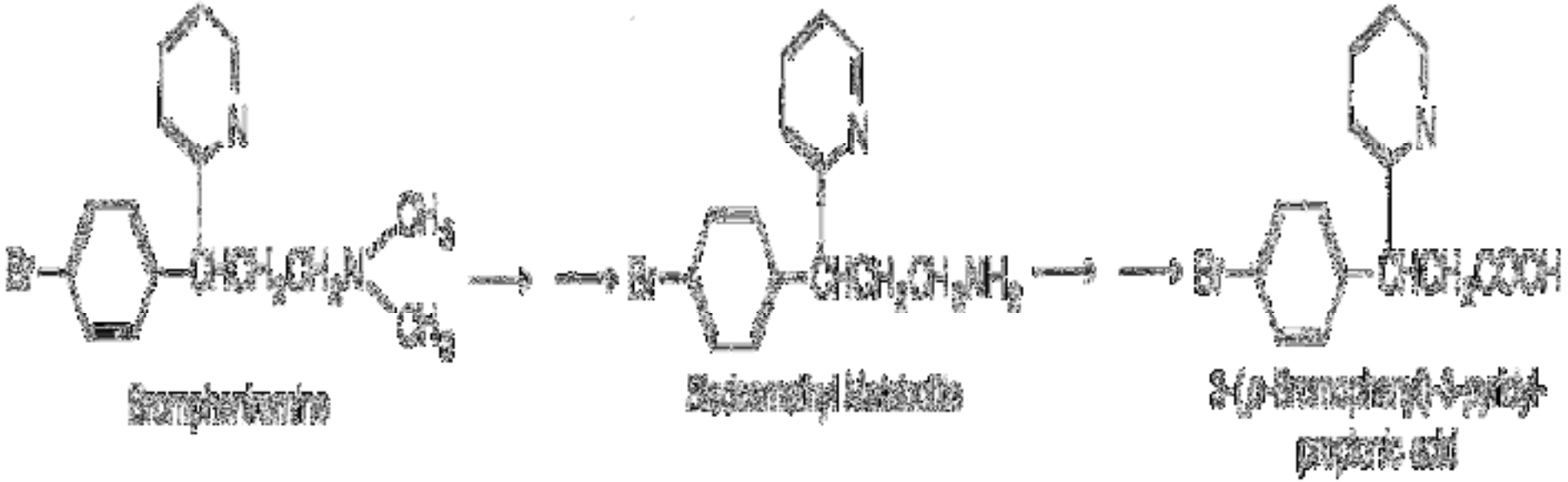
- Drugs that undergo oxidative N-dealkylation:



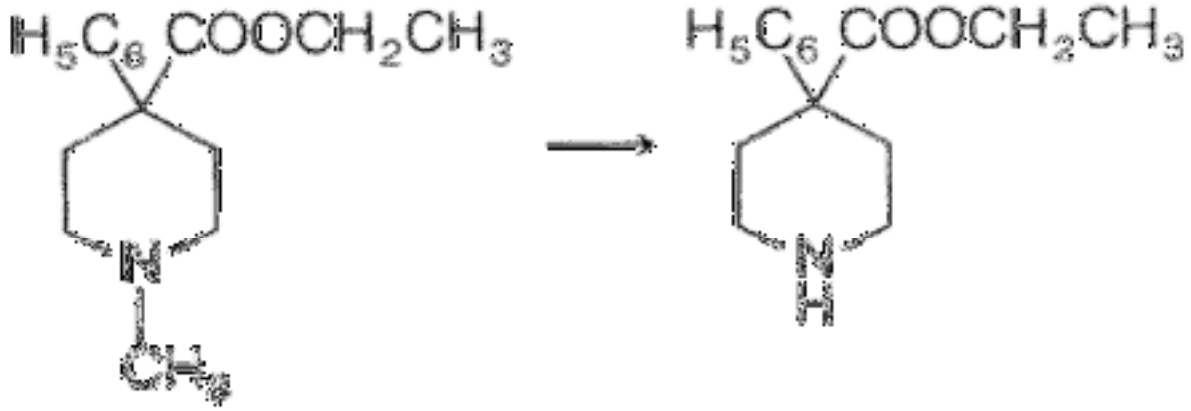




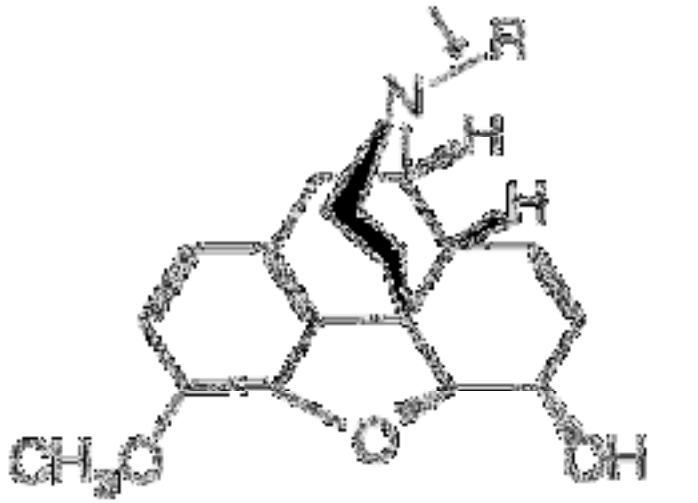
- Many times, bisdealkylation of a tertiary amine leads to the corresponding primary aliphatic amine metabolite, which is susceptible to further oxidation.
- For example, the bis-desmethyl metabolite of the H1-histamine antagonist brompheniramine undergoes **oxidative deamination** and further oxidation to the corresponding propionic acid metabolite.



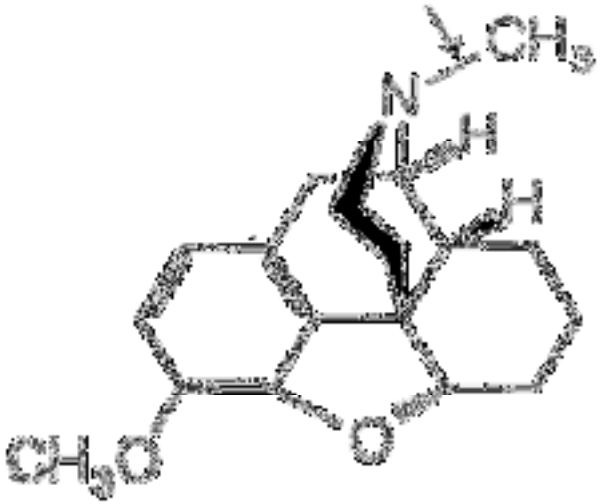
- Morphine derivatives and N-Dealkylation:



Meperidine Normeperidine

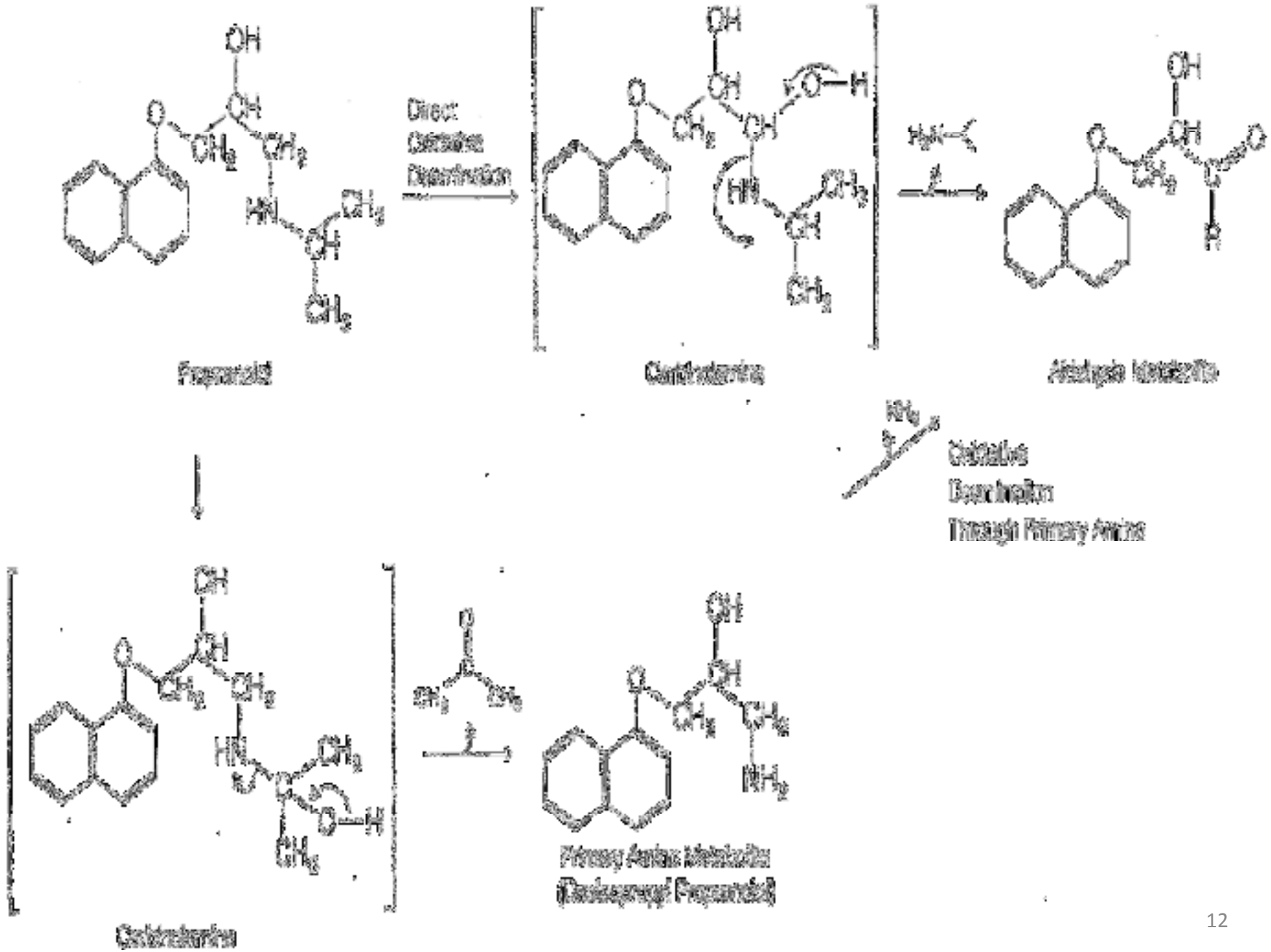


Morphine R = CH_3
N-Ethylnormorphine R = CH_2CH_3

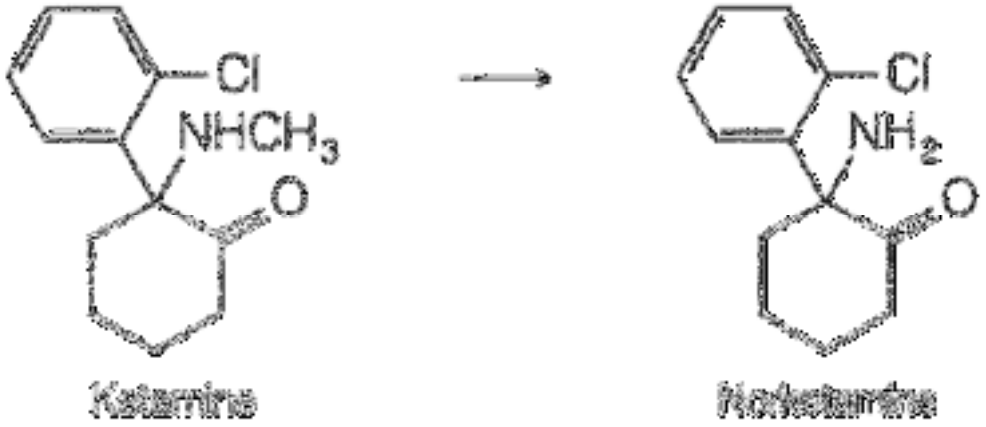


Dextromethorphan

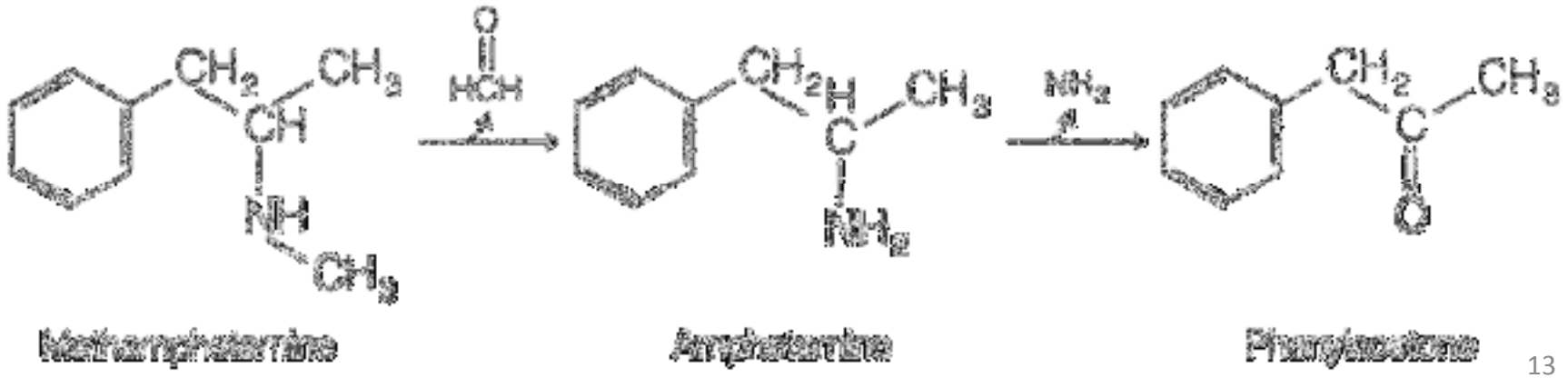
- ***Secondary and Primary Amines.***
- Secondary amines (either parent compounds or metabolites) undergoes oxidative *N*-dealkylation, oxidative deamination, and *N*-oxidation reactions.
- Dealkylation of secondary amines gives rise to the corresponding primary amine metabolite.
- The primary amine metabolites formed from oxidative dealkylation are susceptible to *oxidative deamination*.
- If α-carbon hydroxylation cannot occur in primary amine metabolite, then oxidative deamination is not possible.


Direct
Oxidative
Deamination

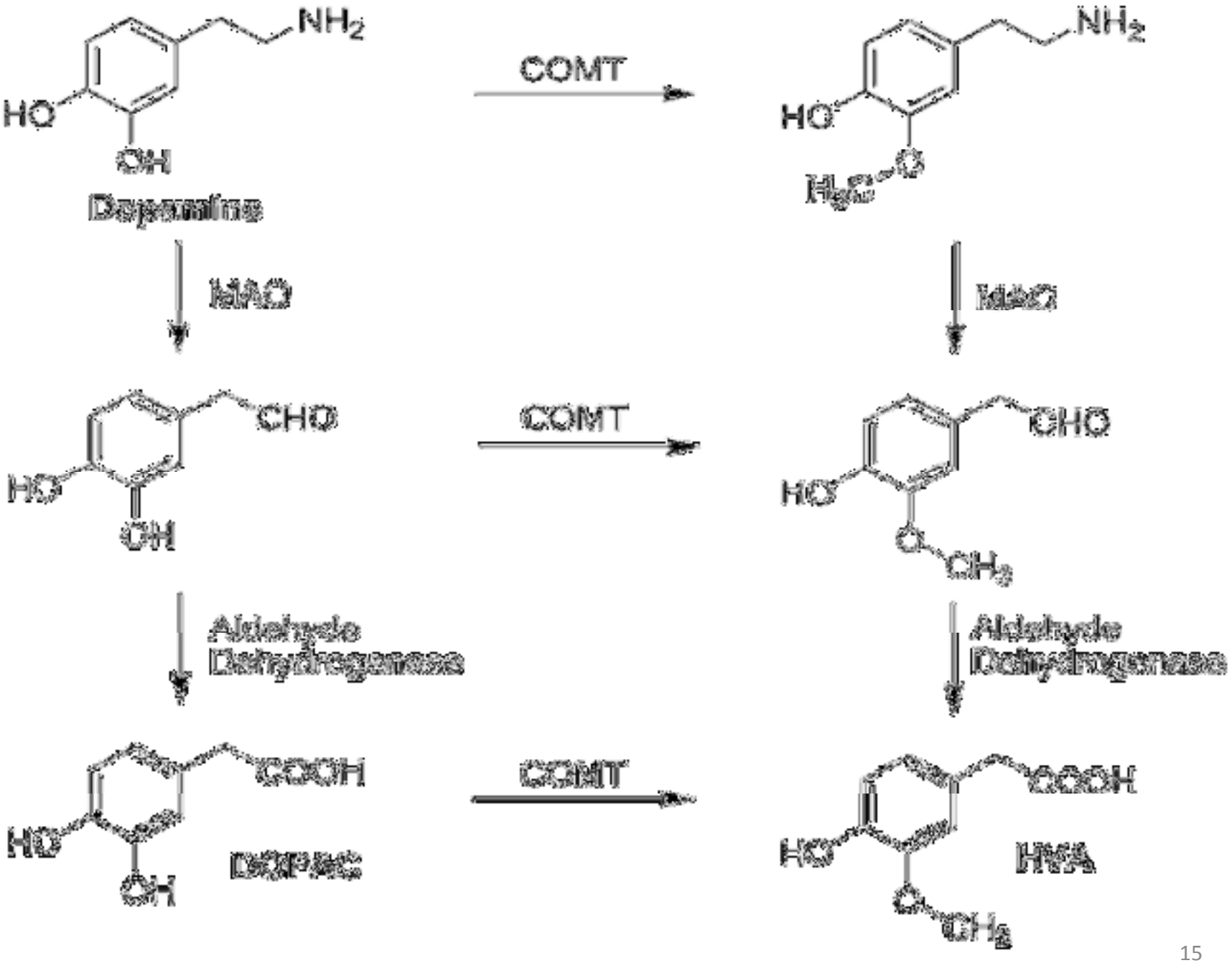
- Oxidative deamination does not occur for norketamine because α-carbon hydroxylation cannot take place.

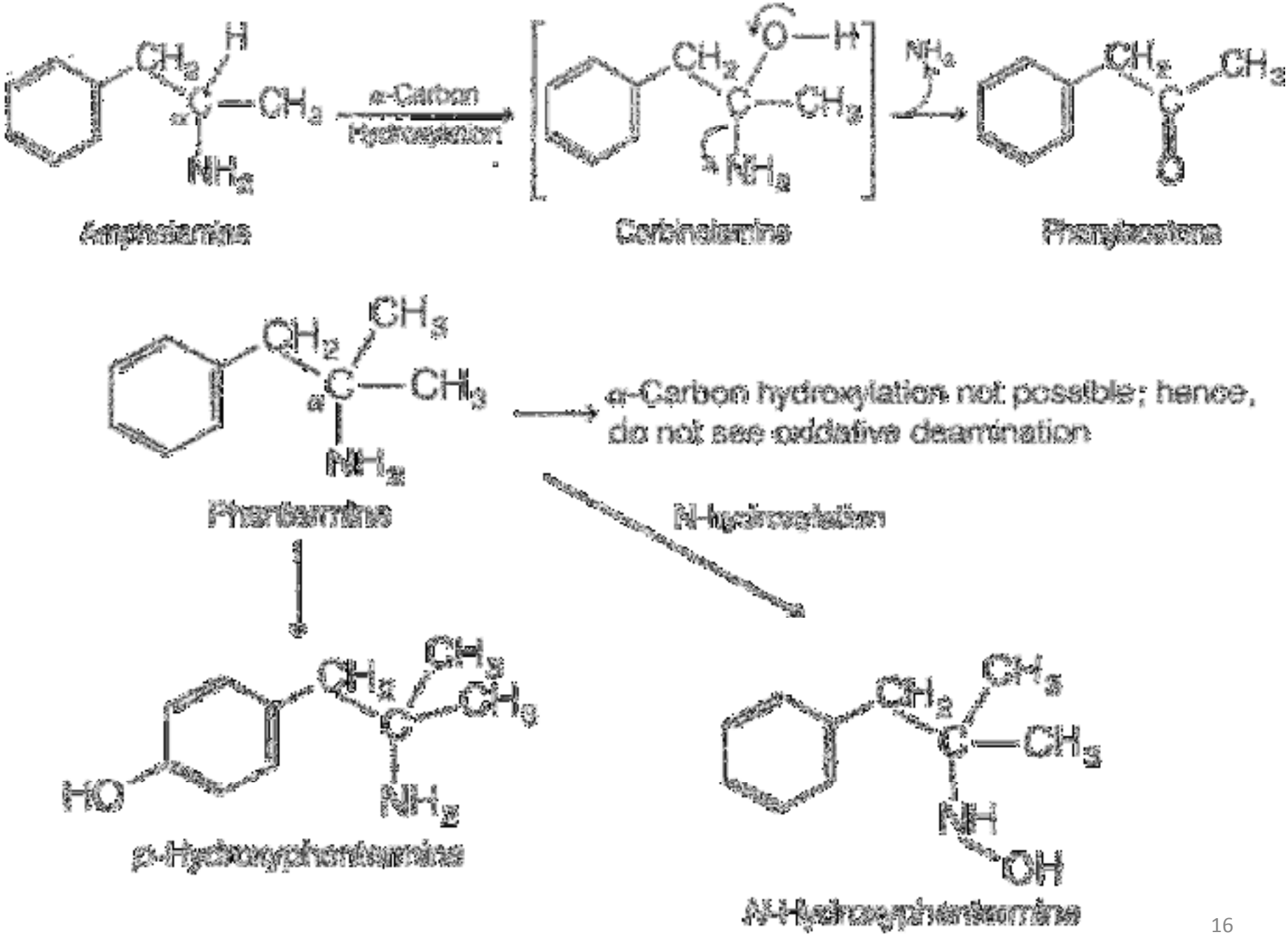


- With methamphetamine, oxidative deamination of primary amine metabolite amphetamine produces phenylacetone.

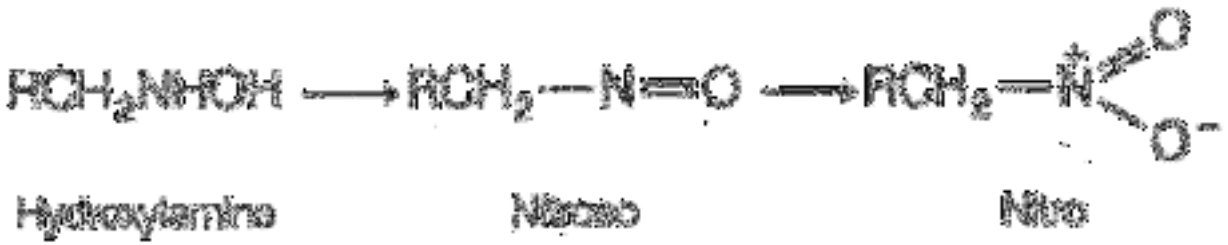


- Primary aliphatic amines (whether parent drugs or metabolites) are biotransformed by oxidative deamination (through the carbinolamine pathway) or by *N*-oxidation.
- Endogenous primary amines (e.g., dopamine, norepinephrine, tryptamine, and serotonin) and xenobiotics based on the structures of these endogenous neurotransmitters are metabolized, however, via oxidative deamination by a specialized family of enzymes called ***monoamine oxidases* (MAOs)**.

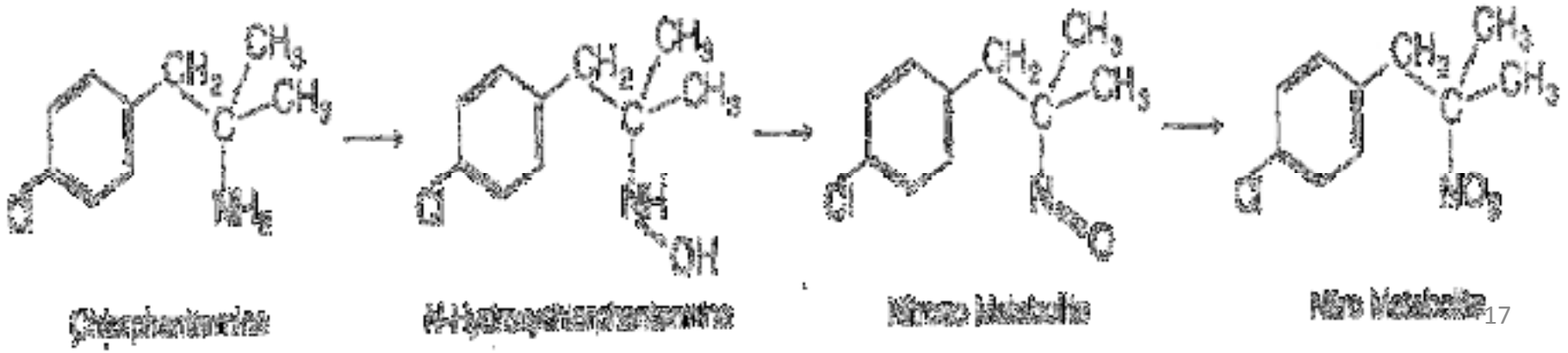

NH2
HO
OH
Dopamine
COMT
NH2
HO
H3C
O
MAO
MAO
CHO
HO
OH
COMT
CHO
HO
O
CH3
Aldehyde
Dehydrogenase
Aldehyde
Dehydrogenase
COOH
HO
OH
DOPAC
COMT
COOH
HO
HVA
O
CH3


α-Carbon Hydroxylation
α-Carbon hydroxylation not possible; hence, do not see oxidative deamination
N-Hydroxylation

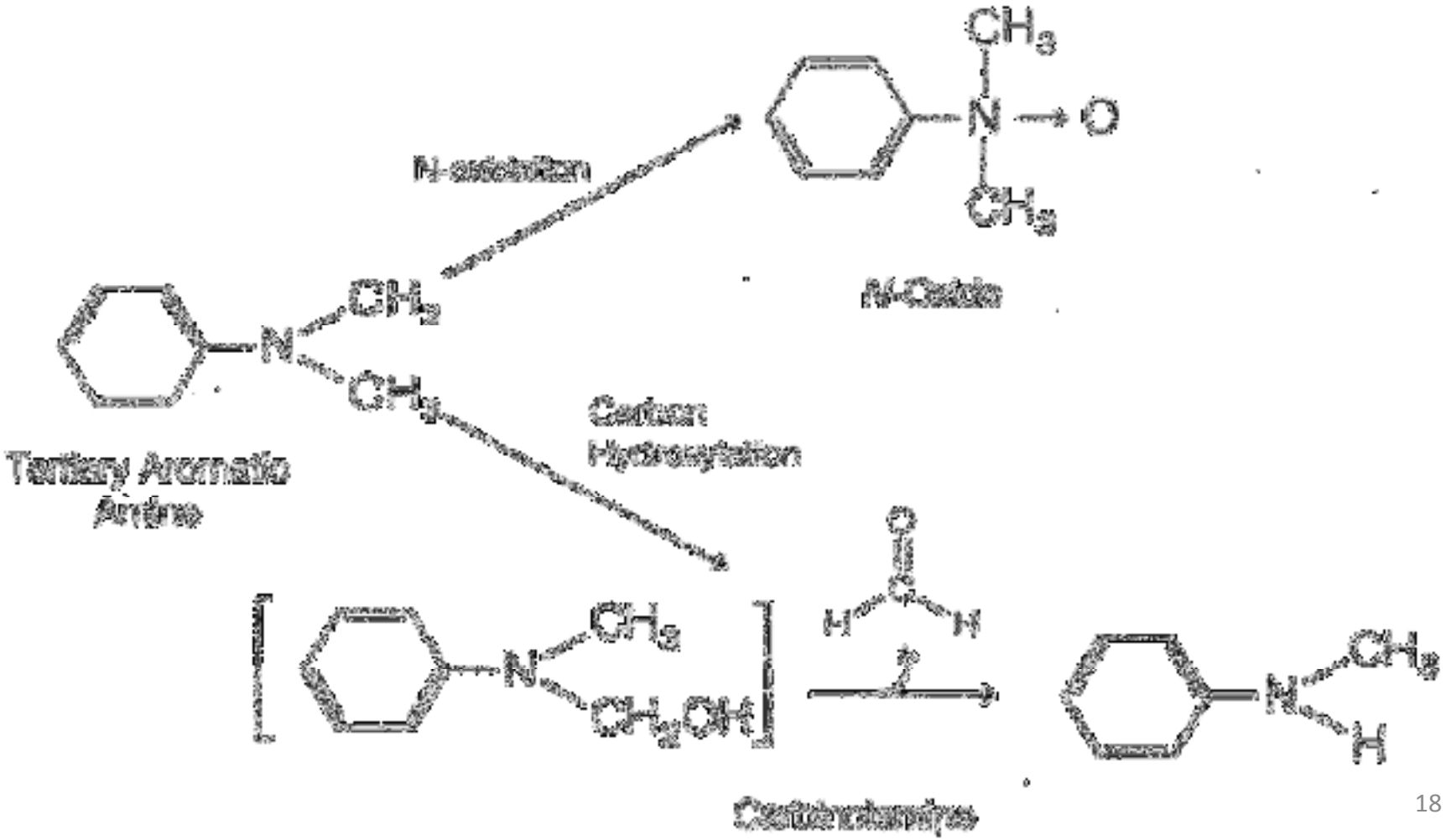
- In general, *N*-hydroxylamines are chemically unstable and susceptible to spontaneous or enzymatic oxidation to the nitroso and nitro derivatives.



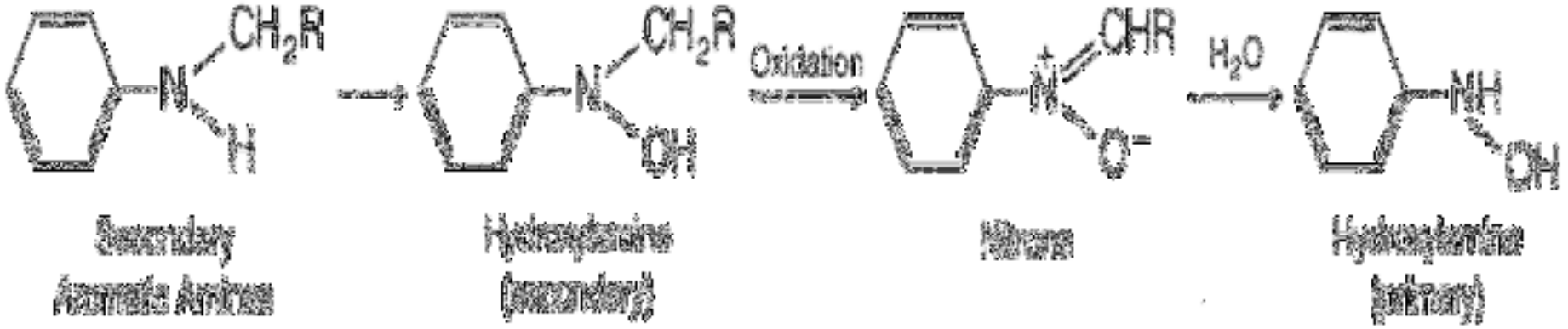
- For example, the *N*-hydroxylamine metabolite of chlorphentermine undergoes further oxidation to the nitroso and nitro products.



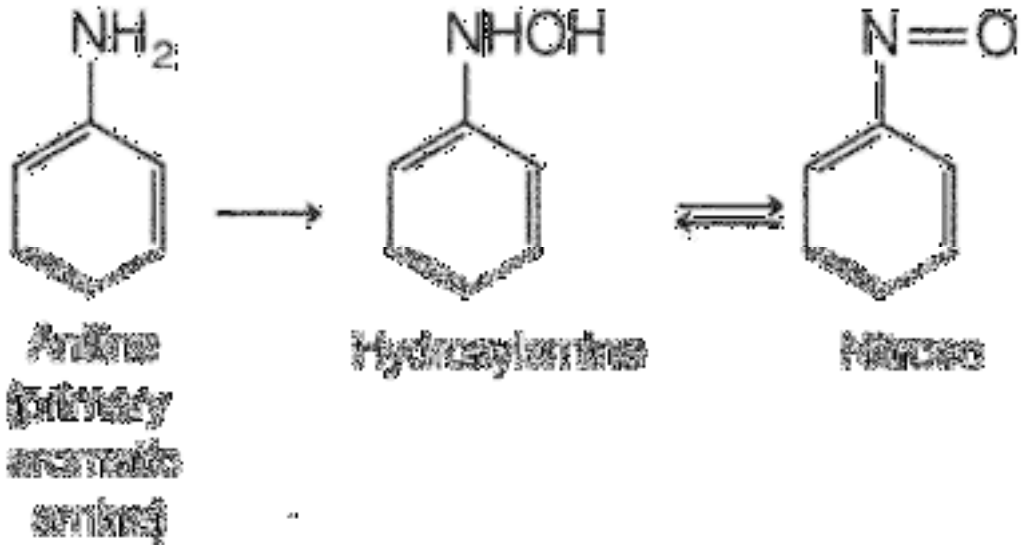
- ***Aromatic Amines and Heterocyclic Nitrogen Compounds.***
- For **tertiary aromatic amines**, such as *N*,*N*-dimethylaniline, oxidative *N*-dealkylation as well as *N*-oxide formation take place.

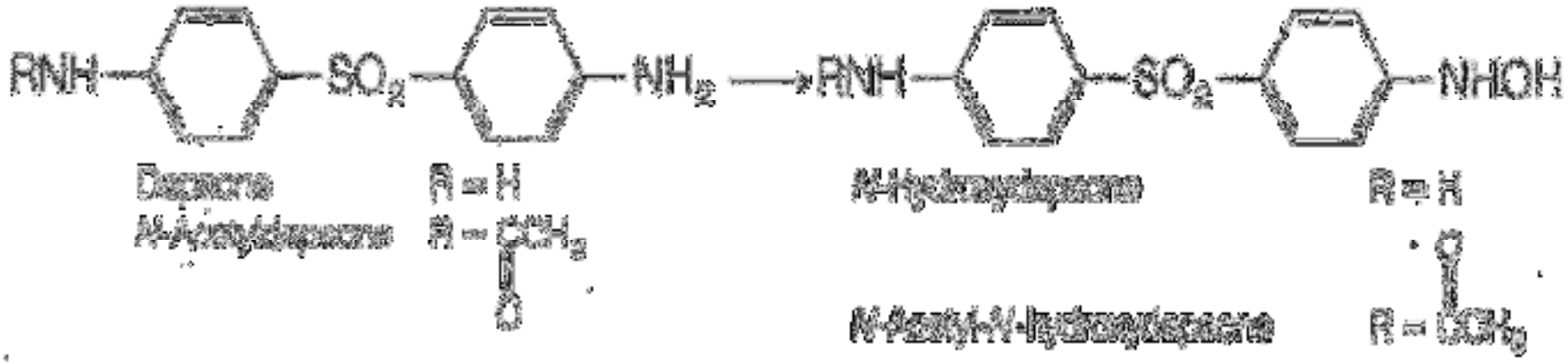


- **Secondary aromatic amines** may undergo *N*-dealkylation or *N*-hydroxylation to give the corresponding *N*-hydroxylamines.
- Further oxidation of the *N*-hydroxylamine leads to nitrone products, which in turn may be hydrolyzed to primary hydroxylamines.

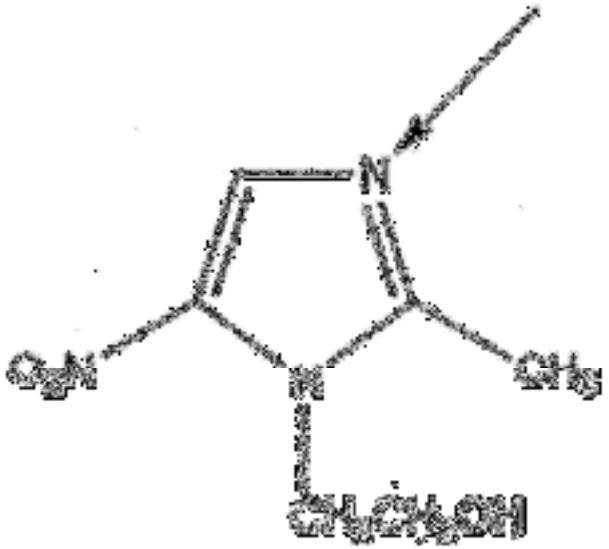


- *N*-oxidation of **primary aromatic amines** generates the *N*-hydroxylamine metabolite.

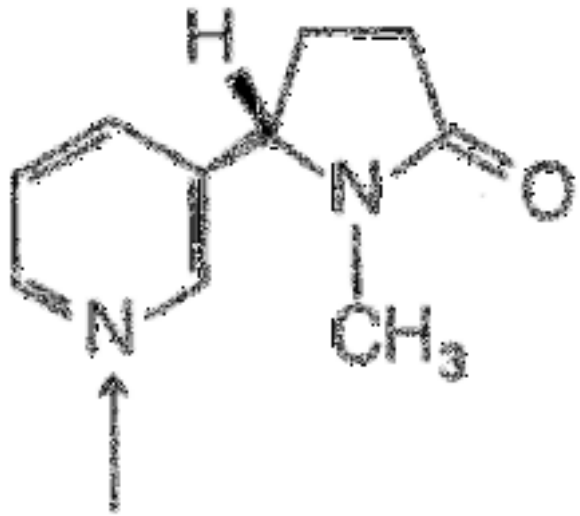




- *N*-oxidation of the nitrogen atoms present in aromatic heterocyclic moieties of many drugs occurs to a minor extent.



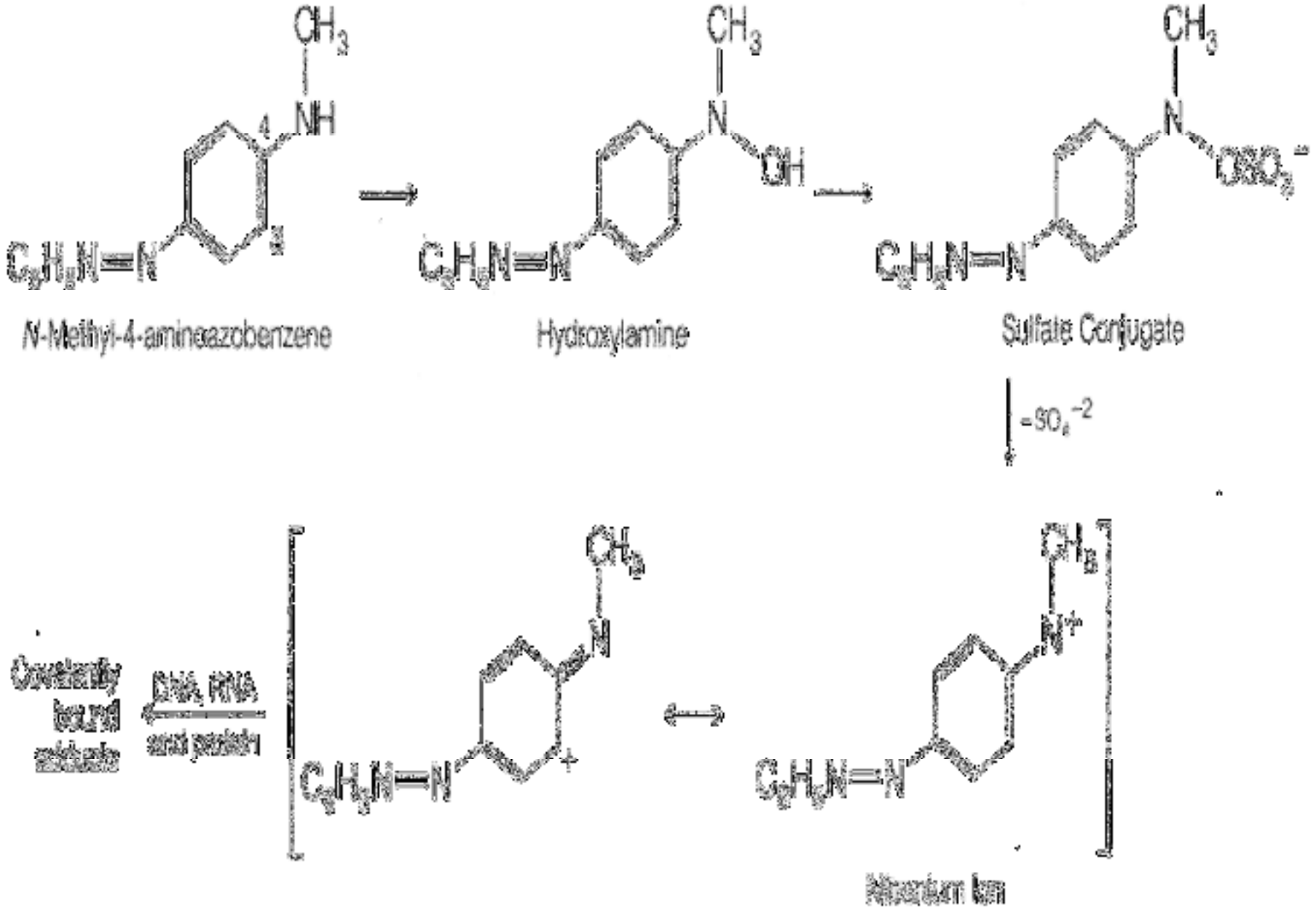
Metronidazole
2-(2-Methyl-6-nitro-imidazol-1-yl)-ethanol



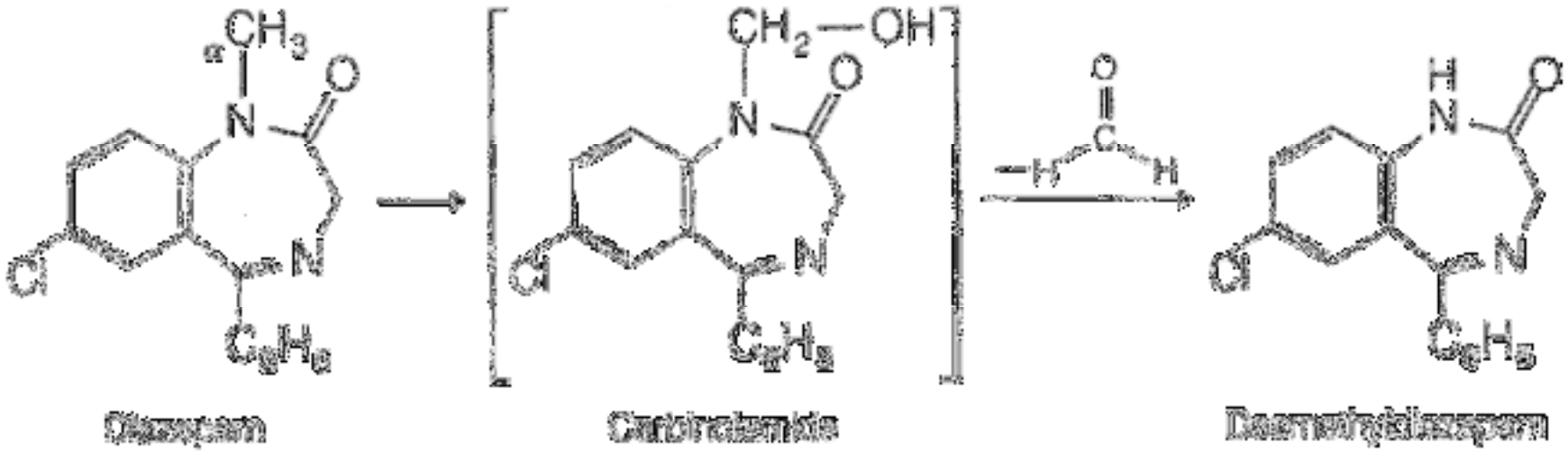
Cotinine

- **Aromatic amines and toxicity:**
- **Methemoglobinemia toxicity** is caused by several aromatic amines, including aniline and dapsone.
- This is a result of the bioconversion of the aromatic amine to its *N*-hydroxy derivative.
- The *N*-hydroxylamine oxidizes the Fe2+ form of hemoglobin to its Fe3+ form.
- This oxidized (Fe3+) state of hemoglobin (called *methemoglobin* or *ferrihemoglobin*) can no longer transport oxygen, which leads to serious hypoxia or anemia, a unique type of chemical suffocation.

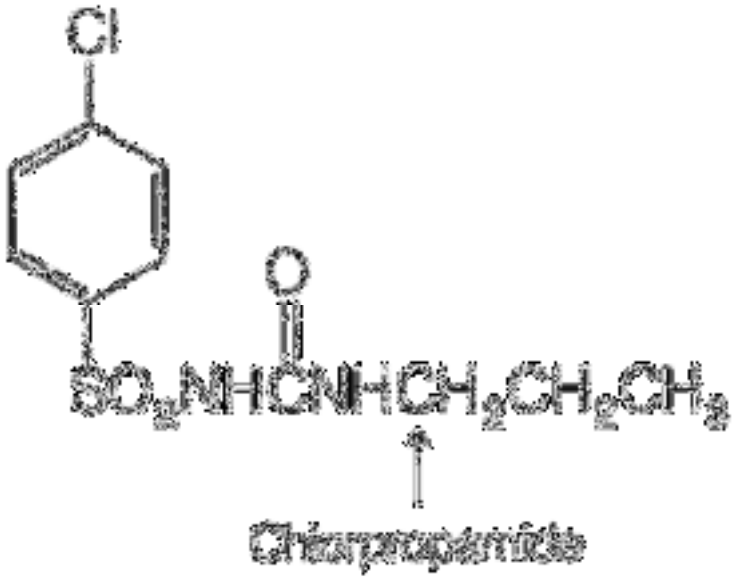
- Diverse aromatic amines (especially azoamino dyes) are known to be **carcinogenic**.
- *N*-oxidation bioactivates these aromatic amines to potentially reactive electrophilic species.
- These reactive electrophilic species covalently bind to cellular protein, DNA, or RNA.

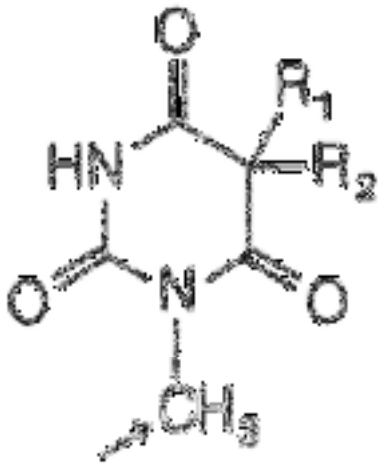

N-Methyl-4-aminoazobenzene
Hydroxylamine
Sulfate Conjugate
$-SO_4^{-2}$
Covalently bound adducts
DNA, RNA and protein
Nitrenium Ion

- ***Oxidation of Amides:***
- Amide functionalities are susceptible to oxidative C-N bond cleavage (via α-carbon hydroxylation) and *N*-hydroxylation reactions.
- Mechanistically, oxidative dealkylation proceeds via an initially formed carbinolamide, which is unstable and fragments to form the *N*-dealkylated product. Example: Benzodiazepines and barbiturates.



- Alkyl groups attached to the amide moiety of some sulfonylureas, such as the oral hypoglycemic chlorpropamide, also are subject to dealkylation to a minor extent.

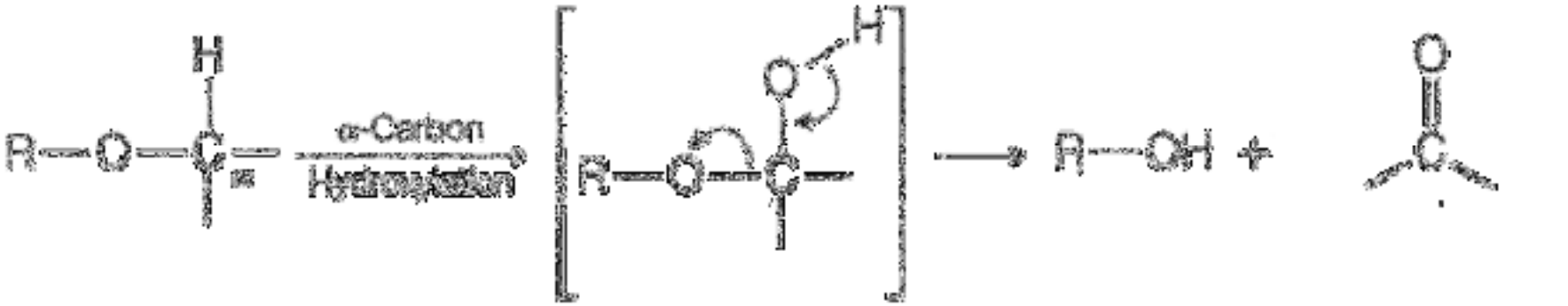


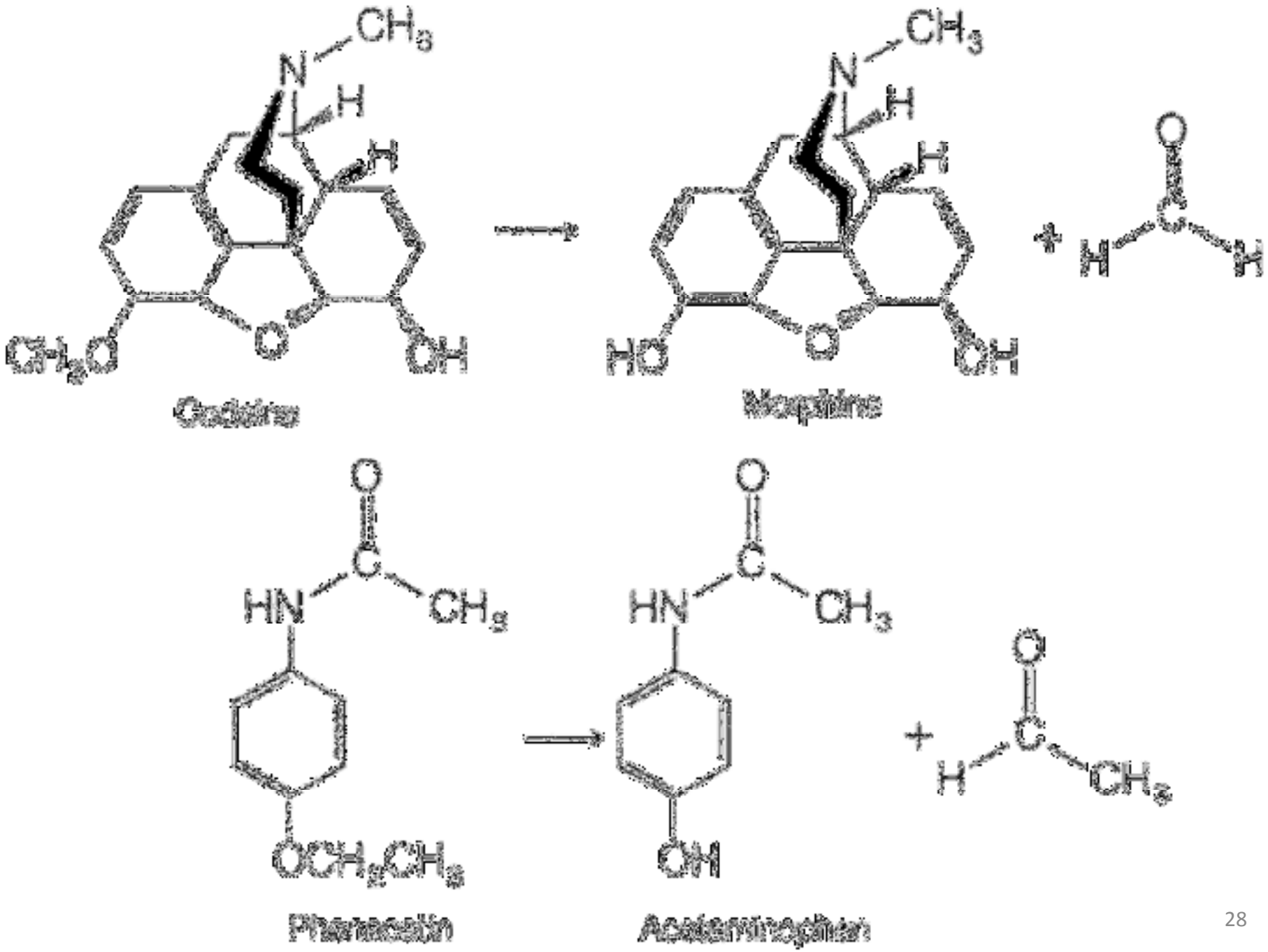


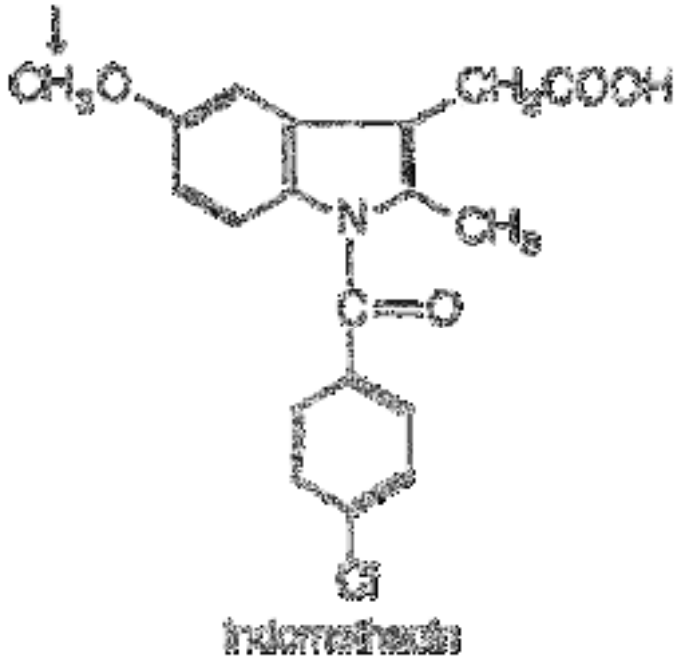
Hexobarbital $R_1 =$  $R_2 = CH_3$

Heptabarbital $R_1 = C_6H_5$, $R_2 = CH_2CH_3$

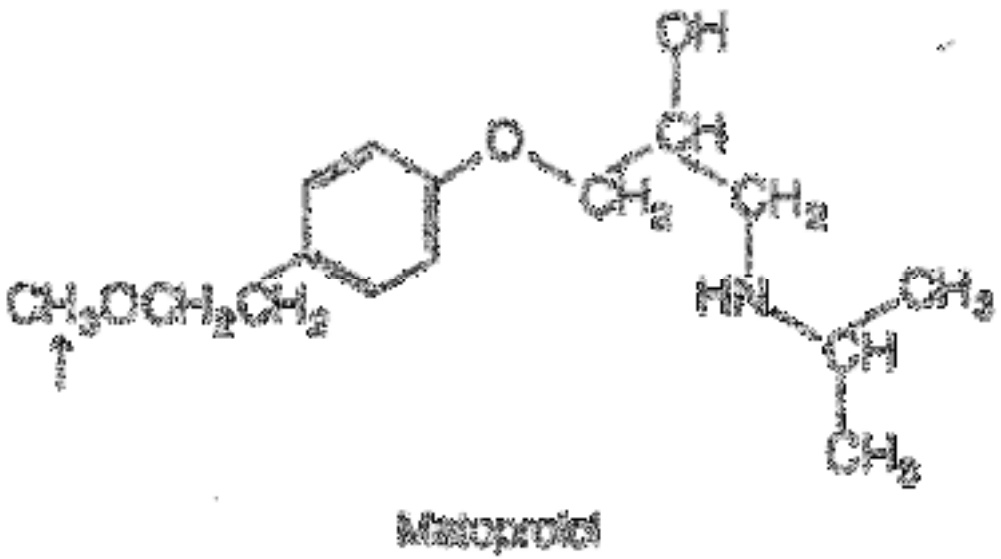
- **OXIDATION INVOLVING CARBON–OXYGEN SYSTEMS:**
- Oxidative *O*-dealkylation of C-O systems is catalyzed by microsomal mixed function oxidases.
- This involves an initial α-carbon hydroxylation to form either a hemiacetal or a hemiketal, which undergoes spontaneous C-O bond cleavage to yield the dealkylated oxygen species (phenol or alcohol) and a carbon moiety (aldehyde or ketone).



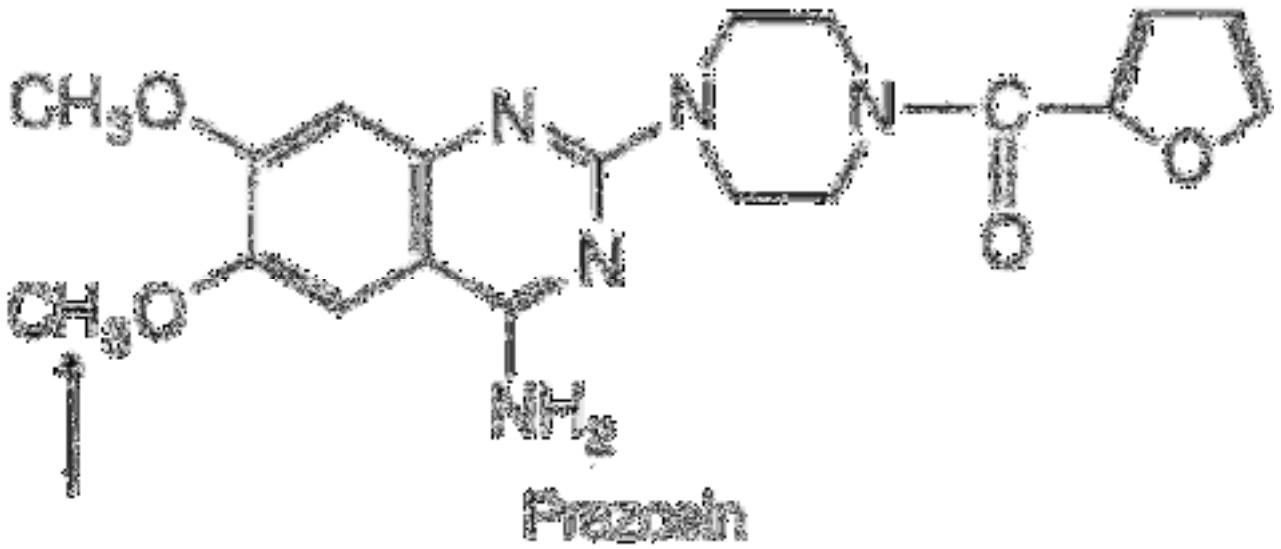

Codeine
Morphine
Phenacetin
Acetaminophen



Indomethacin

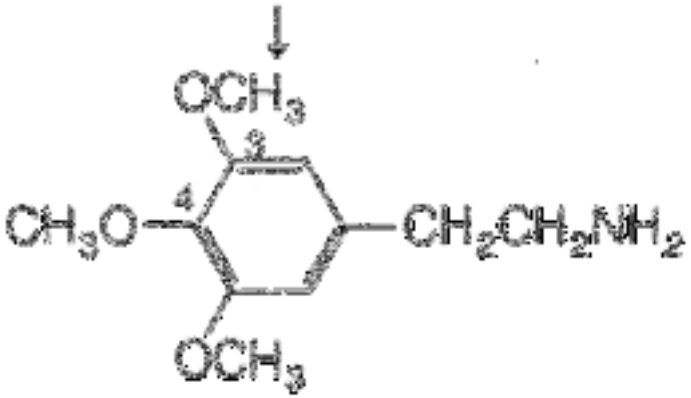


Metoprolol

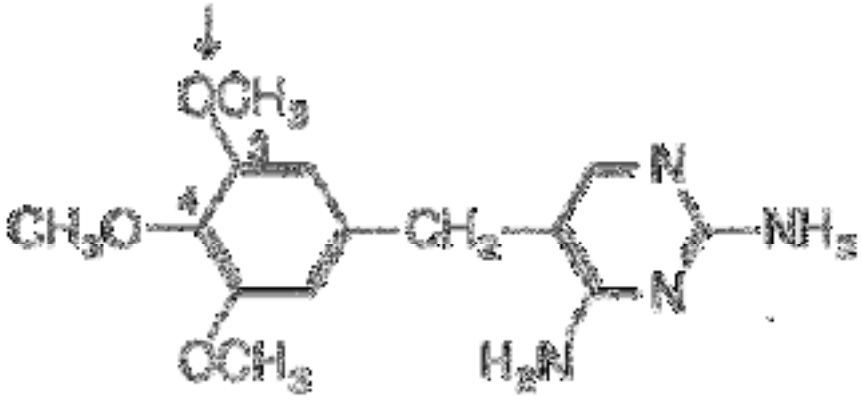


Prazosin

- In many drugs that have several nonequivalent methoxy groups, one particular methoxy group often appears to be *O*-demethylated selectively or preferentially.
- For example, the 3,4,5- trimethoxyphenyl moiety in both mescaline and trimethoprim undergoes *O*-demethylation to yield predominantly the corresponding 3-*O*-demethylated metabolites.
- 4-*O*demethylation also occurs to a minor extent for both drugs.
- The phenolic and alcoholic metabolites formed from oxidative *O*-demethylation are susceptible to conjugation, particularly glucuronidation.

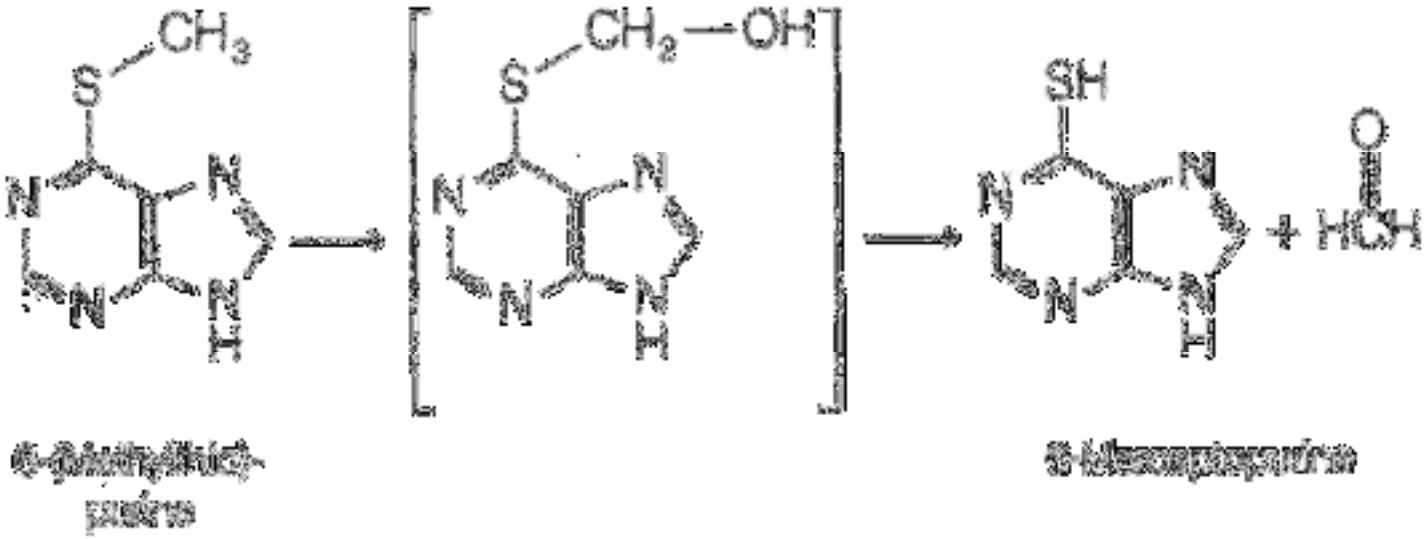


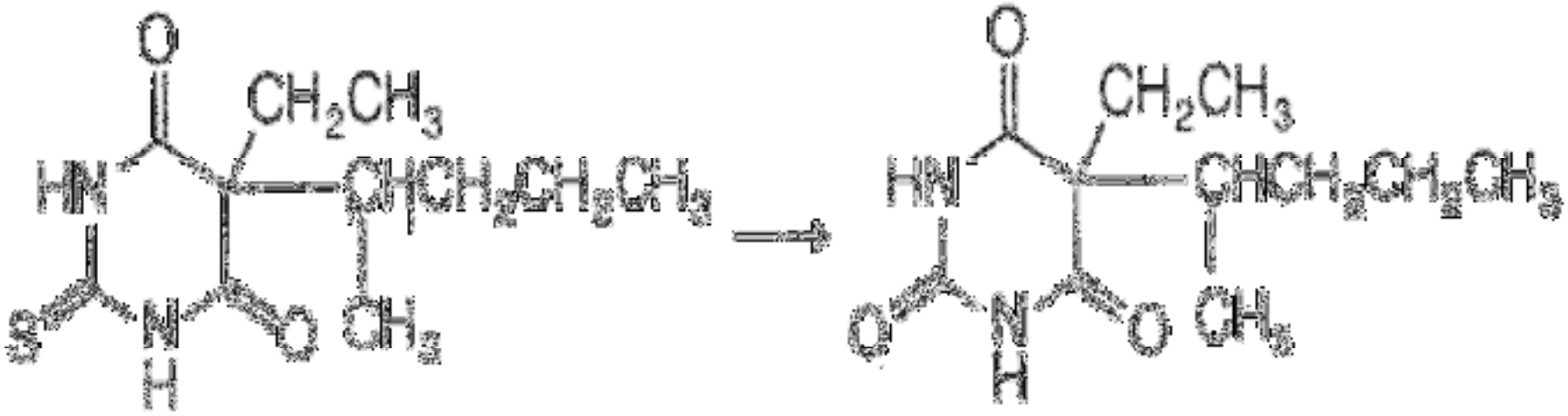
Mescaline

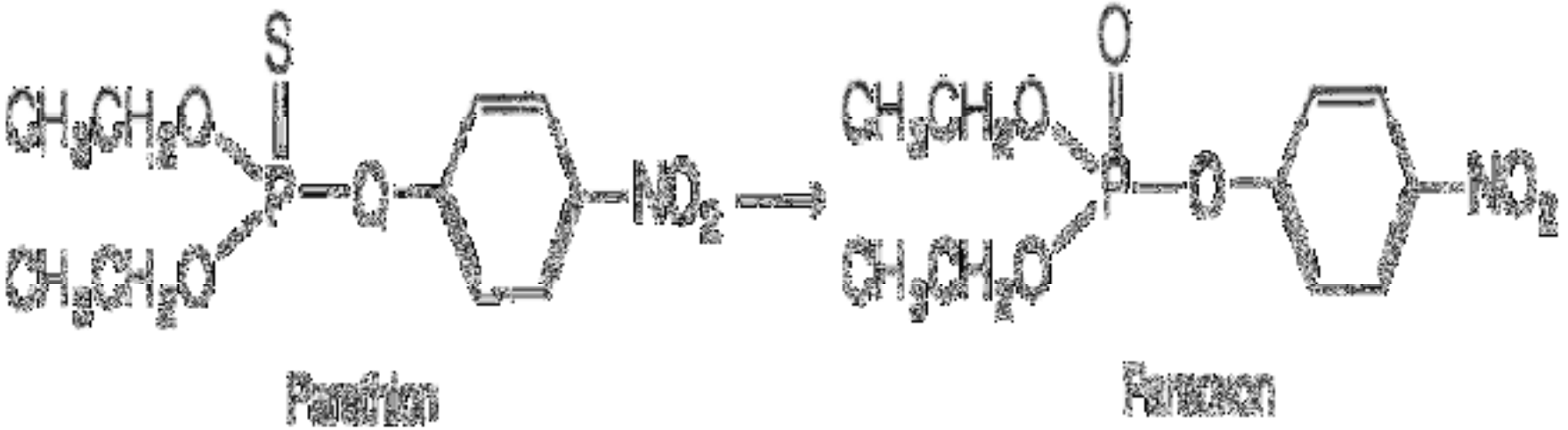


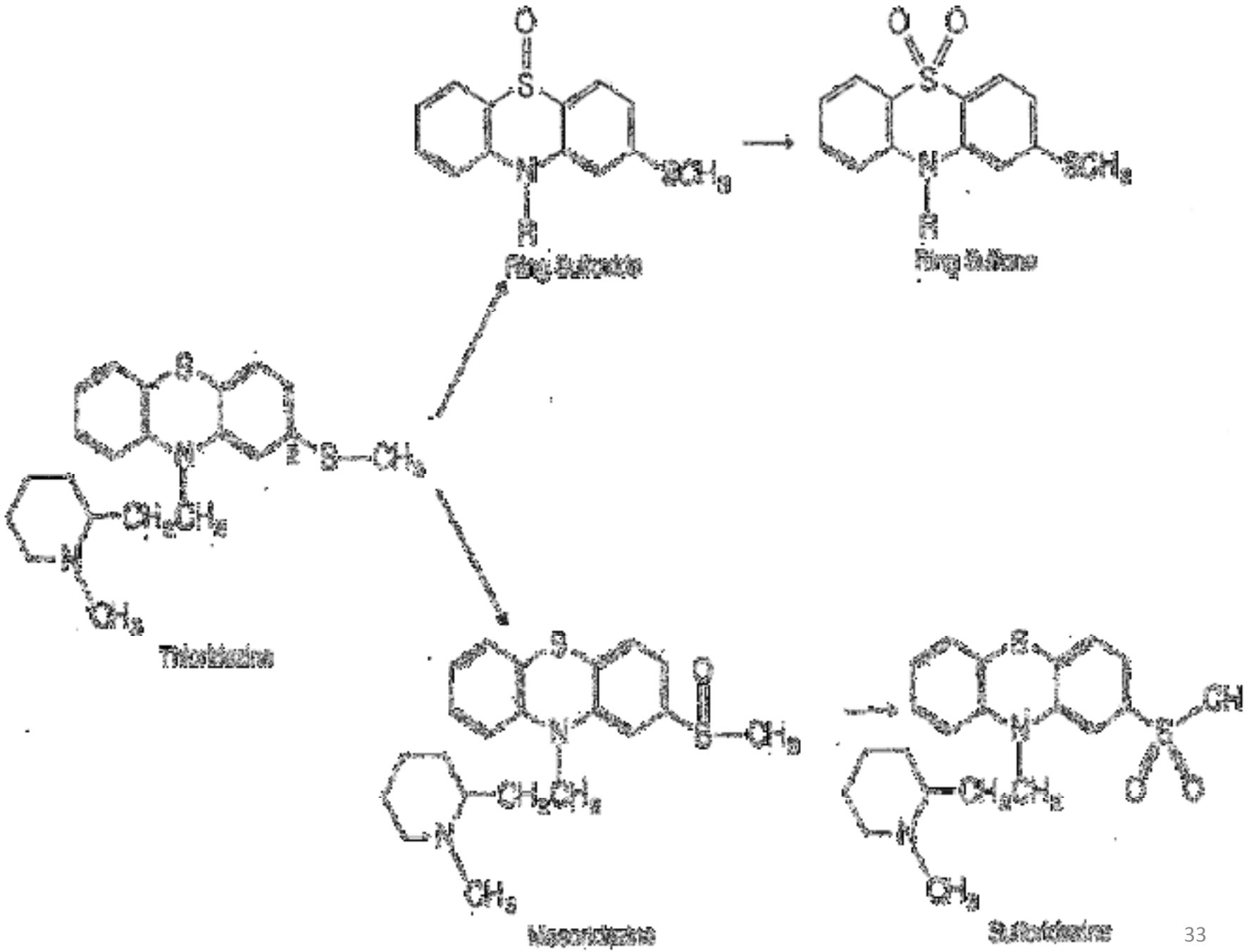
Trimethoprim

- **OXIDATION INVOLVING C–S SYSTEMS:**
- Carbon–sulfur functional groups are susceptible to metabolic *S*-dealkylation, desulfuration, and *S*-oxidation reactions.
- The first two processes involve oxidative C–S bond cleavage.
- *S*-dealkylation is analogous to *O*- and *N*-dealkylation mechanistically (i.e., it involves α-carbon hydroxylation).

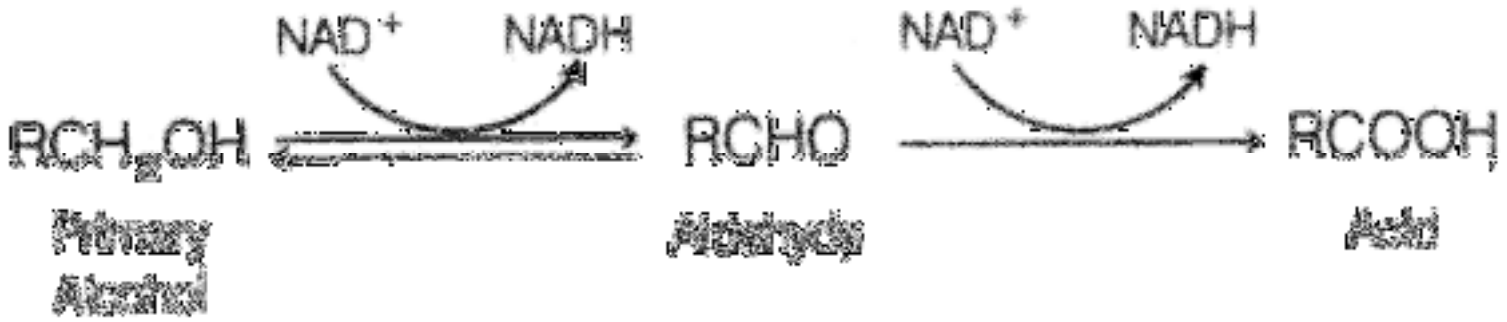



Thiopental
Pentobarbital


Parathion
Paraoxon



- **Oxidation of Alcohols and Aldehydes:**
- Many oxidative processes 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 from oxidation of primary alcohols or oxidative deamination of primary aliphatic amines undergo oxidation to generate polar carboxylic acid derivatives.



- The secondary alcohols are susceptible to oxidation but this reaction is not important because-

➢ reduction of the ketone back to the secondary alcohol, occurs quite readily.

➢ the secondary alcohol group is more likely to be conjugated than the ketone moiety.

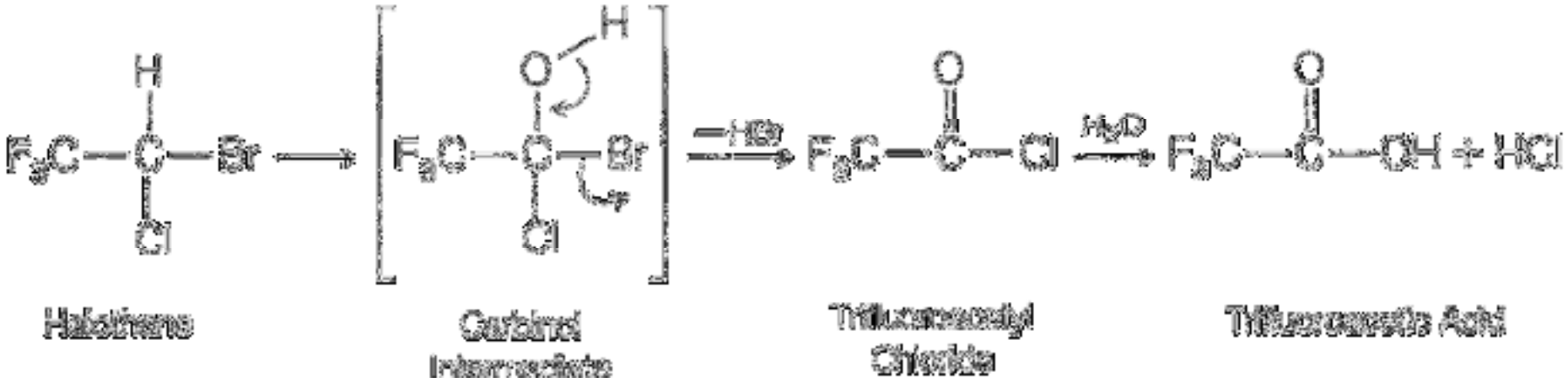
- Enzymes and co-enzymes involved:

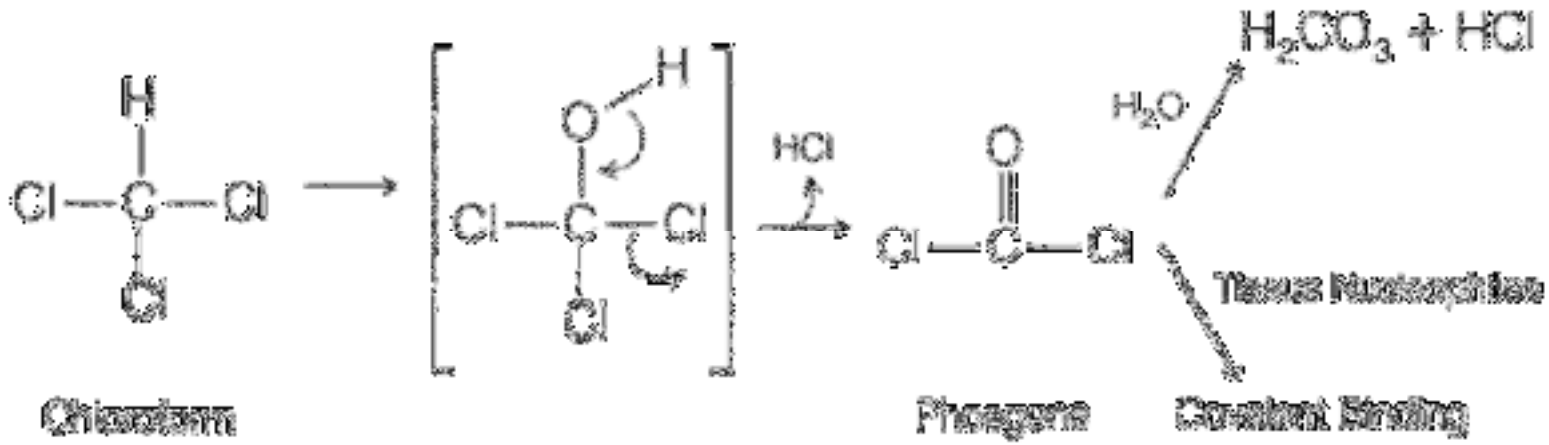
➢ Soluble alcohol dehydrogenases.

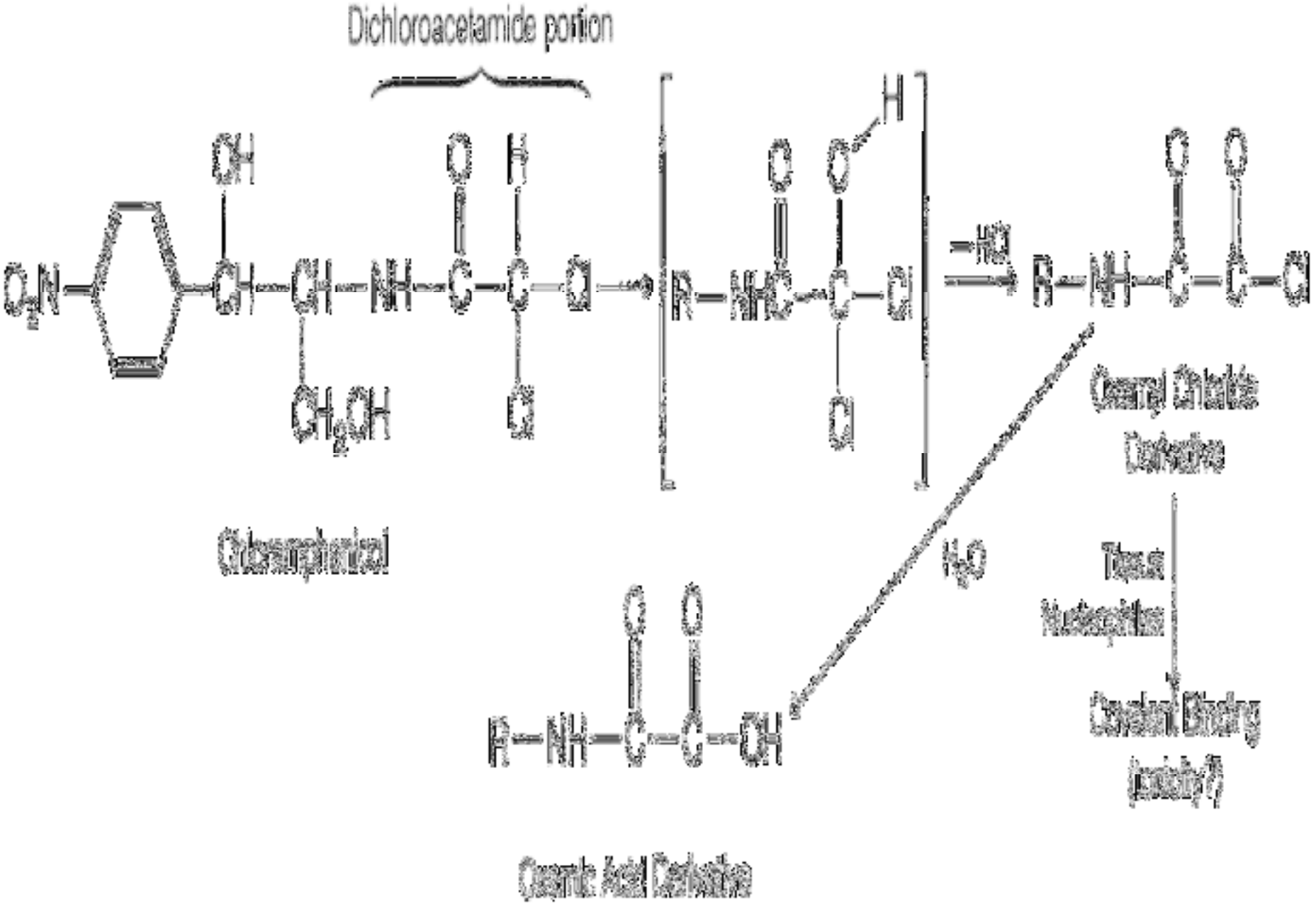
➢ Aldehyde oxidase and Xanthine oxidase.

➢ NAD and NADP.

- **Oxidative dehalogenation:**
- Many halogen-containing drugs and xenobiotics are metabolized by oxidative dehalogenation.

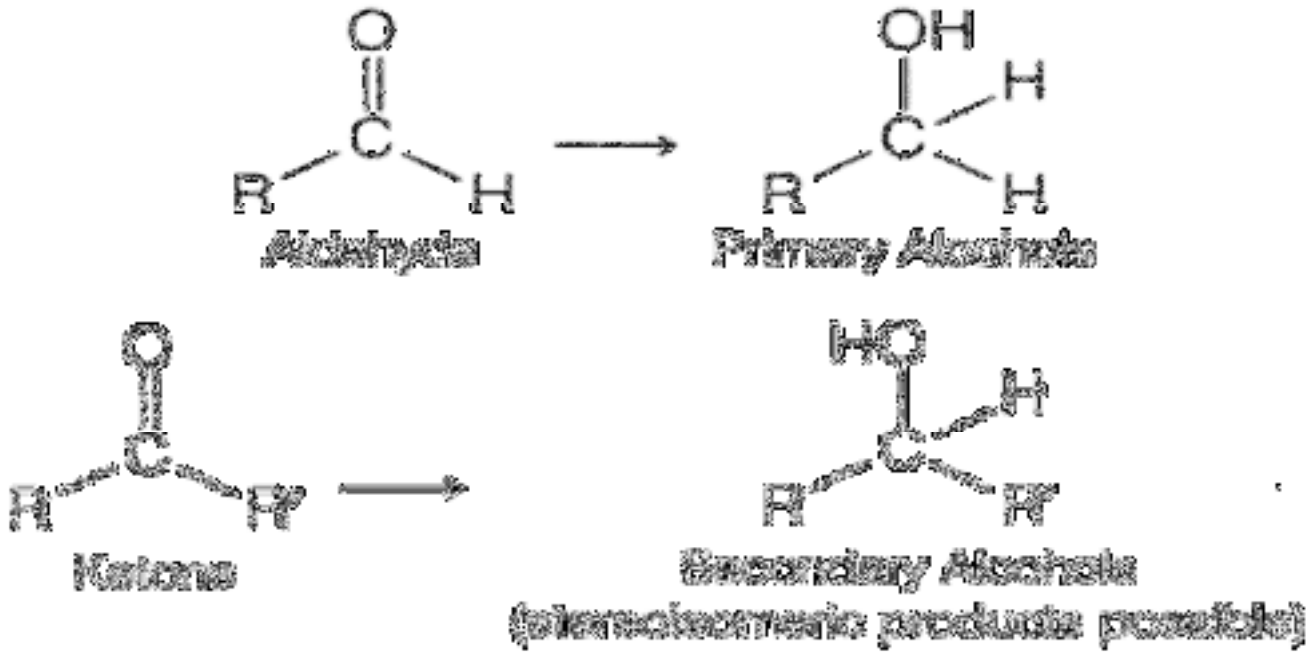





Dichloroacetamide portion
Chloramphenicol
Cleavage Chloride Derivative
Tissue Nucleophiles
Covalent Binding (toxicity?)
Organic Acid Derivative

- **REDUCTIVE REACTIONS**
- Reductive processes 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.
- Hence, reductive processes, as such, facilitate drug elimination.

- **Reduction of Aldehyde and Ketone Carbonyls:**
- Few aldehydes undergo bioreduction because of the relative ease of oxidation of aldehydes to carboxylic acids.
- Ketones are generally resistant to oxidation and are reduced mainly to secondary alcohols.
- Alcohol metabolites arising from reduction of carbonyl compounds generally undergo further conjugation (e.g., glucuronidation).

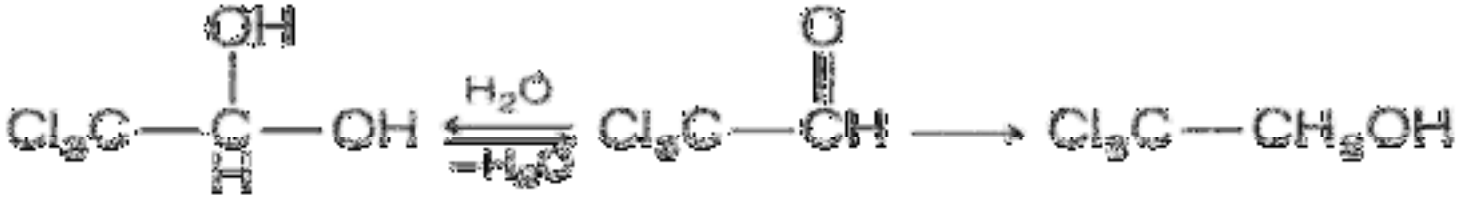


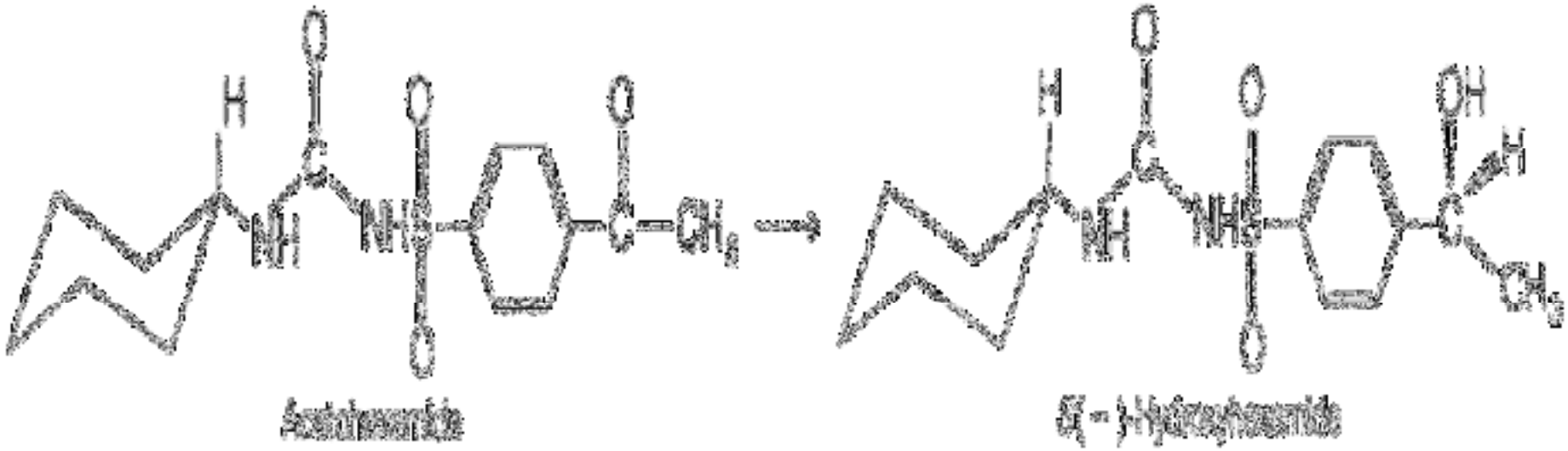
- **Enzymes:**

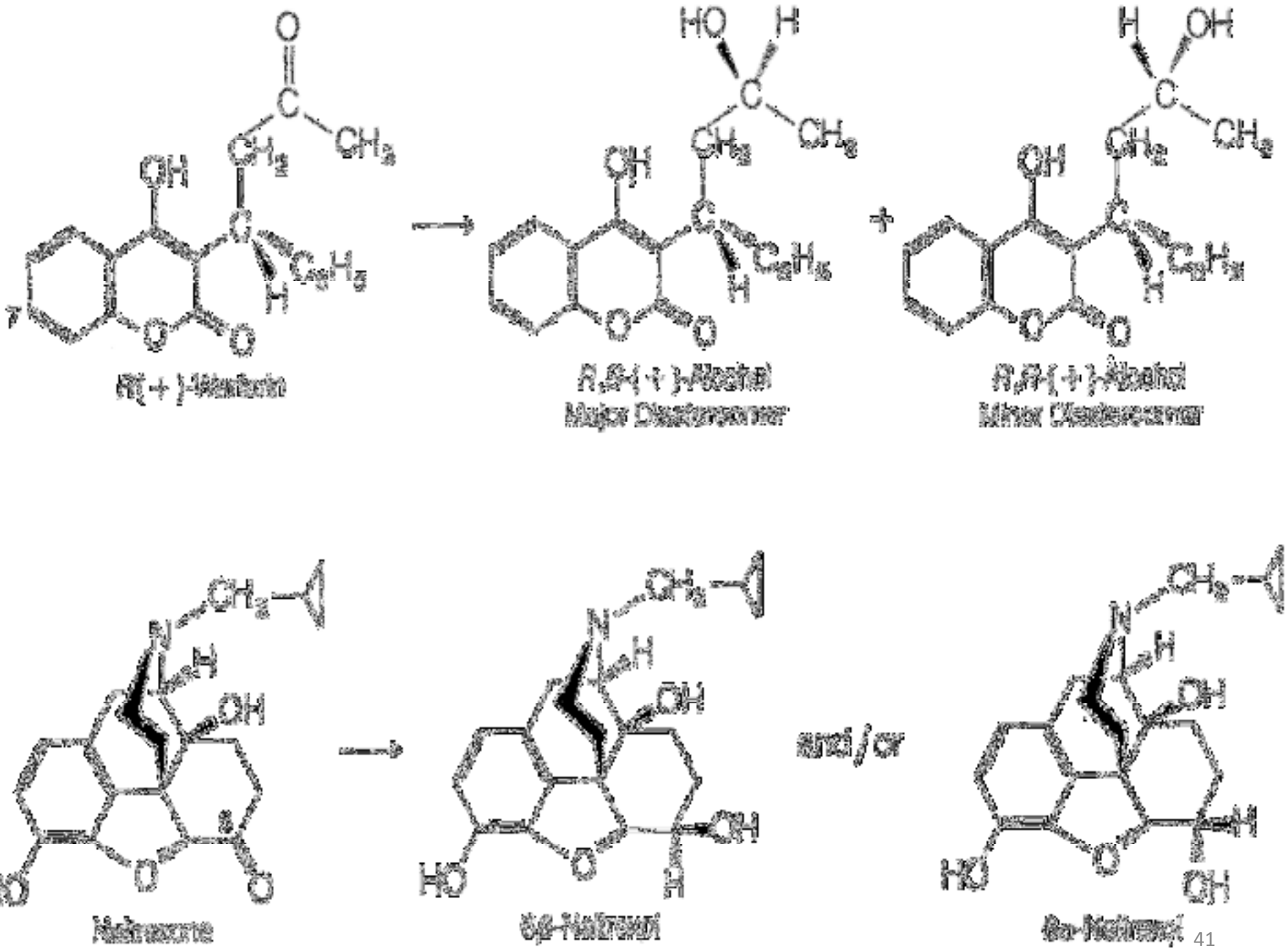
➢ Aldo-keto reductases

➢ Oxidoreductase

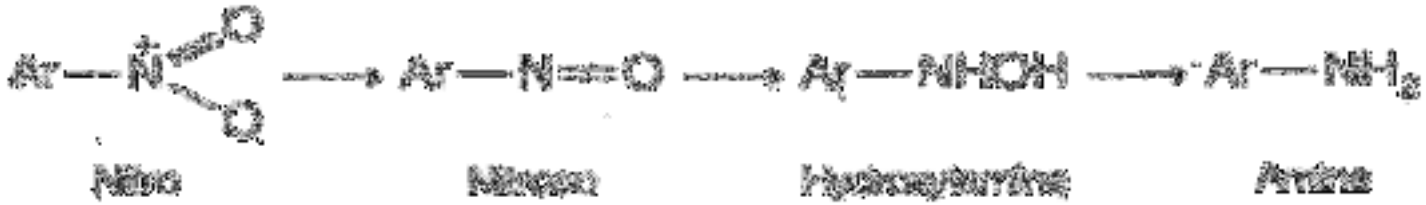
➢ Alcohol dehydrogenase



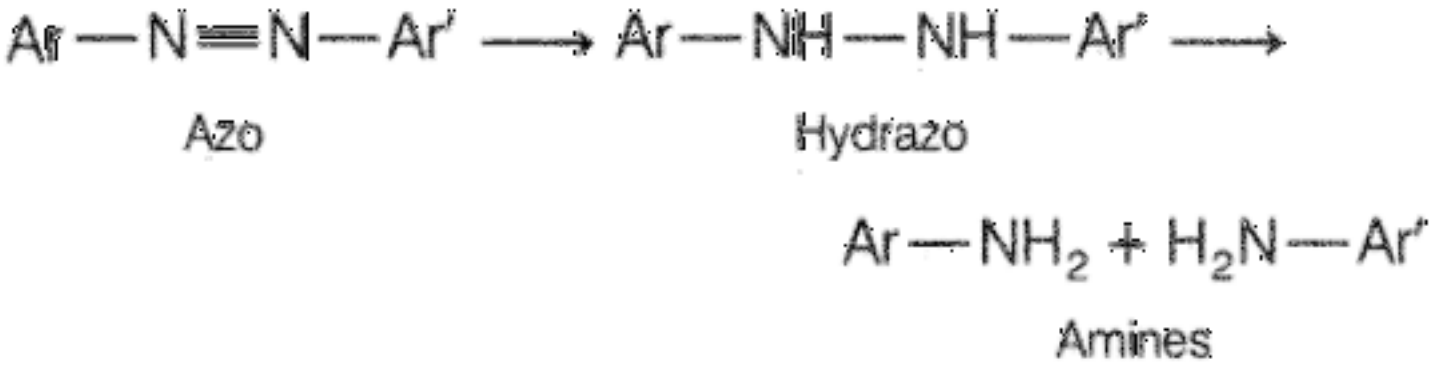


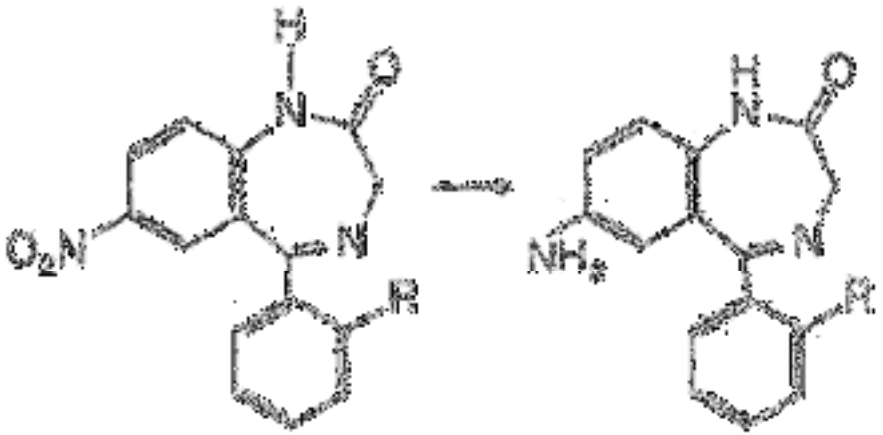


- **Reduction of Nitro and Azo Compounds:**
- Aromatic nitro compounds are reduced initially to the nitroso and hydroxylamine intermediates and finally in to primary amine metabolite.



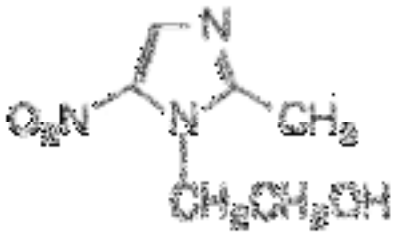
- Azo reduction proceeds via hydrazo intermediate (-NH-NH-) that subsequently is cleaved reductively to yield the corresponding aromatic amines.



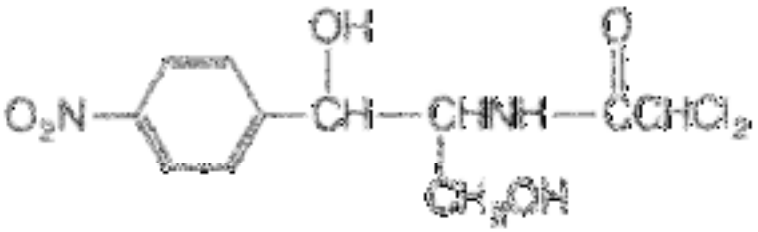


Clonazepam, R = Cl
Nitrazepam, R = H

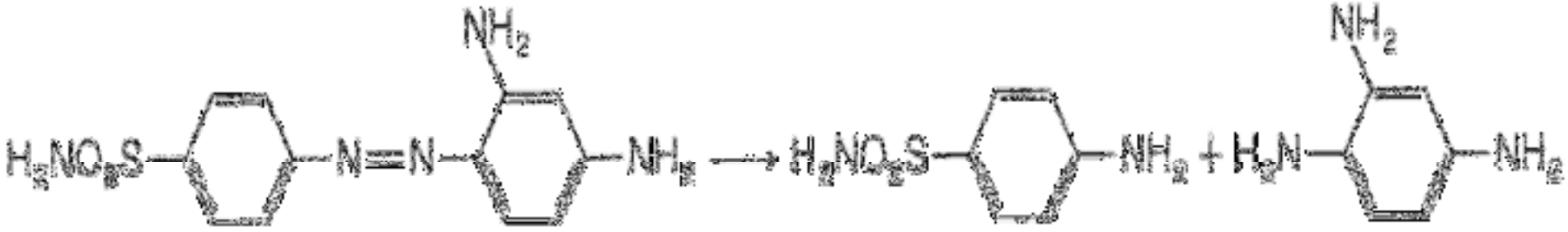
7-Amino Metabolite



Nitroimidazole



Chloramphenicol



Sulfanilamidopyridine (Prontosil)

Sulfanilamide

1,2,4-Diaminobenzene

- **Reduction of *N*-oxides:**
- Reduction of *N*-oxides to the corresponding tertiary amine occurs to some extent.
- If reduction of *N*-oxide metabolites occurs to a significant extent, drug elimination of the parent tertiary amine is delayed.
- For example, imipramine *N*-oxide.
- **Reduction of sulfur-containing functional groups:**
- Reduction of sulfur-containing functional groups such as the disulfide and sulfoxide moieties, also undergo a minor reductive metabolism.
- Reductive cleavage of the disulfide bond in disulfiram and reduction of sulfone & sulfoxide in sulindac are few examples.

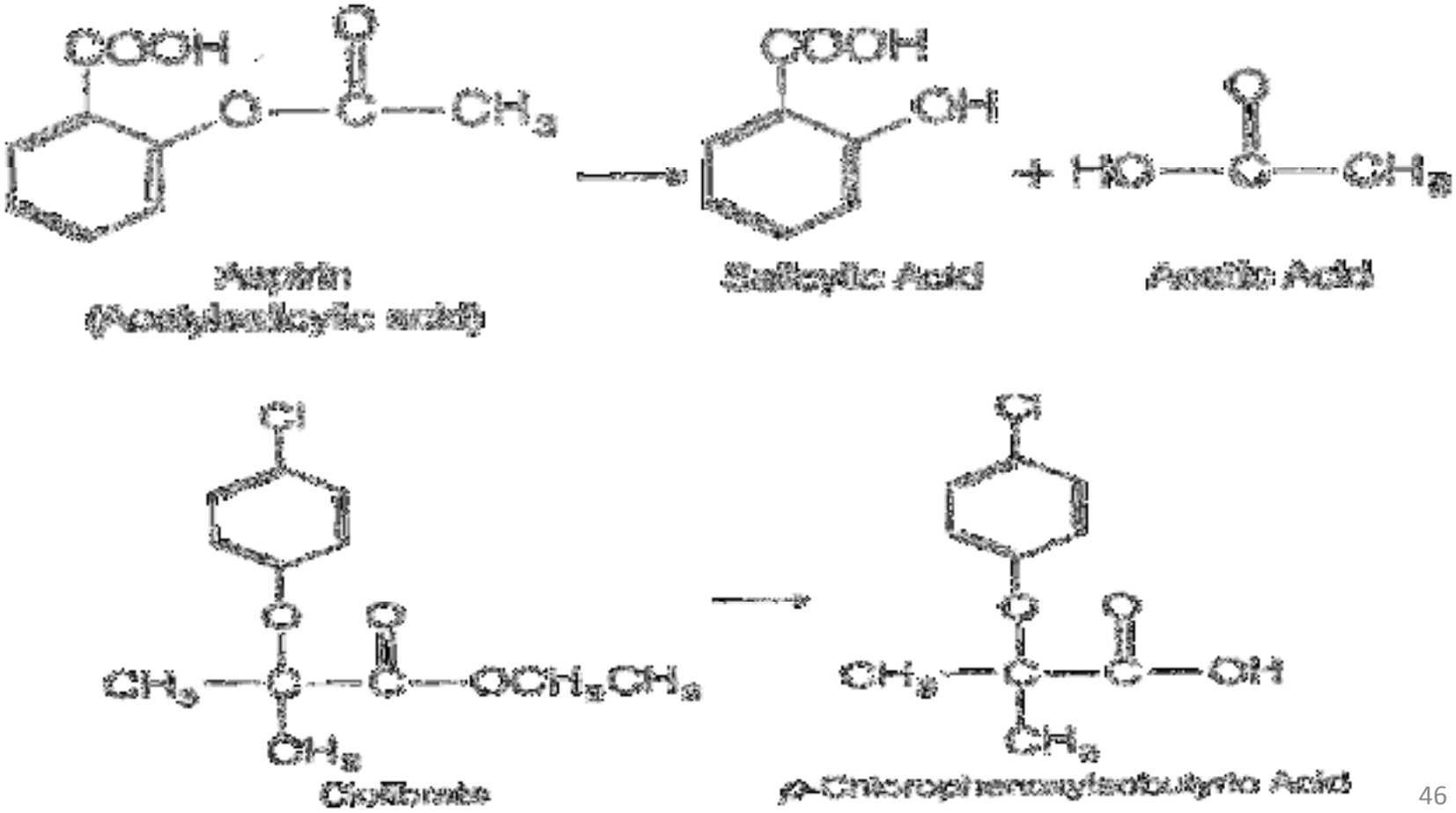
- **HYDROLYTIC REACTIONS**
- **Hydrolysis of Esters and Amides:**
- The metabolism of ester and amide linkages in many drugs is common.
- The metabolites formed (carboxylic acids, alcohols, phenols, and amines) are polar and functionally more susceptible to conjugation and excretion.
- **Enzymes involved:**

➢ Nonspecific esterases

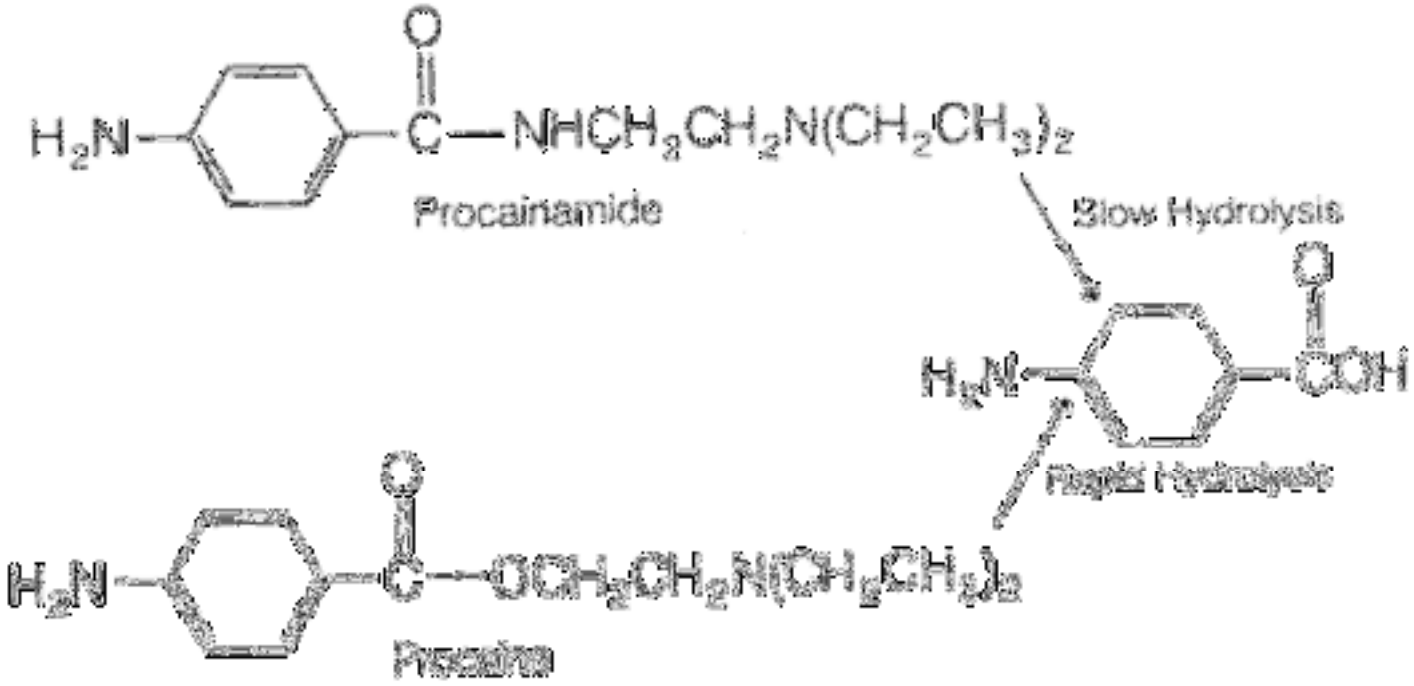
➢ Pseudocholinesterases

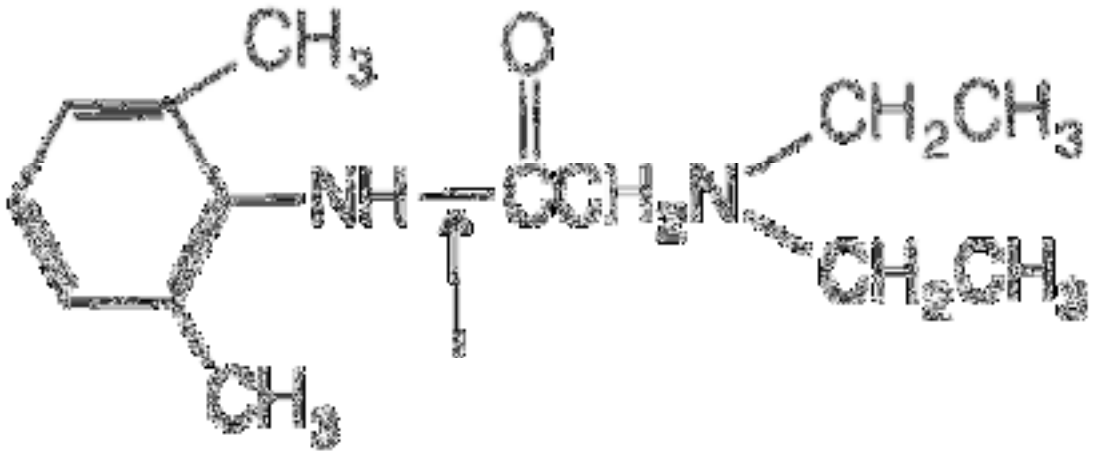
➢ Amidases, esterases, and deacylases

- Hydrolysis is a major biotransformation pathway for drugs containing an ester functionality.
- This is because of the relative ease of hydrolyzing the ester linkage.
- Examples include aspirin, clofibrate, chloramphenicol palmitate, ACE inhibitors, local anesthetics and etc.

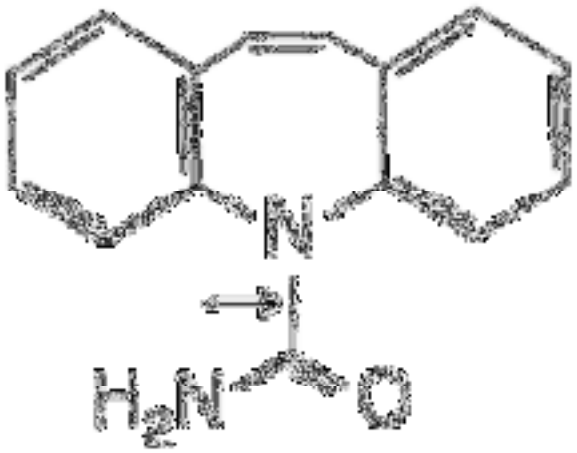


- Amides are hydrolyzed slowly in comparison to esters.
- Example is hydrolysis of the amide bond in procainamide is relatively slow compared with hydrolysis of the ester linkage in procaine.
- Examples include lidocaine, carbamazepine, indomethacin, prazosin, barbiturates, hydantoins and succinimides.

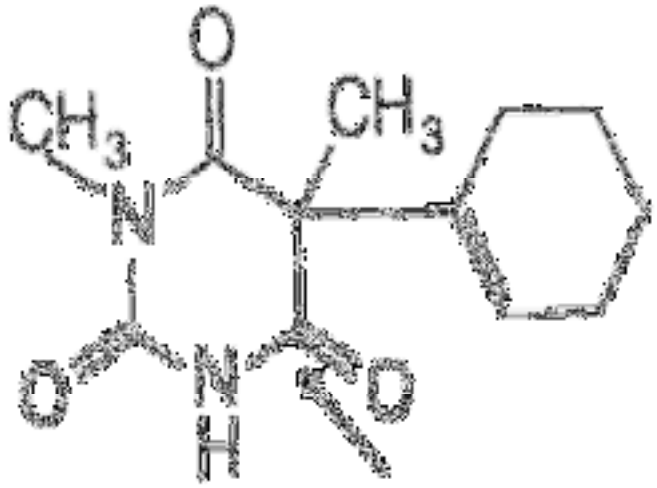




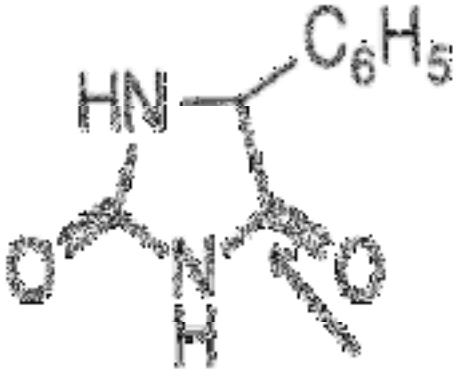
Lidocaine



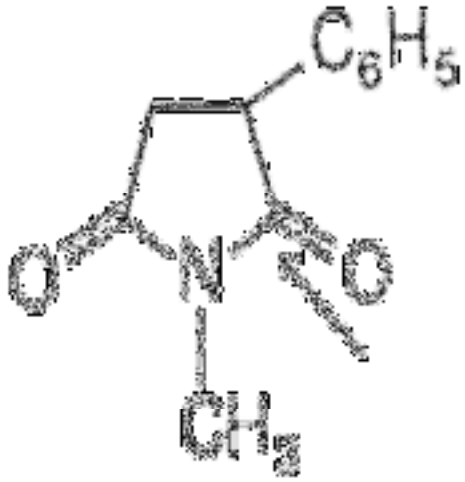
Carbamazepine



Hexobarbital

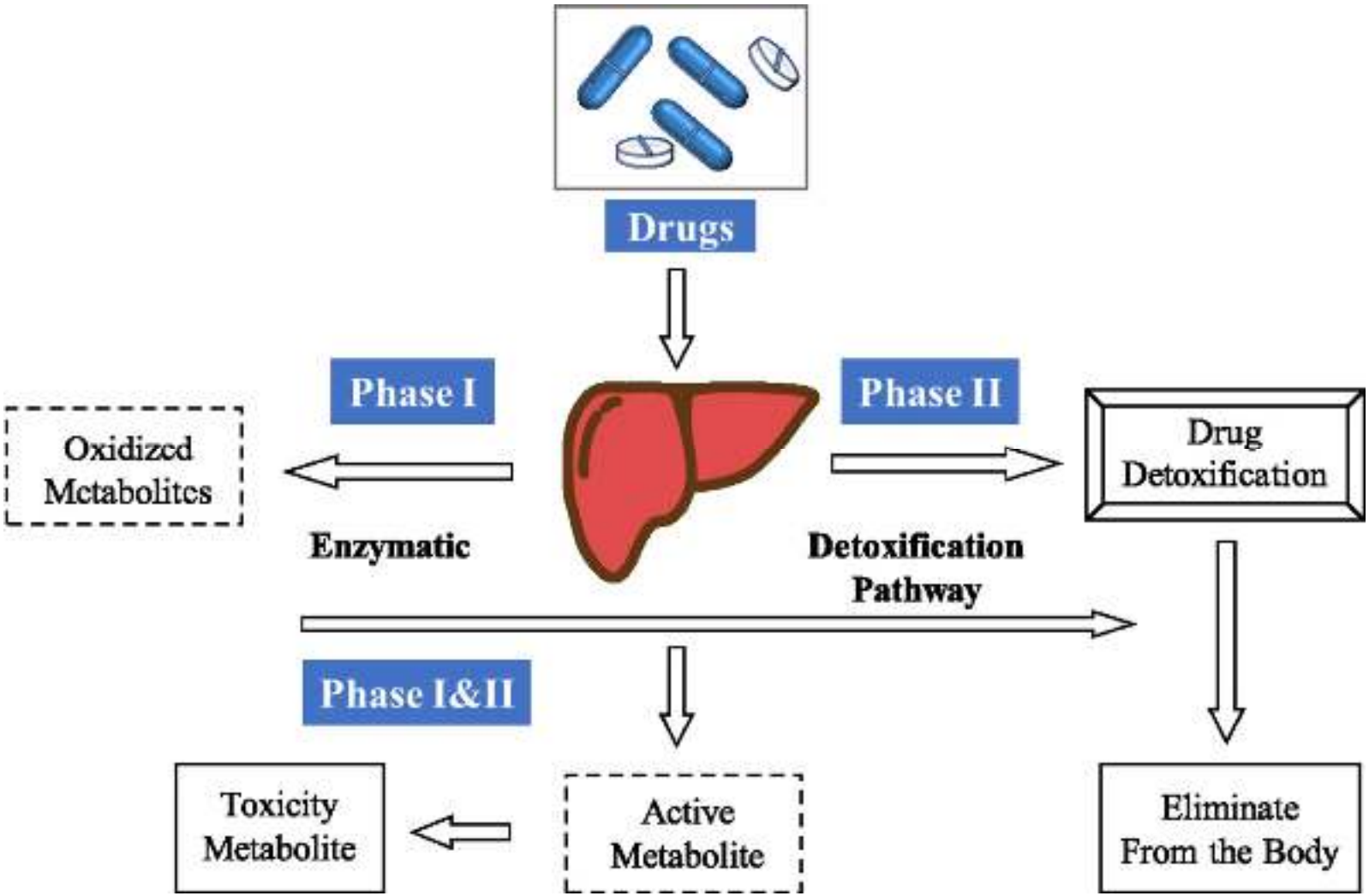


5-Phenylhydantoin

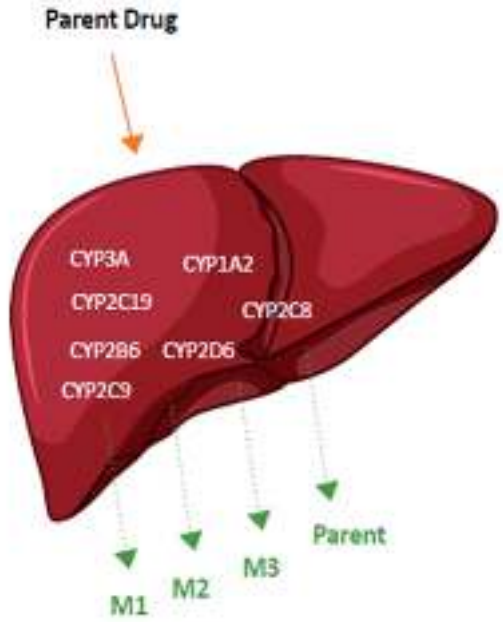


Fluorouracil

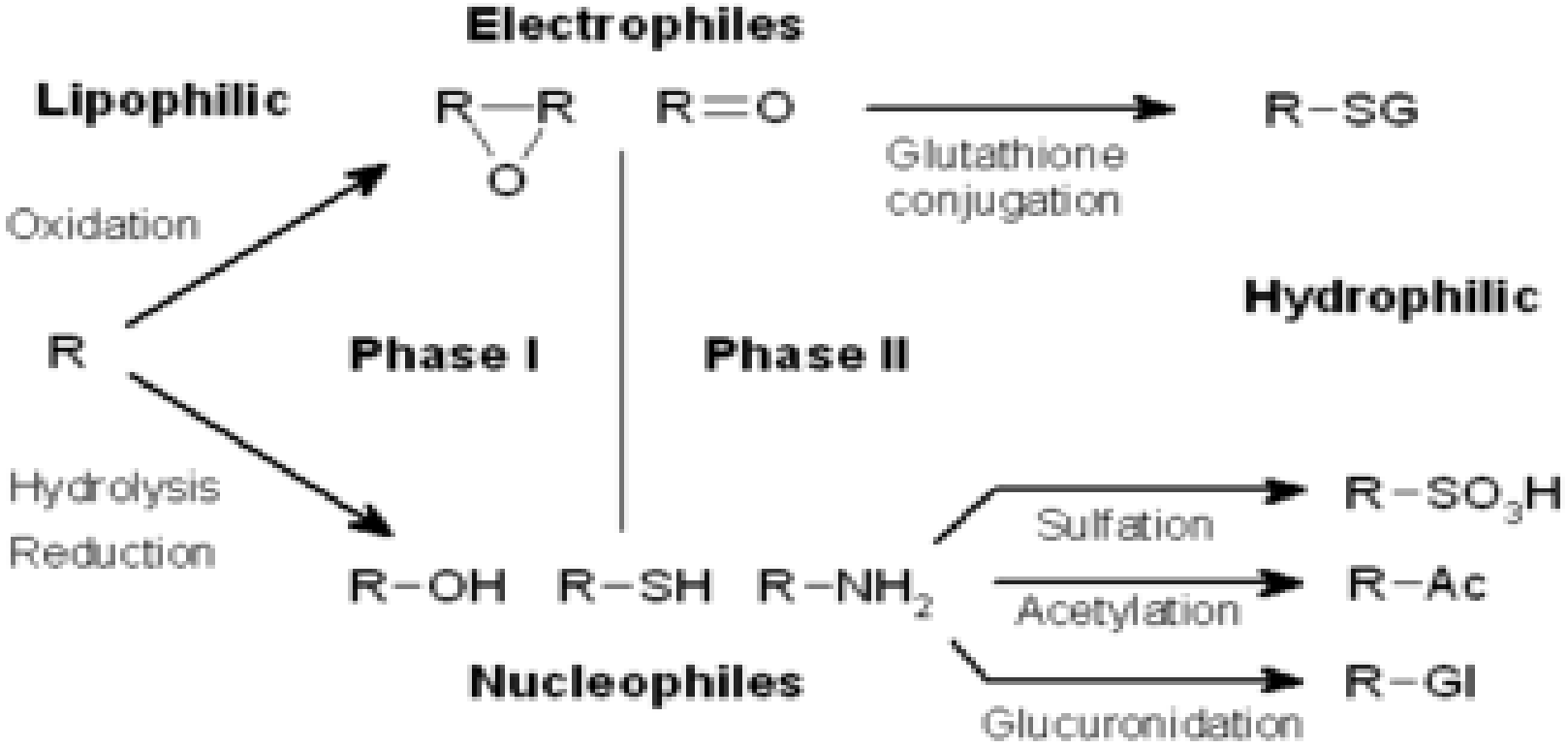
DRUG METABOLISM
PHASE 1 REACTIONS



- **Drug Metabolism / Biotransformation**
- Drug metabolism is the chemical modification of a drug via a biological system to help its elimination by increasing its hydrophilicity.
- Drug metabolism occurs in two phases:
- **Phase I** reactions are mainly oxidative, reductive or hydrolytic.
- **Oxidative reactions play the major role.**
- **CYP-450 enzyme family is the major oxidative enzyme.**
- **Reductases and hydrolases are involved in reductive and hydrolytic reactions, respectively.**



- In **Phase II reactions**, the parent drug or its phase I metabolite is conjugated with an endogenous substrate such as glucuronic acid, sulphate, amino acids and glutathione by specific enzyme systems like glutathione-S-transferases and etc.

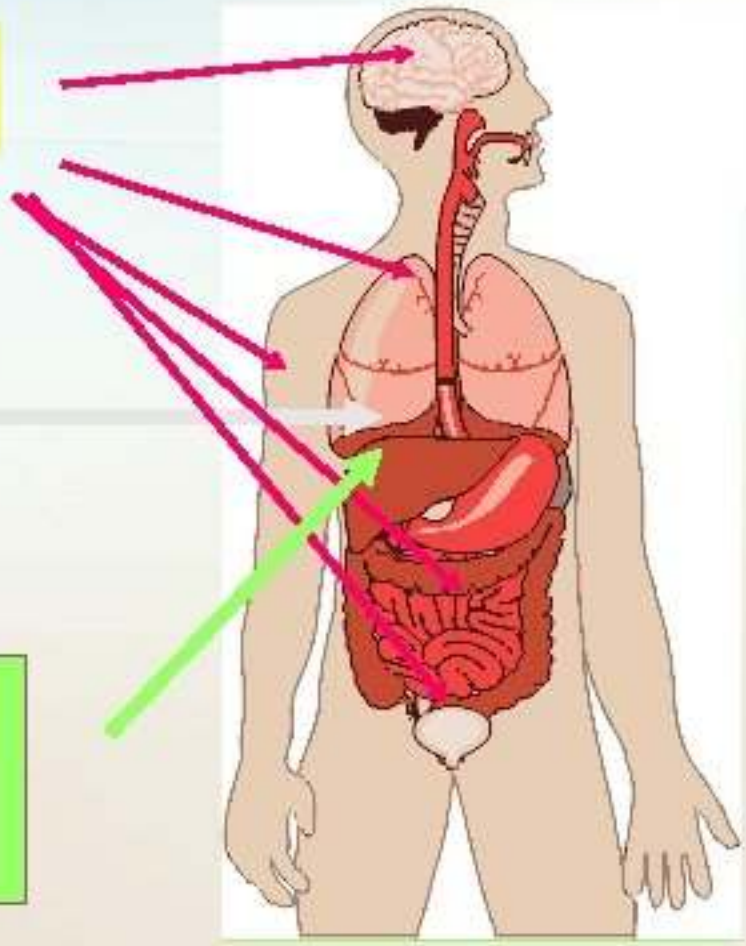


Sites of Drug Metabolism

Extrahepatic microsomal enzymes (oxidation, conjugation)

Hepatic microsomal enzymes (oxidation, conjugation)

Hepatic non-microsomal enzymes (acetylation, sulfation,GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)



- **Significance of drug metabolism:**
- Drug detoxification:
- 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 (TOXICITY).
- 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.

- Bioactivation:
- Many drugs are biotransformed to pharmacologically active metabolites.
- These metabolites may have significant activity that contributes to the pharmacological or toxicological effect(s) of the parent drug.
- Occasionally, the parent compound is inactive when administered and must be metabolically converted to a biologically active drug or metabolite.
- These types of compounds are referred to as *prodrugs*.

- **Phase I or functionalization reactions:**

➢ Oxidation,Reduction and Hydrolysis.

- **Significance:**

➢ To introduce polar functional group(s).
(e.g., OH, COOH, NH2, SH).

➢ To produce a more water-soluble compound.

- **Mechanism:**

➢ By direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation).

➢ By modifying or “unmasking” existing functionalities (e.g., reduction of ketones and aldehydes to alcohols; reduction of ester to COOH).

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

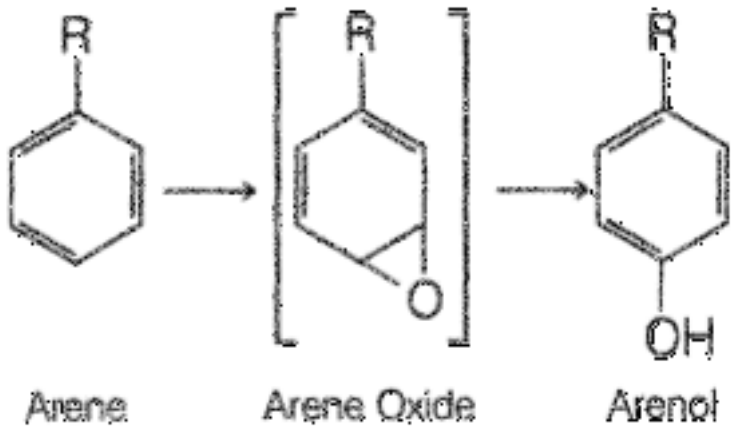
Reduction of aldehydes and ketones
Reduction of nitro and azo compounds
Miscellaneous reductive reactions

Hydrolytic Reactions

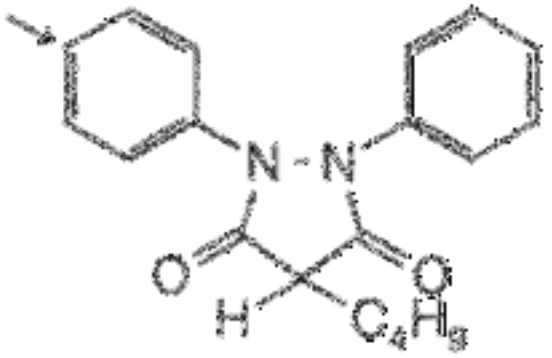
Hydrolysis of esters and amides
Hydration of epoxides and arene oxides by epoxide hydrase

OXIDATIVE REACTIONS

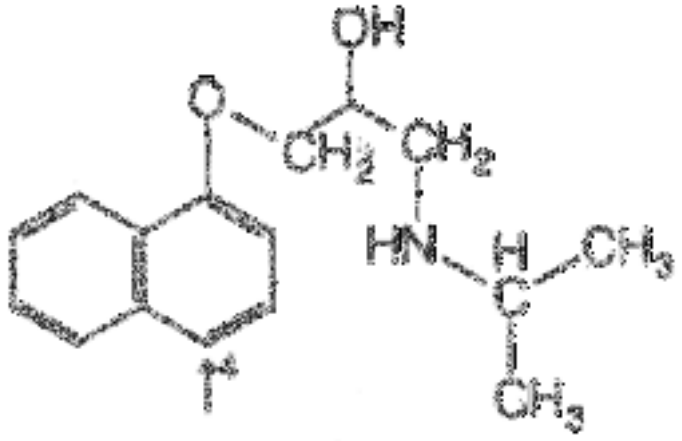
- **Oxidation of aromatic moieties:**
- Drugs with aromatic moieties undergo aromatic hydroxylation to give phenolic metabolites (arenols).
- Initially, arene oxide metabolite is formed in all these reactions.
- Arene oxide is highly unstable, reactive and toxic.



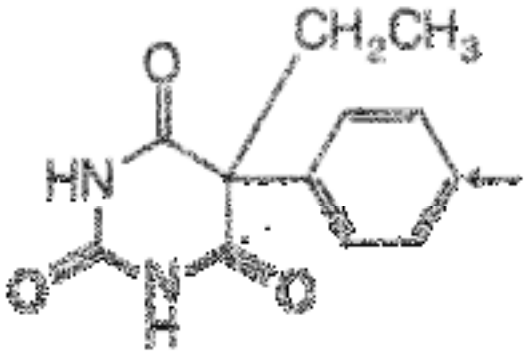
- Aromatic hydroxylation occurs preferably at para or 4th position in majority of drugs with phenyl or aryl rings.

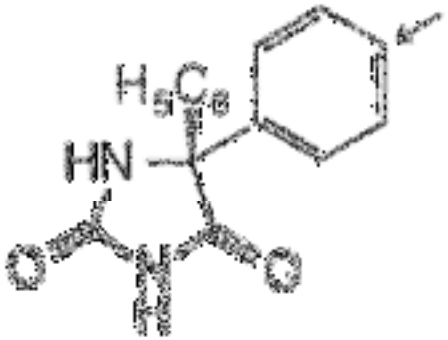


Phenylbutazone

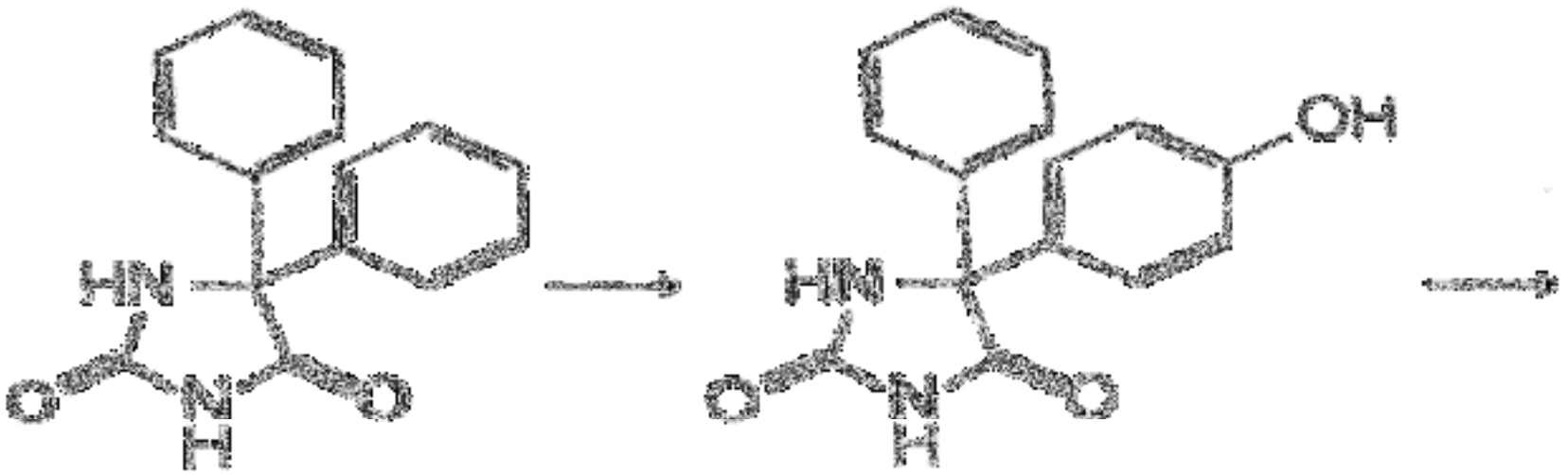


Propranolol

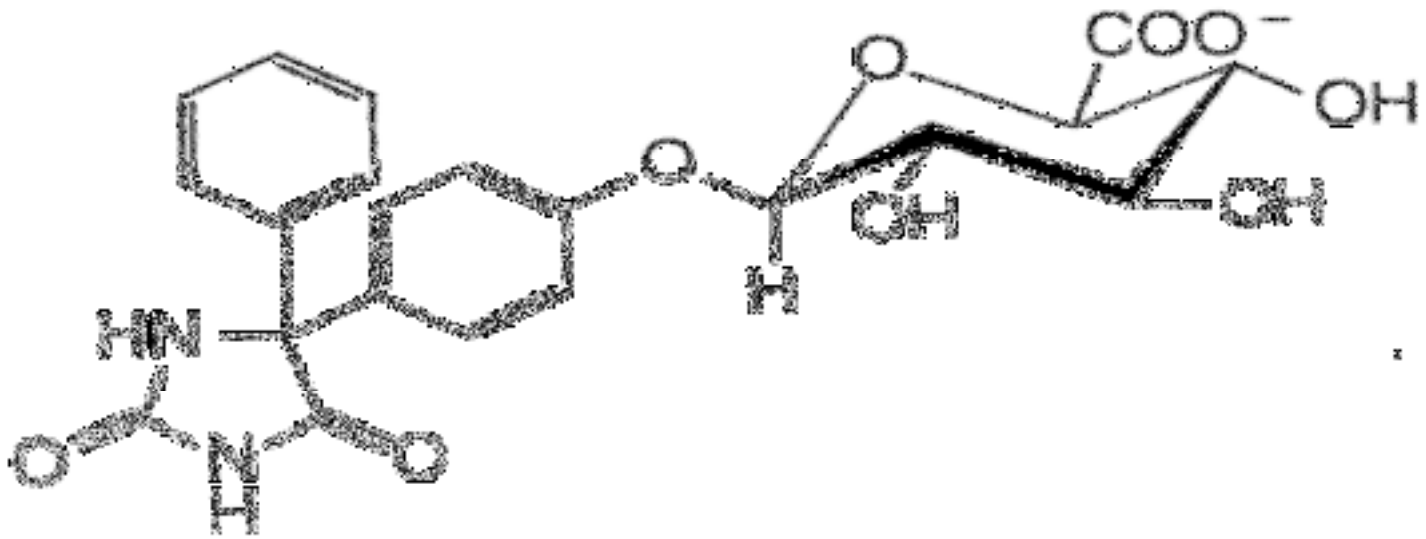




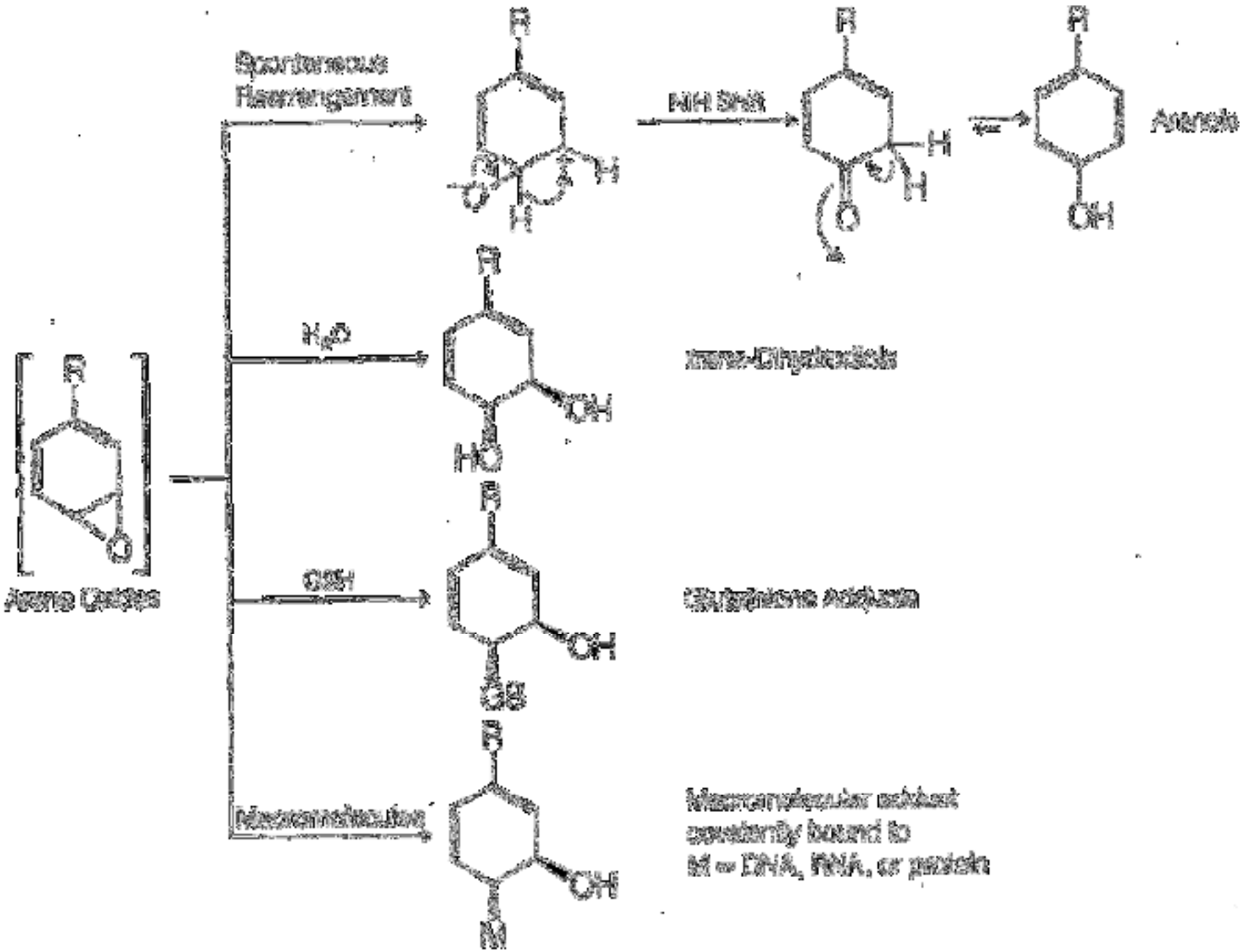
- **Fate of arenol metabolite:**
- Most phenolic metabolites undergo further conversion to polar and water soluble glucuronide or sulfate conjugates, which are readily excreted in the urine.
- For example, *O*-glucuronide conjugate of *p*-hydroxyphenytoin is the major urinary metabolite/conjugate of phenytoin.
- Interestingly, the *para*-hydroxylated metabolite of phenylbutazone, oxyphenbutazone, is pharmacologically active and has been marketed itself as an anti-inflammatory agent.



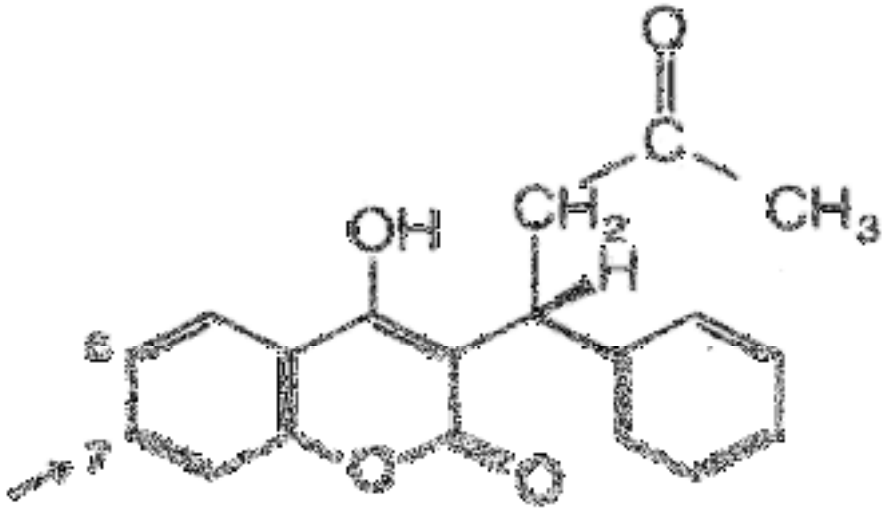
Phenytoin → p-Hydroxyphenytoin →



O-Glucuronide Conjugate


Spontaneous Rearrangement
NIH Shift
Arenols
H_2O
trans-Dihydrodiols
GSH
Glutathione Adducts
Macromolecules
Macromolecular adduct covalently bound to M = DNA, RNA, or protein
Arene Oxides

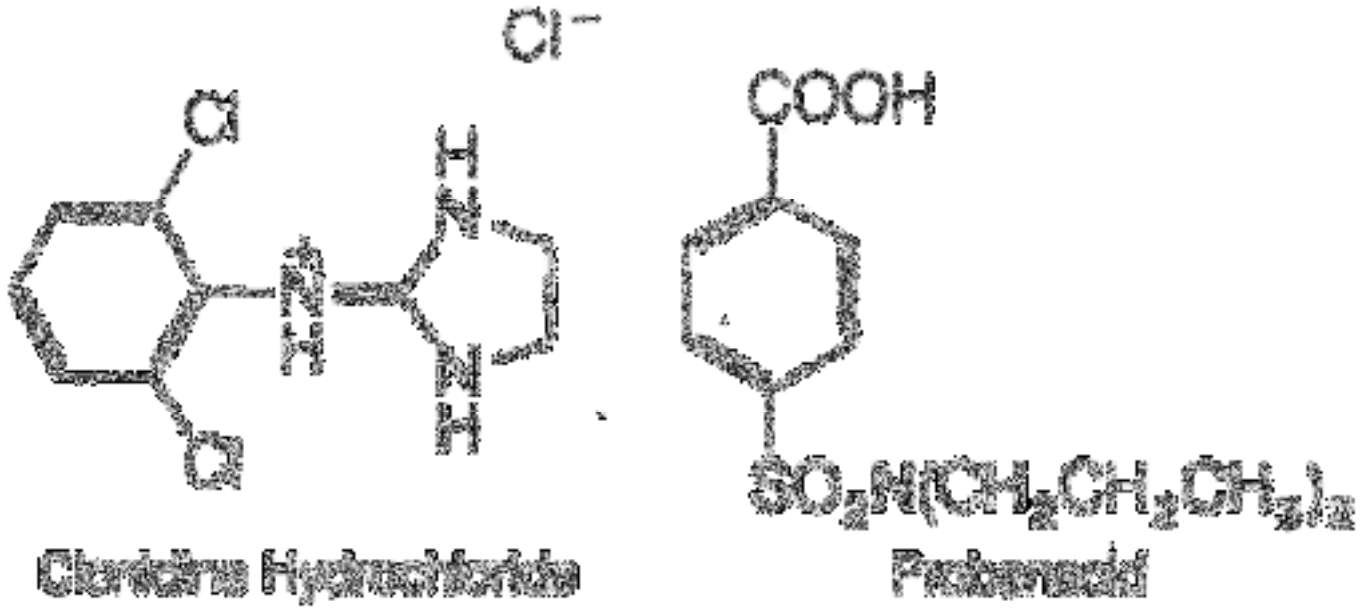
- **Effect of stereochemistry:**
- Sometimes, stereochemical features of drug influence metabolic reactions.
- For example, only the more active *S*(-) warfarin undergo aromatic hydroxylation to 7-hydroxywarfarin in humans.
- In contrast, the (*R*)(+) enantiomer is metabolized by keto reduction.



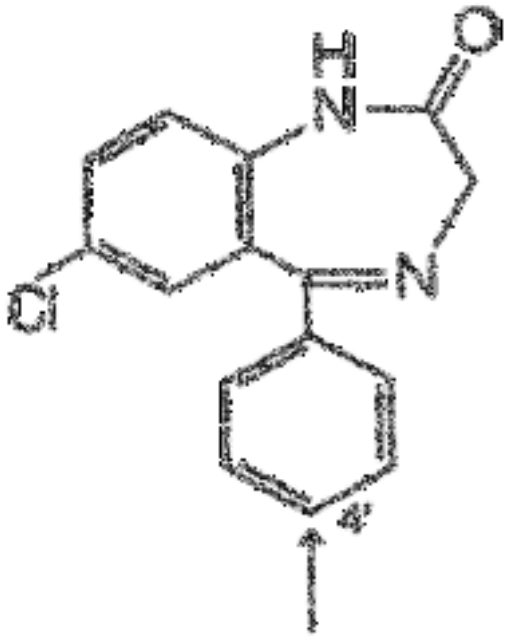
Warfarin
(*S*) – Enantiomer
in Humans

- **Effect of substituents:**
- When an aromatic ring is activated due to electron donating groups (ring activators), aromatic hydroxylation occurs very easily.
- Whereas deactivated aromatic rings (e.g., those containing electron-withdrawing groups Cl, COOH, SO2NHR) are generally slow or resistant to hydroxylation.

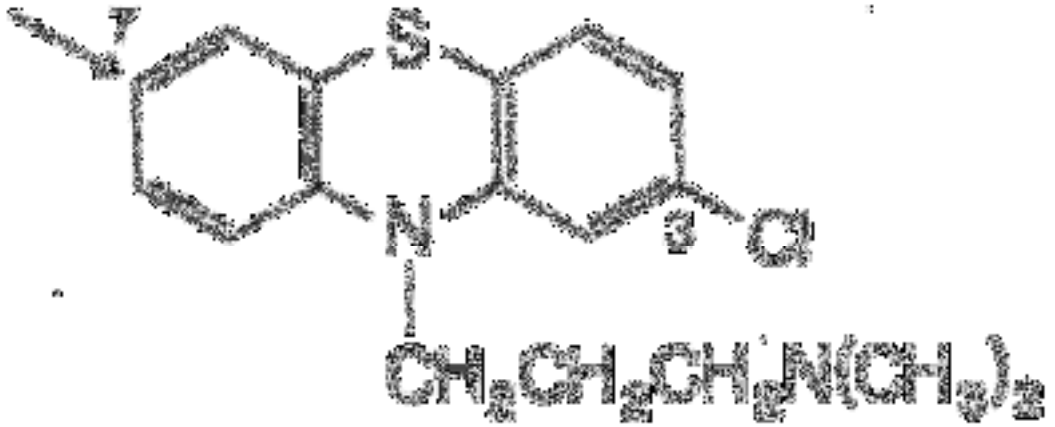
- The deactivating groups (Cl, -H=C) present in the antihypertensive clonidine makes the drug to undergo little aromatic hydroxylation in humans.
- The uricosuric agent probenecid with its electron-withdrawing carboxy and sulfamido groups, do not undergo any aromatic hydroxylation.



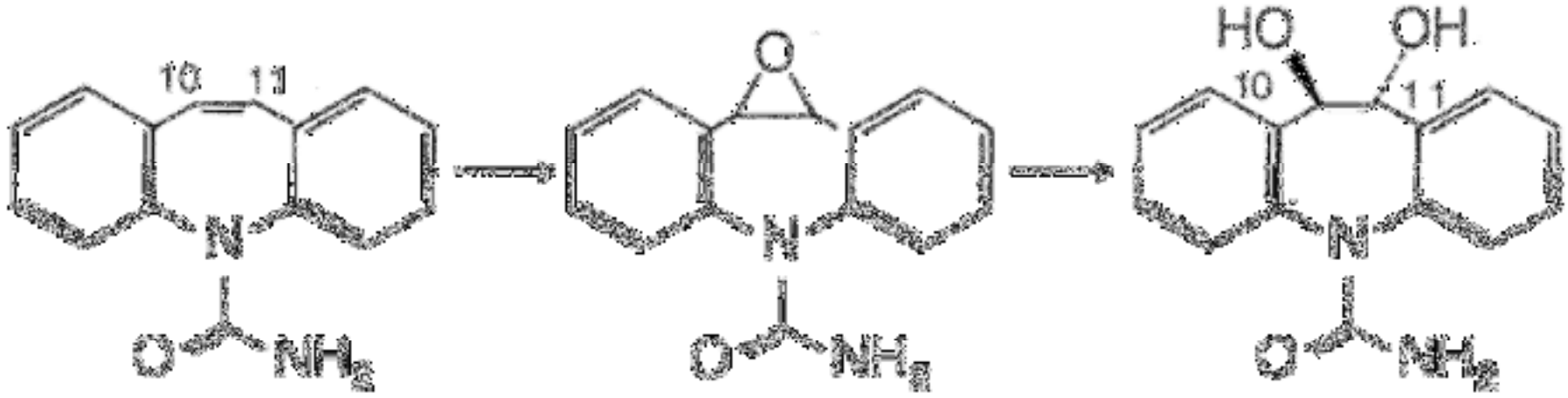
- In compounds with two aromatic rings, hydroxylation occurs preferentially in the more electron-rich ring.
- For example, aromatic hydroxylation of diazepam occurs primarily in the more activated ring to yield 4’-hydroxydiazepam.



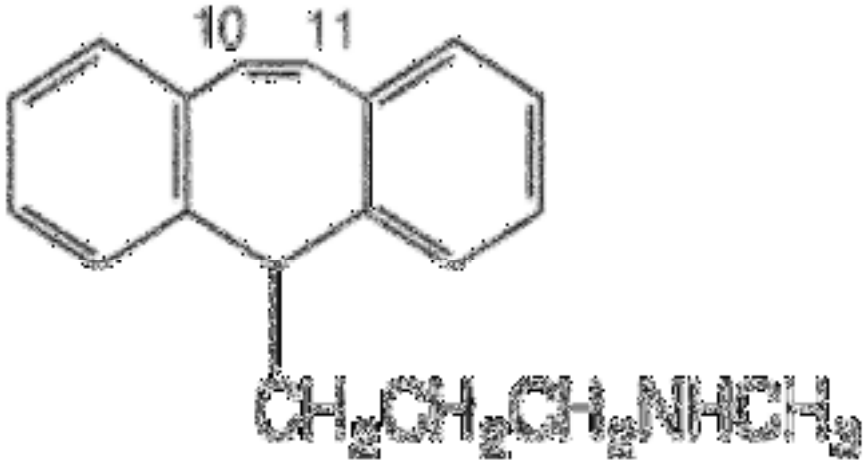
Diazepam



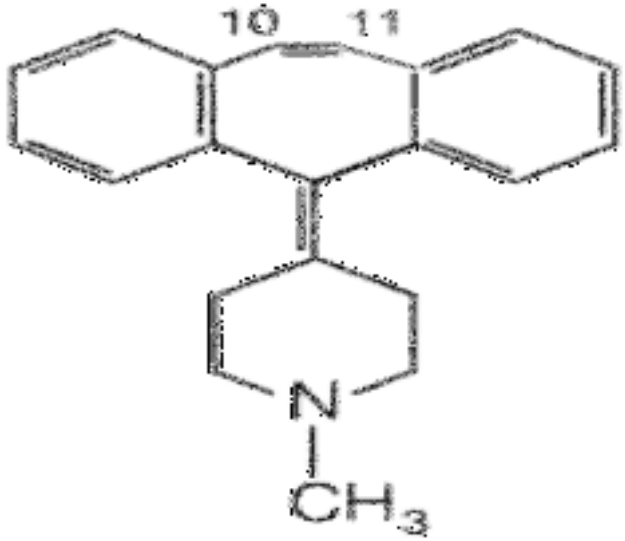
- **Oxidation of Olefins:**
- The metabolic oxidation of olefinic carbon–carbon double bonds leads to the corresponding epoxide (or oxirane).
- Epoxides derived from olefins are somewhat more stable than the arene oxides formed from aromatic compounds.
- Epoxides are susceptible to enzymatic hydration by epoxide hydrase to form *trans*- 1,2-dihydrodiols (also called *1,2-diols* or *1,2-dihydroxy compounds*).
- In addition, several epoxides undergo GSH conjugation.



Carbamazepine | Carbamazepine-10,11-epoxide | trans-10,11-Dihydroxy-carbamazepine

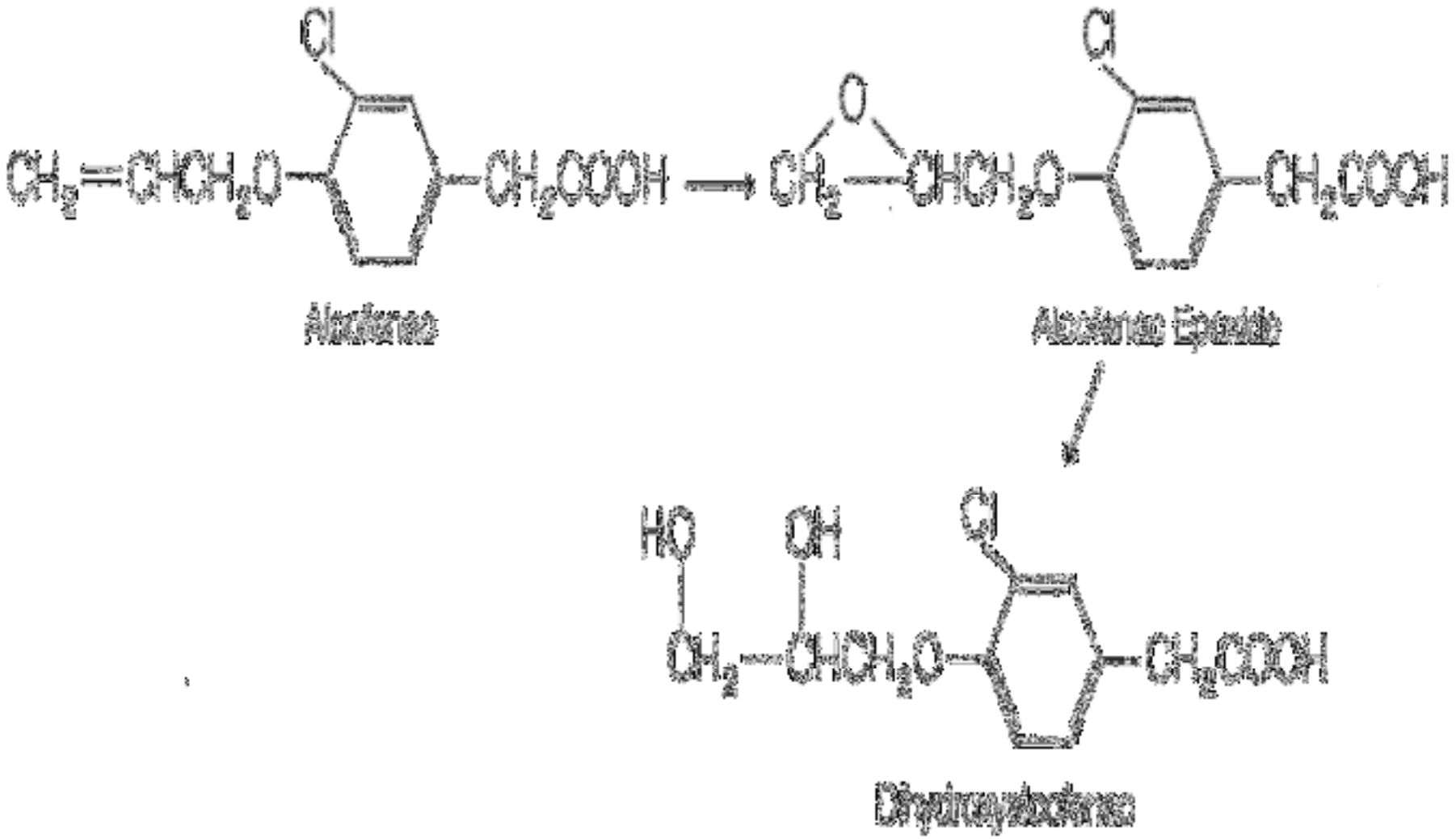


Protriptyline

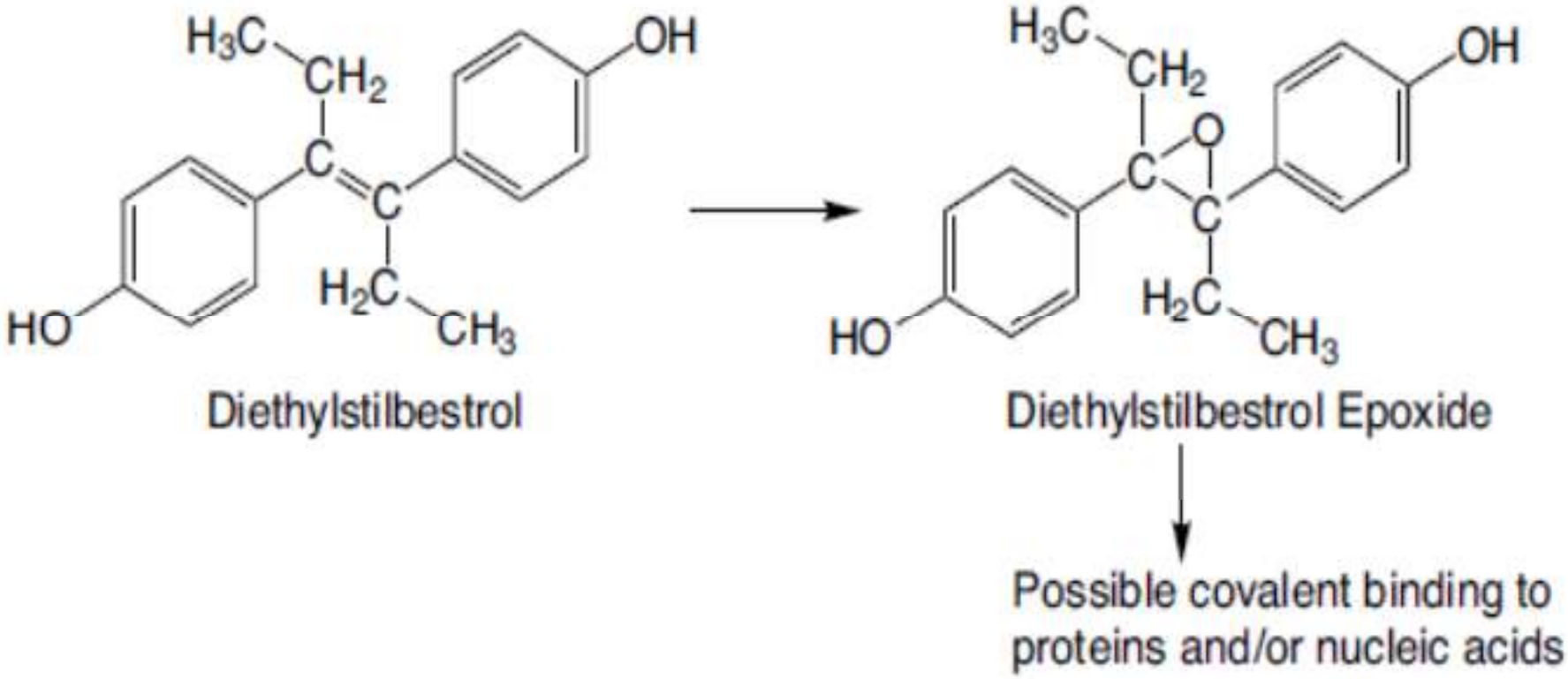


Cyproheptadine

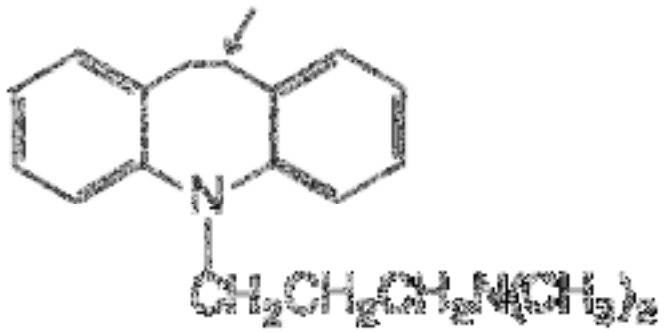
- Sometimes epoxide metabolite is minor metabolite due to their further conversion to 1,2-diols.



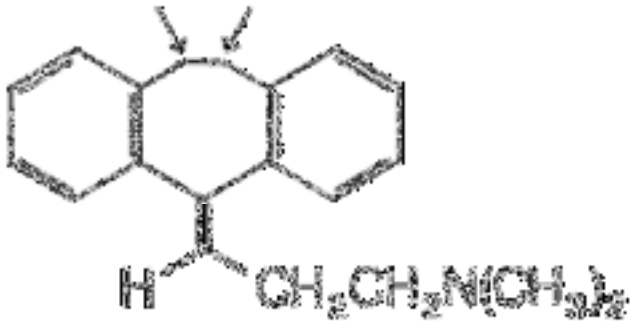
- Some epoxide metabolites bind irreversibly to cellular components and produce cellular toxicity.



- **Oxidation at Benzylic Carbon Atoms:**
- Carbon atoms attached to aromatic rings (benzylic position) are susceptible to oxidation, thereby forming the corresponding alcohol (or carbinol) metabolite.
- Carbinol may undergo further oxidation in to aldehyde or carboxylic acid or alternatively, it may be conjugated directly with glucuronic acid.

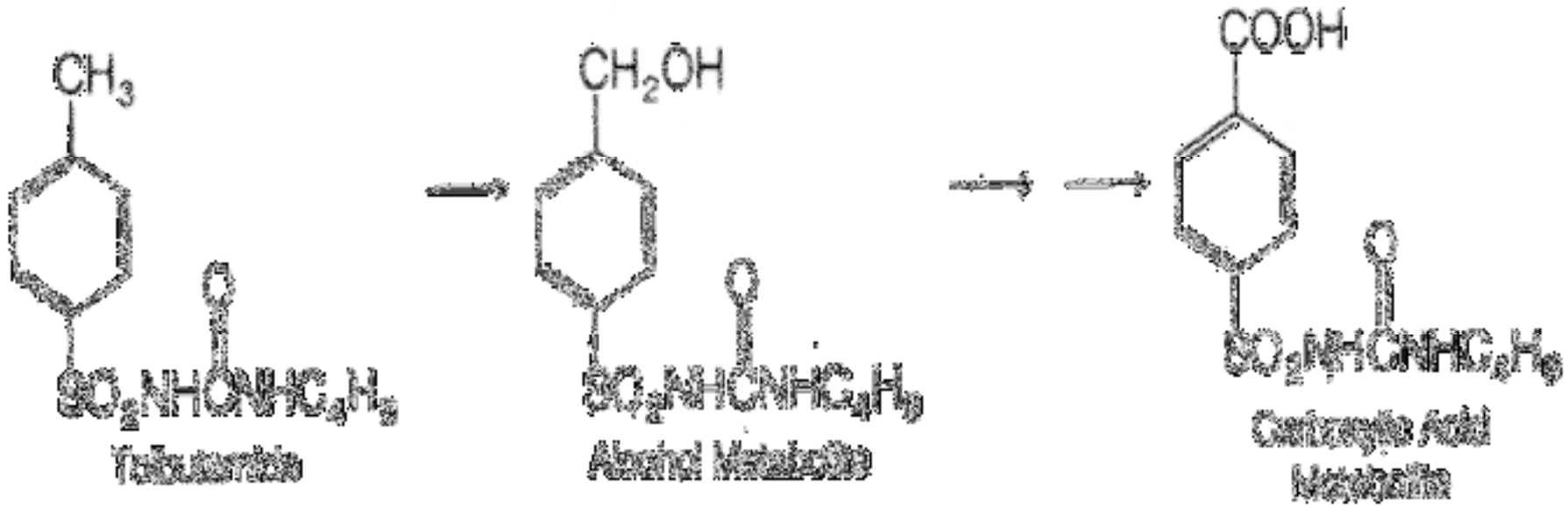


Imipramine

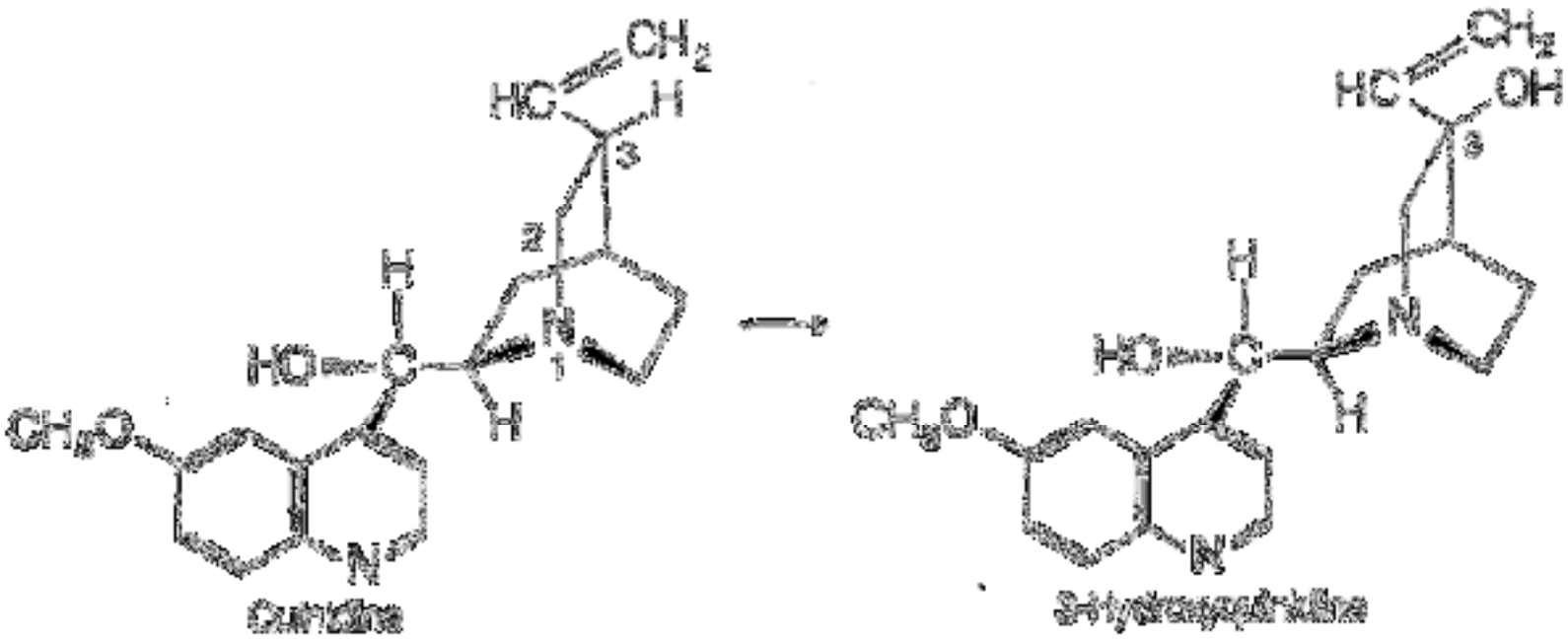


Amitriptyline

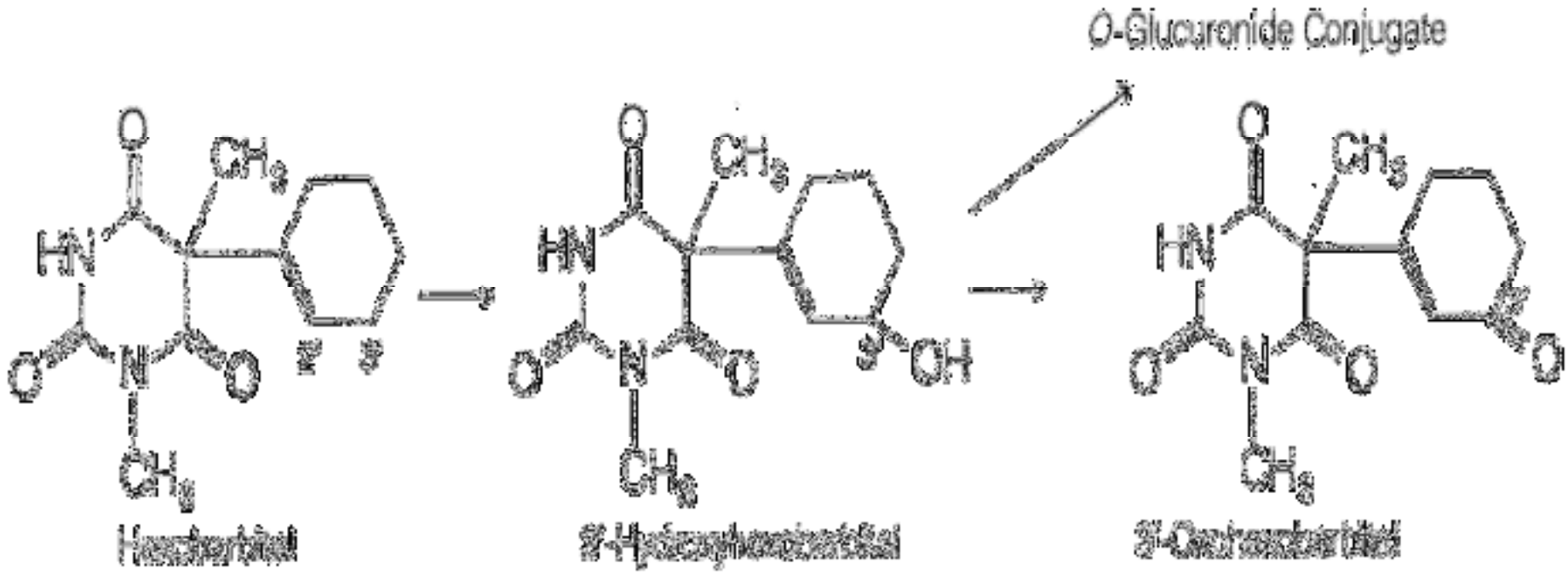
- Primary alcohol metabolites are often oxidized further to aldehydes and carboxylic acids (CH2OH → CHO → COOH), and secondary alcohols are converted to ketones by soluble alcohol and aldehyde dehydrogenases.



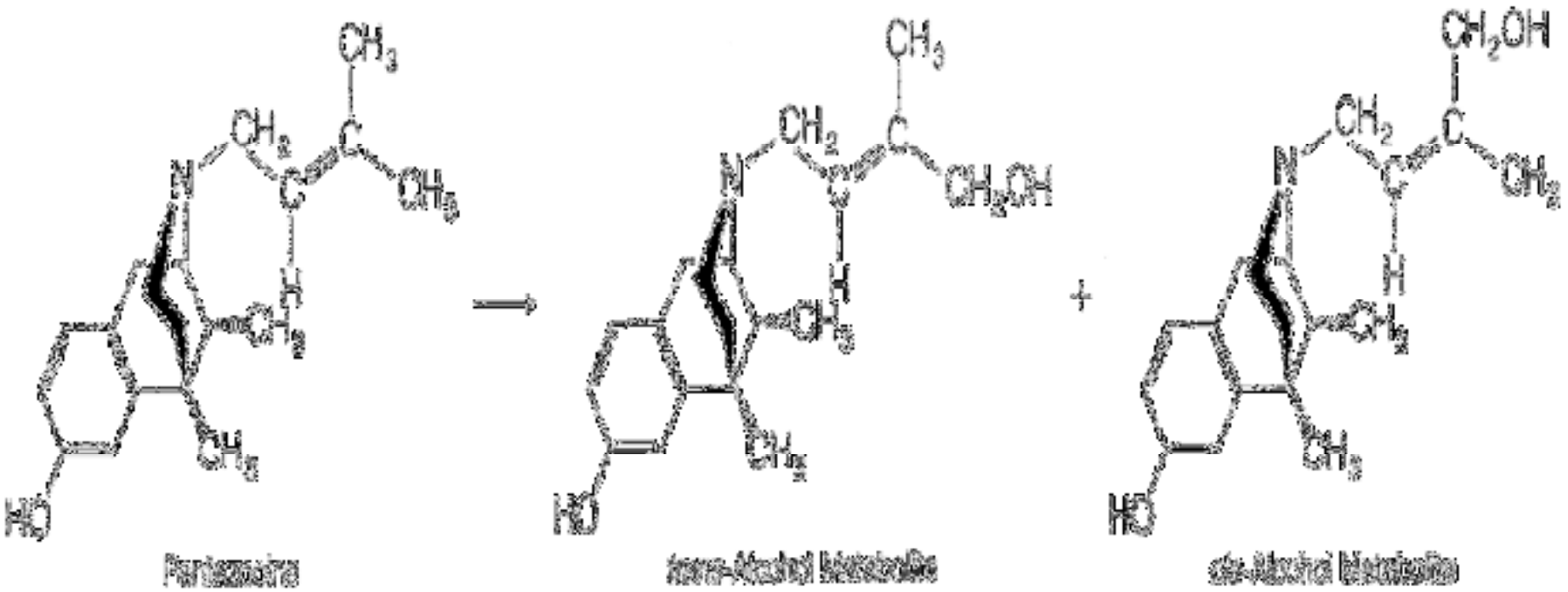
- **Oxidation at Allylic Carbon Atoms:**
- Microsomal hydroxylation at allylic carbon atoms is commonly observed in drug metabolism.
- The antiarrhythmic agent quinidine is metabolized by allylic hydroxylation to 3-hydroxyquinidine, the principal plasma metabolite found in humans.



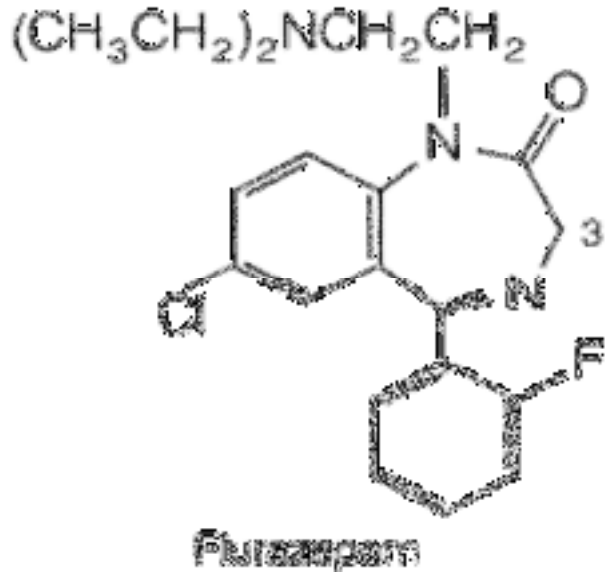
- Studies in humans indicate that the pharmacologically less active (*R*)(-) hexobarbital is metabolized more rapidly than its (*S*)(+)-isomer.



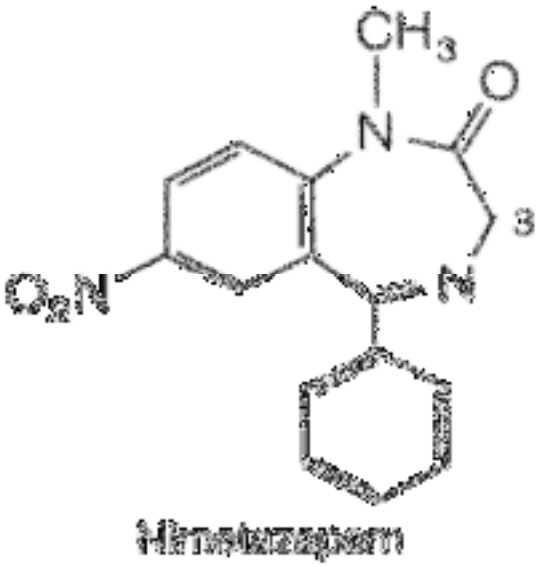
- The analgesic pentazocine also undergoes allylic hydroxylation at two terminal methyl groups of its *N*-butenyl side chain to yield either the *cis* (minor) or *trans* (major) alcohol metabolites.



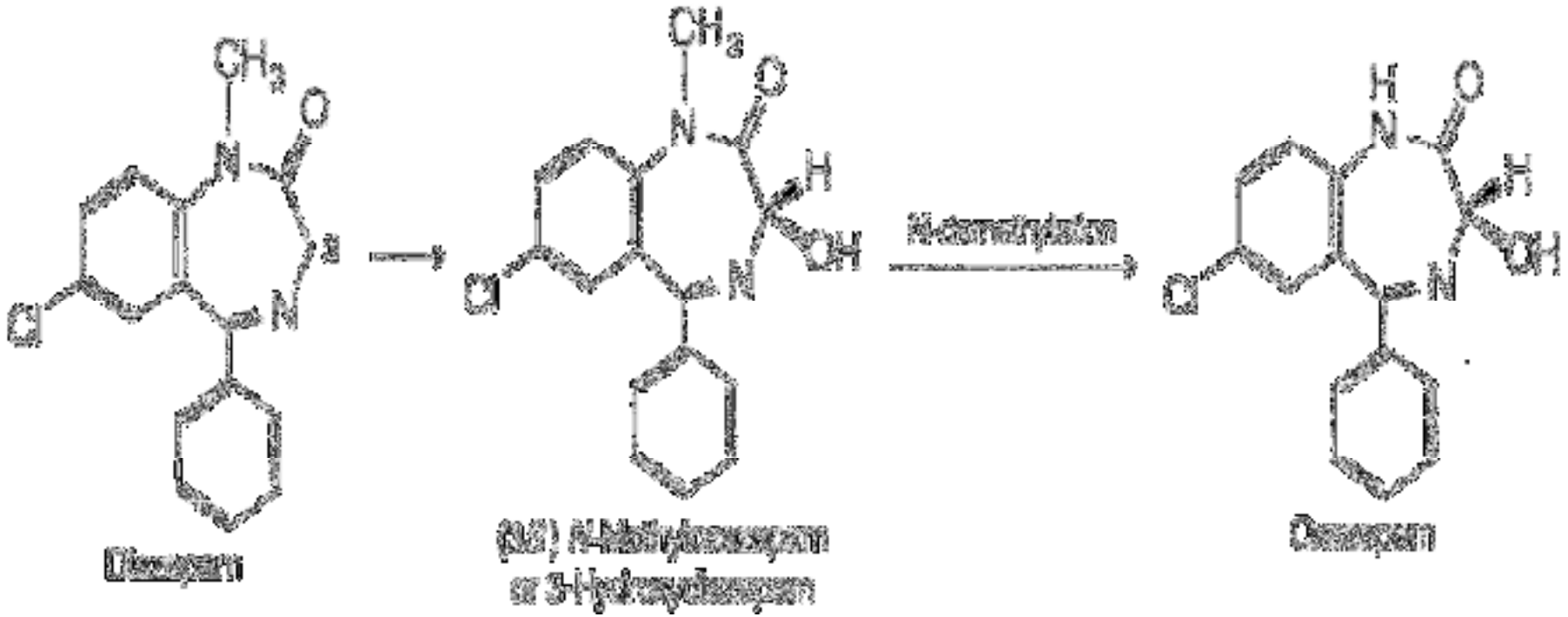
- **Oxidation at Carbon Atoms α to Carbonyls and Imines:**
- The mixed-function oxidase system also oxidizes carbon atoms adjacent (i.e.,α) to carbonyl and imino (C=N) functionalities.
- An important class of drugs undergoing this type of oxidation is the benzodiazepines.



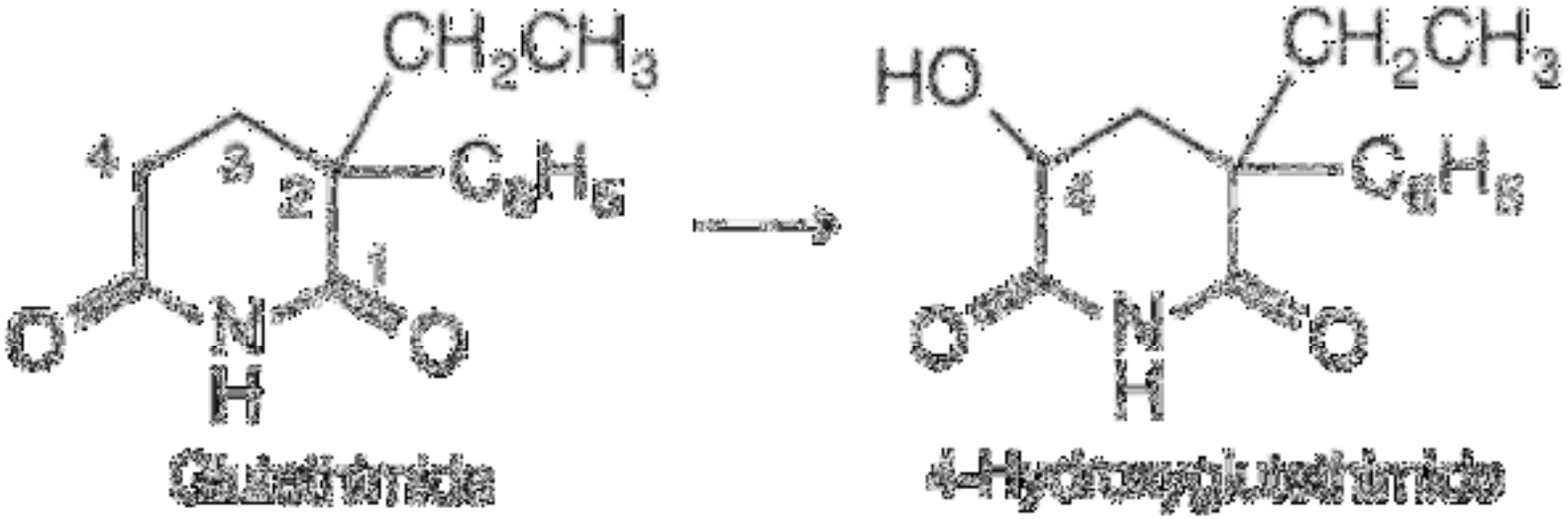
Fluazepam



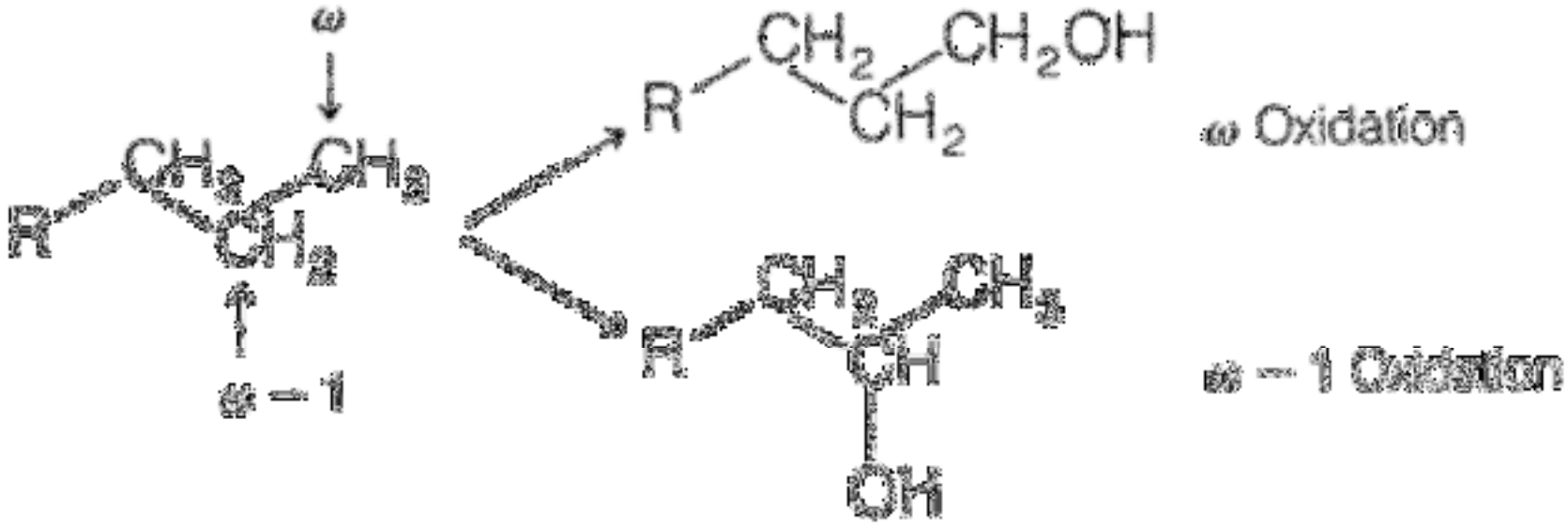
- For example, diazepam and flurazepam are oxidized to their corresponding 3-hydroxy metabolites.
- The C-3 carbon atom undergoing hydroxylation is α to both a lactam carbonyl and an imino functionality.



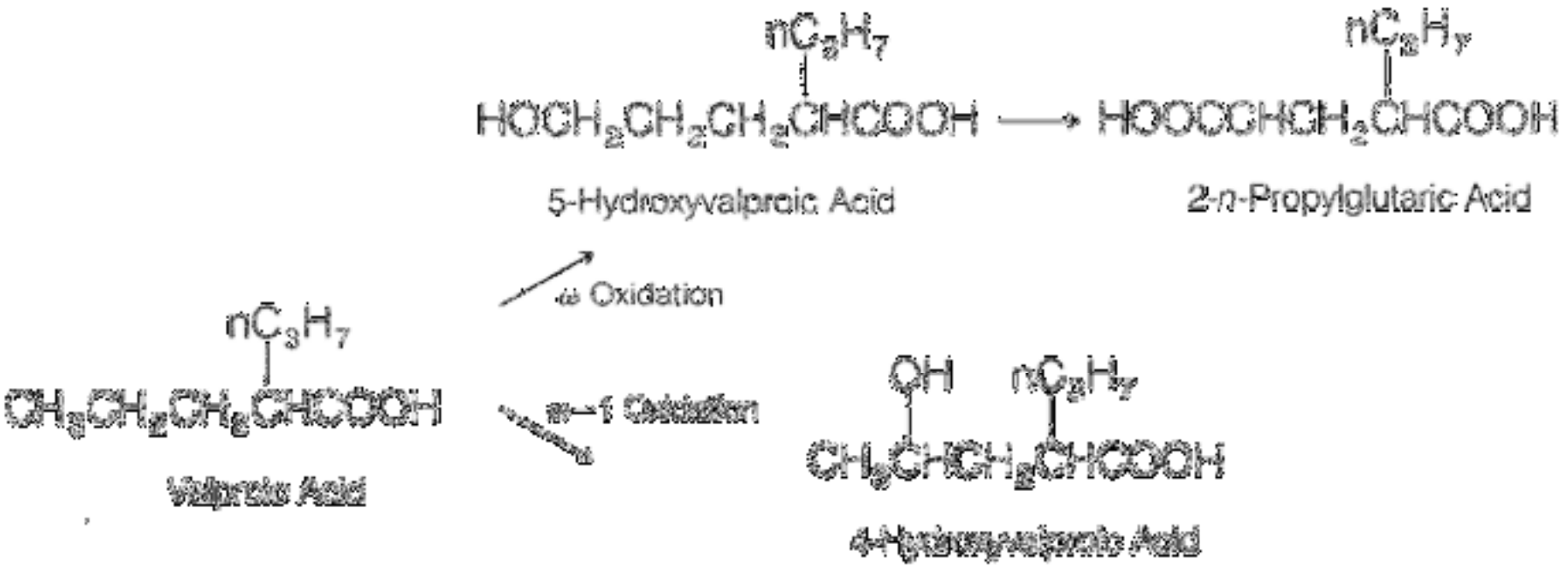
- Hydroxylation of the carbon atom α to carbonyl functionalities generally occurs only to a limited extent in drug metabolism.
- An illustrative example involves the hydroxylation of the sedative–hypnotic glutethimide to 4-hydroxyglutethimide.



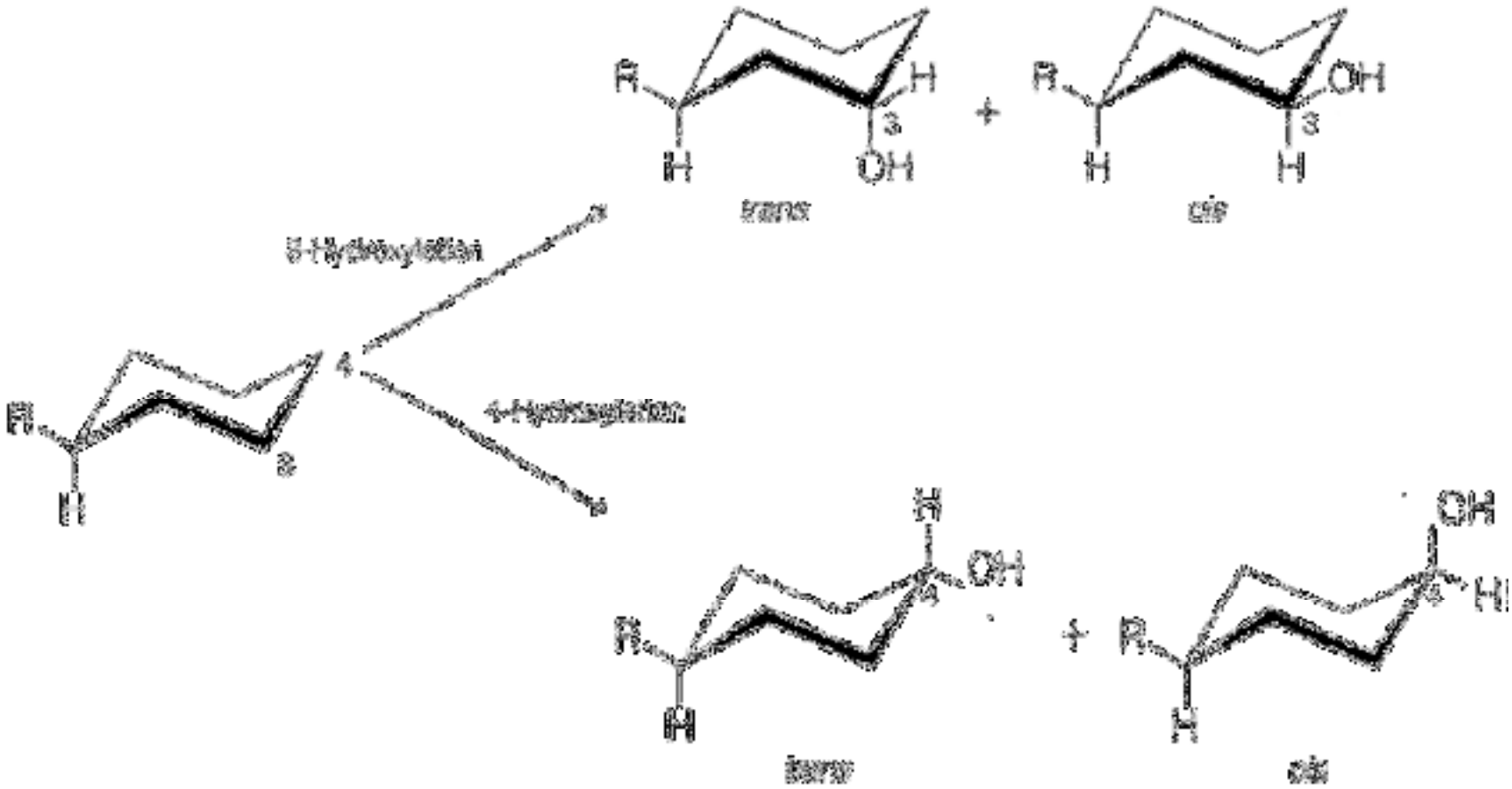
- **Oxidation at Aliphatic and Alicyclic Carbon Atoms:**
- Metabolic oxidation at the terminal methyl group is called ω-*oxidation.*
- Oxidation of the penultimate carbon atom (i.e., next-to-the-last carbon) is called ω*–1 oxidation.*



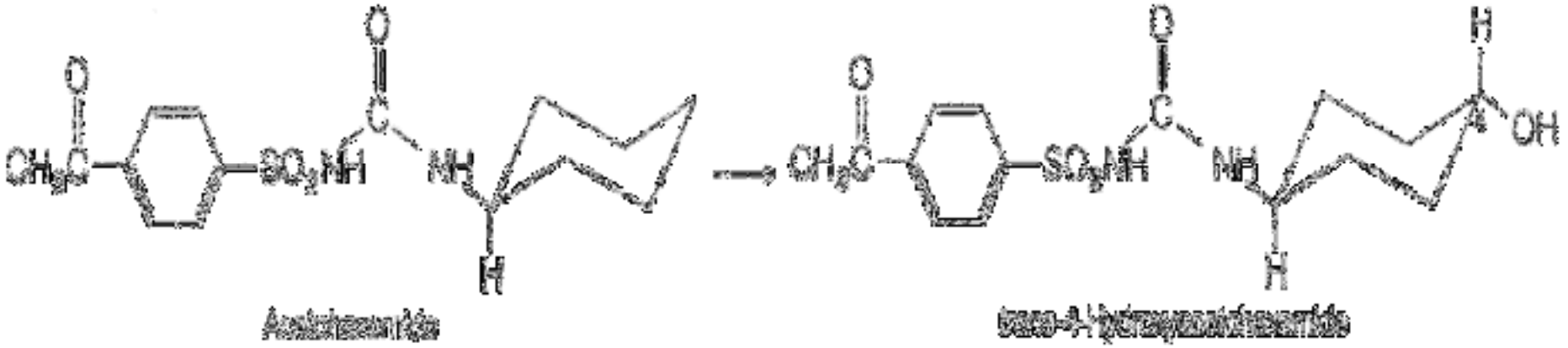
- The initial alcohol metabolites formed from these enzymatic ω and ω–1 oxidations are susceptible to further oxidation to yield aldehyde, ketones, or carboxylic acids.
- Alternatively, the alcohol metabolites may undergo glucuronide conjugation.

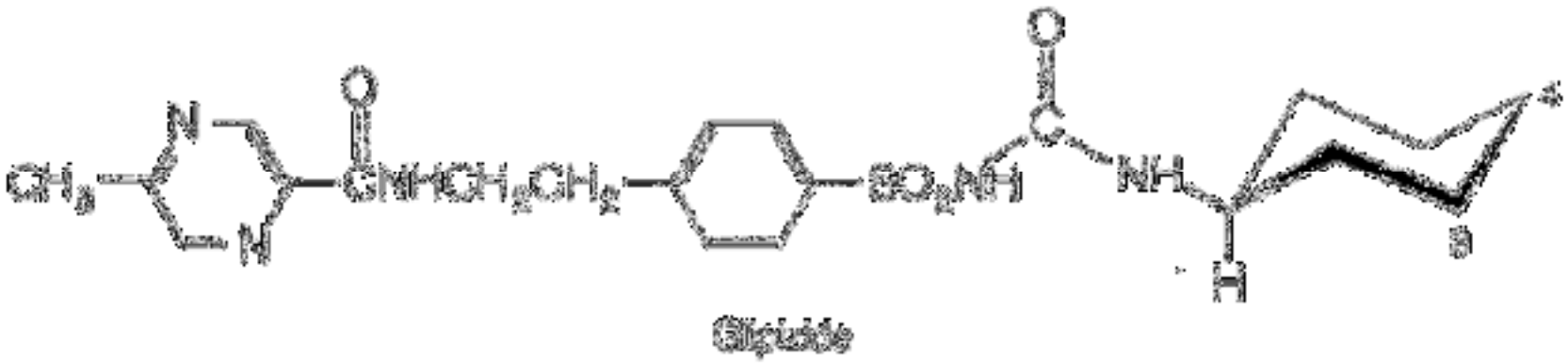


- The cyclohexyl group is commonly found in many drugs and undergoes **alicyclic hydroxylation**.
- Enzymatic introduction of a hydroxyl group into a cyclohexane ring generally occurs at C-3 or C-4 and can lead to *cis* and *trans* conformational stereoisomers.



- An example of this hydroxylation pathway is seen in the metabolism of the oral hypoglycemic agents acetohexamide and glipizide.



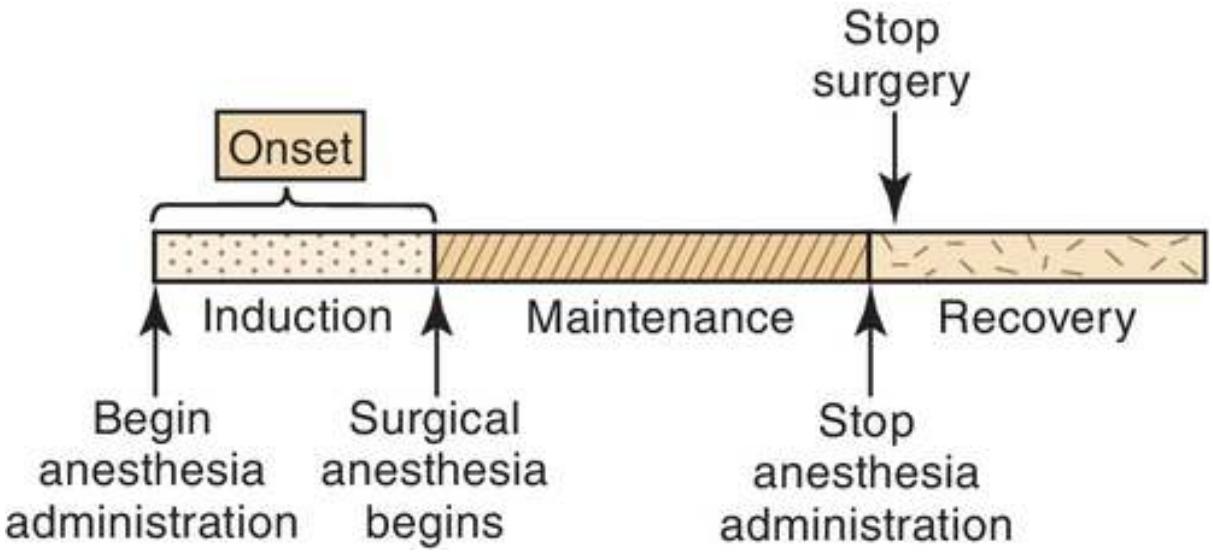


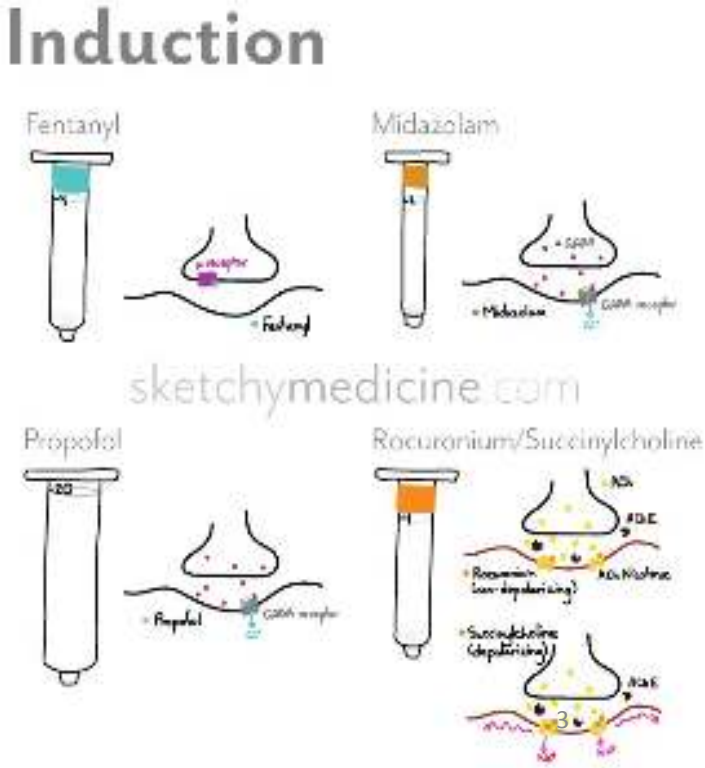
GENERAL ANESTHETICS

Stage	Condition	Behavior/Response
I	Sedation	Motion & breathing reduced
II	Anesthesia	Partial loss of equilibrium Reactive to touch stimuli
III	Surgical anesthesia	Total loss of equilibrium No reaction to touch stimuli
IV	Death	Breathing & heart beat stop Overdose - eventual death

- **INTRODUCTION:**
- General anesthetics are CNS depressants which produce partial or total loss of the sense of pain.
- They induce controlled and reversible depression of CNS.
- They show wide structural variation and so SAR can’t be framed out.
- They are non-specific in action.
- They interact with specific receptors like GABA-A or NMDA.
- Some of them are simple general cellular poisons.

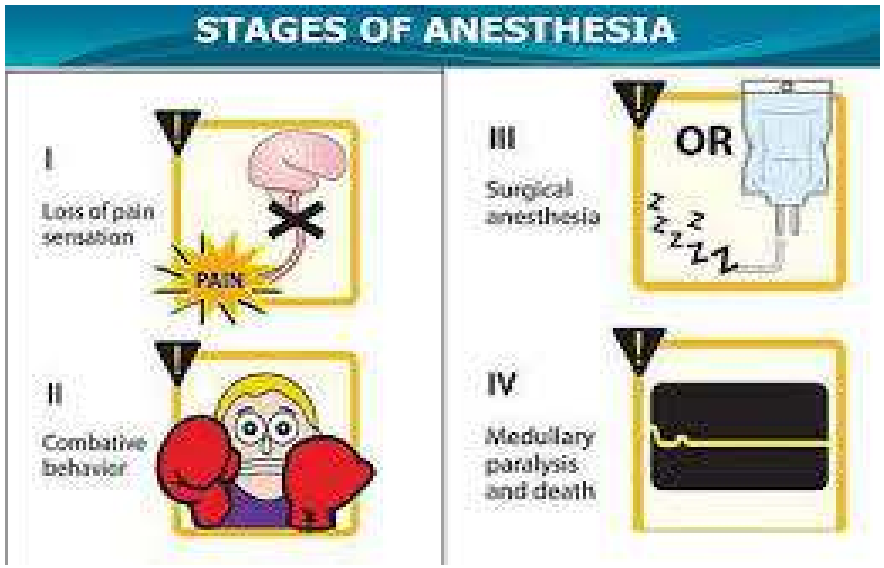
- **STAGES OF ANESTHESIA:**
- **1. Stage of analgesia:**
- There is a gradual depression of cortical centers in this stage.
- Analgesia is produced before consciousness is lost.





- **2. Stage of delirium or excitement:**
- This stage extends from loss of consciousness to the beginning of surgical anesthesia.
- It is associated with shout, excitement, increased muscular activity, breath holding and hyper ventilation.
- Pupil dilation and increased BP is observed.
- Struggling, increased tone of skeletal muscle and vomiting are undesirable features.
- These features can be prevented by pre-anesthetic medication.

- **3. Stage of surgical anesthesia:**
- It is characterized by a gradual loss of refluxes, regular respiration and relaxation of skeletal muscle.
- Roving eyeball movements are observed.
- This stage is the desired one for surgeries.



- **4. Stage of respiratory paralysis:**
- This stage is characterized by respiratory and vasomotor paralysis and heart stops to beat.
- This stage represents an overdose or toxic level that should be avoided.

- **CLASSIFICATION OF GENERAL ANESTHETICS:**
- General anesthetics are classified into two major groups based on their physical state.
- They are volatile or inhalation anesthetics that are gases or highly volatile liquids and intravenous anesthetics that are liquids or solutions.
- **VOLATILE/INHALATION ANESTHETICS:**
- These are sub classified based on chemical nature.
- Hydrocarbons, Halogenated Hydrocarbons, Ethers and Inorganic compounds.

- **Hydrocarbons:**
- Many of short chain alkanes,alkenes and alkynes are capable of producing anesthesia.
- The anesthetic property is directly proportional to chain length.
- Only cyclopropane is used as general anesthetic.
- 15-20% of cyclopropane is mixed with 80-85% of oxygen is sufficient to achieve stage of anesthesia.
- Cyclopropane is highly potent and non-irritant.
- **Now a day, hydrocarbons are not preferred because of their flammability and toxicity.**

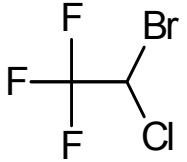
- **Halogenated Hydrocarbons:**
- Chloroform ($CHCl_3$) is an earliest anesthetic but its hepatotoxicity seriously limited its utility.
- The addition of halogen to hydrocarbon backbone increases potency and decreases flammability.
- As an anesthetic agent, chloroform is very potent. But it causes cancers, hepatotoxicity and nephrotoxicity.
- Fluorinated hydrocarbons are safer than other halogenated hydrocarbons.

- Example for fluorinated hydrocarbon is halothane.
- It is a non-flammable, nonexplosive anesthetic.
- It is mixed with air or oxygen to produce anesthesia.
- Halothane produces rapid onset and recovery from anesthesia with high potency.
- It can be given alone or in combination with nitrous oxide.
- Enflurane and isoflurane are isomeric halogenated ethers with high potent anesthetic property.
- Both are non-flammable and produce fewer side effects.

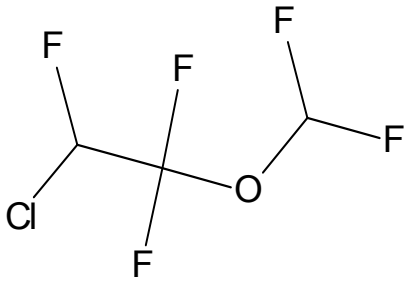
- **Ethers:**
- Many ethers possess general anesthetic property but most of them are either toxic or highly flammable liquids.
- Clinically useful ether anesthetic is diethyl ether.

Cyclopropane

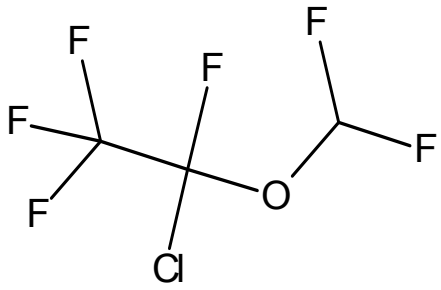
Halothane



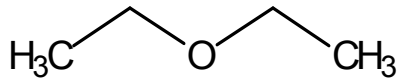
Enflurane



Isoflurane



Diethyl ether



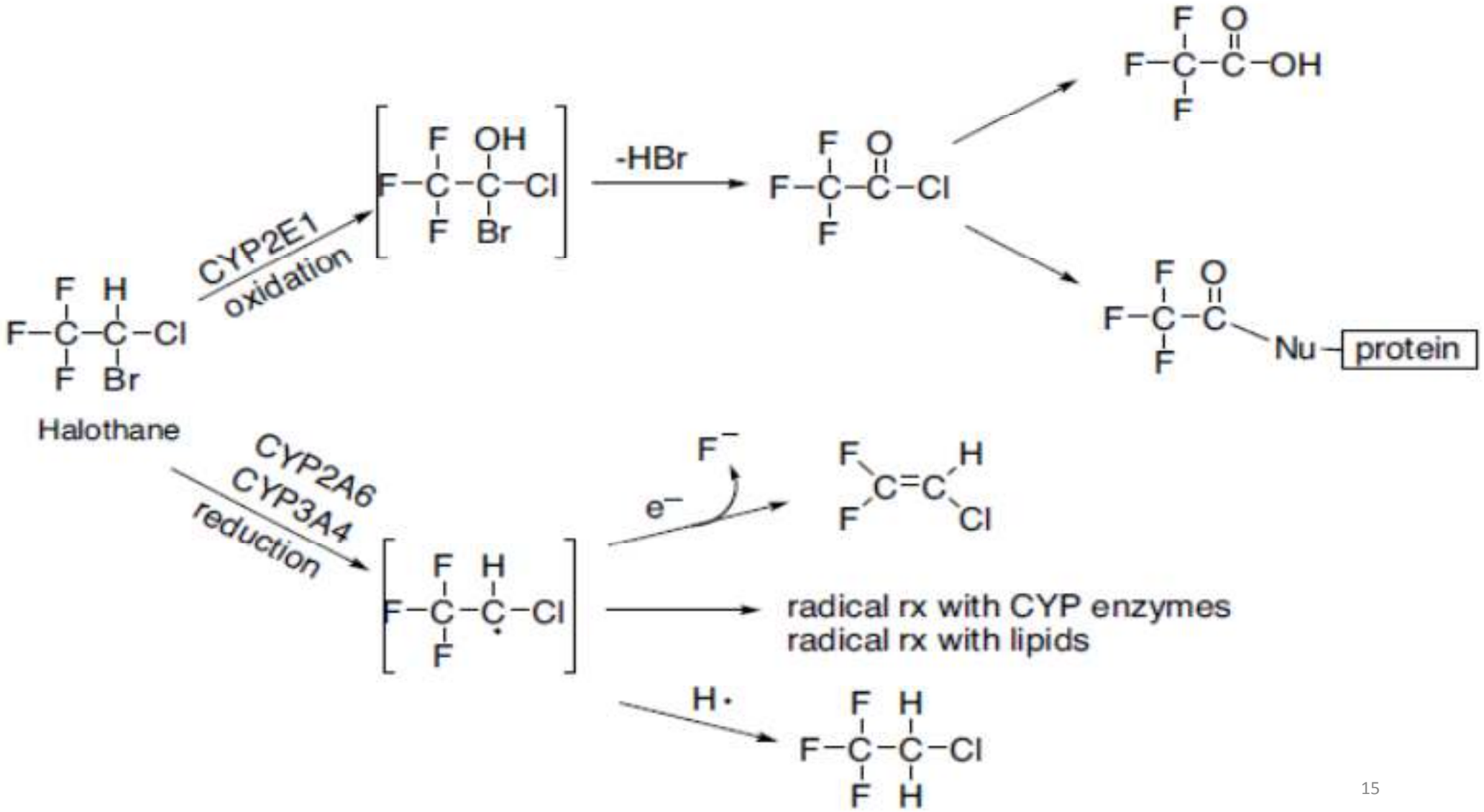
- **Inorganic compounds:**
- Nitrous oxide (N_2O) is commonly called as “laughing gas” or dinitrogen monoxide.
- It is a gas at room temperature and is least potent of the inhalation anesthetics used today.
- When administered alone, it cannot produce surgical anesthesia.
- It is generally mixed with oxygen to produce anesthesia.
- Most commonly it is used in combination with other general anesthetics.
- When administered alone, it is used during certain procedures like dental extraction in which full surgical anesthesia is not required.

- **Mechanism of Action of the Inhaled Anesthetics**

- The mechanism of action of the inhaled anesthetics is not known.
- Most theories of the inhaled anesthetics leave room for the possibility of multiple mechanisms, receptors, and regions of the nervous system (spinal cord and brain) to explain their action.
- It seems likely that the individual anesthetic molecules act with different potencies on multiple receptors that lead to similar clinical states of anesthesia.
- Some of theories of anesthetic action are MEYER-OVERTON THEORY and THEORY OF INTERACTION WITH ION CHANNELS.

- **HALOTHANE**
- Halothane is a non-flammable, non-pungent, volatile, liquid, halogenated (F, Cl, and Br) ethane (bp 50°C), introduced in 1956.
- Halothane may increase heart rate, cause cardiac arrhythmias, increase cerebral blood flow, and increase intracranial pressure.
- It can undergo spontaneous oxidation when exposed to ultraviolet light to yield HCl, HBr, Cl, Br, and phosgene (COCl2).
- To prevent oxidation it is packaged in amber bottles with a low concentration of thymol (0.01%) as a stabilizer.

- The drug has a high potency (MAC 0.75%), a blood:gas partition coefficient of 2.4, and high adipose solubility.
- Halothane undergoes both reductive and oxidative processes with up to 20% of the dose undergoing metabolism.
- The trifluoroacetyl chloride metabolite is electrophilic and can form covalent bonds with proteins leading to immune responses and halothane hepatitis upon subsequent halothane exposure.
- Halothane hepatitis is rare with 1 case reported for every 6,000 to 35,000 patients exposed.

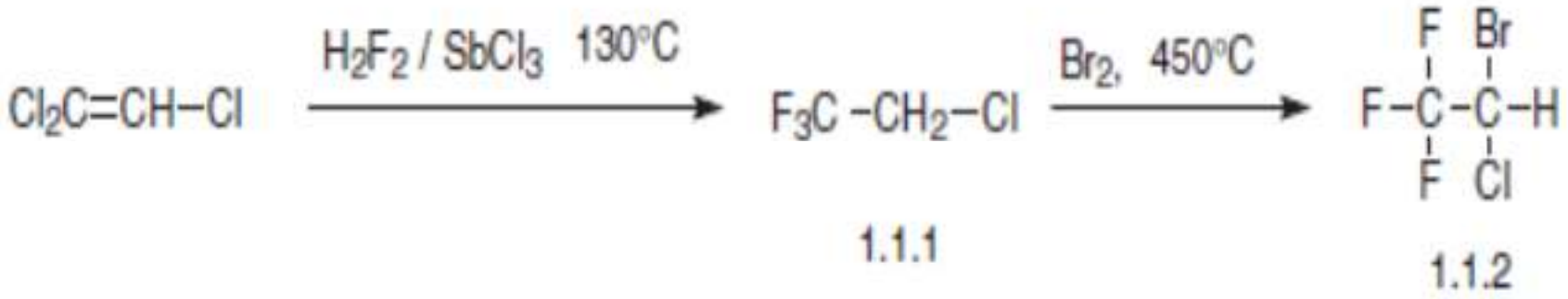

Halothane
CYP2E1
oxidation
-HBr
CYP2A6
CYP3A4
reduction
e⁻
F⁻
H·
radical rx with CYP enzymes
radical rx with lipids
Nu
protein

- The use of inhaled anesthetics and halothane in particular can produce malignant hyperthermia (MH) in genetically susceptible individuals.
- This results in an increase in body temperature, tachycardia, tachypnea, acidosis, and rhabdomylolysis.
- MH is a result of the excessive release of calcium from the sarcoplasmic reticulum (SR).
- MH has been reported to occur with all anesthetics agents and with succinylcholine, a depolarizing neuromuscular blocker.
- The combination of halothane and succinylcholine appears to trigger a great extent of the MH episodes.

- ***Synthesis of Halothane:***

- Halothane, 2-bromo-2-chloro-1,1,1-trifluorethane (1.1.2), is made by the addition of hydrogen fluoride to tricholoroethylene and simultaneous substitution of chlorine atoms in the presence of antimony(III) chloride at 130 °C.

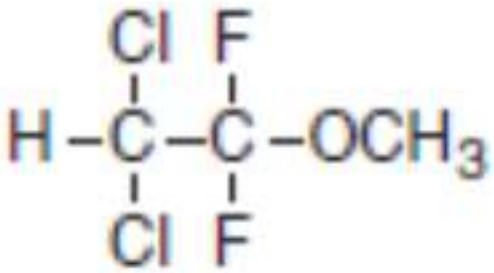
- The resulting 2-chloro-1,1,1-trifluorethane (1.1.1) undergoes further bromination at 450 °C to form halothane.



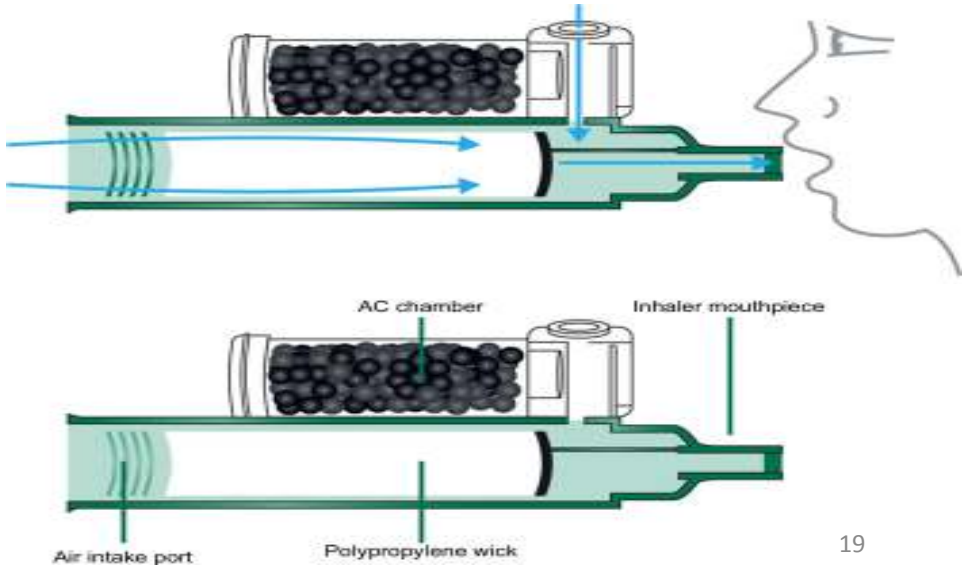
1.1.1

1.1.2

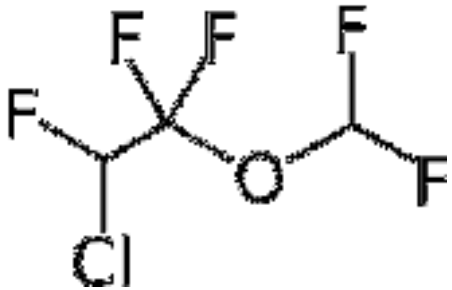
- **METHOXYFLURANE**
- Methoxyflurane is a volatile liquid (bp 105°C) with a high blood:gas partition coefficient and thus a slow induction and prolonged recovery.
- Approximately 75% of the drug undergoes metabolism yielding dichloroacetate, difluoromethoxyacetate, oxalate, and fluoride ions.
- The intrarenal inorganic fluoride concentration, as a result of renal defluorination, may be responsible for the nephrotoxicity seen with methoxyflurane.



- Both the concentration of F generated and the duration for which it remained elevated were factors in the development of methoxyflurane nephrotoxicity.
- Methoxyflurane was removed from the U.S. market in 2000 because of safer alternatives.
- Both isoflurane and enflurane produce less fluoride ion upon metabolism than methoxyflurane.

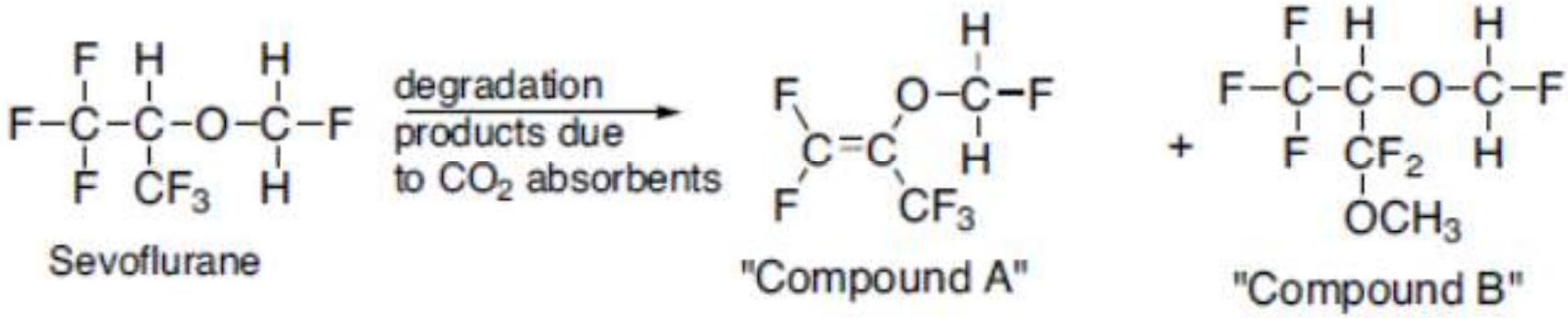


- **ENFLURANE**
- Enflurane is a volatile liquid (bp 56.5°C) with a blood: gas partition coefficient of 1.8 and an MAC of 1.68%.
- Approximately 2% to 8% of the drug is metabolized primarily at the chlorofluoromethyl carbon.
- Little chlorofluoroacetic acid is produced suggesting minor metabolism at the difluoromethyl carbon.
- Difluoromethoxydifluoroacetate and fluoride ion have been reported as metabolites.



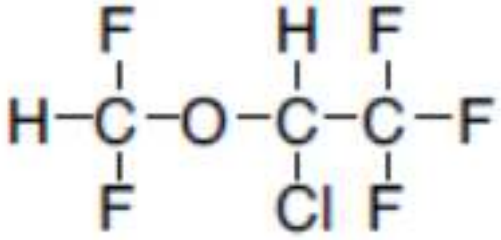
- Enflurane may increase heart rate, cause cardiac arrhythmias, increase cerebral blood flow, and increase intracranial pressure but all to a smaller degree than halothane.
- Enflurane also causes electroencephalographic (EEG) patterns consistent with electrical seizure activity.
- It has caused tonic–clonic convulsive activity in patients when used at high concentrations or during profound hypocarbic periods.
- Enflurane is therefore not recommended in patients with seizure disorders.

- **SEVOFLURANE**
- Sevoflurane is a volatile, nonpungent, nonflammable, and nonexplosive liquid with a boiling point of 58.6°C.
- The blood:gas partition coefficient is 0.65, the oil:gas partition coefficient is 50, and the MAC is 2.1%.
- Sevoflurane reacts with desiccated carbon dioxide adsorbents, to produce compounds (A and B) with known toxicity.



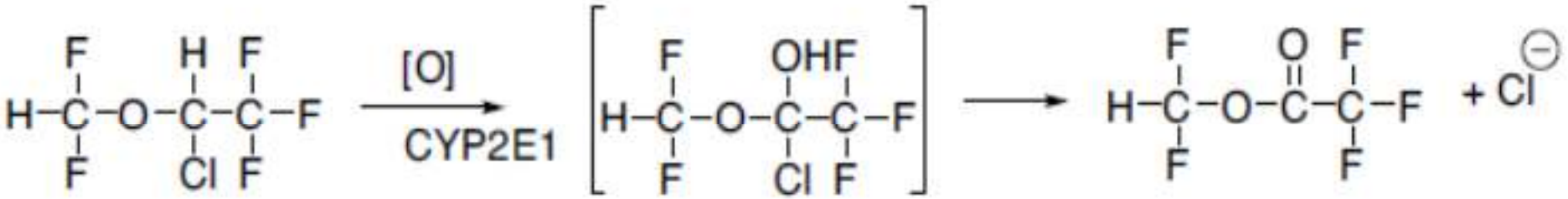
- The type of CO2 absorbent used, the temperature of the absorbent, and the duration of exposure can influence the degree to which sevoflurane breaks down.
- The major breakdown product, compound A, pentafluoroisopropenyl fluoromethyl ether, (PIFE, C4H2F6O) has been studied extensively.
- Compound A is nephrotoxic in rats and nonhuman primates and remains a theoretical risk to humans.
- Sevoflurane breakdown by CO2 absorbents generates heat and has resulted in sporadic operating room fires.

- **ISOFLURANE**
- Isoflurane is a volatile liquid (bp 48.5°C) with an MAC of 1.15, a blood:gas partition coefficient of 1.43 and high solubility in fat.
- Isoflurane is a structural isomer of enflurane.
- It is a known respiratory irritant, but less so than desflurane.
- Approximately 0.2% of the administered drug undergoes metabolism, the rest is exhaled unchanged.



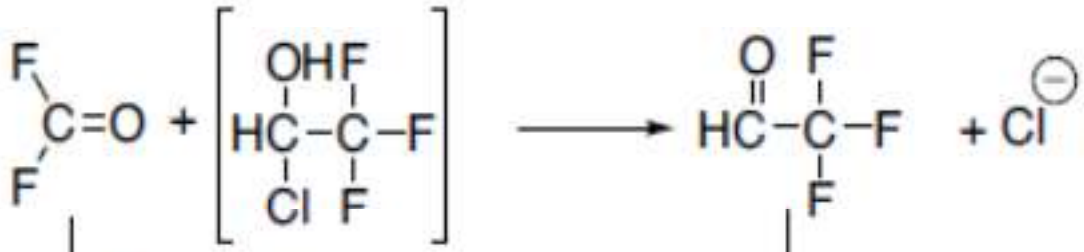
Isoflurane

- The metabolism of isoflurane yields low levels of the nephrotoxic fluoride ion as well as a potentially hepatotoxic trifluoroacetylating compound.
- The relatively low concentrations of these compounds have resulted in very low risks of hepatotoxicity and nephrotoxicity.
- There have been no reports of seizures caused by isoflurane and only transient increases in heart rate have been reported.

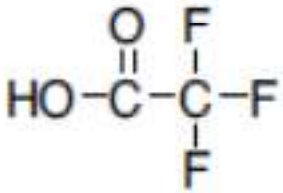


Isoflurane

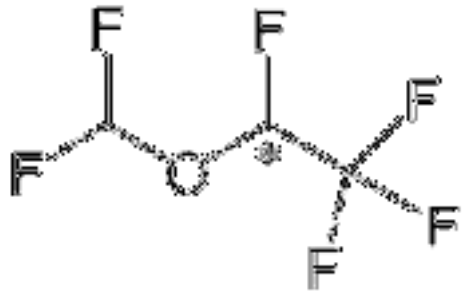
minor | [O]



H_2O



- **DESFLURANE**
- Desflurane is a nonflammable, colorless, very volatile liquid packaged in amber-colored vials. The boiling point is 22.8°C, and it requires a vaporizer specifically designed for desflurane.
- Desflurane has a blood:gas partition coefficient of 0.42, an MAC of 7.3% and an oil:gas partition coefficient of 18.7.
- The low blood:gas partition coefficient leads to fast induction times and short recovery times.



- Desflurane is not recommended for induction anesthesia in children because of the high incidence of laryngospasms (50%), coughing (72%), breath holding (68%), and increase in secretions (21%).
- Desflurane can produce a dose-dependent decrease in blood pressure and concentrations exceeding 1 MAC may cause transient increases in heart rate.
- Desflurane can react with desiccated carbon dioxide absorbents to produce carbon monoxide that may result in elevated levels of carboxyhemoglobin.
- Desflurane is metabolized minimally with less than 0.02% of the administered dose recovered as urinary metabolites.
- Desflurane produces minimal free fluoride ion and very little trifluoroacetic acid and has not been reported to cause either kidney or liver damage.

NON-INHALATION ANESTHETICS

- In order to place a patient under narcosis in modern anesthesiology, multiple drugs are used both prior to using inhalation anesthetics and during the procedure.
- The compounds used (with a few special exceptions) are formally classified as non-inhalation anesthetics.
- They represent other pharmacological classes like analgesics, tranquilizers, neuroleptics, and others.

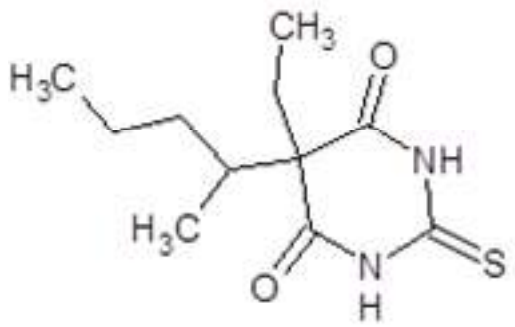
- It is worth mentioning that during non-inhalation anesthesia, control and regulation during the procedure is significantly harder than with inhalation anesthesia.
- However, the simplicity of intravenous anesthesia equipment and the various combinations (neuroleptanalgesia, ataragesia, tranquilizeresia) make the general anesthetic options extremely beneficial in clinical use.

- For general anesthesia, ketamine and ethomidate are used as short-acting, special drugs for noninhalation narcosis, as are a number of drugs that belong to completely different chemical classes, including: short-acting barbiturates (thiopental, methohexital), opioid analgesics (morphine, fentanyl), and also a number of benzodiazepine tranquilizers (diazepam, lorazepam, and midazolam).

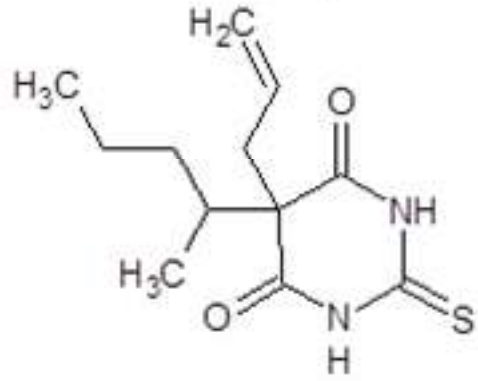
- **Ultra short acting Barbiturates:**
- These are used intravenously to produce a rapid unconsciousness for surgical anesthesia.
- These agents may be used initially to induce anesthesia, which then can be maintained during the surgical procedure with inhalation anesthetics.
- The induction is smooth, rapid and pleasant.

- These are positive allosteric modulators of GABA-A receptor and helps in opening of chloride ion channels resulting in CNS depression.
- Presence of sulfur atom at 2nd position of barbiturate ring (thiobarbiturates) greatly enhances the lipophilicity and therefore thiobarbiturates easily crosses BBB.
- Eg: Methohexital, Thiopental and Thiamylal.

Thiopental

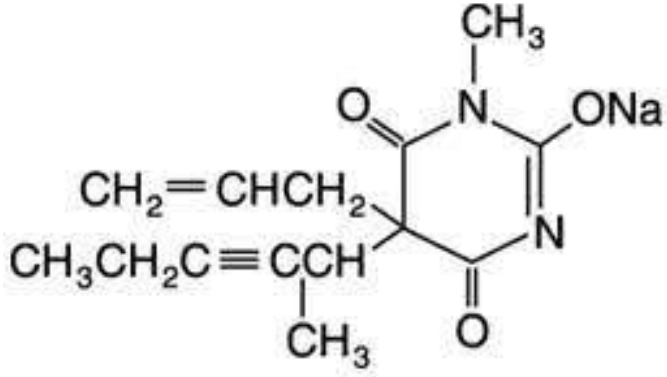


Thiamylal



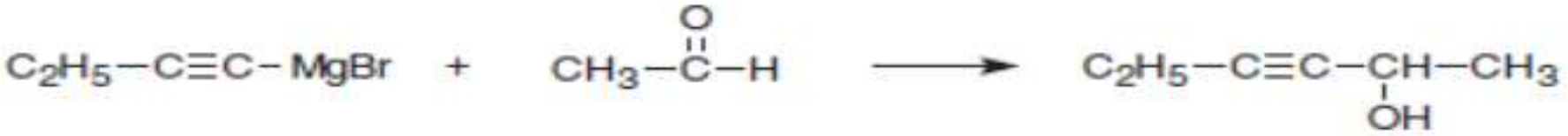
- Thiopental is an extremely short-acting barbiturate that makes anesthesia pleasant and smooth for the patient.
- When using the usual therapeutic doses, coming back into consciousness happens 15 min after administration.
- Thiopental has a straightforward dose-requiring oppressive effect on the myocardium, central nervous system, and to a lesser effect acts on the smooth muscle of blood vessels. It is used for narcosis in brief surgical operations.

- **Methohexital** is also an extremely short-lasting barbiturate, and it is used in same circumstances as is thiopental.
- It has a slightly shorter active time than thiopental; however, this difference is insignificant in clinical situations.
- Methohexital is a barbiturate substituted at N-1 by a methyl group and at C-5 by allyl and 1-methylpent-2-ynyl groups.

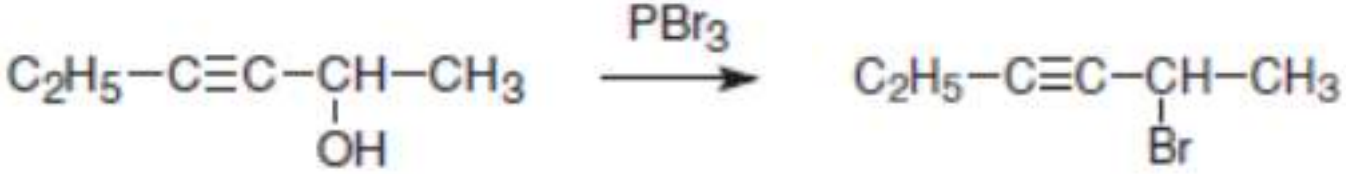


- ***Synthesis of Methohexital:***

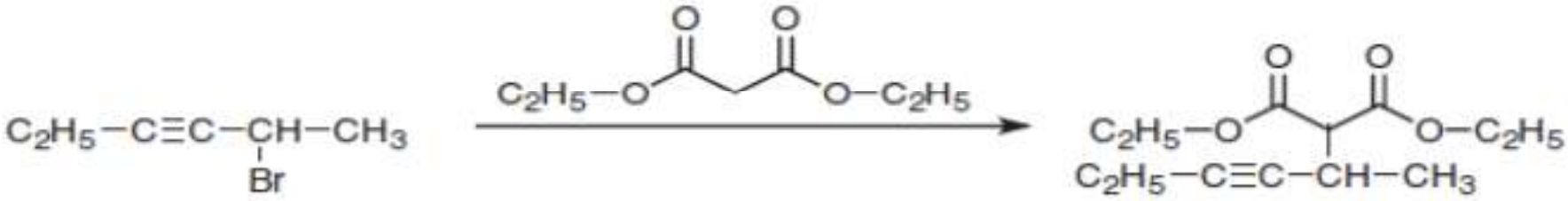
- **Butyne magnesium bromide reacts with acetaldehyde to give hexyne carbinol.**



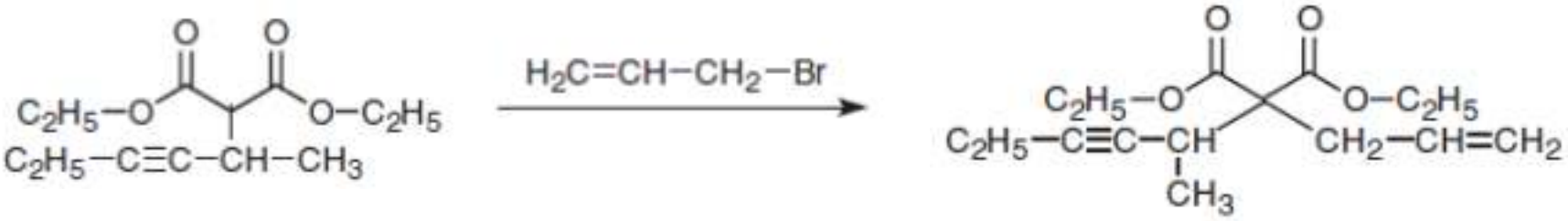
- **Bromination of this carbinol using phosphorous tribromide gives 2-bromo-3-hexyne.**



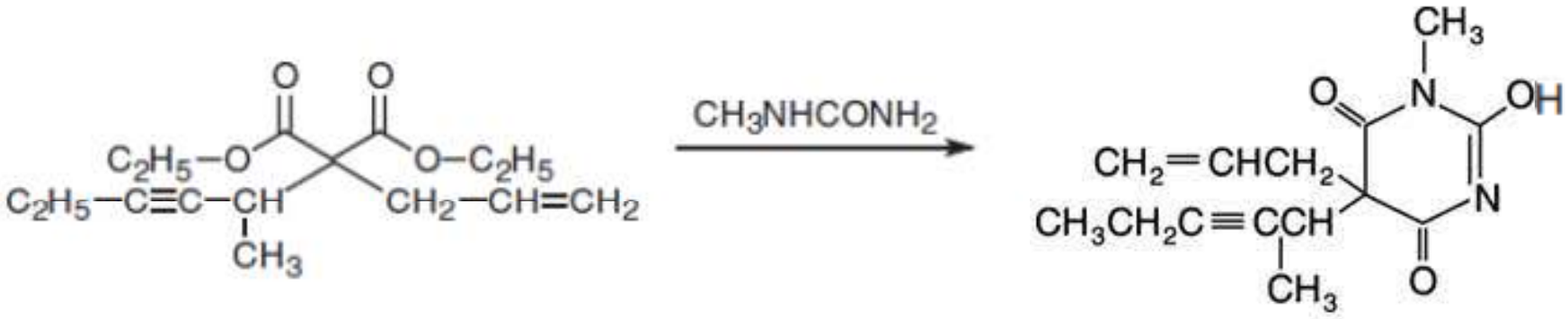
- **Condensation of 2-bromo-3-hexyne and diethyl malonate (nucleophilic addition) gives (1-methyl-2-pentynyl) malonic ester.**



- Allylation of this alkylated malonic ester gives allyl-(1-methyl-2-pentynyl) malonic ester.

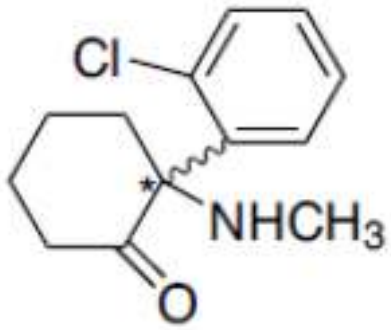


- Interaction of obtained dialkyl malonic ester with N-methylurea, gives desired methohexital.

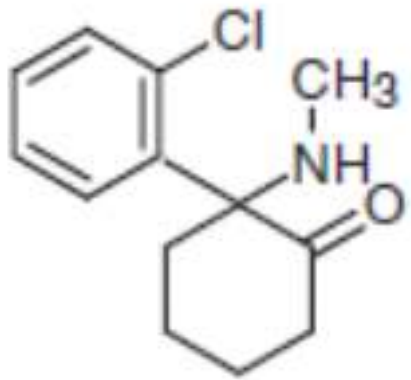


- **Ketamine:**

- Ketamine is marketed as the racemic mixture.
- Ketamine is a rapid-acting agent that can be used for induction, used as the sole agent for general anesthesia or combined with other agents.
- Unlike the proposed mechanism of action for most anesthetics, ketamine does not act at the GABAA receptor.



Ketamine



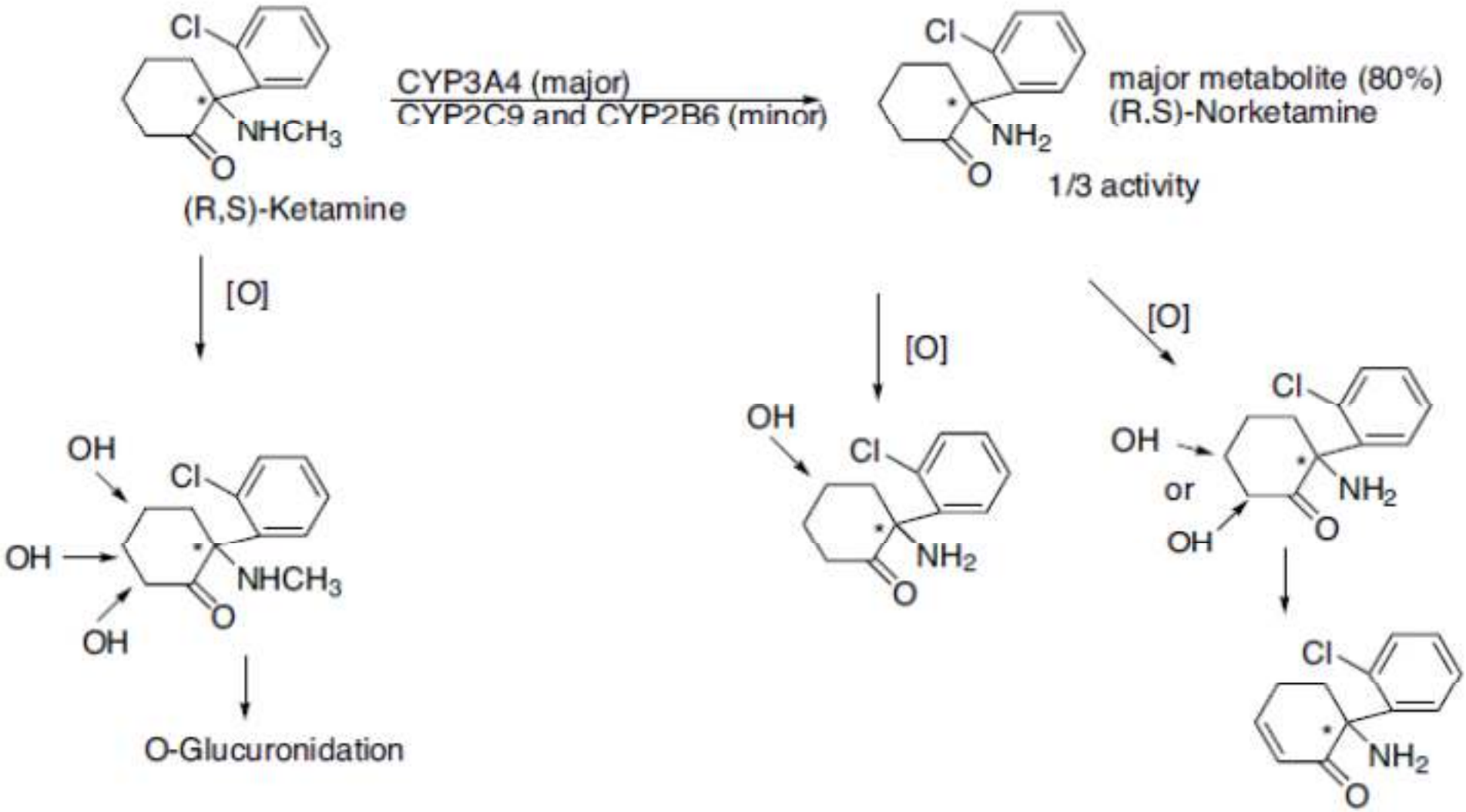
- Ketamine acts as a noncompetitive antagonist at the glutamate, NMDA receptor, a nonspecific ion channel receptor.
- The NMDA receptor contains four well-studied binding sites.
- The primary binding site binds L-glutamate, NMDA, and aspartate.
- The allosteric site binds glycine, which facilitates primary ligand binding.
- There is also a magnesium binding site that blocks ion flow through the channel.

- Fourth site is phencyclidine (PCP) binding site that blocks the ion channel when occupied.
- Ketamine is believed to bind to the PCP binding site in a stereo-selective manner and block the ion flow in the channel.
- By blocking the flow of calcium ions into the cell, ketamine prevents the calcium concentration from building and triggering excitatory synaptic transmissions in the brain and spinal cord.

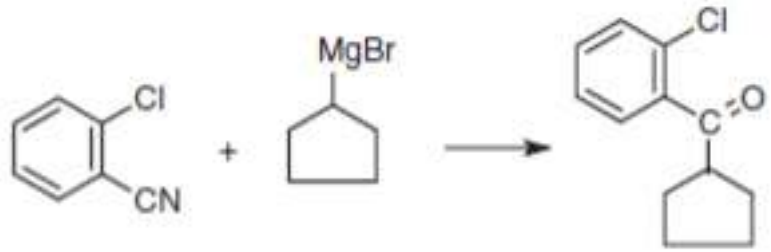
- Ketamine causes a transient increase in blood pressure after administration and is contraindicated in patients whom a significant elevation of blood pressure would constitute a serious hazard.
- Ketamine has also been found to bind to mu, delta, and kappa opioid receptors as well as the sigma receptors.
- The S(+) ketamine is two to three times more potent than the R(-) ketamine as an analgesic.
- Ketamine has different effects at different doses on the opioid receptors and the use of ketamine as a postoperative analgesic or for chronic pain requires more study.

- Ketamine is classified as a “dissociative anesthetic,” and psychological manifestations during emergence of anesthesia occur in 12% of patients.
- These vary from pleasant dreamlike states to vivid hallucinations and delirium.
- The duration is usually for only a few hours but patients have reported recurrences taking place up to 24 hours postoperatively.
- Like other dissociative anesthetics, ketamine is abused for its hallucinatory effects.

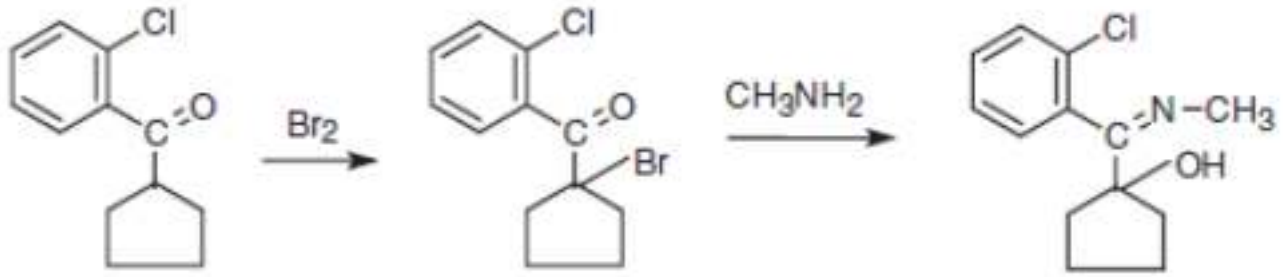
- Ketamine is metabolized via *N*-demethylation to form the main metabolite norketamine.
- Norketamine has about one third the potency of the parent compound.
- Minor metabolic metabolic pathways include hydroxylation of the cyclohexanone ring; hydroxylation followed by glucuronide conjugation, and hydroxylation followed by dehydration to the cyclohexanone derivative.


Cl
NHCH3
O
(R,S)-Ketamine
CYP3A4 (major)
CYP2C9 and CYP2B6 (minor)
Cl
NH2
O
major metabolite (80%)
(R.S)-Norketamine
1/3 activity
[O]
[O]
[O]
OH
Cl
NHCH3
O
OH
OH
OH
Cl
NH2
O
OH
or
OH
Cl
NH2
O
Cl
NH2
O
O-Glucuronidation

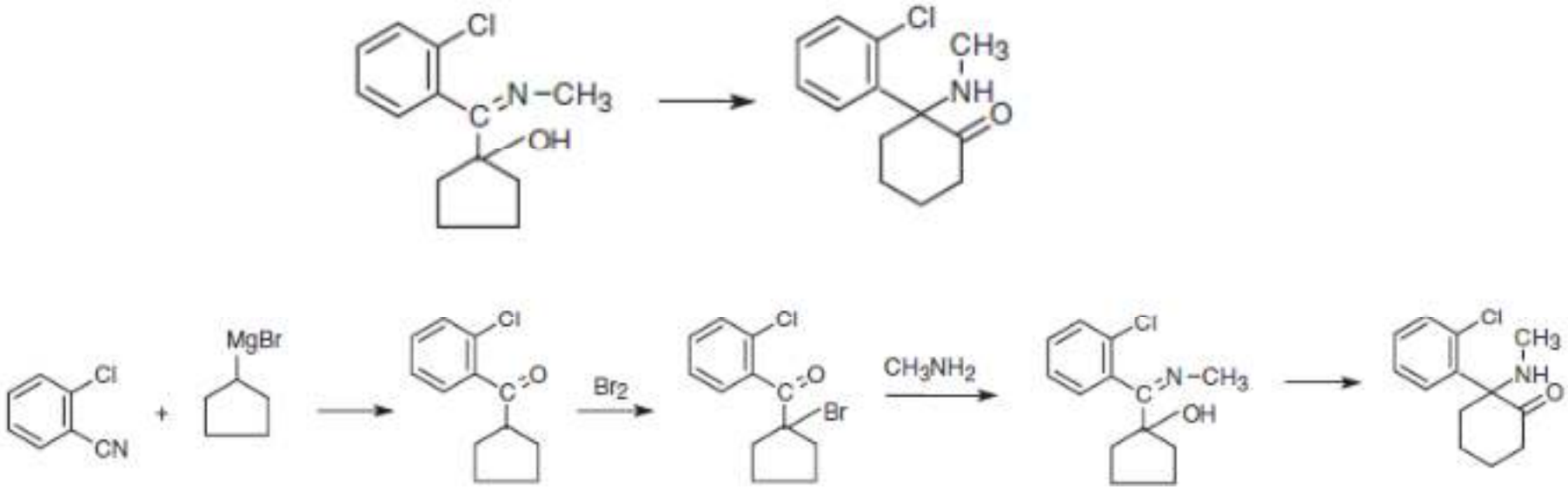
- **Synthesis of Ketamine:**
- 2-chlorobenzonitrile, which reacts with cyclopentylmagnesium bromide to give 1-(2-chlorobenzoyl)cyclopentane.



- The next step is bromination using bromine to the corresponding bromoketone, which upon interaction with an aqueous solution of methylamine forms the methylamino derivative.



- During this reaction a simultaneous hydrolysis of the tertiary bromine atom occurs.
- On further heating the reaction product in decaline, a ring expansion rearrangement occurs, causing formation of ketamine.

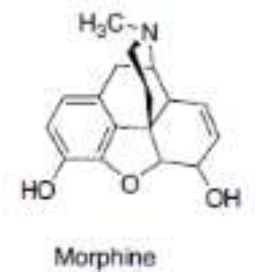


The History of Medicinal Chemistry

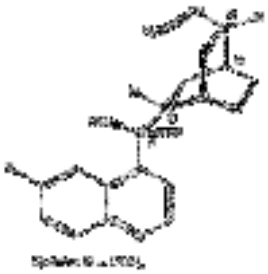
There is a long history of plants being used to treat various diseases. They figure in the records of early civilisations in Babylon, Egypt, India and China. The therapeutic properties of plants were described by the Ancient Greeks and by the Romans and are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus. Some metals and metal salts were also used at this time.

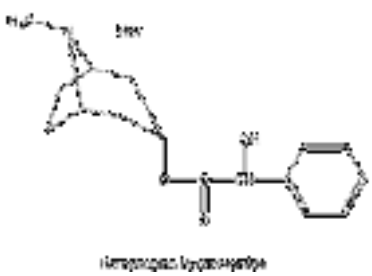
In the Middle Ages various 'Materia Medica and pharmacopeas brought together traditional uses of plants. The herbals of John Gerard (1596), John Parkinson (1640) and Nicolas Culpeper (1649) provide an insight into this widespread use of herbs. Exploration in the seventeenth and eighteenth centuries led to the addition of a number of useful tropical plants to those of European origin.

The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry. Their development is intertwined. The isolation of a number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud.



Morphine

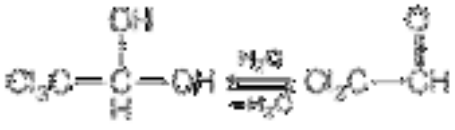




General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)).

Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery.

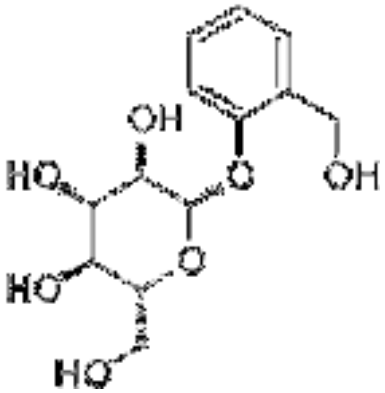
The hypnotic activity of chloral (trichloroethanal) (1869) was also reported.



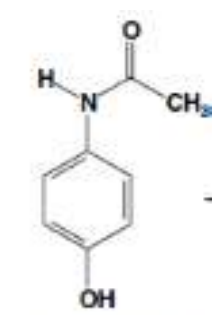
Chloral Hydrate Chloral

Many of the developments after the 1860s arose from the synthesis of compounds specifically for their medicinal action. Although the use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin and of salicylic acid were developed in the 1860s and 1870s.

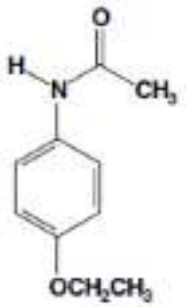
Salicin



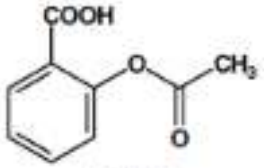
Acetaminophen (paracetamol) and phenacetin (1886) were also recognized as pain-killers.



Acetaminophen



Phenacetin

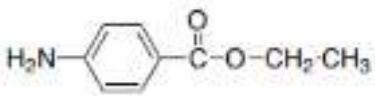


Aspirin

Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899. However its mode of action was not established until 1971.

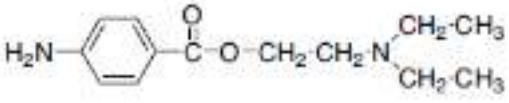
The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time. Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) and procaine (1905). The barbiturates, veronal (1903) and phenobarbital (1911) were introduced as sleeping tablets.

Cocaine

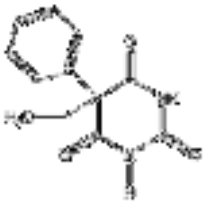


Benzocaine

Phenobarbital



Procaine

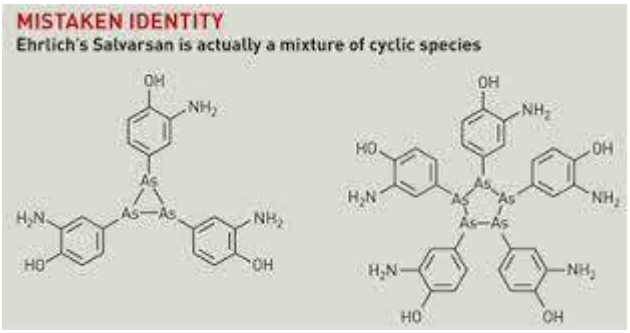


Once ideas of chemical structure were formulated in the mid-nineteenth century, the first theories of the relationships between chemical structure and biological activity began to emerge.

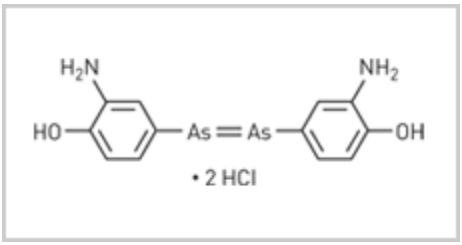
Thus Crum-Brown and Fraser (1869) noted that a 'relationship exists between the physiological action of a substance and its chemical composition' leading to the idea that cells can respond to the signals from specific molecules.

On the basis of observations that certain dyes selectively stained micro-organisms, Ehrlich in the 1890s put forward the idea that there were specific receptors for biologically active compounds - 'lock and key' relationships.

This led to the examination in 1904 of dyestuffs such as trypan red for the treatment of trypanosomiasis and the development (1907) of salvarsan for the treatment of syphilis by what turned out to be a false structural analogy.

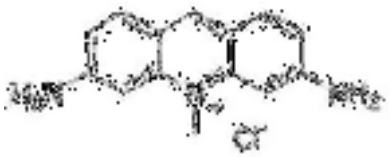


Salvarsan (correct structure)

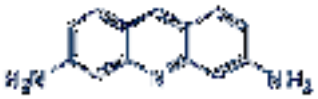


In the First World War acriflavine and proflavine dyestuffs were used for the treatment of sepsis in wounds. The work of Meyer and Overton (1899-1901) to relate a physical property (the oil: water distribution co-efficient) to biological activity (anaesthesia) were the first rudimentary QSAR. Another quantitative measurement that was made was the chemotherapeutic index, which was the ratio of the minimum curative dose to the maximum tolerated dose (CD50/LD50).

Acriflavine

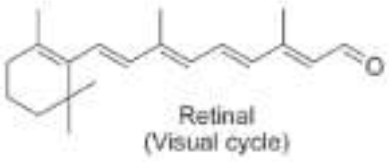


Proflavine



The action of acetylcholine on nerve tissue had been recognized in the late nineteenth century. Barger and Dale (1910) examined the response of various tissues to acetylcholine agonists and showed that there were different receptor sub-types; some responding to muscarine and others to nicotine.

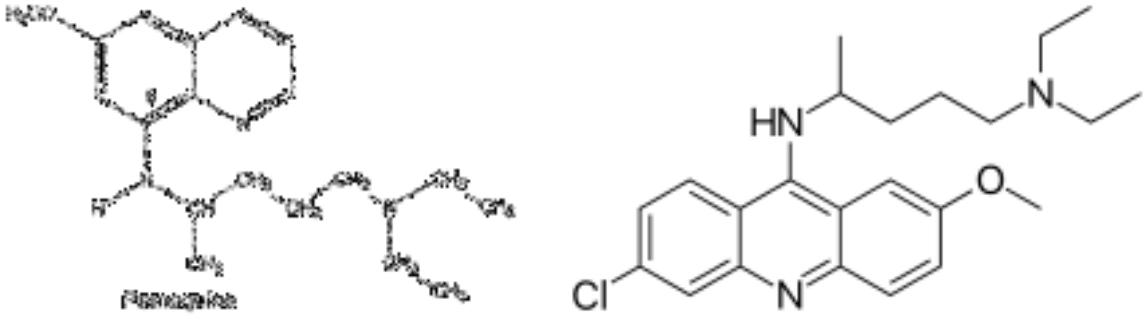
The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins. It was also a period in which there was exposure of many Europeans to tropical diseases.



The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentary and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness.

Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) and later chloroquine (1943) and paludrine (1946) were introduced as quinine replacements.

Mepacrine



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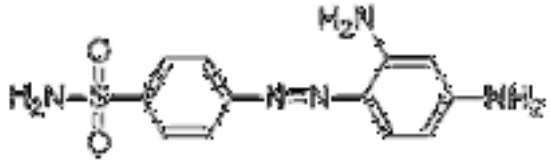
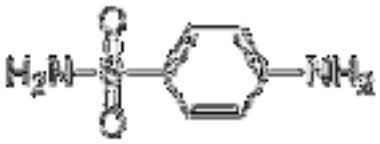
Prontosil



Sulfanilamide

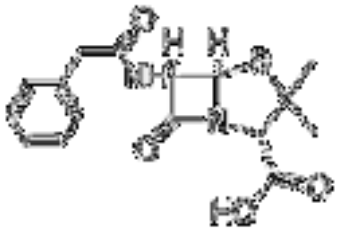


With the onset of the Second World War, there was a need for new antibiotics. In 1929 Fleming had observed that a strain of *Penicillium notatum* inhibited the growth of a Staphylococcus.

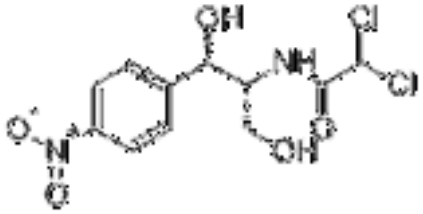
In 1940-1941 Chain, Florey and Heaton isolated benzylpenicillin. After considerable chemical work, the β-lactam structure for the penicillins was established.

The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including streptomycin (1944), chloramphenicol (1949) and the tetracyclines such as aureomycin (1949).

Benzylpenicillin



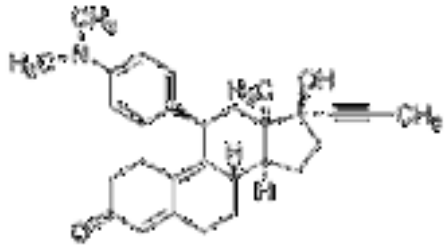
Chloramphenicol



Several different aspects of medicinal chemistry developed in parallel through the second half of the twentieth century. Although they did not develop independantly, it is easier to follow their progression by considering them separately.

The structures of the steroid hormones were established in the 1930s and 1940s. The discovery in 1949 of the beneficial effect of cortisone in alleviating the inflammation associated with rheumatism provided the stimulus for synthetic activity in this area. A number of anti-inflammatory semi-synthetic corticosteroids such as prednisolone, betamethasone and triamcinolone became available in the late 1950s and 1960s.

Animal experiments to develop steroidal oral contraceptives were carried out before the Second World War but the first preparations containing a synthetic estrogen and progestogen were not available until 1959. Subsequent preparations have been developed to reduce the estrogen level. Mifepristone, which is an anti-progestogen and forms the basis of the 'morning-after pill', was introduced in 1985. Whereas many of the medicines that had been developed prior to this time were administered for only short periods of time, this was not true of the steroids and concerns developed over the effects of long-term therapy.



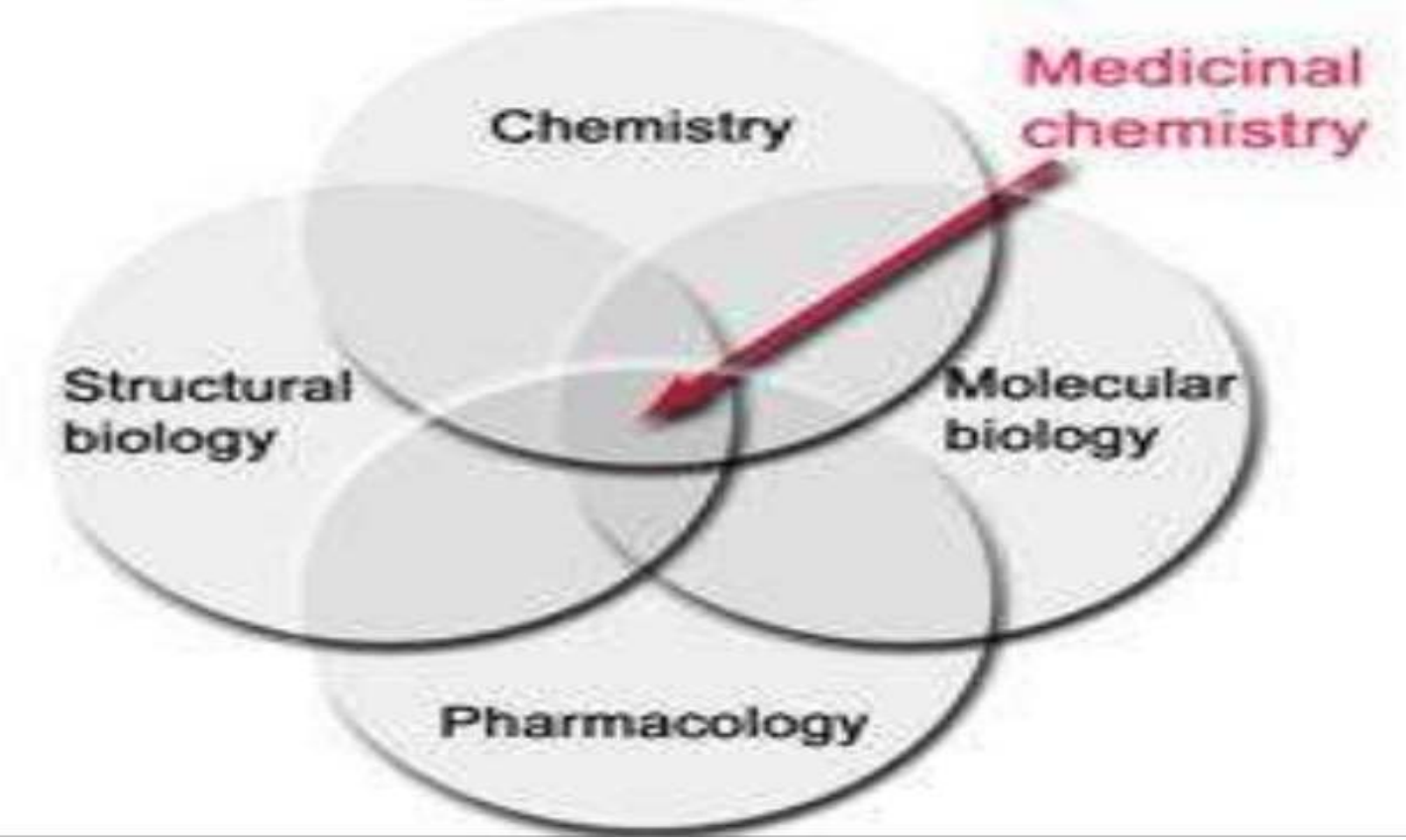
Problems associated with separating the anti-inflammatory activity from the mineralcorticoid activity of the cortical steroids led to interest in the development of non-steroidal anti-inflammatory agents (NSAIDs). The long-term use of aspirin as a pain-killer for arthritic conditions brought side-effects such as stomach ulcers. Indomethacin and ibuprofen were introduced in 1965 and 1971 respectively as alternatives.

During the 1960s the prostaglandin hormones were implicated in inflammation and in the protection of the stomach against ulcers. In 1971 aspirin was shown to inhibit the biosynthesis of the prostaglandins from arachidonic acid by the enzyme system, cyclo-oxygenase. The subsequent realization that there were several forms of cyclo-oxygenase provided the framework for developing selective non-steroidal anti-inflammatory agents that only targeted some of the multiple activities of the prostaglandins. One result was the introduction in 1999 of celecoxib and rofecoxib as selective cyclooxygenase (COX-2) inhibitors. Recently cardiovascular side effects of these compounds have begun to emerge and rofecoxib has been withdrawn.

A number of developments took place in the 1960s, which changed medicinal chemistry. It was found that a drug, thalidomide, which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children. The consequences of this teratogenic effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines. Unfortunately there was some tardiness in the recognition of this side-effect. Second in 1964 Hansch published correlations between substituent effects (Hammett parameters) and the biological activity of some aromatic compounds. These QSAR began to provide a framework for the systematic development of drugs and for decisions to be made in the planning of a research programme.

The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine (1976) and then ranitidine (1981). The reasoning behind this work had a major impact on the development of medicinal chemistry.

UNIT- I
Introduction to Medicinal Chemistry



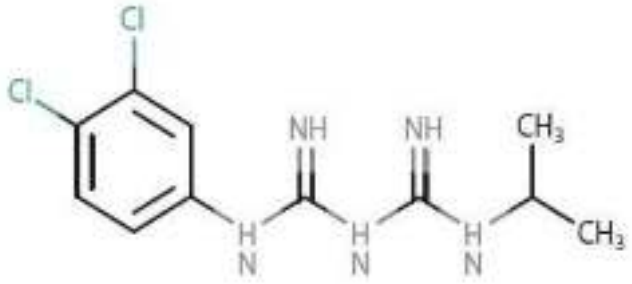
- History and development of medicinal chemistry.
- Physicochemical properties in relation to biological action.
- Ionization, Solubility, Partition Coefficient, Hydrogen bonding, Protein binding, Chelation, Bioisosterism, Optical and Geometrical isomerism.
- Drug metabolism principles- Phase I and Phase II. Factors affecting drug metabolism including stereo chemical aspects.

The History Of Medicinal Chemistry

- There is a long history of plants being used to treat various diseases.
- They figure in the records of early civilisations in Babylon, Egypt, India and China.
- The therapeutic properties of plants were described by the Ancient Greeks and by the Romans and are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus.
- Some metals and metal salts were also used at this time.

- In the Middle Ages various 'Materia Medica and pharmacopeas brought together traditional uses of plants.
- The herbals of John Gerard (1596), John Parkinson (1640) and Nicolas Culpeper (1649) provide an insight into this widespread use of herbs.
- Exploration in the seventeenth and eighteenth centuries led to the addition of a number of useful tropical plants to those of European origin.

- The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry.
- Their development is intertwined. The isolation of a number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud.



- General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)).
- Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery.
- The hypnotic activity of chloral (trichloroethanal) (1869) was also reported.

- Many of the developments after the 1860s arose from the synthesis of compounds specifically for their medicinal action.
- Although the use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin and of salicylic acid were developed in the 1860s and 1870s.
- p-Hydroxyacetanilide (paracetamol) and phenacetin (1886) were also recognized as pain-killers.

- Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899.
- However its mode of action was not established until 1971.
- The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time.
- Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) and procaine (1905).
- The barbiturates, veronal (1903) and phenobarbital (1911) were introduced as sleeping tablets.

- Once ideas of chemical structure were formulated in the mid-nineteenth century, the first theories of the relationships between chemical structure and biological activity began to emerge.
- Thus Crum-Brown and Fraser (1869) noted that a 'relationship exists between the physiological action of a substance and its chemical composition' leading to the idea that cells can respond to the signals from specific molecules.
- On the basis of observations that certain dyes selectively stained micro-organisms, Ehrlich in the 1890s put forward the idea that there were specific receptors for biologically active compounds - 'lock and key' relationships.

- This led to the examination in 1904 of dyestuffs such as trypan red for the treatment of trypanosomiasis and the development (1907) of salvarsan for the treatment of syphilis by what turned out to be a false structural analogy.
- In the First World War acriflavine and proflavine dyestuffs were used for the treatment of sepsis in wounds.
- The work of Meyer and Overton (1899-1901) to relate a physical property (the oil: water distribution co-efficient) to biological activity (anaesthesia) were the first rudimentary QSAR.
- Another quantitative measurement that was made was the chemotherapeutic index, which was the ratio of the minimum curative dose to the maximum tolerated dose (CD50/LD50).

- The action of acetylcholine on nerve tissue had been recognized in the late nineteenth century.
- Barger and Dale (1910) examined the response of various tissues to acetylcholine agonists and showed that there were different receptor sub-types; some responding to muscarine and others to nicotine.
- The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins.

- It was also a period in which there was exposure of many Europeans to tropical diseases.
- The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentary and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness.
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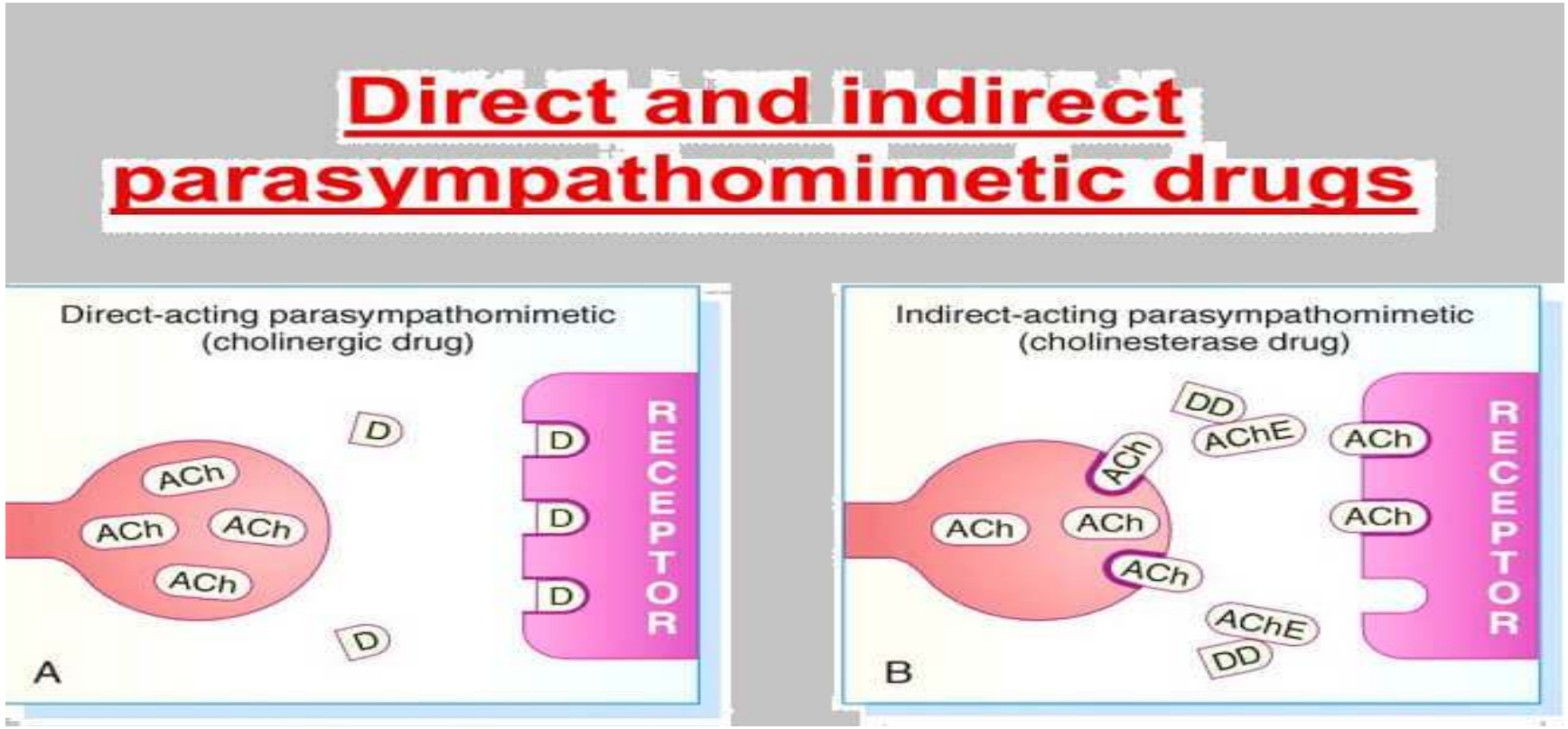
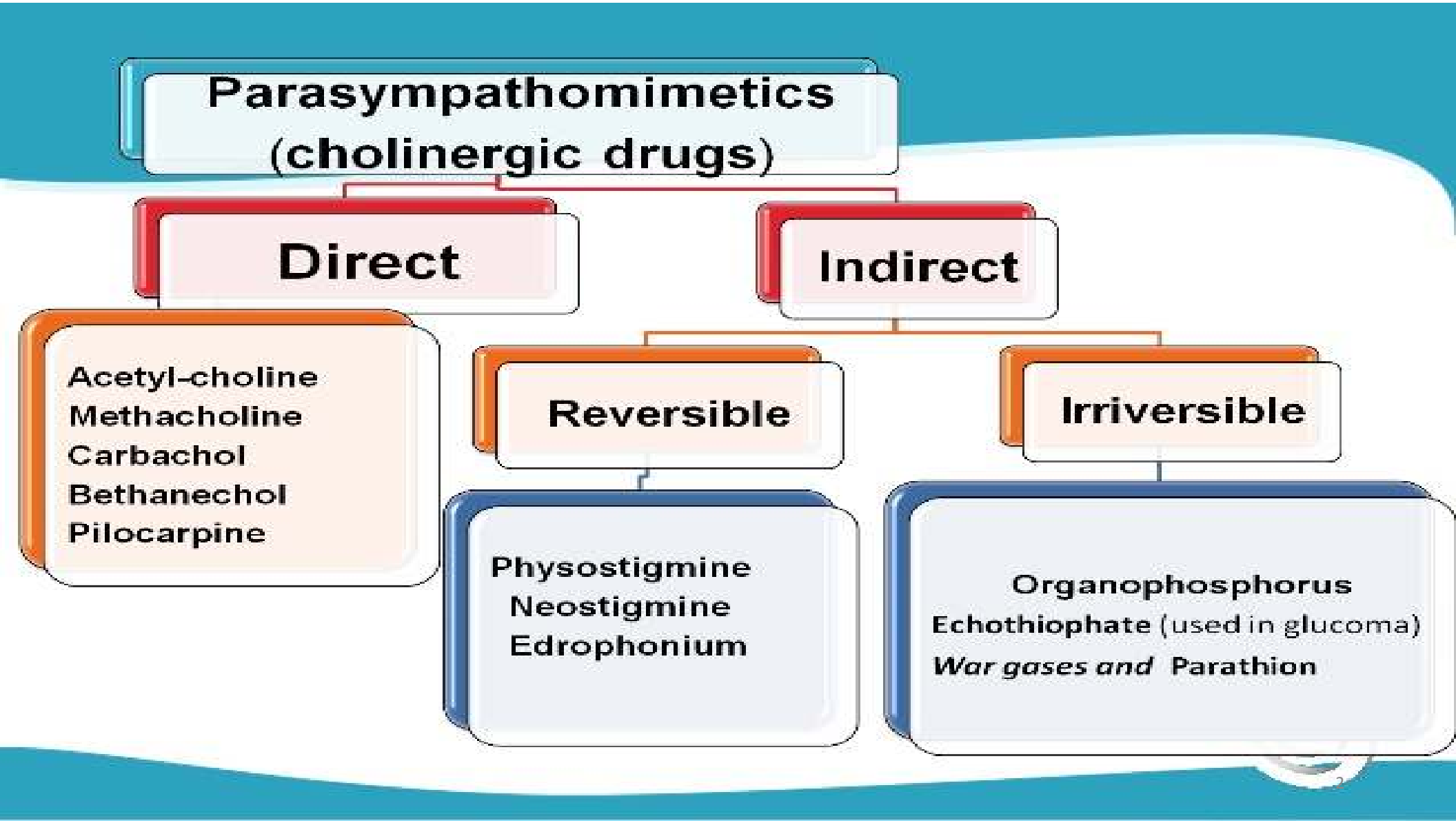
INDIRECT ACTING PARASYMPATHOMIMETICS

(Cholinesterase Inhibitors)




Parasympathomimetics
(cholinergic drugs)
Direct
Indirect
Acetyl-choline
Methacholine
Carbachol
Bethanechol
Pilocarpine
Reversible
Irriversible
Physostigmine
Neostigmine
Edrophonium
Organophosphorus
Echothiophate (used in glucoma)
War gases and Parathion

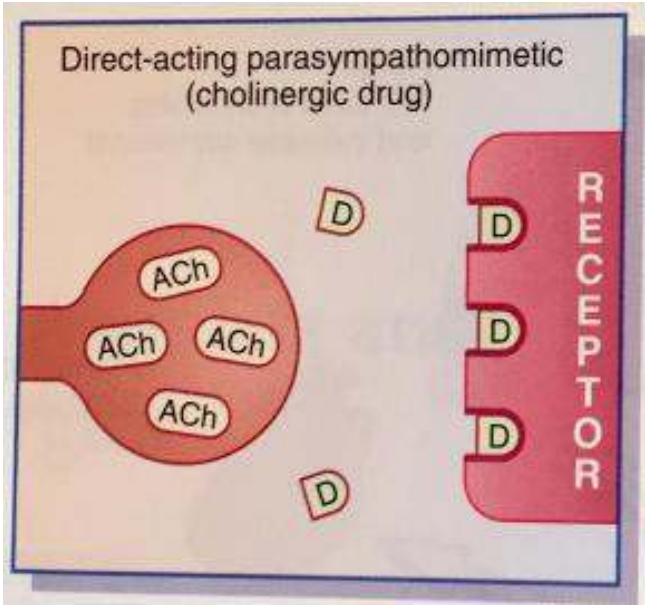
Direct-acting Parasympathomimetic agents

- **Choline Esters:**
- Acetylcholine.
- Carbachol.
- Methacholine.
- Bethanechol.

- **Cholinomimetic Alkaloids:**
- Muscarine.
- Pilocarpine.
- Arecholine.
- Oxotramorine.
- Cevimeline.
- Nicotine.
- Lobeline.
- Dimethyl phenyl piperazinium (DMPP).
- Varenicline.

- **Tertiary alkaloids:**
- Pilocarpine.
- Nicotine.
- Lobeline.

- **Quaternary amines:**
- Muscarine.

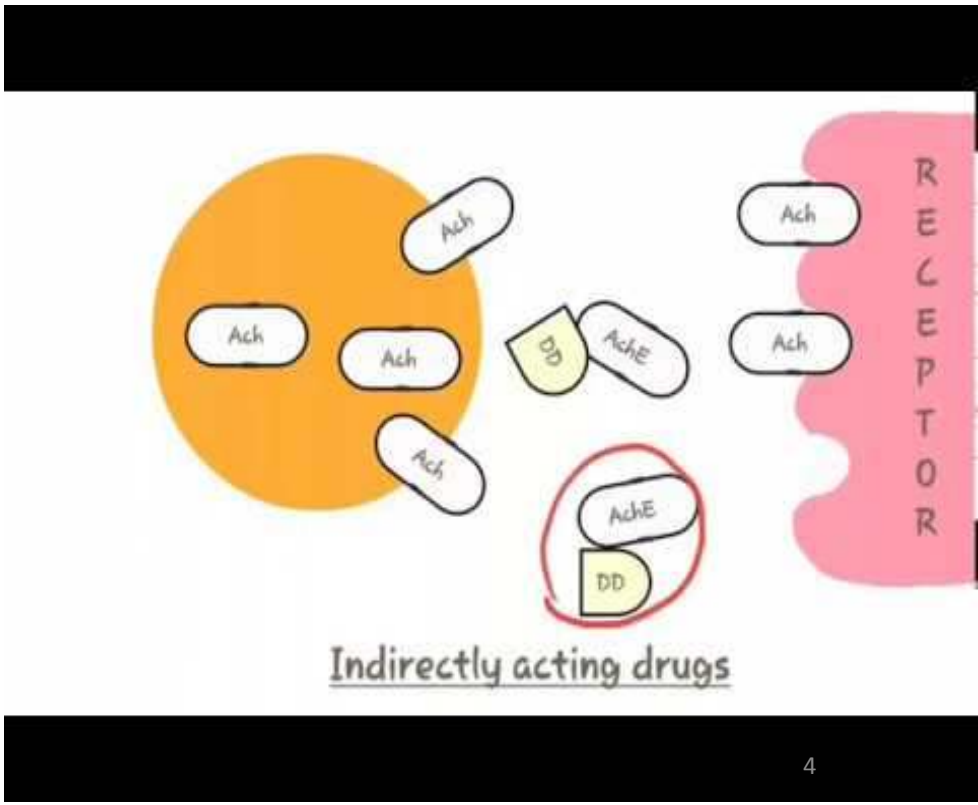


Indirect-acting parasympathomimetic agents (Cholinesterase Inhibitors)

- **Reversible:**

Physostigmine,
Neostigmine*,
Pyridostigmine,
Edrophonium chloride,
Tacrine hydrochloride,
Ambenonium chloride,
Demecarium,
Donepezil,
Rivastigmine,
Galantamine,
Metrifonate.

- **Irreversible:**
- Echothiophate iodide,
- Isofluorphate,
- Parathione,
- Malathion.
- War Gases.
- Insecticides.



- **Cholinesterases:**

- There are two types of cholinesterases in humans.

➢ Acetylcholinesterase (AChE)

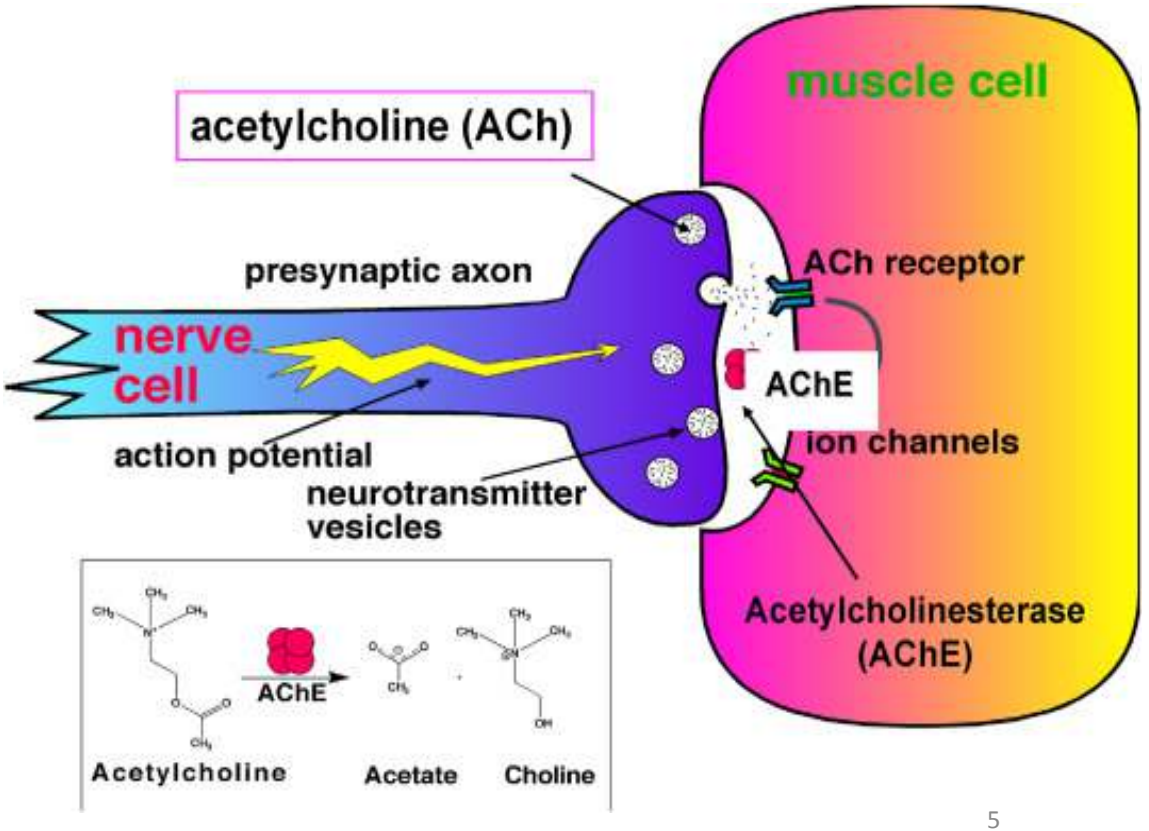
➢ Butyrylcholinesterase (BuChE)

(Pseudocholinesterase)

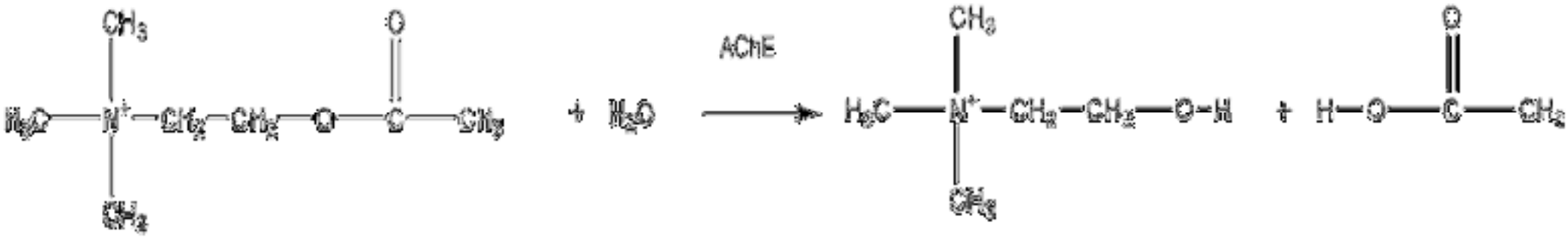
- They differ in

➢ their location in the body

➢ their substrate specificity



- **AChE** is associated with the outside surface of glial cells in the synapse and catalyzes the hydrolysis of ACh to choline and acetic acid.



- **Inhibition of AChE** prolongs the duration of the neurotransmitter in the junction and produces pharmacological effects similar to ACh.
- These inhibitors are indirect-acting cholinergic agonists.

- **Therapeutic uses:**
- They are used in the treatment of-
  - Myasthenia gravis,
  - Atony in the GI tract, and
  - Glaucoma.
- More recently, they have received attention as symptomatic drug treatments in patients suffering from **Alzheimer disease**.
- They are also useful as agricultural insecticides and nerve gases.

- **BuChE** (pseudocholinesterase) is located in human plasma.
- Its biological function is not clear.
- It has catalytic properties similar to those of AChE.
- The substrate specificity is broader.
- It may hydrolyze dietary esters and drug molecules in the blood.

- **Structural Requirements for Enzyme Inhibition:**
- The active center of AChE consists of several major domains:

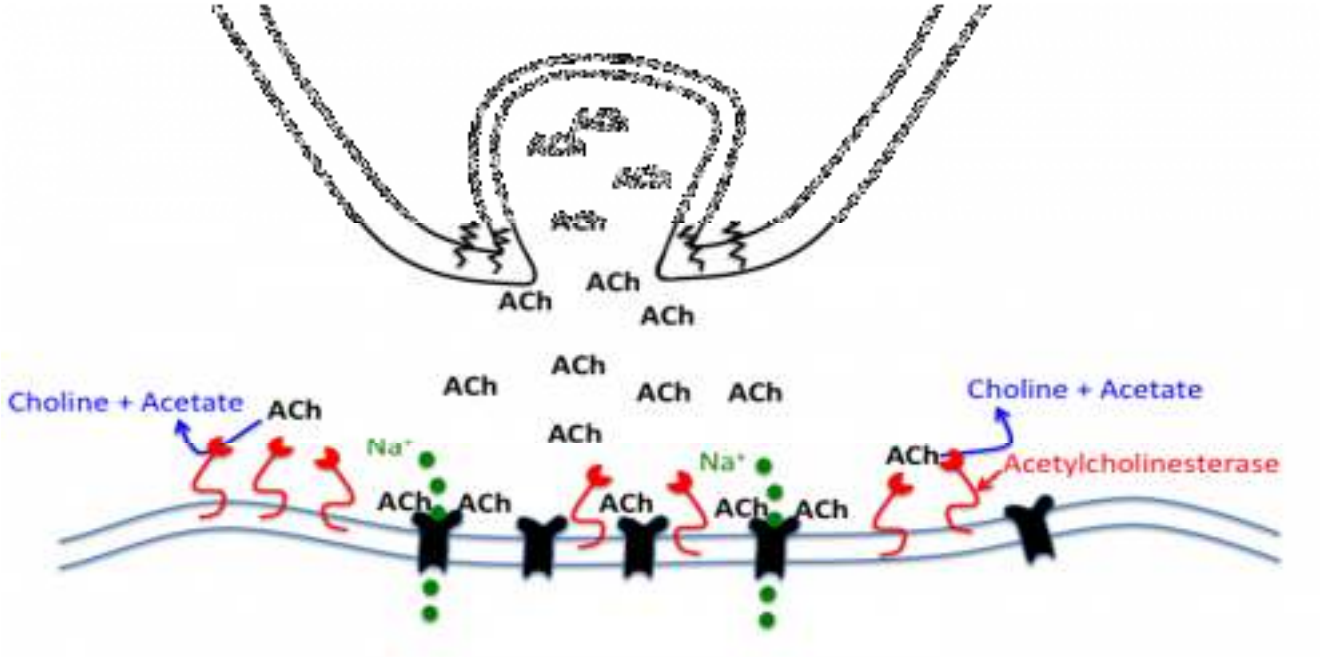
➢ an **anionic site**, to which the trimethylammonium group binds;

➢ an **esteratic site**, which causes hydrolysis of the ester portion of ACh;

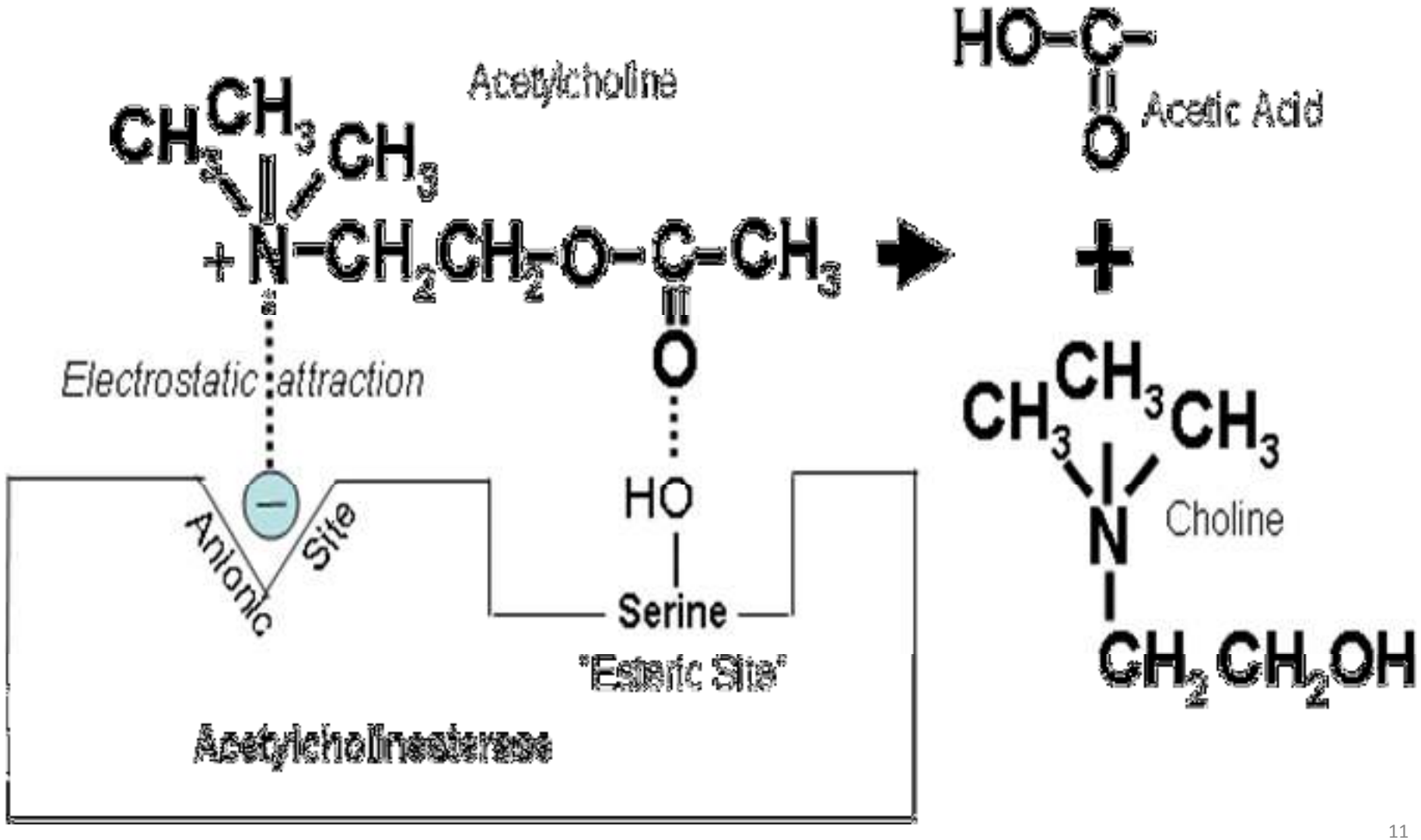
➢ **hydrophobic sites**, which bind aryl substrates, other uncharged ligands, and the alkyl portion of the acyl moiety of ACh.

- Three different pharmacophoric groupings may react with the **esteratic site of AChE**.

  - Acetyl,
  - Carbamyl,
  - Phosphoryl.



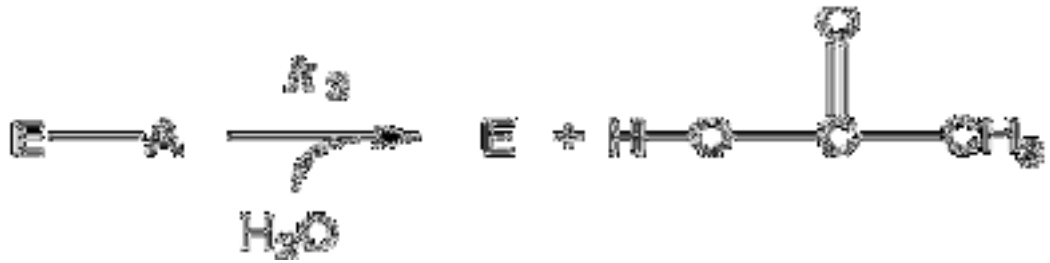
- Although the chemical reactions are similar, the **kinetic parameters** for each type of substrate differ and result in differences between toxicity and usefulness.


Acetylcholine
Acetic Acid
Electrostatic attraction
Anionic Site
Serine
"Esteric Site"
Acetylcholinesterase
Choline

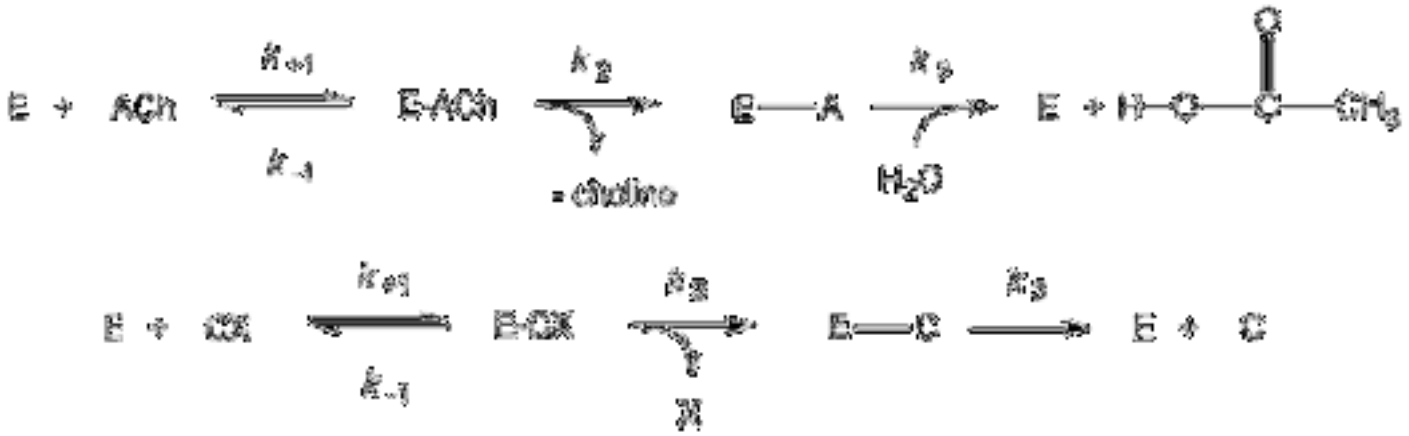
- **The initial step in the hydrolysis of ACh by AChE is a reversible enzyme–substrate complex formation. The association rate (*k*1) and dissociation rate (*k*1) are relatively large.**

- **The enzyme–substrate complex, EA–ACh, may also form an acetyl-enzyme intermediate at a rate (*k*2) that is slower than either the association or dissociation rates.**

- **Choline is released from this complex with the formation of the acetyl-enzyme intermediate, EA. This intermediate is then hydrolyzed to regenerate the free enzyme and acetic acid.**

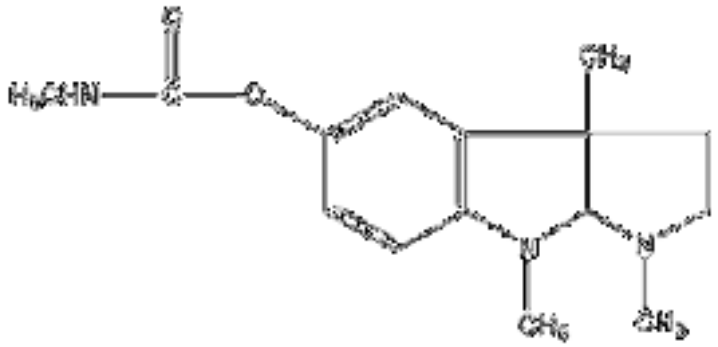


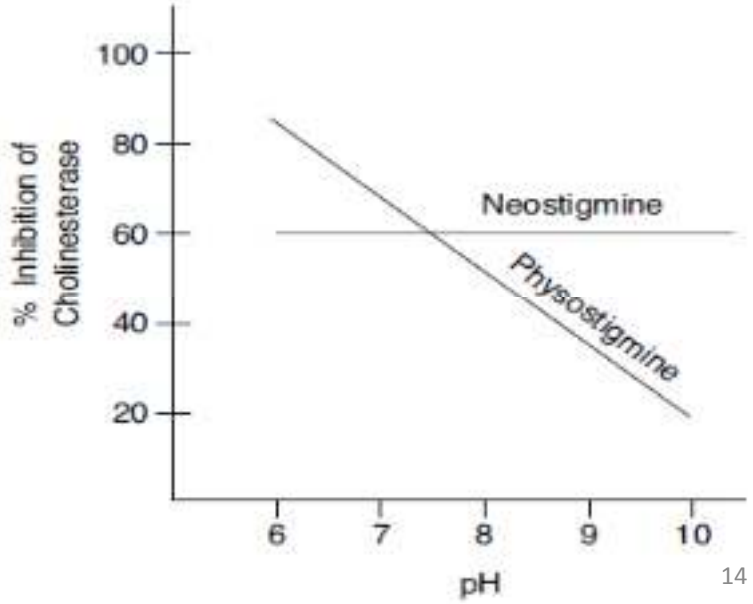
- **The acetylation rate, *k*2, is the slowest step in this sequence and is rate-limiting.**



REVERSIBLE INHIBITORS

- **PHYSOSTIGMINE:**
- Physostigmine is an indole alkaloid obtained from the dried ripe seed of *Physostigma venenosum*.
- It is a relatively poor carbamylating agent of AChE.
- Its cholinesterase-inhibiting properties vary with the pH of the medium **(WHY?)**.

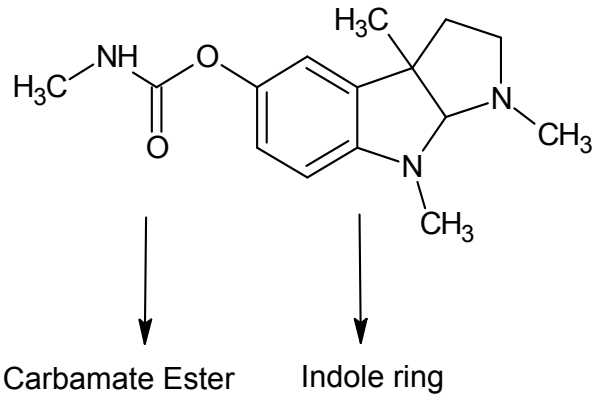




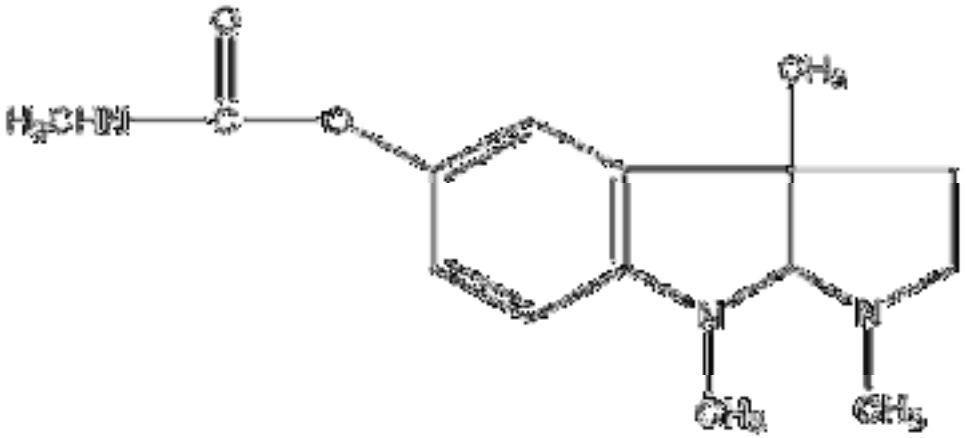
- Mechanism of Inhibition:
- When aryl carbamate inhibitors like physostigmine bind to the enzyme, hydrolysis of carbamate occurs.
- This transesterifies the serine residue with carbamic acid forming "CARBAMYLATED ENZYME".
- **Aryl carbamates are more efficient than alkyl carbamates like carbachol and betanechol due to better affinity.**

Calabar bean

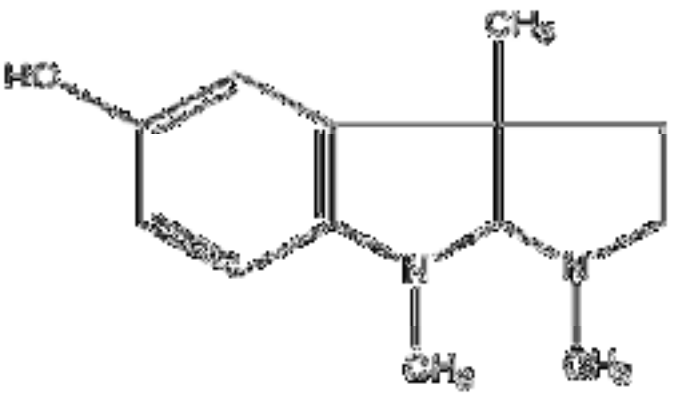
Physostigmine



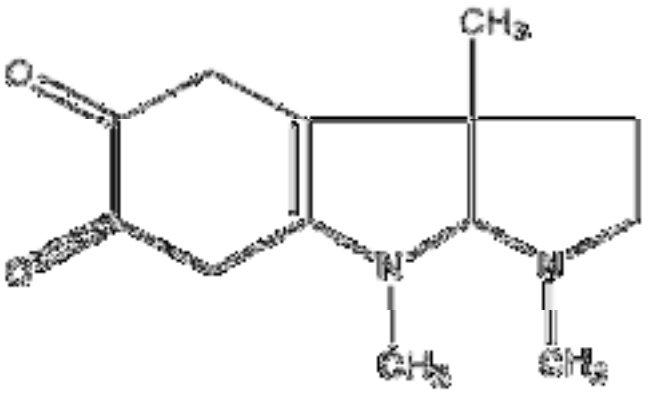
- It is quite sensitive to heat, light, moisture, and bases, undergoing rapid decomposition.
- In solution, it is hydrolyzed to methyl carbamic acid and eseroline, neither of which inhibits AChE.
- Eseroline is oxidized to a red compound, rubreserine, and then further decomposed to eserine blue and eserine brown.
- Addition of sulphite or ascorbic acid prevents oxidation of the phenol, eseroline, to rubreserine.
- Hydrolysis does take place, however, and the physostigmine is inactivated.
- **Solutions are most stable at pH 6** and should never be sterilized by heat.



Physostigmine



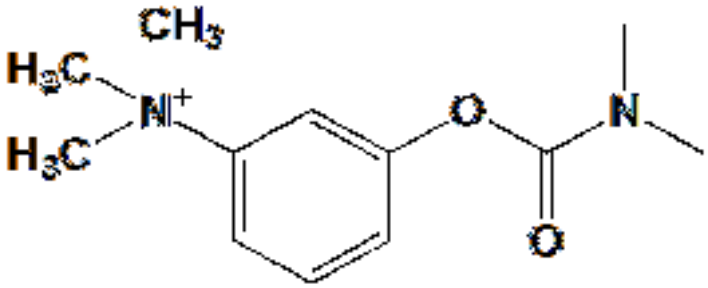
Eserolina



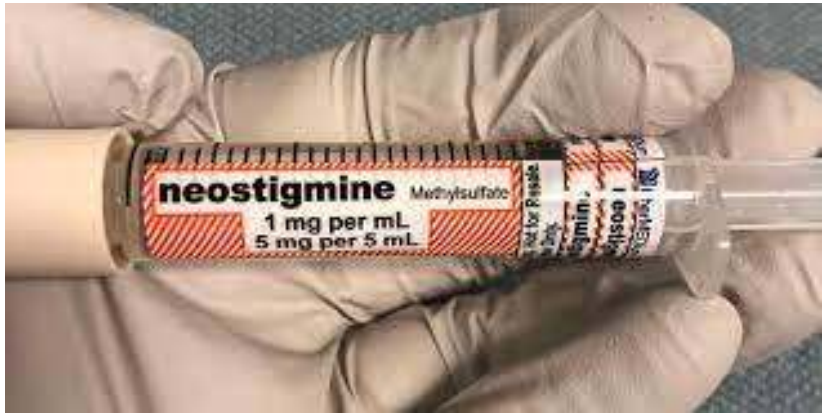
Rubreserine

- It has been used in ophthalmology for the **treatment of glaucoma**.
- It has been used in the **treatment of overdoses of anticholinergic compounds**.
- It has ability to cross BBB and now it is being investigated as indirect cholinomimetic for use in the **treatment of Alzheimers disease** and other **cognitive disorders**.

- **NEOSTIGMINE:**
- It is a synthetic compound that resemble physostigmine structurally .
- It retains the substituted carbamate group , benzene ring and nitrogen atom of first heterocyclic ring of physostigmine.
- The distance between ester and quaternary nitrogen is same as that found in acetylcholine and physostigmine.



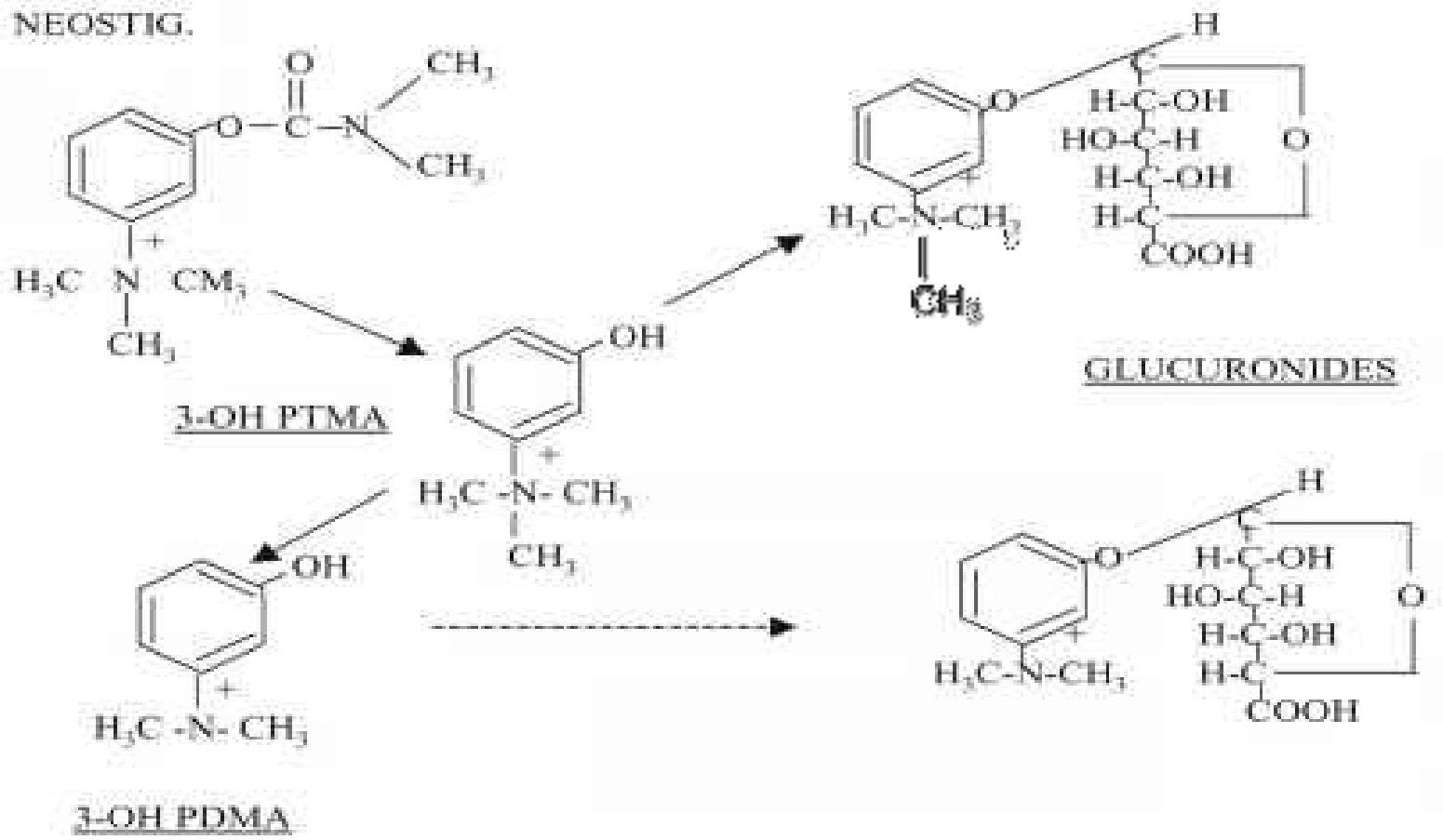
Neostigmine



- When a trimethylamine group was placed *meta t*o a dimethylcarbamate group in benzene, better inhibition of cholinesterase was observed.
- Neostigmine is a more active and useful agent.
- Although physostigmine contains a methylcarbamate functional group, greater chemical stability toward hydrolysis was obtained with the dimethylcarbamyl group in neostigmine

- **Pharmacokinetics:**
- It has a half-life of about 50 minutes after oral or intravenous administration.
- About 80% of a single intramuscular dose is excreted in the urine within 24 hours;
- Approximately 40% is excreted unchanged, and the remainder is excreted as metabolites.
- It is metabolized in 10 minutes to 3-hydroxyphenyltrimethyl ammonium (weakly active).

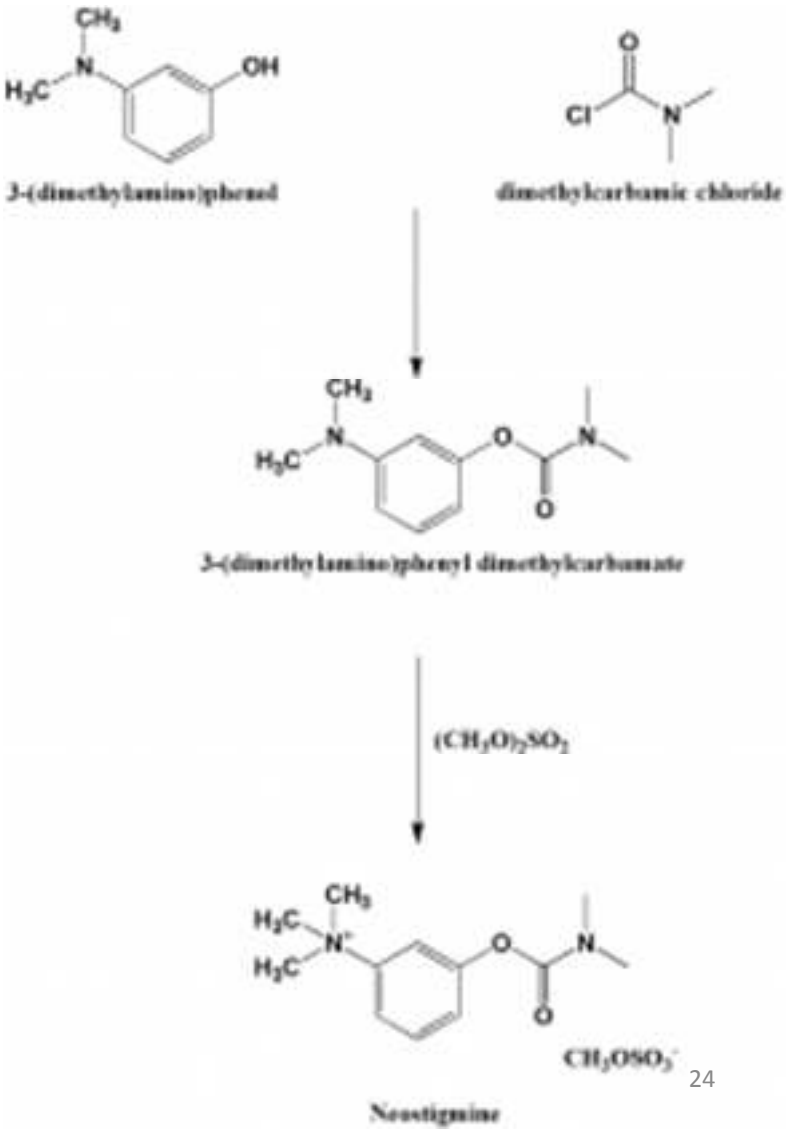
- **Metabolism of Neostigmine:**
- 3-OH PTMA – 3-Hydroxyphenyl trimethyl ammonium metabolite
- 3-OH PDMA – 3-Hydroxyphenyl dimethyl ammonium metabolite



- **Therapeutic Uses:**
- It can not cross BBB and so lacks central activity.
- It is used as an antidote to nondepolarizing neuromuscular blocking drugs and in the treatment of myasthenia gravis.
- It is used as prophylactic agent in postoperative abdominal distension and urinary retention.
- It is also used to prevent atony of the intestinal, skeletal, and bladder musculature.

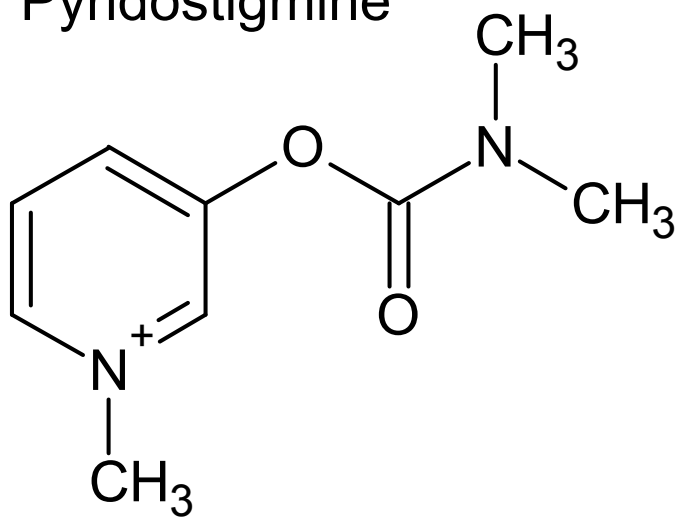
Synthesis of Neostigmine:

- i. Reaction of 3-dimethyl amino phenol and N-dimethylcarbonyl chloride to form Neostigmine.
- ii. Alkylation of the neostigmine using dimethylsulfate gives neostigmine methylsulfate.

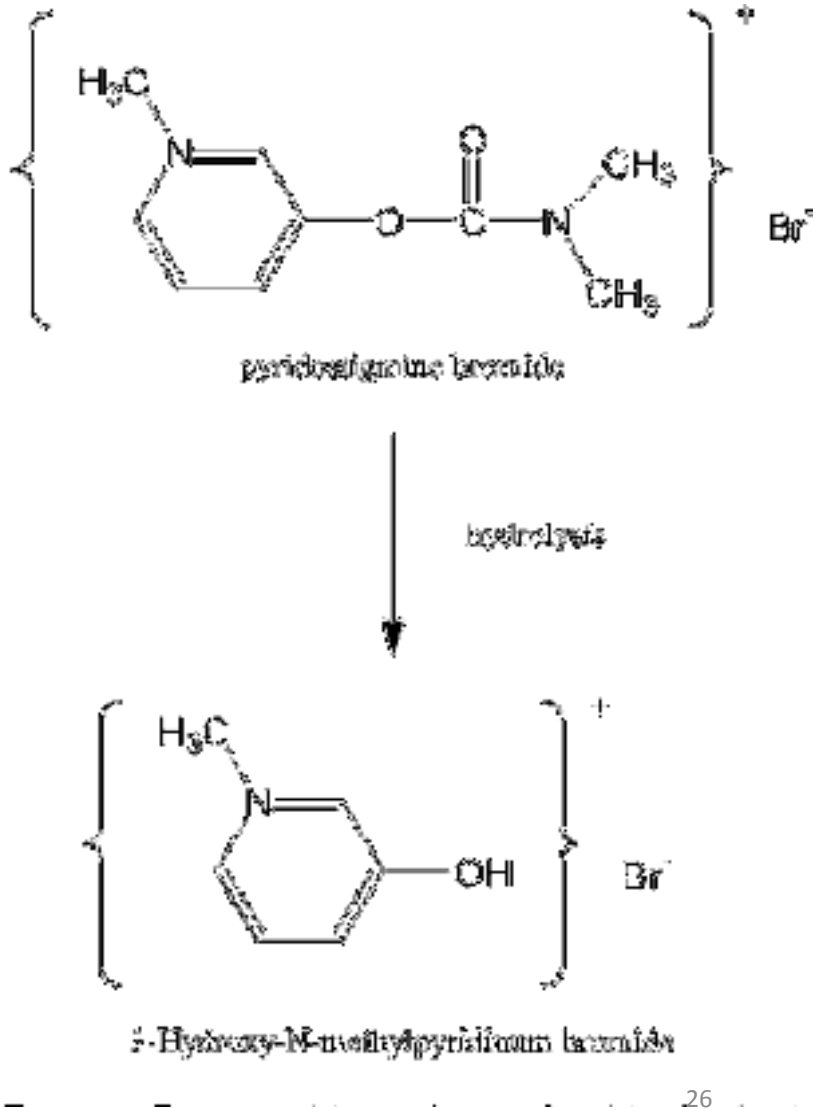


- **PYRIDOSTIGMINE:**
- It is closely related to neostigmine that incorporates charged nitrogen in to a pyridine ring.
- It acts by the same mechanism as physostigmine but lacks central activity.
- It is about one fifth as toxic as neostigmine.
- It appears to function in a manner similar to that of neostigmine and is the most widely used anticholinesterase agent for treating myasthenia gravis.

Pyridostigmine

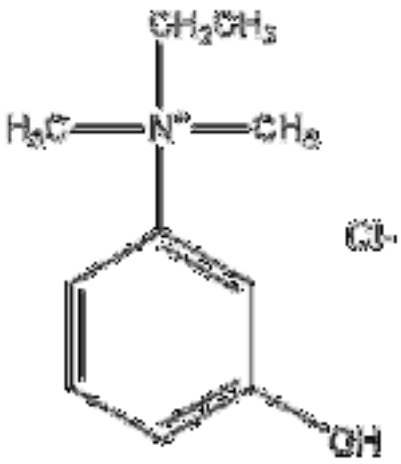


- The liver enzymes and plasma cholinesterase metabolize the drug.
- The principal metabolite is 3-hydroxy-*N*-methylpyridinium.
- Orally administered pyridostigmine has a half-life of 90 minutes and a duration of action of between 3 and 6 hours.



- Pyridostigmine is orally active and has longer duration of action & lower incidence of side effects than neostigmine.
- It is a better choice for oral therapy of myasthenia gravis.
- It is used parenterally to reverse the effects of non-depolarising neuromuscuar blocking agents.

- ***EDROPHONIUM CHLORIDE:***
- **IUPAC-ethyl(*m*-hydroxyphenyl)dimethylammonium chloride.**



- It is bitter and very soluble in water and alcohol.
- Edrophonium chloride injection has a pH of 5.2 to 5.5.
- On parenteral administration, it has a more rapid onset and shorter duration of action than neostigmine, pyridostigmine, or ambenonium.
- It is a specific anticurare agent and acts within 1 minute to alleviate overdose of *d*-tubocurarine, dimethyl *d*-tubocurarine, or gallamine triethiodide.

- The drug is also used to terminate the action of any one of these drugs when the physician so desires.
- It is of no value in terminating the action of the depolarizing (i.e., noncompetitive) blocking agents, such as decamethonium and succinylcholine.
- In addition to inhibiting AChE, edrophonium chloride has a direct cholinomimetic effect on skeletal muscle, which is greater than that of most other anticholinesterase drugs.

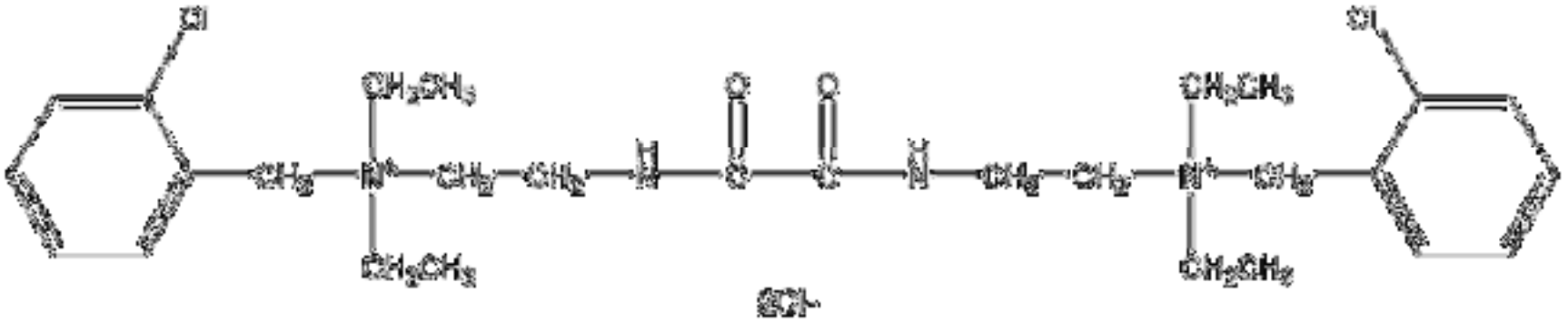
- ***Ambenonium Chloride:***

- ***IUPAC*-(iminoethylene)]bis[(*o*-chlorobenzyl)diethylammonium] dichloride**

- Because of its quaternary ammonium structure, ambenonium chloride is absorbed poorly from the GI tract.

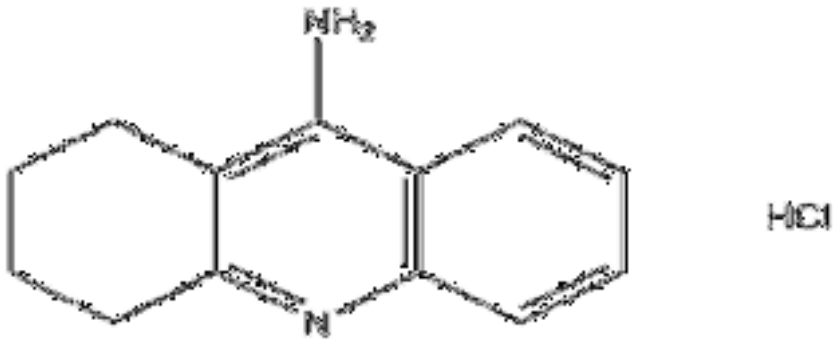
- In moderate doses, the drug does not cross the blood-brain barrier.

- It is not hydrolyzed by cholinesterases.



- It is used for the treatment of myasthenia gravis in patients who do not respond satisfactorily to neostigmine or pyridostigmine.
- It possesses a relatively prolonged duration of action and causes fewer side effects in the GI tract than the other anticholinesterase agents.
- The dosage requirements vary considerably, and the dosage must be individualized according to the response and tolerance of the patient.

- ***Tacrine Hydrochloride:***
- **IUPAC - 1,2,3,4-tetrahydro-9-aminoacridine hydrochloride.**
- It is an aminoacridine synthesized as nonclassical AChEI.
- It binds to both acetylcholinesterase and butyrylcholinesterase.
- It has been used in the treatment of Alzheimer disease for several years.



Tacrine Hydrochloride

- The drug has been used to increase the levels of Ach.
- The use of the drug is not without controversy, as conflicting results on efficacy have been reported.
- The drug has been used in mild-to-moderate Alzheimer dementia.
- Its use in the treatment of Alzheimers disease is now limited due to hepatotoxicity.

IRREVERSIBLE INHIBITORS

- Phosphate esters are chemically more stable than the carbamate esters(reversible inhibitors).
- This led to the design of derivatives of phosphoricacid , phosphonic acid and pyrophosphoric acid.
- These act as inhibitors by the same mechanism as carbamate inhibitors.
- But they leave the enzyme esterified as phosphate ester.
- As the duration of action of these phosphate esters is much longer than carbamate esters, they are referred as **IRREVERSIBLE INHIBITORS**.

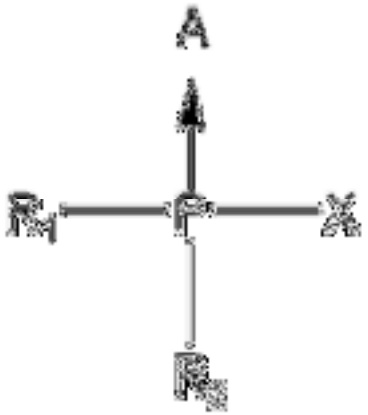
- Phosphate esters:

- Both AChE and BuChE are inhibited irreversibly by phosphate esters.

- They are highly toxic.

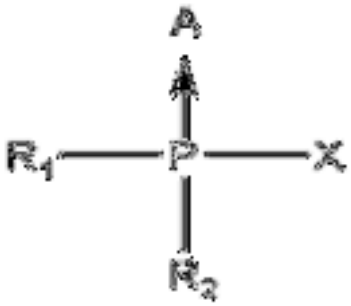
- The compounds belong to a class of organophosphorous esters.

- **SAR:** **<u>A general formula for such compounds</u>**



where R_1 = alkoxy
R_2 = alkoxyl, alkyl, or tertiary amine
X = a good leaving group
(e.g. F, CN, thiocyanate, p-nitrophenyl)

- ***'A'*** is usually oxygen or sulfur but may also be selenium.



- When *A* is other than oxygen, biological activation is required.
- **Phosphorothionates [*R*1R2P(S)X]** have much poorer electrophilic character than their oxygen analogs and are much weaker hydrogen bond-forming molecules because of the sulfur atom.
- Their anticholinesterase activity is 105-fold weaker than their oxygen analogs.
- ***X*** is the leaving group when the molecule reacts with the enzyme.

- Typical leaving groups include fluoride, nitrile, and *p*-nitrophenoxy.
- The *R* groups may be alkyl, alkoxy, aryl, aryloxy, or amino.
- The *R* moiety imparts lipophilicity to the molecule and contributes to its absorption through the skin.
- These chemicals are **nerve poisons** and have been **used in warfare, in bioterrorism**, and as **agricultural insecticides**.
- They permit ACh to accumulate at nerve endings and increase ACh-like actions.

- **Mechanism of Irreversible Inhibition:**

- Inhibition of AChE by organophosphorous compounds takes place in two steps:

➢ Association of enzyme and inhibitor.

➢Phosphorylation step.

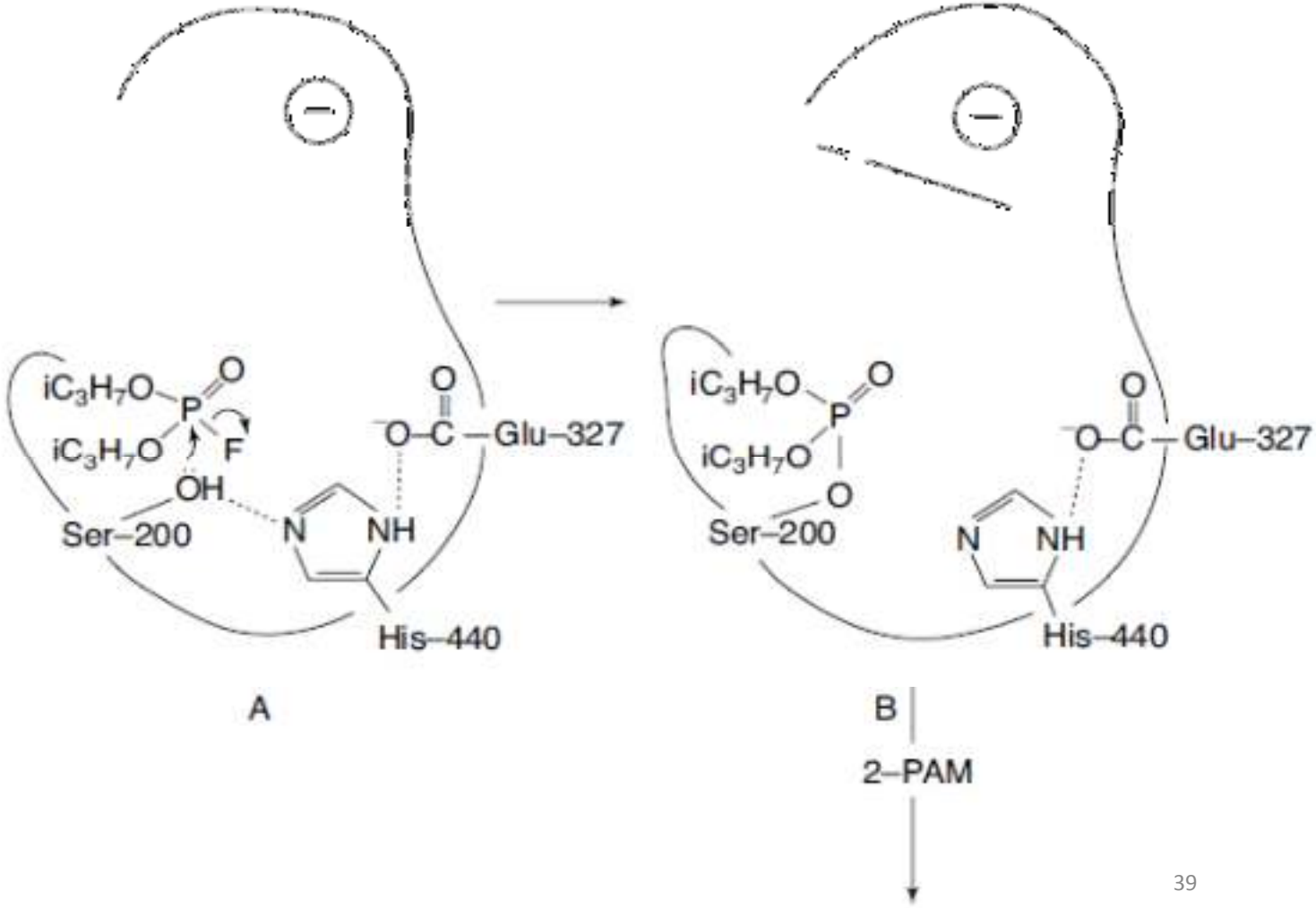
- This is completely analogous to acylation by the substrate.

- Stereospecificity is mainly caused by interactions of enzyme and inhibitor at the esteratic site.

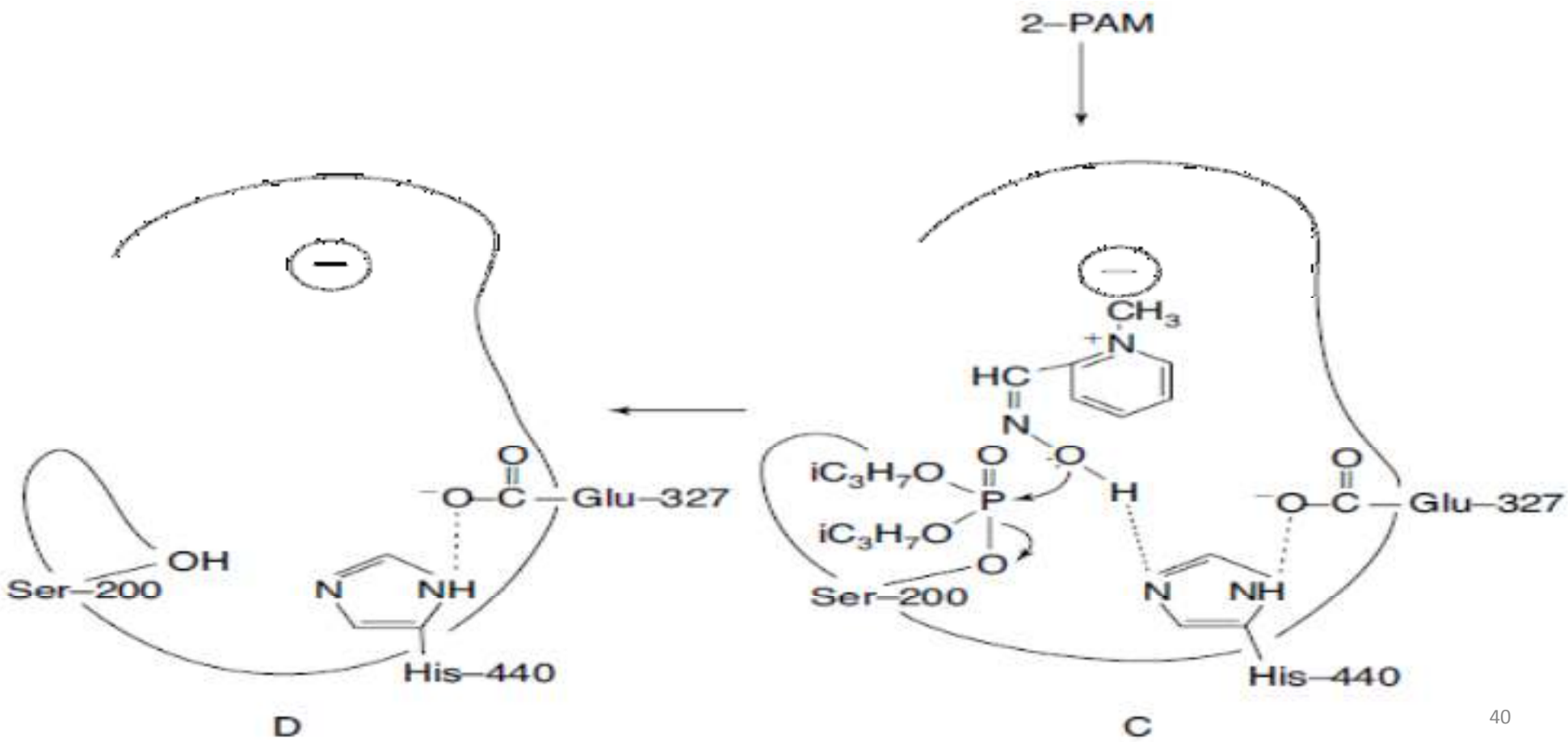
- The serine residue at the esteratic site forms a stable phosphoryl ester with the organophosphorous inhibitors.

Phosphorylation and reactivation of cholinesterase:

- **A. Phosphorylation of serine by isofluorphate.**
- **B. Phosphorylated serine at the esteratic site.**



- **C.** Nucleophilic attack on phosphorylated residue by 2-PAM.
- **D.** Free enzyme.

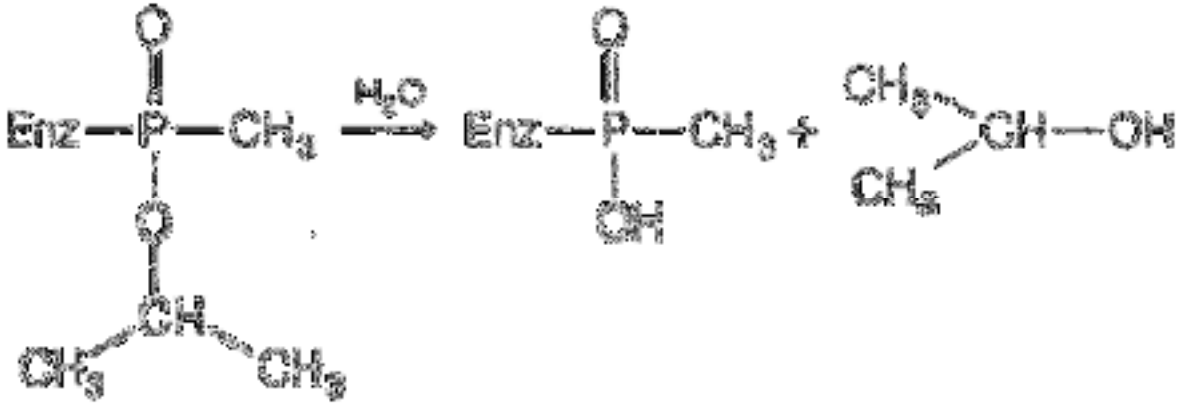


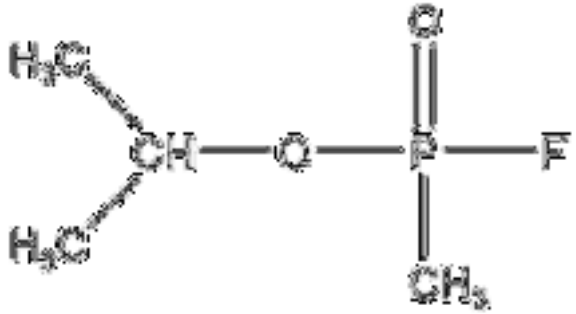
- **Reactivation/Regeneration of Enzyme:**
- Nucleophilic attack on the phosphorylated enzyme cause regeneration of the free enzyme.
- Substances such as choline, hydroxylamine, and hydroxamic acid have led to the development of more effective **cholinesterase reactivators**, such as nicotinic hydroxamic acid and pyridine-2-aldoxime methiodide (2-PAM).

- **Enzyme Aging:**

- Cholinesterases that have been exposed to phosphorylating agents (e.g., sarin) become **refractory to reactivation by cholinesterase reactivators**.

- The process is called *aging* and occurs both in vivo and in vitro with AChE and BuChE. Aging occurs by **partial hydrolysis of the phosphorylated moiety** that is attached to the serine residue at the esteratic site of the enzyme.

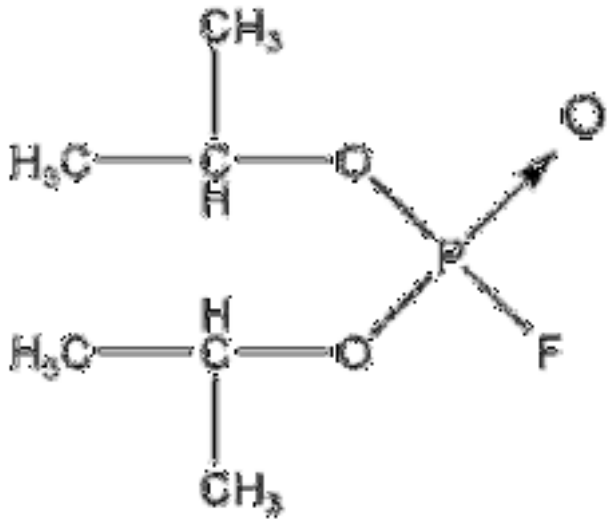




Sarin

- **TOXICITY:**
- Phosphate esters used as insecticidal agents are toxic.
- Symptoms of toxicity are nausea, vomiting, excessive sweating, salivation, miosis, bradycardia, low blood pressure, and respiratory difficulty, which is the usual cause of death.
- The organophosphate insecticides of low toxicity, such as malathion, generally cause poisoning only by ingestion of relatively large doses.
- Parathion or methylparathion, however, cause poisoning by inhalation or dermal absorption.
- Because these compounds are so long acting, cumulative and serious toxic manifestations may result after several small exposures.

- ***Isofluorphate:*** ***(D*iisopropylphosphorofluoridate**)



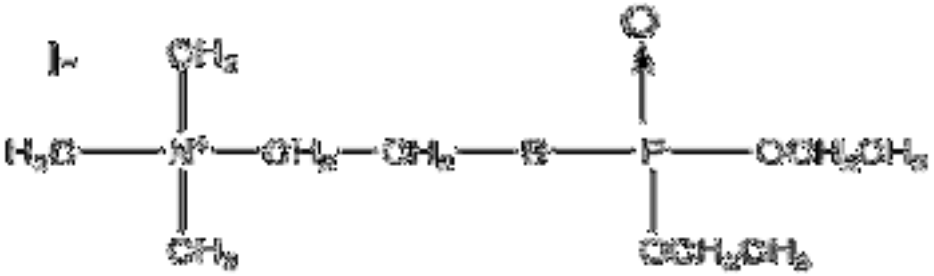
- It irreversibly inhibits cholinesterase.
- Its activity lasts for days or even weeks.
- New cholinesterase may be synthesized in plasma, erythrocytes, and other cells.
- A combination of **atropine sulfate** and **magnesium sulfate** can be used as **antidotes** against the toxic effects of isofluorphate.

- Atropine sulfate counteracts the muscarinic effect, and magnesium sulfate counteracts the nicotinic effect of the drug.
- Isofluorphate must be handled with extreme caution.
- Contact with eyes, nose, mouth, and even skin should be avoided because it can be absorbed readily through intact epidermis and more so through mucous tissues.
- Isofluorphate has been used in the **treatment of glaucoma**.

- ***Echothiophate Iodide:*** **[(2-mercaptoethyl)trimethylammonium iodide]**

- It is a long-lasting irreversible cholinesterase inhibitor.

- It is a quaternary salt.



- **When applied locally, its distribution in tissues is limited.**

- **This can be very desirable.**

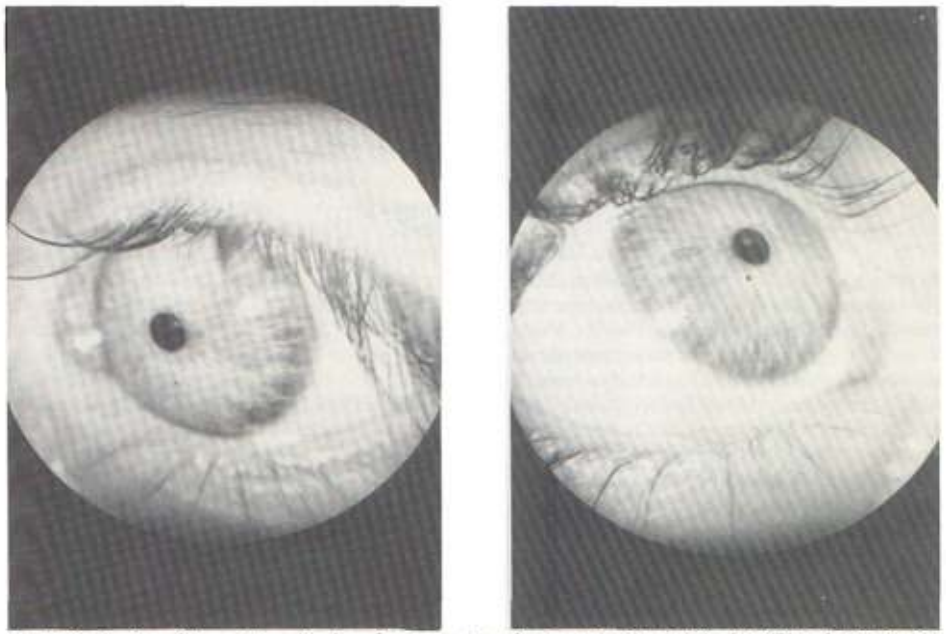
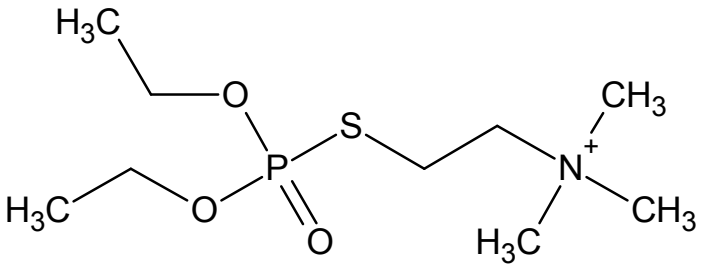


Fig. 1: Shallowing of the anterior chamber after four weeks of treatment with echothiophate (Phospholine) iodide .06 per cent every night.

- It is used as a long-acting anticholinesterase agent in the **treatment of glaucoma**.

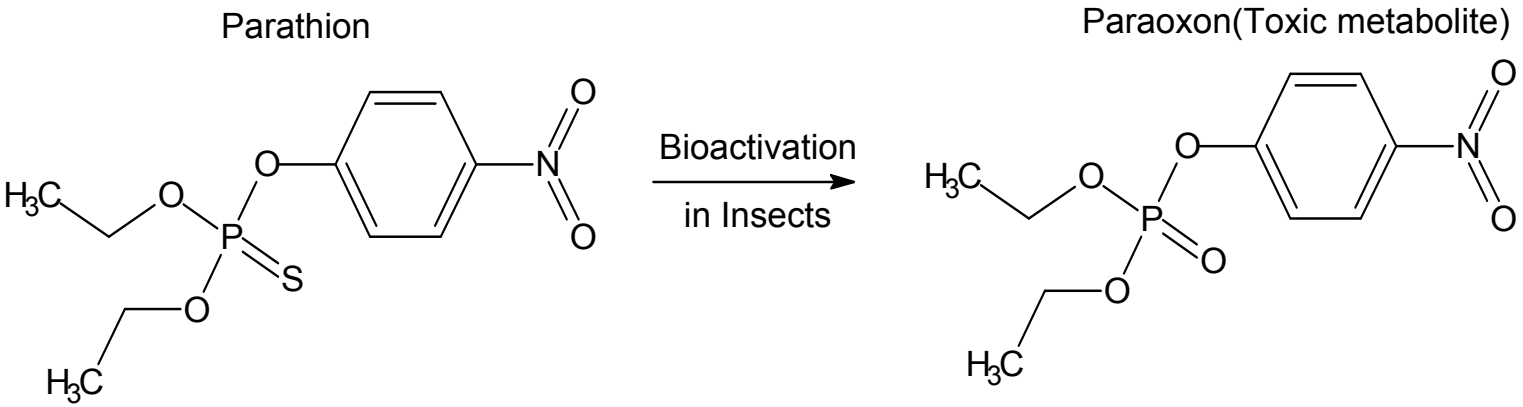
- It is applied topically as a solution and is the only irreversible inhibitor used in the treatment of glaucoma.
- It decreases the intraocular pressure which can be observed up to 4 weeks.
- Its use must be reserved for patients who do not respond to reversible inhibitors and other drugs.
- Because of its **toxicity(cataractogenicity)** , echothiophate is not used systemically.

Echothiophate



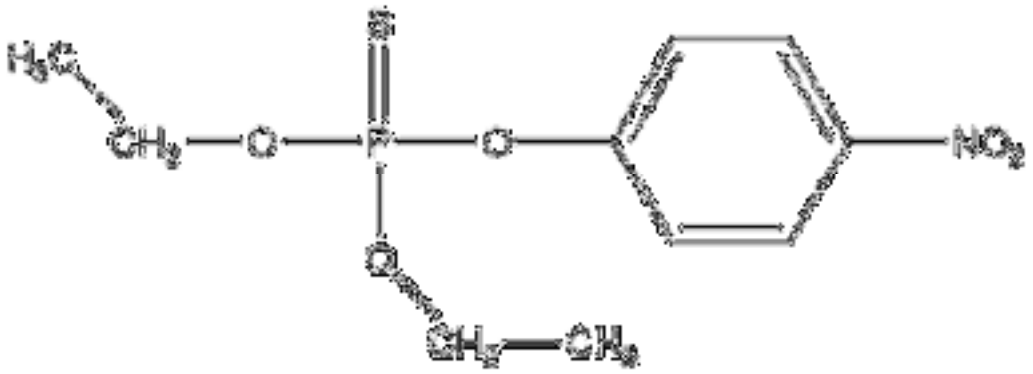
- **INSECTICIDAL INHIBITORS (ORGANOPHOSPHORUS COMPOUNDS):**
- A number of lipophilic derivatives of phosphoester inhibitors were designed as insecticides.
- They also have high vapor pressure.
- This combination of physicochemical properties ie lipophilicity and vapor pressure make them very potent and should be used with extreme caution.

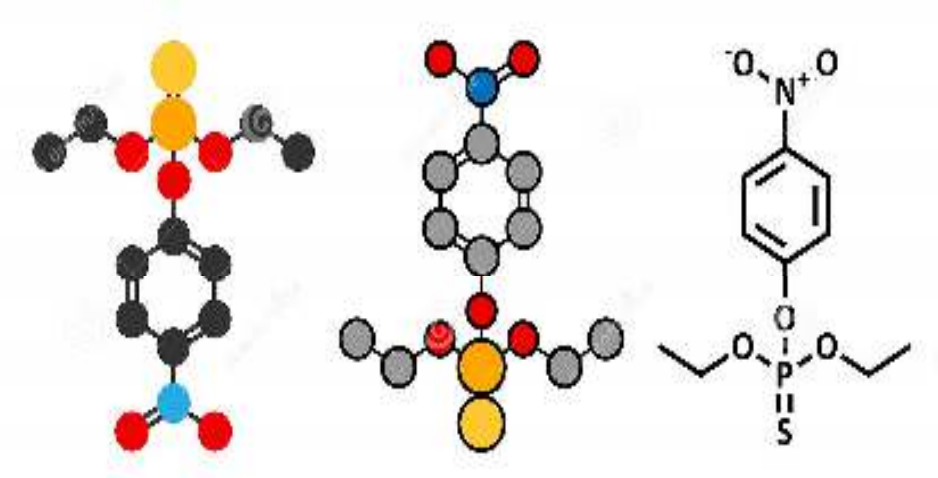
- Most of them are used in agriculture and their exposure to humans and other mammals is fatal.
- Some of these compounds have a sulfur atom bonded to phosphorus atom.
- These compounds have little inhibitory effect but rapidly **bioactivated via desulfurization** in insects to give oxo derivatives which are more potent.



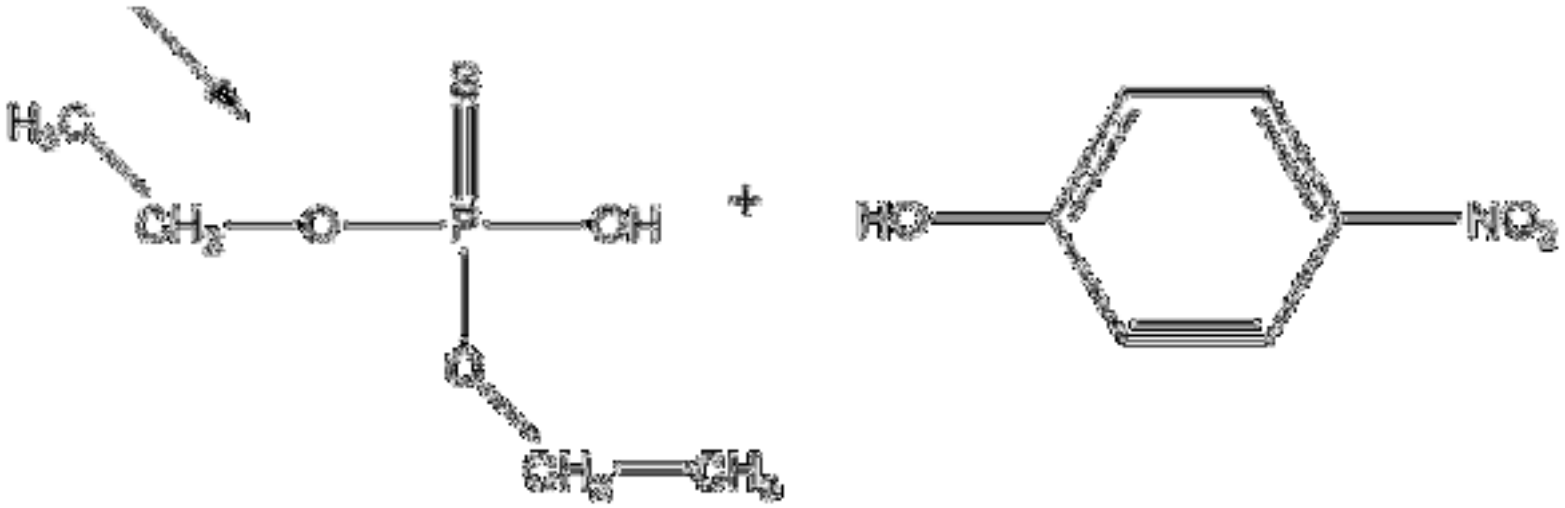
- ***Parathion:*** **(*O*,*O*-diethyl *O*-*p*-nitrophenylphosphorothioate)**

- Synonym:Thiophos It is decomposed at a pH above 7.5.
- Parathion is used as an agricultural insecticide.
- It is a relatively weak inhibitor of cholinesterase;

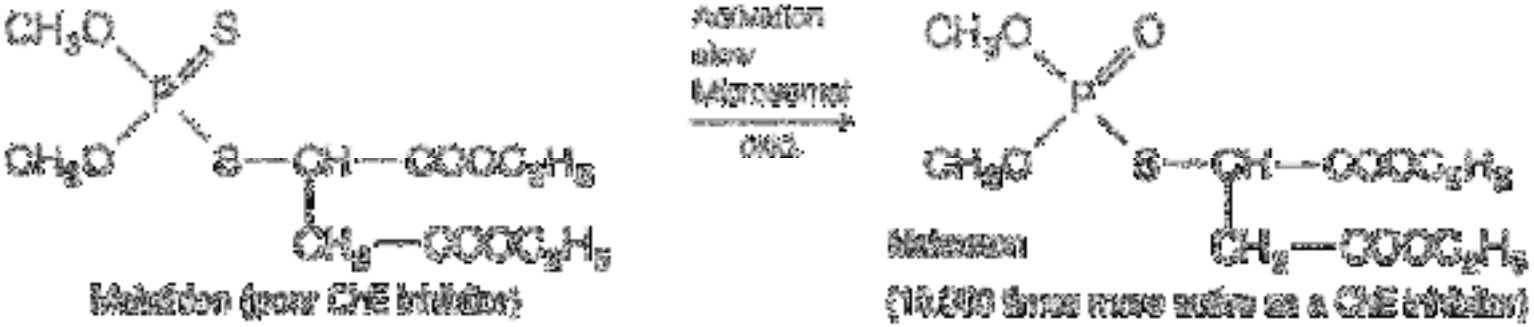




- **Bio-Activation and Inactivation:**
- Hepatic enzymes and insect enzymes convert parathion to paraoxon.
- **Paraoxon is a more potent inhibitor of cholinesterase**.
- Parathion is also metabolized by liver microsomes to yield *p*-nitrophenol and **diethylthiophosphate** (inactivate).

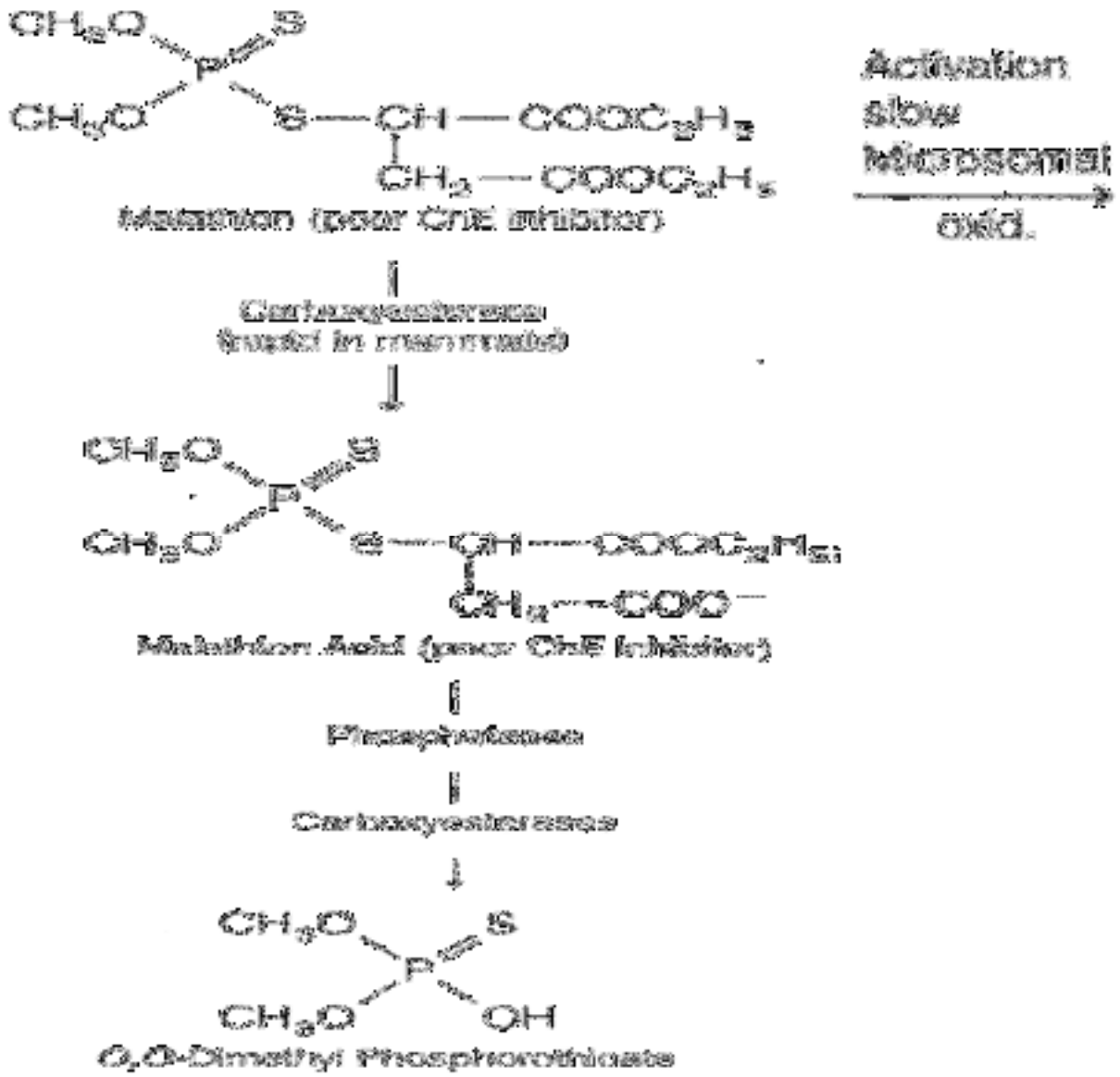


- **MALATHION:**
- It is a poor inhibitor of cholinesterases.
- It is bioactivated at different rates in humans and insects.
- Therefore, it is considered relatively safe insecticide.
- Microsomal oxidation, which causes desulfuration, occurs slowly to form the phosphothioate (malaoxon).

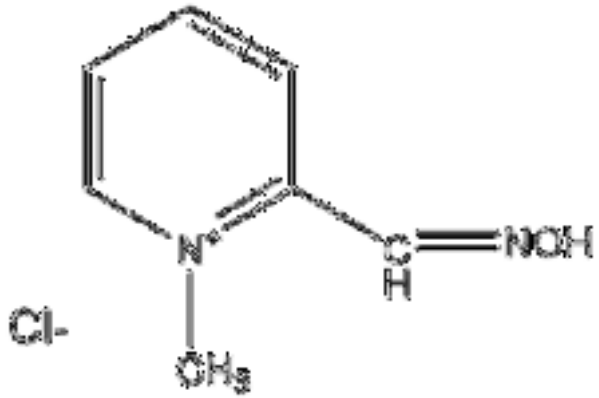


- Malaoxon is 10,000 times more active than the malathion as a cholinesterase inhibitor.
- Insects detoxify the malaoxon by a phosphatase, forming dimethyl phosphorothioate(inactive).
- Humans, however, can rapidly hydrolyze malathion by a carboxyesterase enzyme, yielding malathion acid (inactive).

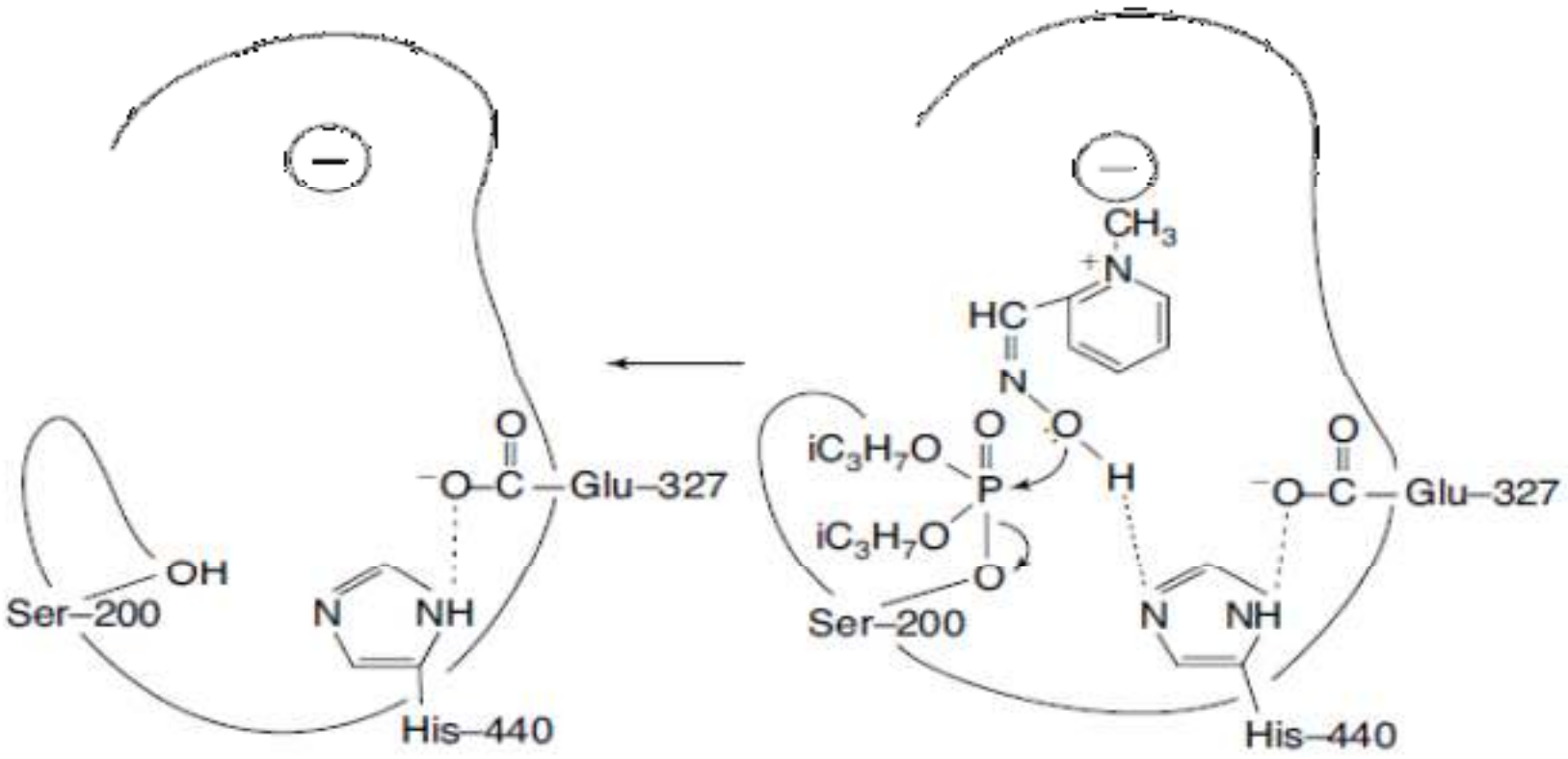
- Phosphatases and carboxyesterases further metabolize malathion acid to dimethylphosphothioate.
- It is a dithiophosphate ester used both as an aerial insecticide and clinically in the treatment of lice infestations of hair and scalp.
- It is also bioactivated to phosphate ester in insects but less toxic to humans and other mammals than other irreversible inhibitors.


Activation
slow
Microsomal
oxid.
Malaoxon
(10,000 times more active as a ChE inhibitor)
Phosphatases (specific)
Dimethyl Phosphate
(inactive)

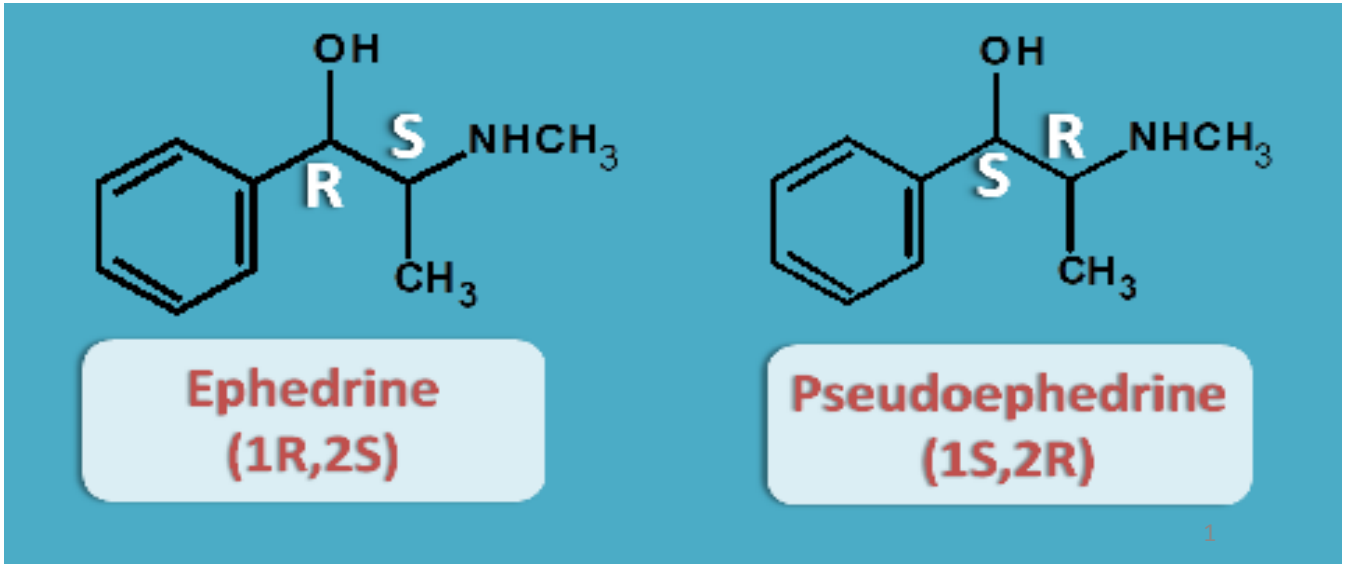
- **Cholinesterase reactivator: Pralidoxime chloride.**
- Organophosphorus compounds are highly toxic in nature. They are widely used as insecticides and as nerve poisons in war. This stimulated the research to find antidotes for these agents.
- Eg: PRALIDOXIME is used subcutaneously , intramuscularly or intravenously to treat organophosphorus poisoning.



- It is effective against some phosphates that have a quaternary nitrogen.
- It is also an effective antagonist for some carbamates, such as neostigmine methylsulfate and pyridostigmine bromide.



INDIRECT ACTING SYMPATHOMIMETICS AND SYMPATHOMIMETICS WITH MIXED MECHANISM

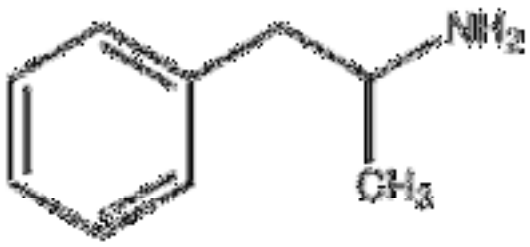


INDIRECT-ACTING SYMPATHOMIMETICS

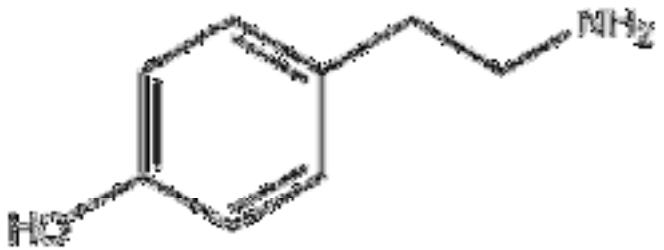
- They act by releasing endogenous NE.
- They also enter the nerve ending by active-uptake process and displace NE from its storage granules.
- **General SAR:**
- The presence of the catechol OH groups enhances the potency of indirect-acting phenylethylamines (similarity with direct acting drugs).
- However, therapeutically used drugs are not catechol derivatives and, in most cases, do not even contain an OH moiety.

- The presence of a β–hydroxyl group decreases, and an α-methyl group increases, the effectiveness of indirect-acting agents (contrast with direct acting drugs).
- The presence of nitrogen substituents decreases indirect activity, with substituents larger than methyl groups rendering the compound virtually inactive.
- Phenylethylamines that contain a tertiary amino group are also ineffective as NE-releasing agents.

- Given the foregoing structure–activity considerations, it is easy to understand why amphetamine and *p*-tyramine are often cited as prototypical indirect-acting sympathomimetics.
- Amphetamine- type drugs exert their primary effects on the CNS.
- Amphetamine is a CNS stimulant and categorized as analeptic.

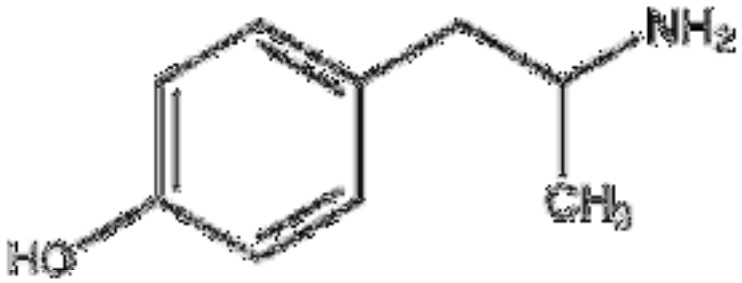


Amphetamine
Log P = 2.81



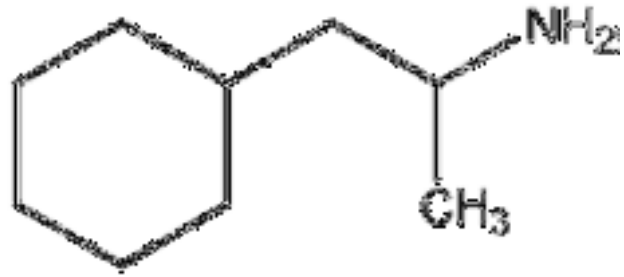
p-Tyramine

- ***Hydroxyamphetamine***
- It is an effective, indirect-acting sympathomimetic drug.
- It differs from amphetamine in the presence of *p*-OH group and so it has little or no CNS-stimulating action.
- It is used to dilate the pupil for diagnostic eye examinations and for surgical procedures on the eye.
- It is sometimes used with cholinergic blocking drugs like atropine to produce a mydriatic effect, which is more pronounced than that produced by either drug alone.



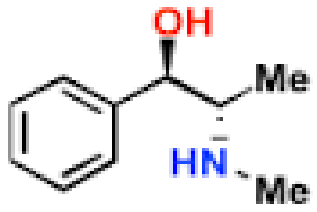
Hydroxyamphetamine
Log P = 1.07
pKa = 10.71

- ***Propylhexedrine***
- It is another analog of amphetamine in which the aromatic ring has been replaced with a cyclohexane ring.
- This drug produces vasoconstriction and a decongestant effect on the nasal membranes, but it has only about one half the pressor effect of amphetamine and produces decidedly fewer effects on the CNS.
- Its major use is for a local vasoconstrictive effect on nasal mucosa in the symptomatic relief of nasal congestion caused by the common cold, allergic rhinitis, or sinusitis.

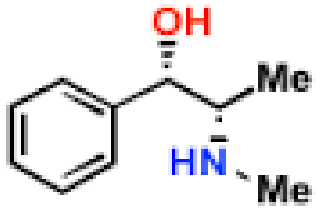


Propylhexedrine

- ***L-(+)-Pseudoephedrine.***
- IUPAC: (1*S*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol;
- It is the (*S*,*S*) diastereoisomer of ephedrine.
- Threo isomer of Ephedrine.
- Whereas ephedrine has a mixed mechanism of action, L-(+)-pseudoephedrine acts mostly by an indirect mechanism and has no direct activity.

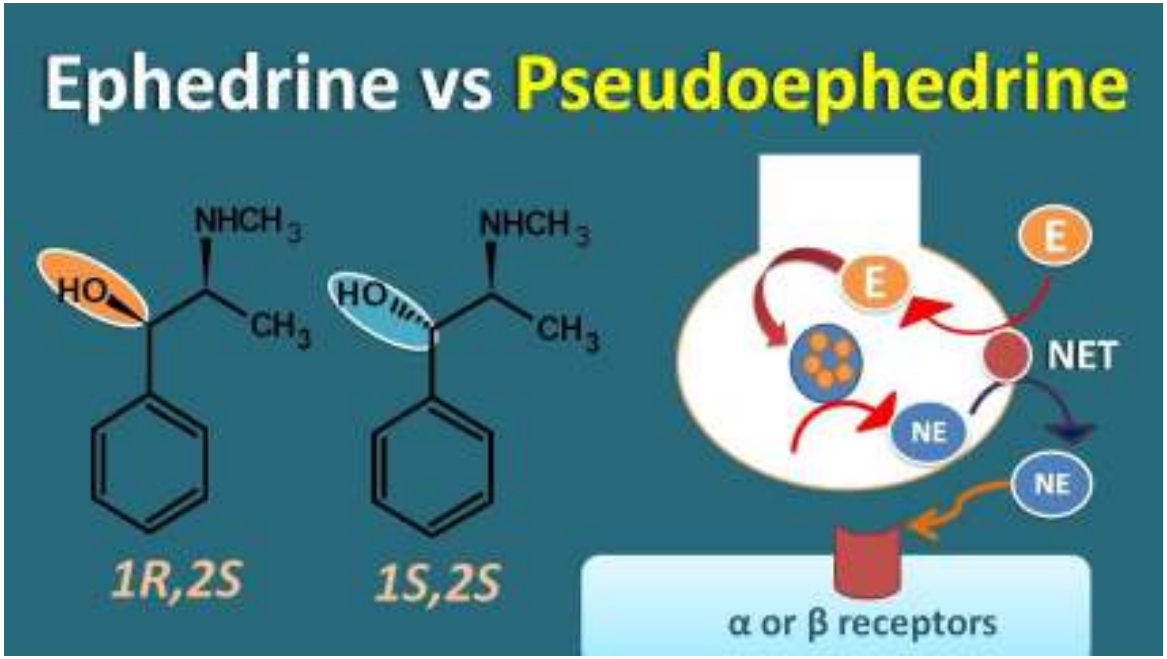


Ephedrine



Pseudoephedrine

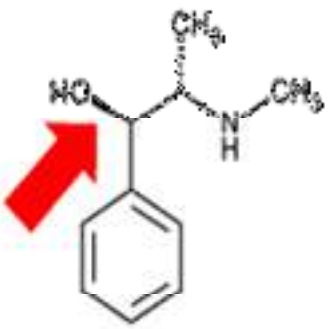
- **The structural basis for this difference in mechanism is the stereochemistry of the carbon atom possessing the β-OH group.**
- **In pseudoephedrine, this carbon atom possesses the (*S*) configuration, the wrong stereochemistry at this center for a direct-acting effect at adrenoceptors.**
- *Watch video ---> (https://youtu.be/n63Xk-TjNVw)*



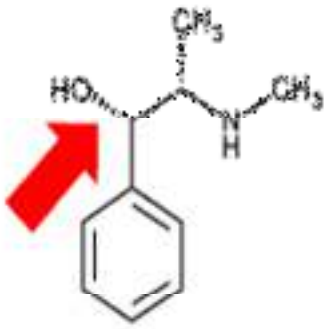
- It crosses the BBB (log P 1.05, pKa 9.38).
- But produces little CNS effects due to lack of direct activity.
- It is a naturally occurring alkaloid from the *Ephedra* species.
- This agent is found in many OTC nasal decongestant and cold medications.
- **Although it is less prone to increase blood pressure than ephedrine, it should be used with caution in hypertensive individuals, and it should not be used in combination with MAO inhibitors (why?).**

- Pseudoephedrine is a phenethylamine and an diastereomer of ephedrine with sympathomimetic property.
- Pseudoephedrine displaces norepinephrine from storage vesicles in presynaptic neurones.
- Thereby releasing norepinephrine into the neuronal synapses where it stimulates primarily alpha-adrenergic receptors.
- It also has weak direct agonist activity at alpha- and beta- adrenergic receptors.

- Receptor stimulation results in vasoconstriction and decreases nasal and sinus congestion.
- It has less CNS effects and mainly used for respiratory tract decongestion.
- **'L' is not related to optical isomerism.**
- **A molecule is L when the arrangement of groups around a stereocenter is the same as the arrangement of groups about the stereocenter of (S)-glyceraldehyde.**

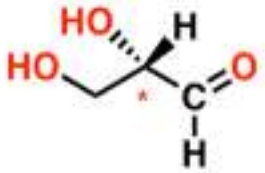


Ephedrine

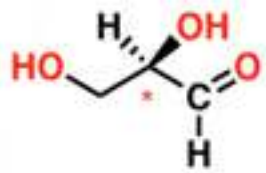


Pseudoephedrine

The simplest sugar: glyceraldehyde $C_3H_6O_3$
a "triose"



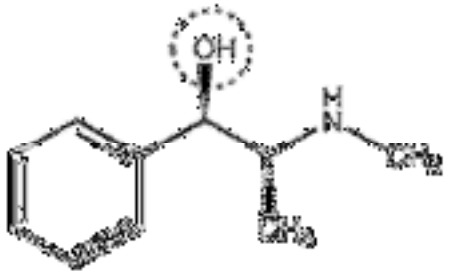
(S)-(–)-glyceraldehyde



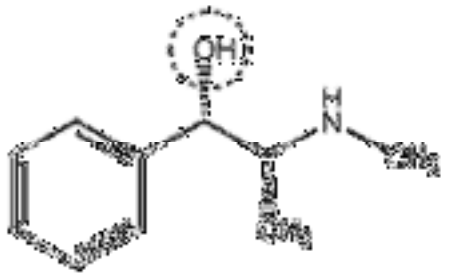
(R)-(+)-glyceraldehyde

correct (1R, 2S) configuration

Ephedrine = *erythro* racemate
cis
Mixed mechanism of action



Enantiomers



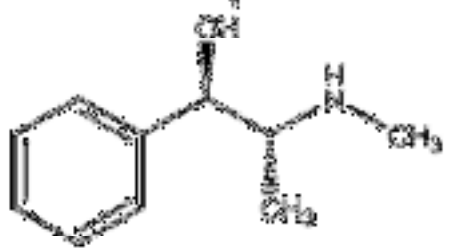
(1S,2S)-D-(-)-Ephedrine
Direct activity on α and β
Some indirect activity.
The most active of the four isomers
as a pressor amine

(1R,2R)-L-(+)-Ephedrine
Mixed mechanism of action
but primarily indirect activity

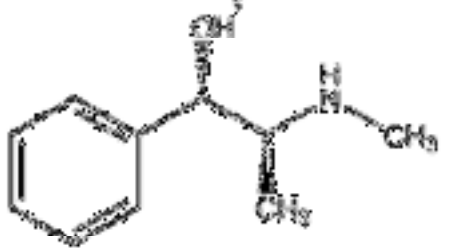
Diastereomers

Diastereomers

Pseudoephedrine = *threo* racemate
trans
Principally, indirect-acting



Enantiomers



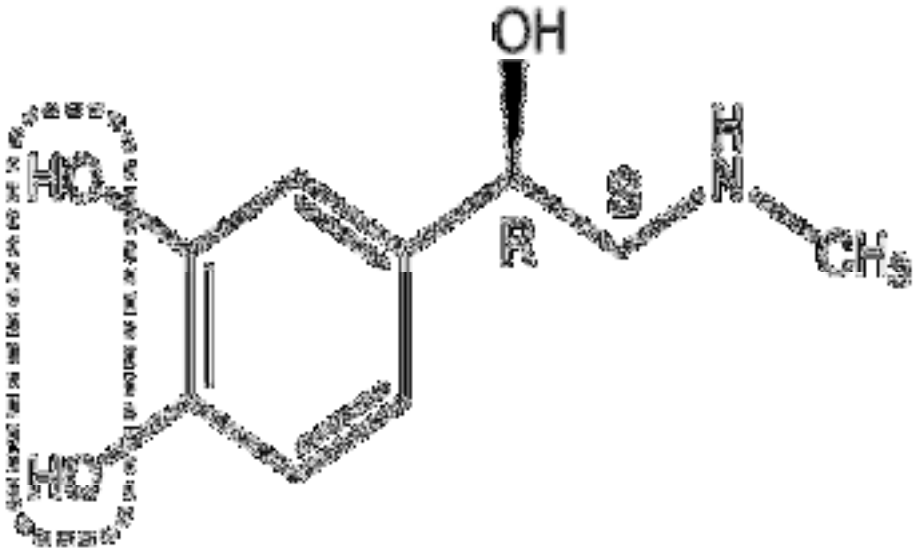
(1S,2S)-D-(-)-Pseudoephedrine

(1R,2R)-L-(+)-Pseudoephedrine
Virtually no direct activity
Mainly indirect activity

Sympathomimetics with a Mixed Mechanism of Action

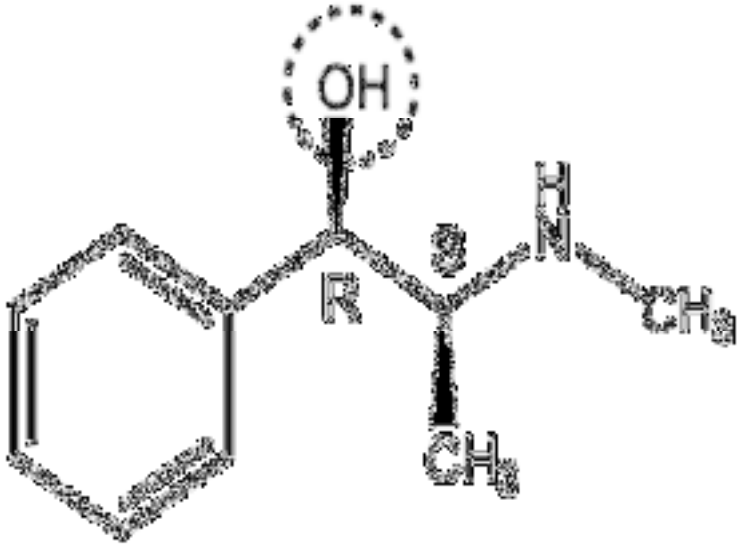
- These phenylethylamines with a mixed mechanism of action usually have no hydroxyls on the aromatic ring but do have a β-hydroxyl group.
- ***D-(-)-Ephedrine.***
- The pharmacological activity of (1*R*,2*S*)-D-(-)-ephedrine resembles that of epinephrine.
- The drug acts on both α- and β-receptors.
- Its ability to activate β –receptors is responsible for its earlier use in asthma.
- It is the classic example of a sympathomimetic with a mixed mechanism of action.

- Due to lack of H-bonding phenolic OH groups, ephedrine is less polar (log P 1.05, pKa 9.6).
- It crosses the BBB far better than do other catecholamines.
- Therefore, ephedrine has been used as a CNS stimulant and exhibits side effects related to its action in the brain.
- It causes more pronounced stimulation of the CNS than epinephrine.
- The drug is not metabolized by either MAO or COMT and therefore has more oral activity and longer DOA than epinephrine.



Epinephrine
Log P = -1.23

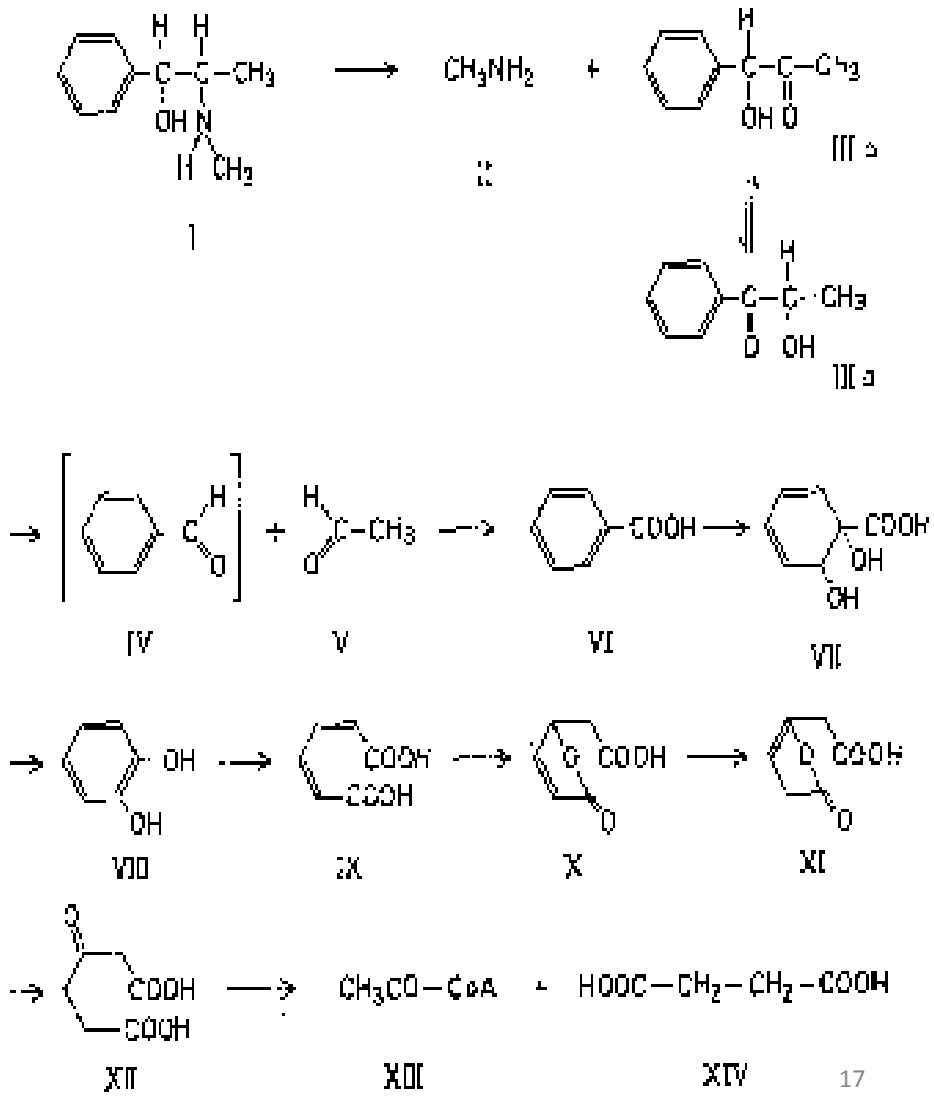
correct (1R) (2S) configuration



(1R)-Ephedrine
Log P = 1.06

- **Stereochemistry:**
- Ephedrine has two asymmetric carbon atoms; thereby creating four optically active isomers.
- The *erythro* racemate is called *ephedrine*, and the *threo* racemate is known as *pseudoephedrine* (ψ-ephedrine).
- Natural ephedrine is the D (-) isomer, and it is the most active of the four isomers as a pressor amine.
- This is largely because of the correct (1*R*,2*S*) configuration for optimal direct action at adrenergic receptors.

- **Photodegradation:**
- Ephedrine decomposes gradually and darkens when exposed to light.
- **Bascity:**
- The free alkaloid is a base, and an aqueous solution of the free alkaloid has a pH above 10.
- The salt form has a pKa of 9.6.



- **Route of administration and therapeutic uses:**
- Ephedrine and its salts are used **orally, intravenously, intramuscularly, and topically** for various conditions, such as-

➢ allergic disorders and colds,

➢ hypotensive conditions, and

➢narcolepsy.

- It is **used locally** -

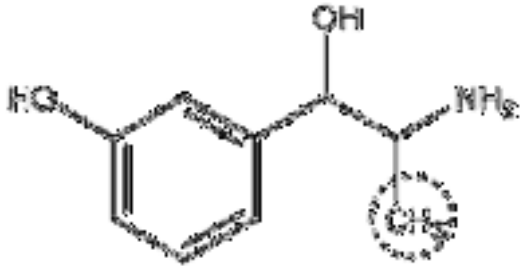
➢To constrict the nasal mucosa and cause decongestion,

➢To dilate the pupil or the bronchi.

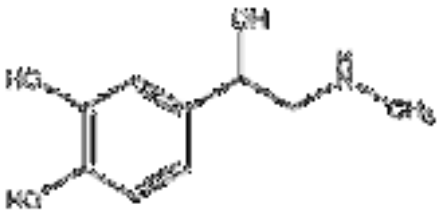
- **Systemically**, it is effective for asthma, hay fever, and urticaria.

- In recent years, various companies have begun marketing extracts of *Ephedra* shrubs (Ma huang) for weight loss and enhancement of athletic performance.
- Herbalists also market them as “alternative medicines” for cold and cough relief.
- It has been estimated that nearly one third of young, obese women have used a weight-loss supplement containing *Ephedra*.

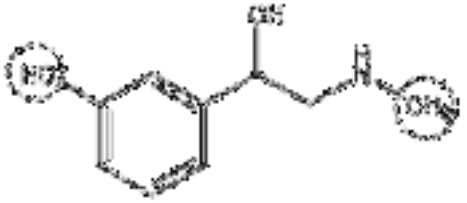
- ***Metaraminol***
- It is the *N*-desmethyl-α-methyl analog of phenylephrine.
- It possesses a mixed mechanism of action, with its direct-acting effects mainly on α1- receptors.
- It is used parenterally as a vasopressor in the treatment and prevention of the acute hypotensive state occurring with spinal anesthesia.
- It also has been used to treat severe hypotension brought on by other traumas that induce shock.



Metaraminol



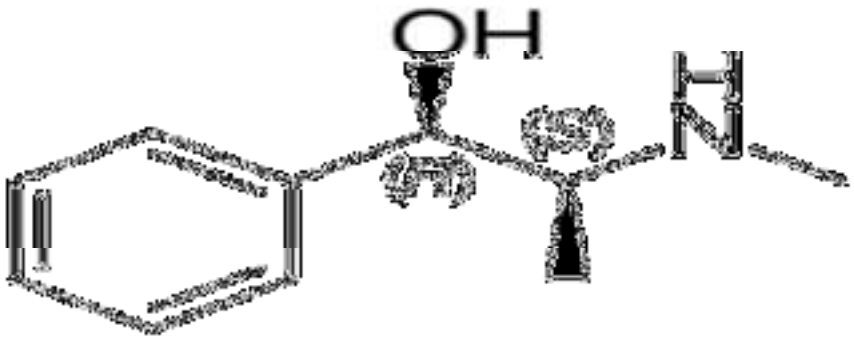
Epinephrine (E)



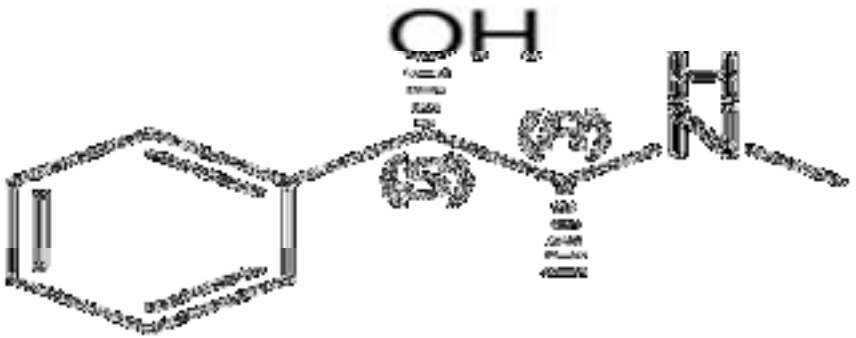
Phenylephrine

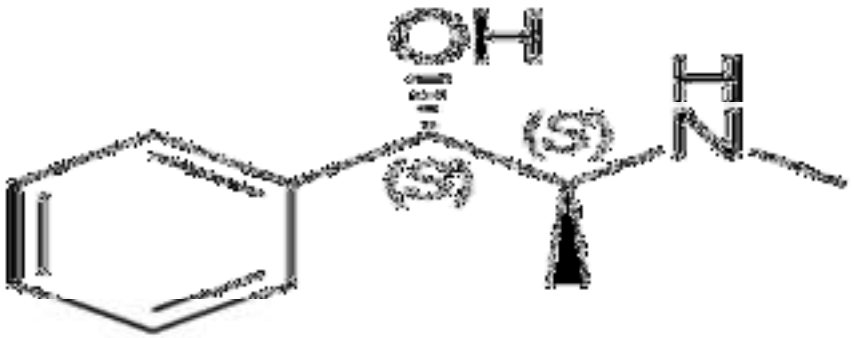
STEREOCHEMICAL FEATURES OF EPHEDRINE & PSEUDOEPHEDRINE

(1*R*,2*S*)-(−)-Ephedrine
(−)-*erythro*-Ephedrine

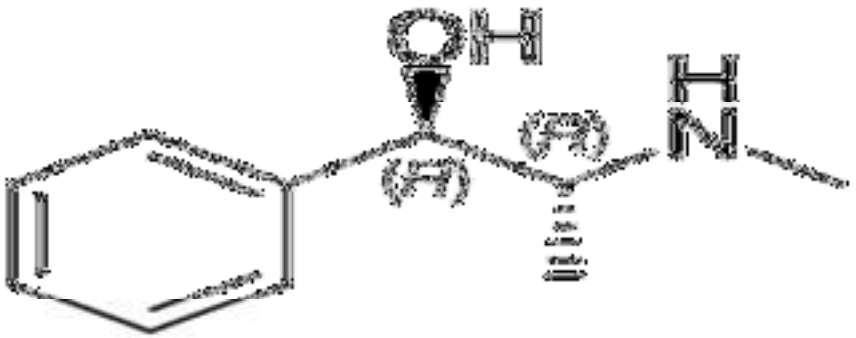


(1*S*,2*R*)-(+)-Ephedrine
(+)-*erythro*-Ephedrine





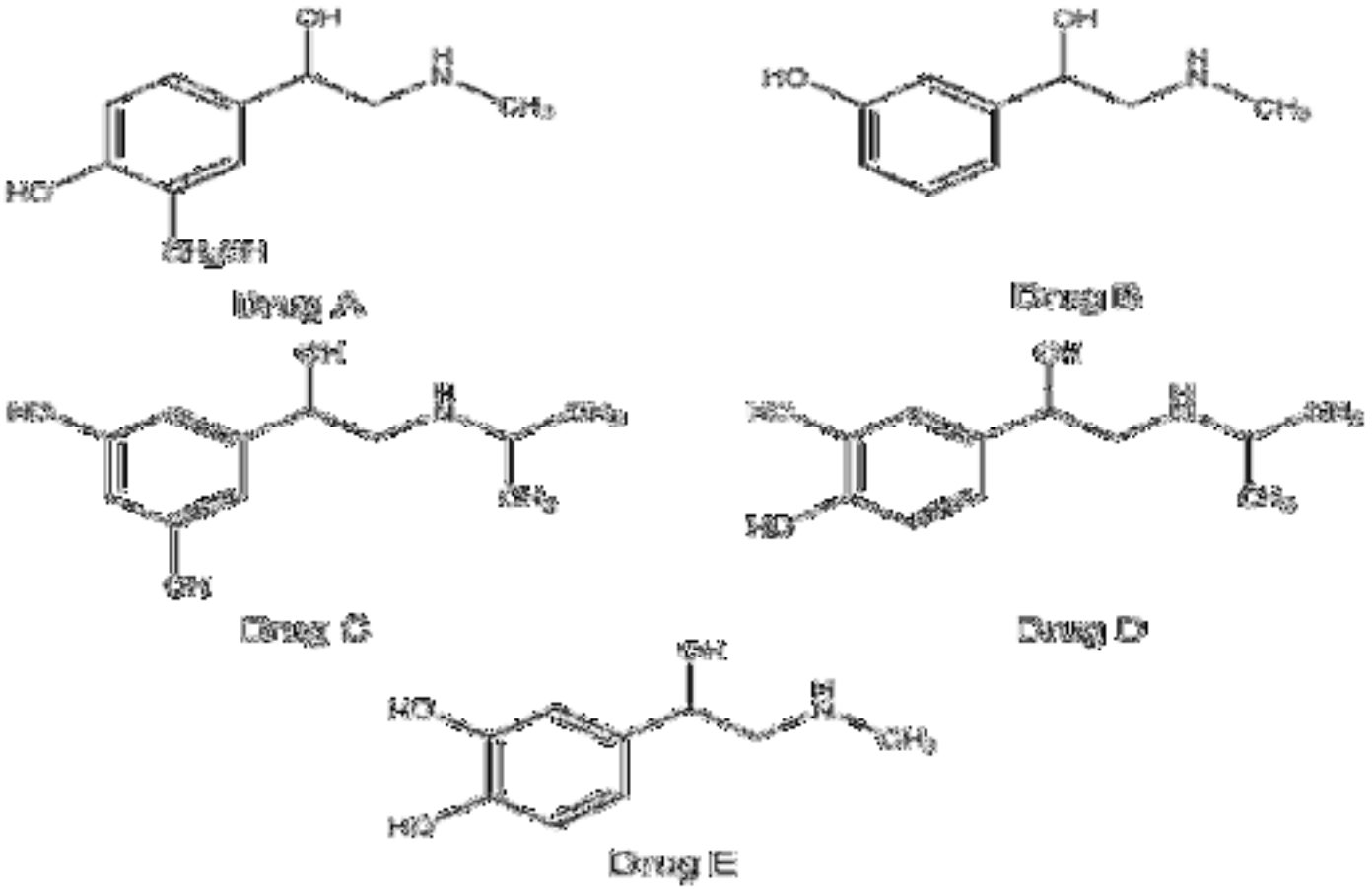
(1*S*,2*S*)-(+)-Pseudoephedrine
(+)-*threo*-Ephedrine



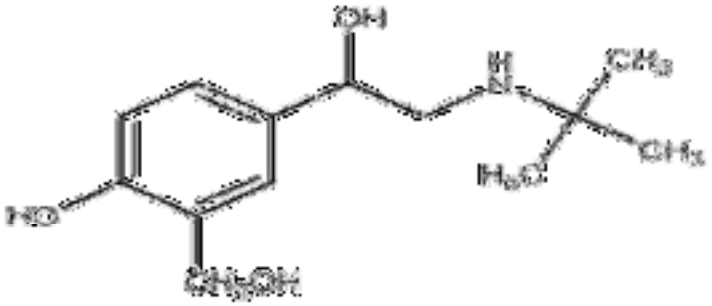
(1*R*,2*R*)-(−)-Pseudoephedrine
(−)-*threo*-Ephedrine

EXERCISE - Practice problems

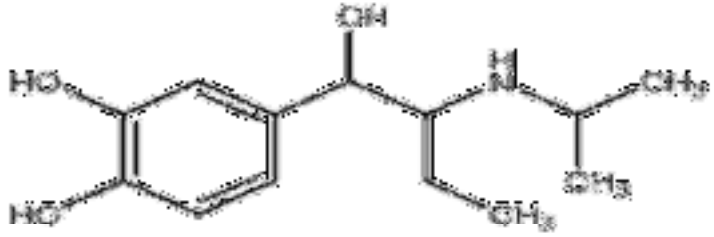
- 1. Which of the following drugs would be resistant to metabolism by COMT and why?



- 2. Which of the drug(s) shown would be the least orally active and have the shortest duration of action and why?

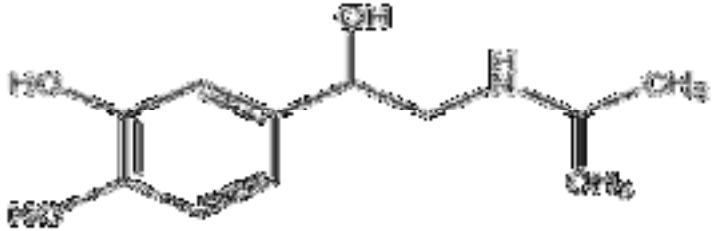


Drug A

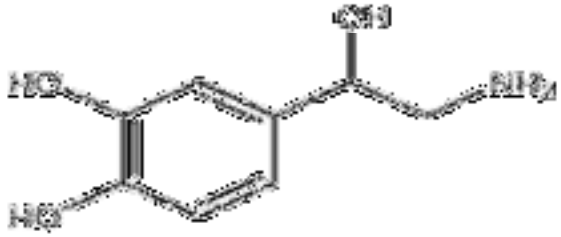


Drug B

Drug C

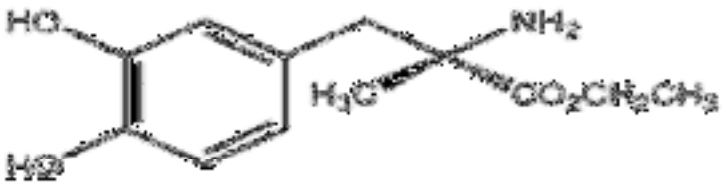


Drug D

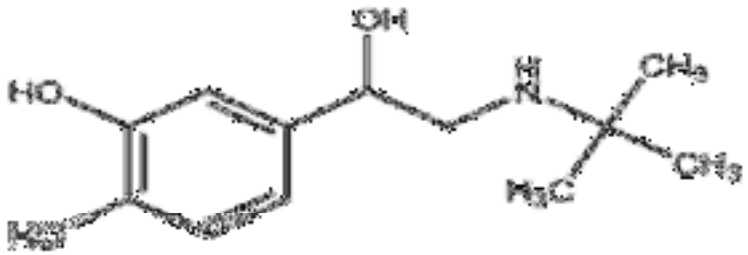


Drug E

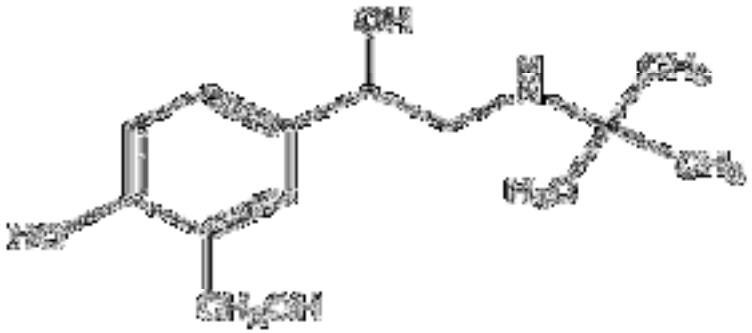
- 3. Which of the following drugs is the most likely to be selective β2-agonist?



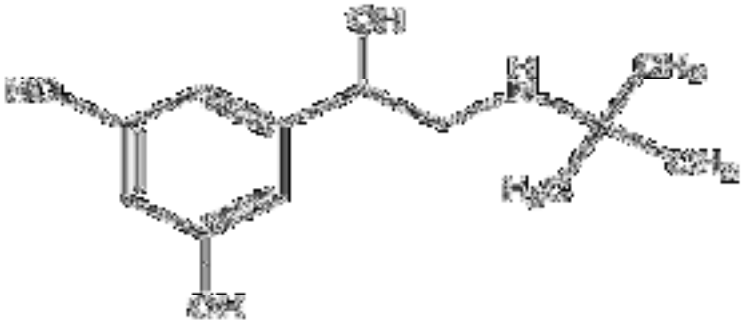
Drug A



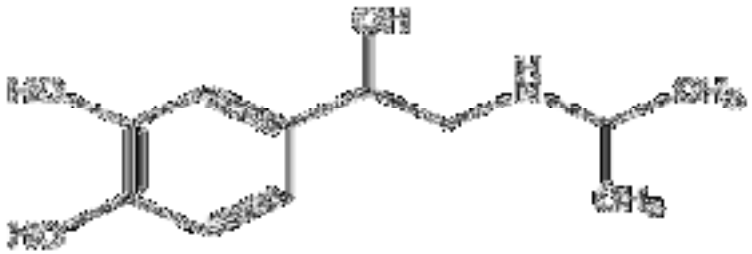
Drug B



Drug C

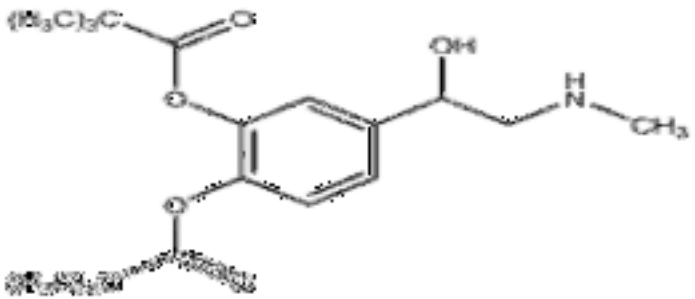


Drug D

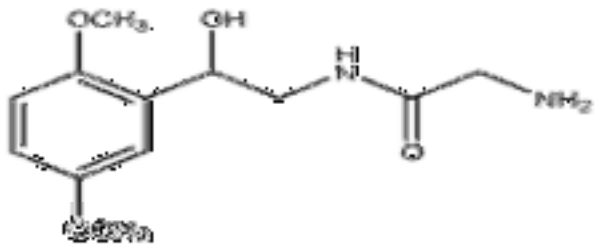


Drug E

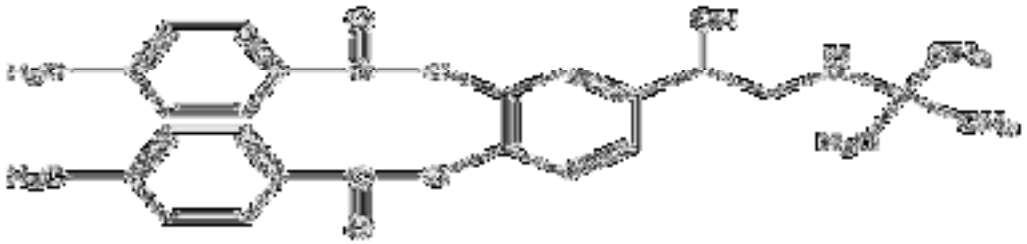
- 4. Which of the following drugs is considered to be a prodrug?



Drug A



Drug B



Drug C

Drug D

Drug E

- 5. What functional group interactions between the catecholamines and adrenoceptors are most likely?
- 6. Which functional groups are considered pharmacophores of catecholamines?

- Try to answer all questions and share soft copies in MC 1 channel, MS Teams.
- Refer online class PPTs and *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry.*
- *Good Luck.*

NARCOTIC ANALGESICS

- **Introduction:**
- **The terms *analgesics and analgetic drugs are often used* to describe a diverse group of pain medications such as**

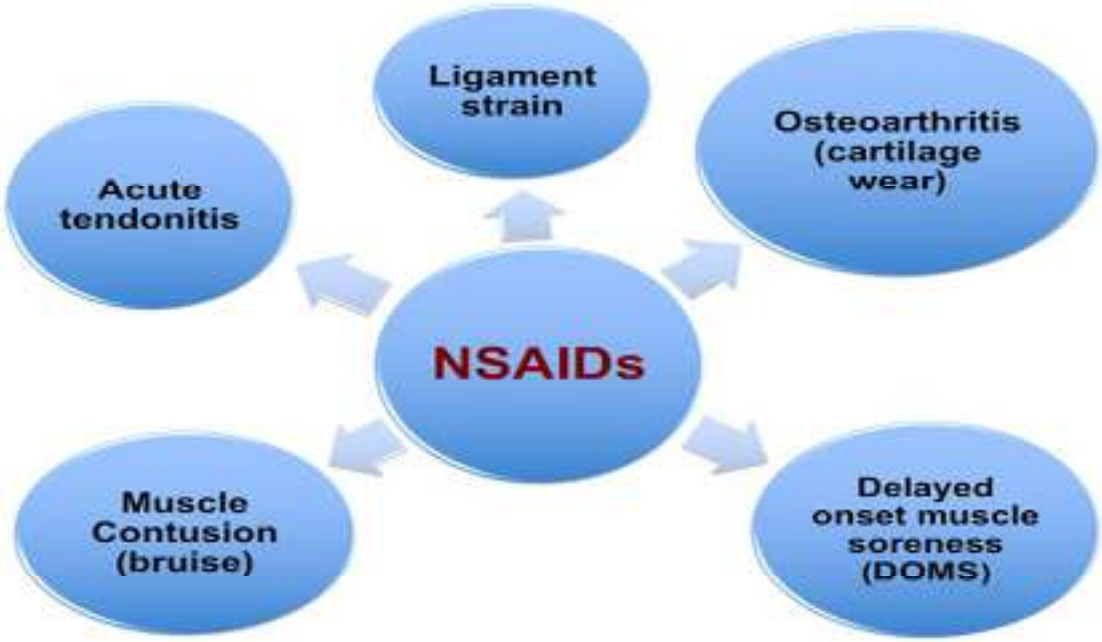
- **Opioids**
- **NSAIDs**
- **Triptans**
- **Analgesic adjuvants**
- **Each of these class has very different mechanisms of action for relieving pains.**

1. Opioids (or narcotic analgesics):

- **Play a major role in the relief of acute pain and in the management of moderate to severe chronic pain.**

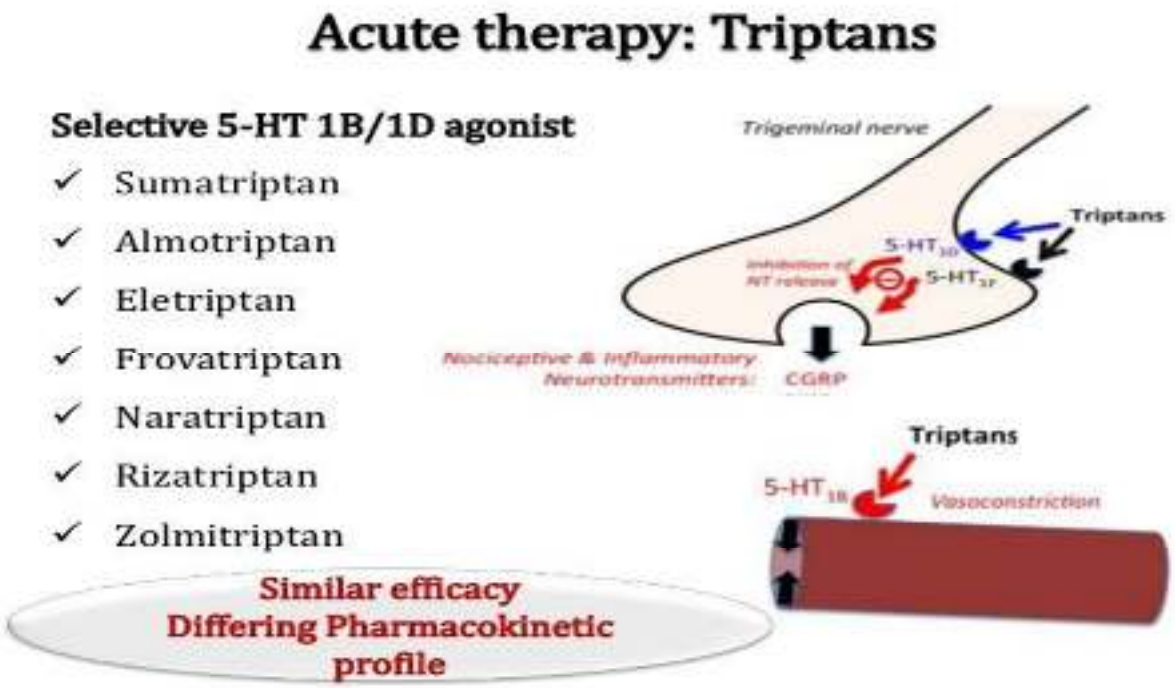
2. NSAIDs and acetaminophen:

- **Most widely used analgesic drugs for relieving mild to moderate pain and reducing fever.**



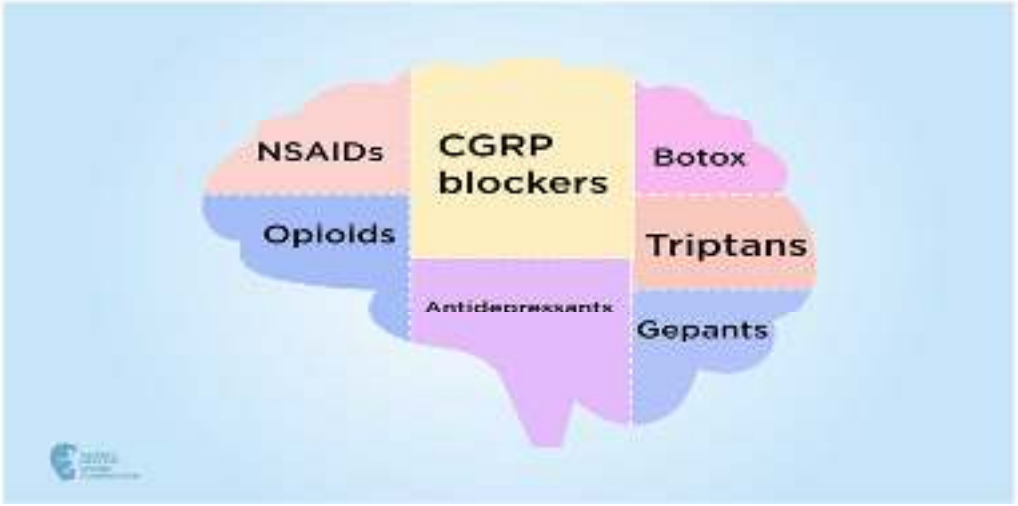
3. Triptans (the antimigraine medications):

- **Specifically designed and targeted for acute and abortive treatment of migraine and cluster headaches.**

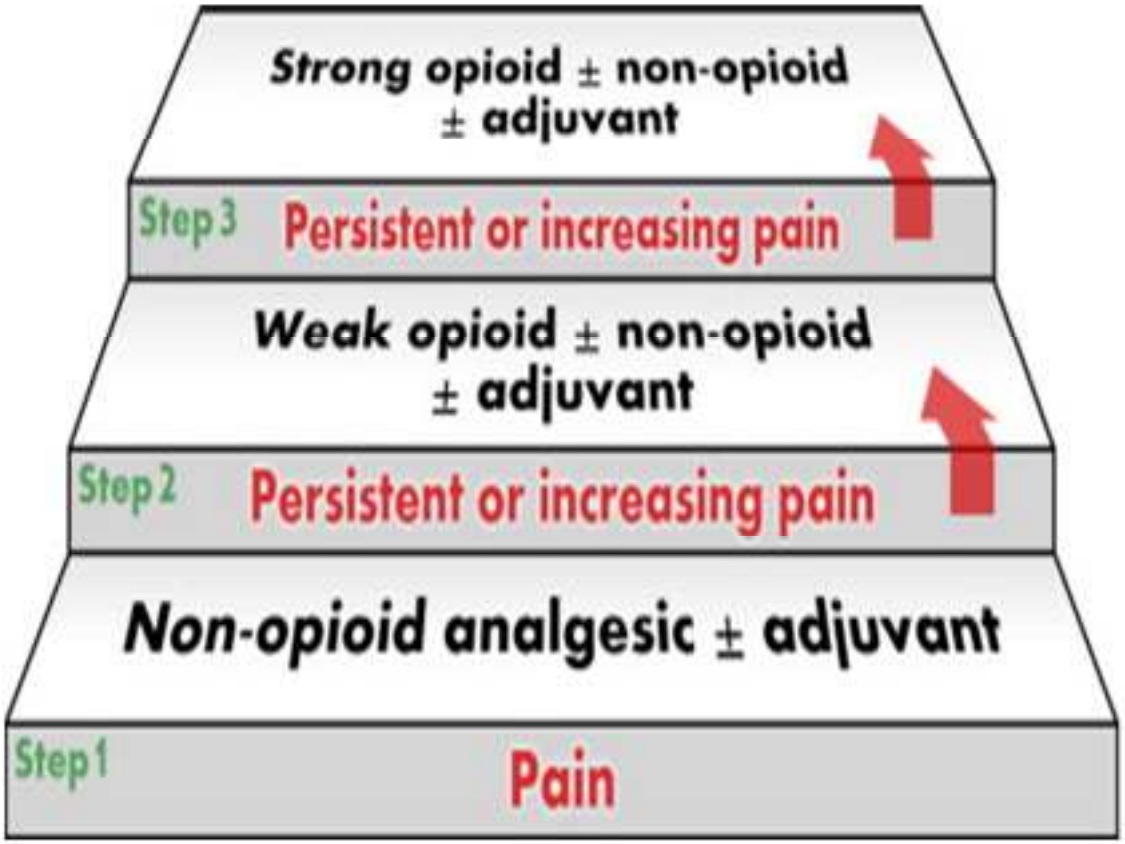


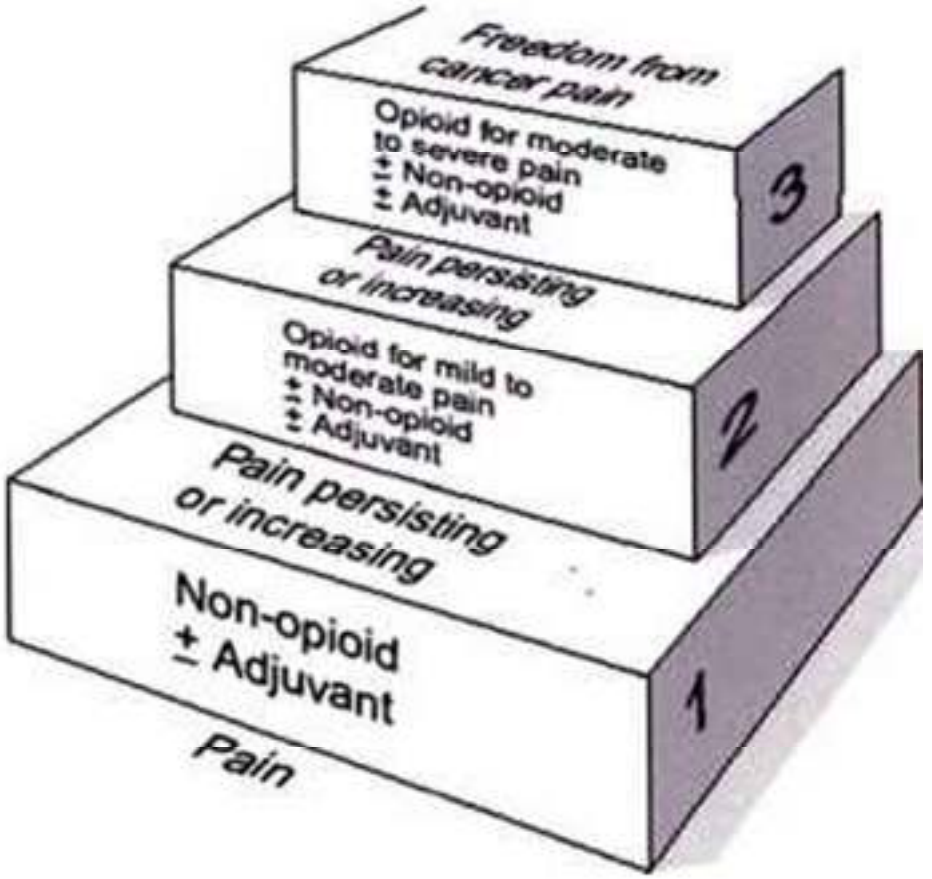
4. Analgesic adjuvants (a new emerging class of analgesics):

- **Include tricyclic antidepressants such as amitriptyline, anticonvulsants such as gabapentin and pregabalin, and topical analgesics such as lidocaine patches that can be used to treat neuropathic pains.**



WHO Analgesic Ladder



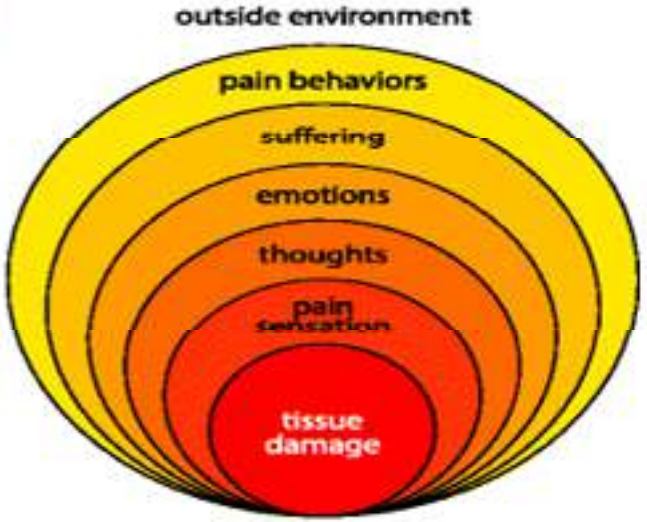


- **Origin of Pain:**
- **Pain differs in its underlying causes, symptoms, and neurobiological mechanisms.**
- **Classification of Pain:**
- **It has been classified into three major types:**

➢ **Physiological (nociceptive)**

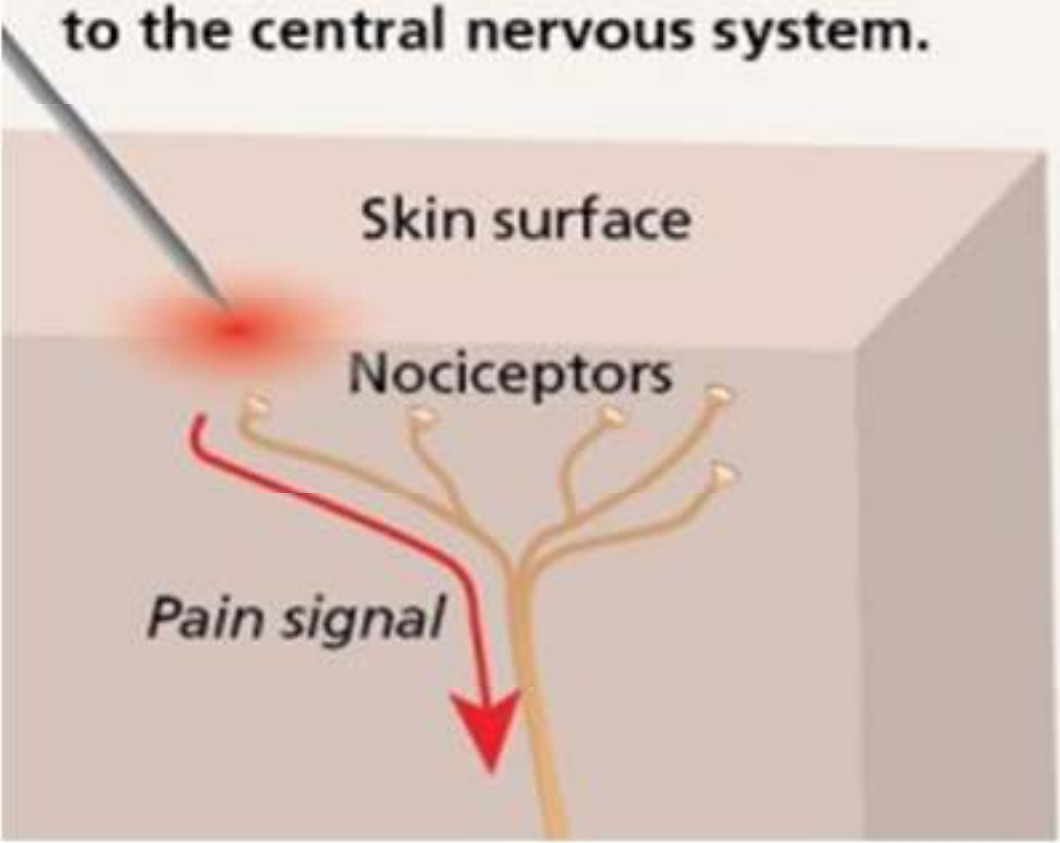
➢ **Inflammatory**

➢ **Neuropathic**



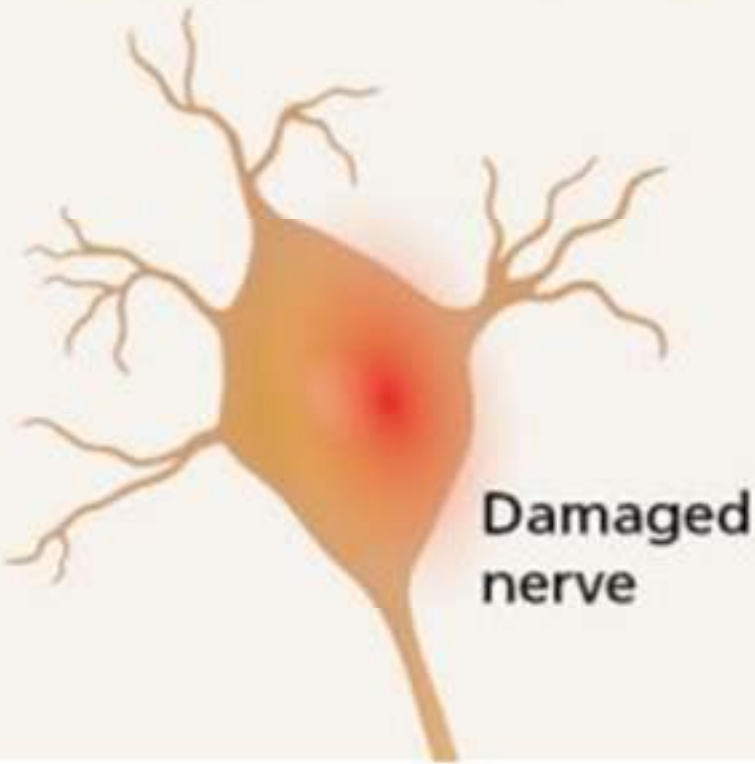
Nociceptive Pain

Special nerve endings called nociceptors send pain signals to the central nervous system.



Neuropathic Pain

Caused by dysfunction in the nervous system or damage to the nerve itself.



- **Acute and chronic pain:**
- **Pain may be acute or chronic.**
- **Acute pain is often severe but usually lasts only until the removal of the source that triggered the pain.**
- **Acute pain includes nociceptive, somatic, or visceral pain, postoperative and posttraumatic pain, burn pain, acute pain during childbirth, acute headache, etc.**
- **Acute and postoperative pains are most often treated with the opioid analgesics.**

- **Chronic pain last longer than 6 months.**
- **Chronic pain can be further divided into-**

➢ **Chronic malignant pain (e.g., cancer, AIDS, amyotrophic lateral sclerosis, multiple sclerosis, end-stage organ failure)**

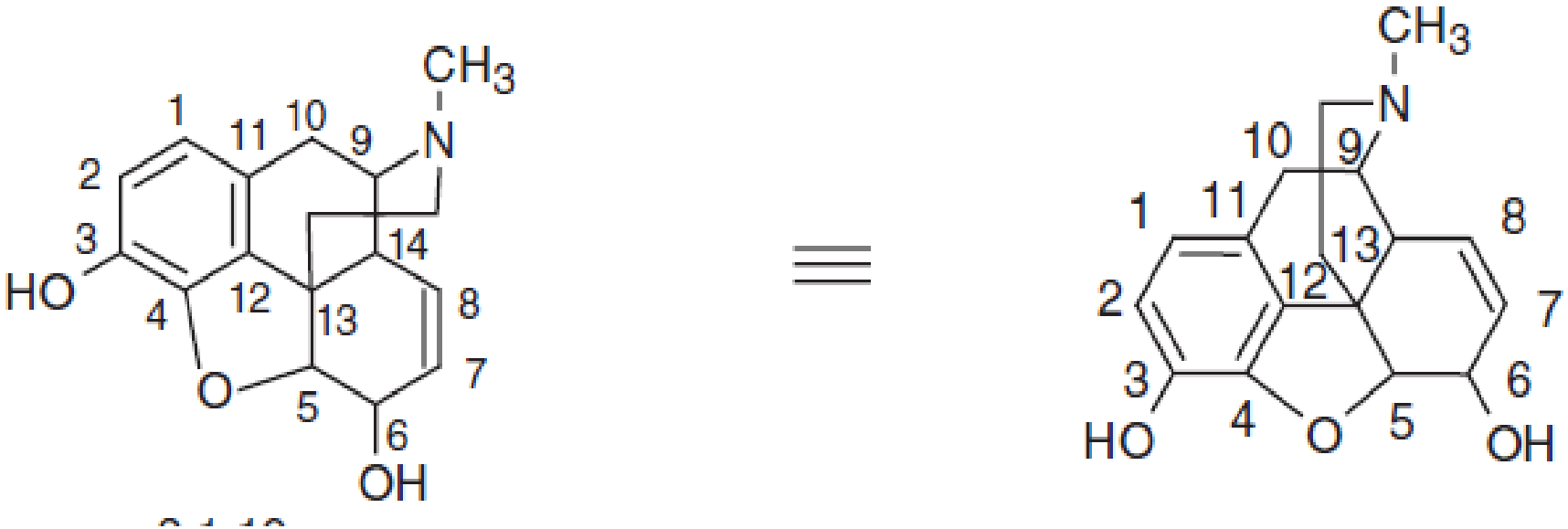
➢ **Chronic non-malignant pain (e.g., lower-back pain, chronic degenerative arthritis, osteoarthritis (OA), rheumatoid arthritis (RA), migraine and chronic headache).**

- **Pain therapy (non-opiate) in patients with chronic pain only provides transient pain relief but does not resolve the underlying pathological process.**

OPIATE ALKALOIDS/OPIOID ANALGESICS

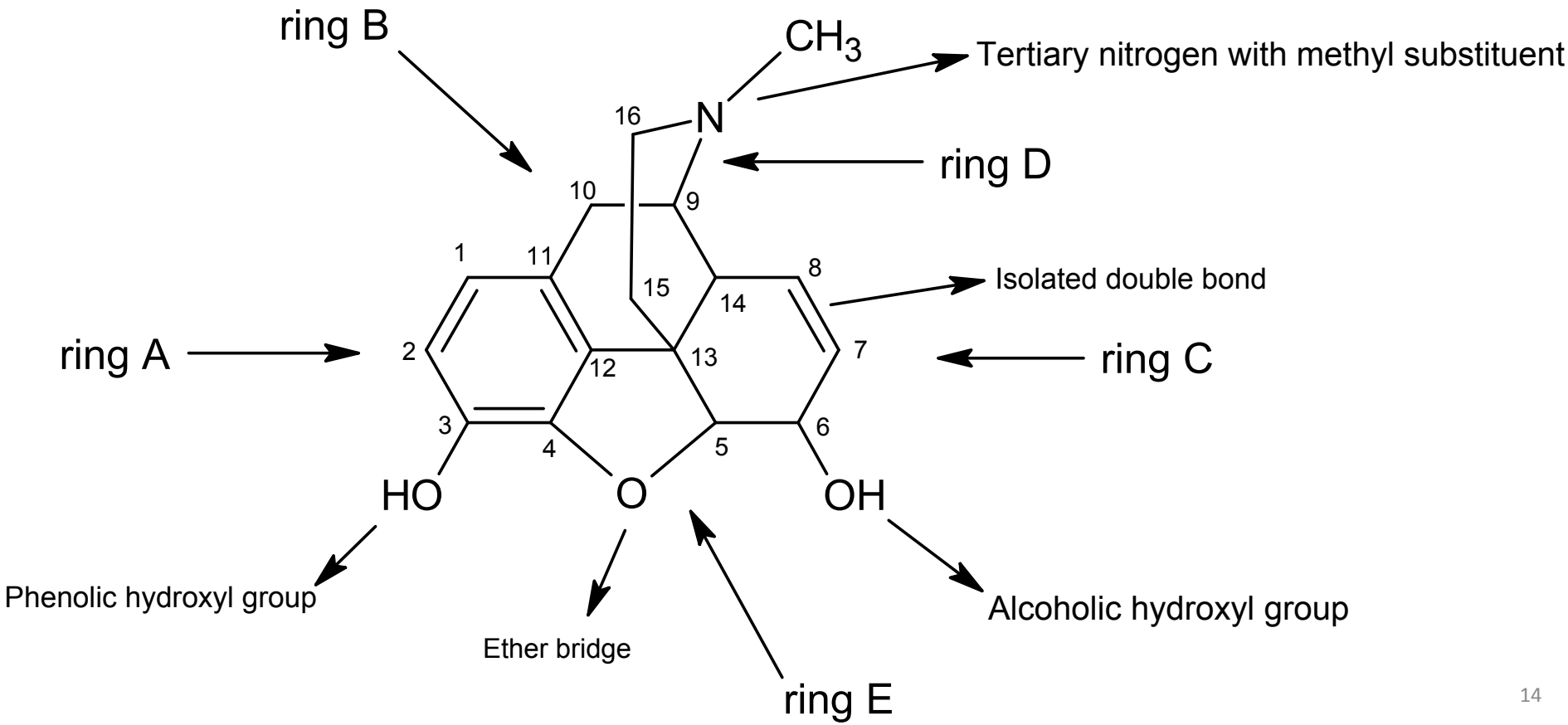
- Opiate alkaloids are the natural compounds which have been extracted from opium-the sticky exudate obtained from the opium poppy ie *Papaver somniferum.*
- 'Opioid' cover all narcotic analgesics, whether they be synthetic, semi-synthetic or natural compounds.

- **Opium contains a complex mixture of over 20 alkaloids including phenanthrene and isoquinoline derivatives.**
- **The principle alkaloid in the mixture, and the one responsible for analgesic activity, is morphine (named after Greek? Roman? God of dreams-Morpheus).**

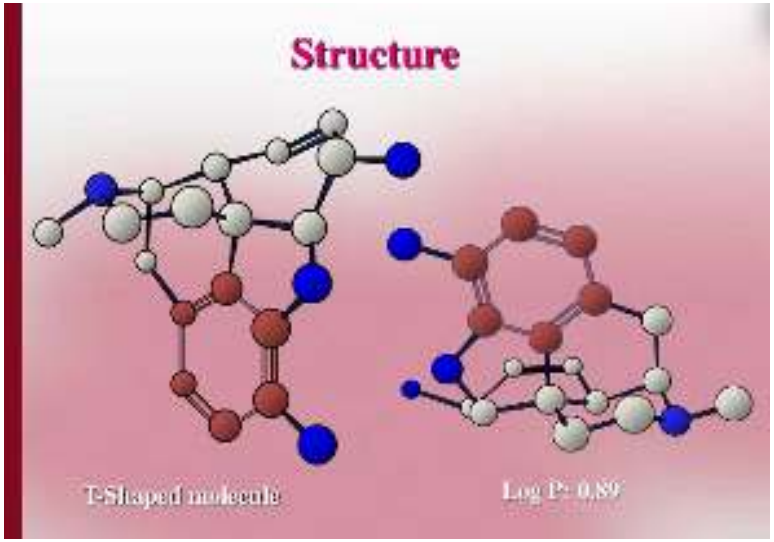


- **Basic nucleus and Peripheral groups in Morphine**

Morphine



- **Chemistry:**
- **Morphine is a pentacyclic molecule containing five rings numbered A-E and has a pronounced T shape.**
- **Three rings A,B and C are approximately in same plane.**
- **Rings D and E are at right angles to rings A,B and C.**



- It is basic in nature because of tertiary amino group.
- It also contains some peripheral or functional groups like-

➢ Phenolic hydroxyl at 3rd position

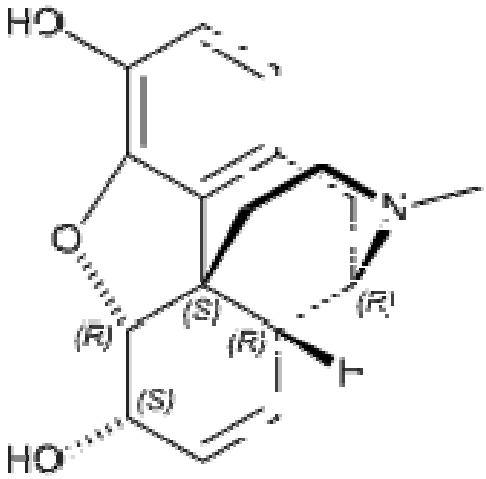
➢ Alcoholic hydroxyl at 6th position

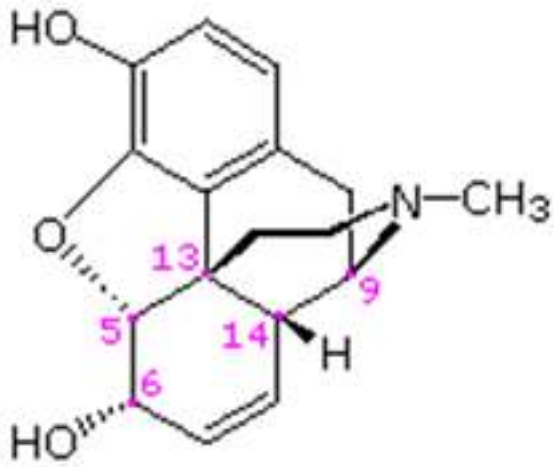
➢ Isolated double bond between 7th and 8th positions

➢ Ether bridge connecting 4th and 5th positions

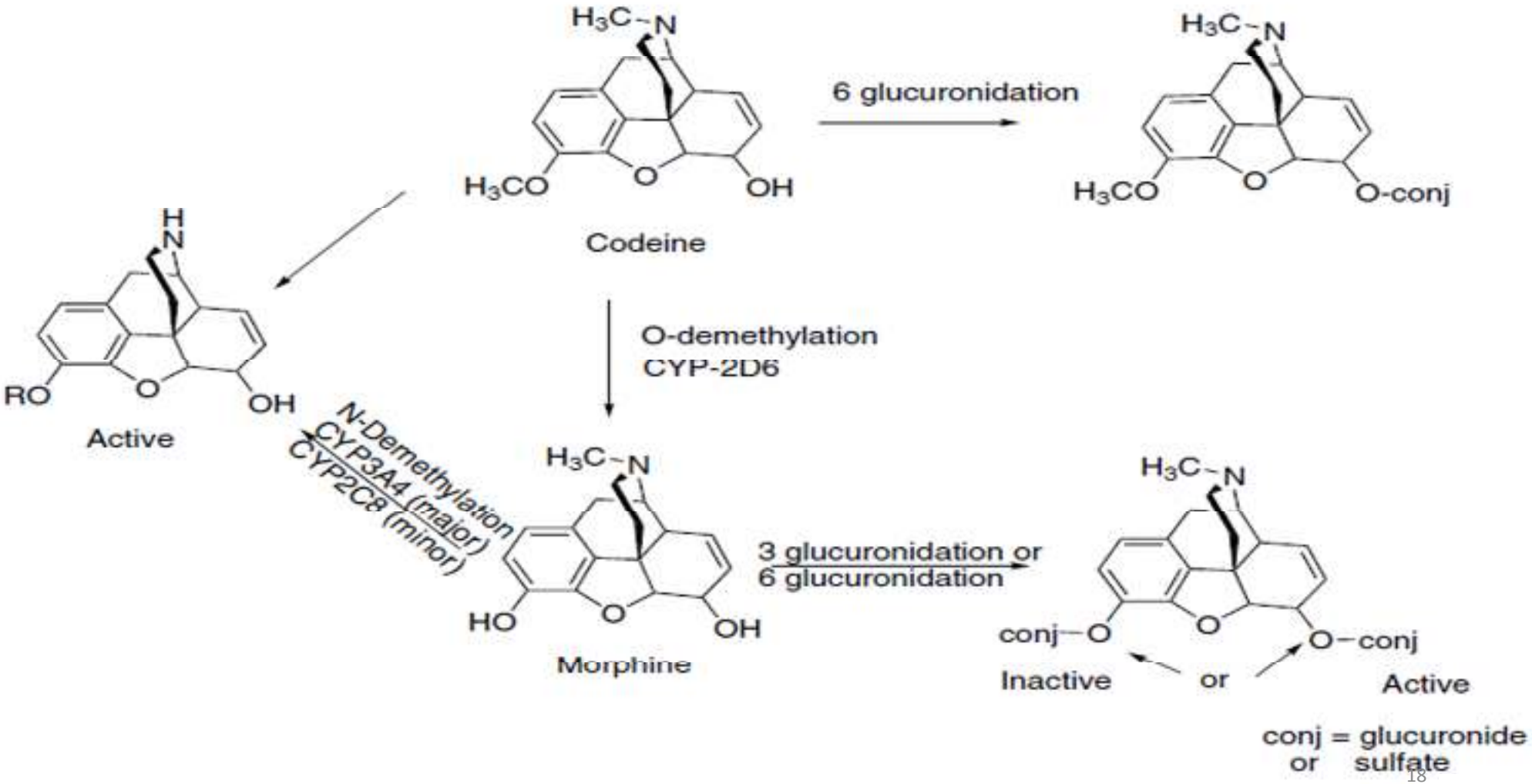
➢ Methyl group attached to tertiary nitrogen atom

- **Stereochemistry:**
- **Morphine contains 5 chiral centers and has 16 optical isomers (not 32 because of the restriction of C-9 to C-13 ethanamino bridge).**
- **The naturally occurring, active form of morphine is the levorotatory with the stereochemistry 5(R), 6(S), 9(R), 13(S), and 14 (R).**



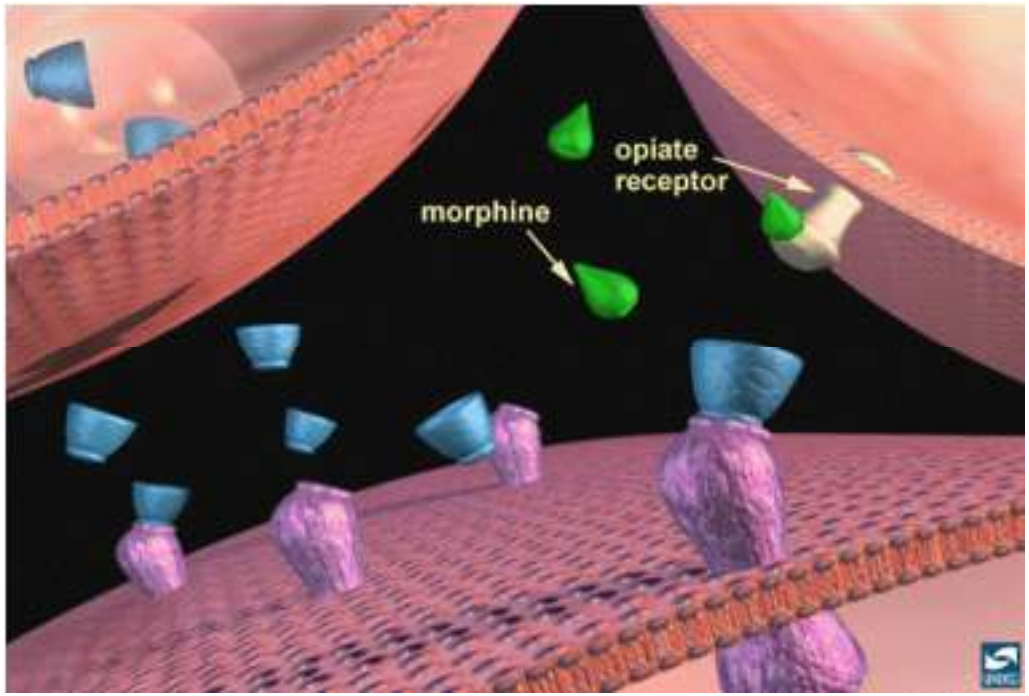


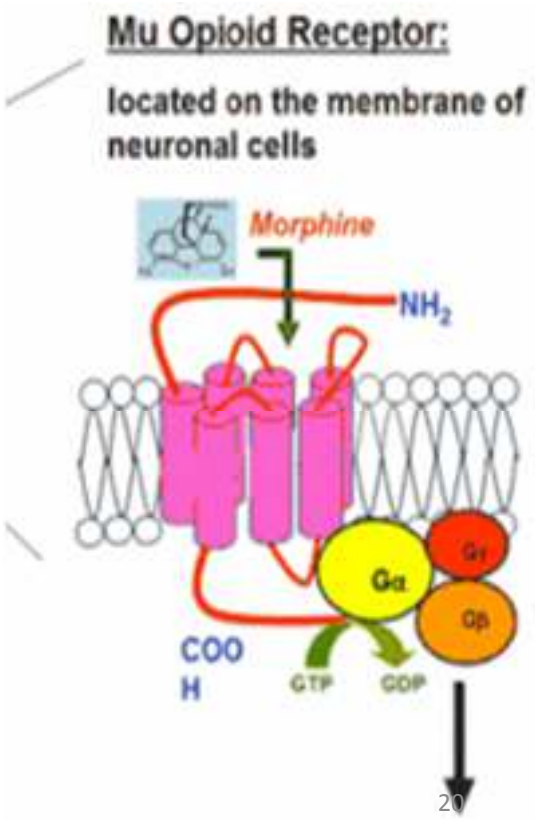
Metabolism of Morphine and Codeine



- **Morphine is extensively metabolized via phase II conjugation to morphine-3-glucuronide, morphine-6-glucuronide, and, to a lesser extent, the N-demethylated metabolite.**
- **6-Glucuronide conjugate and N-Demethyl metabolite are pharmacologically active.**

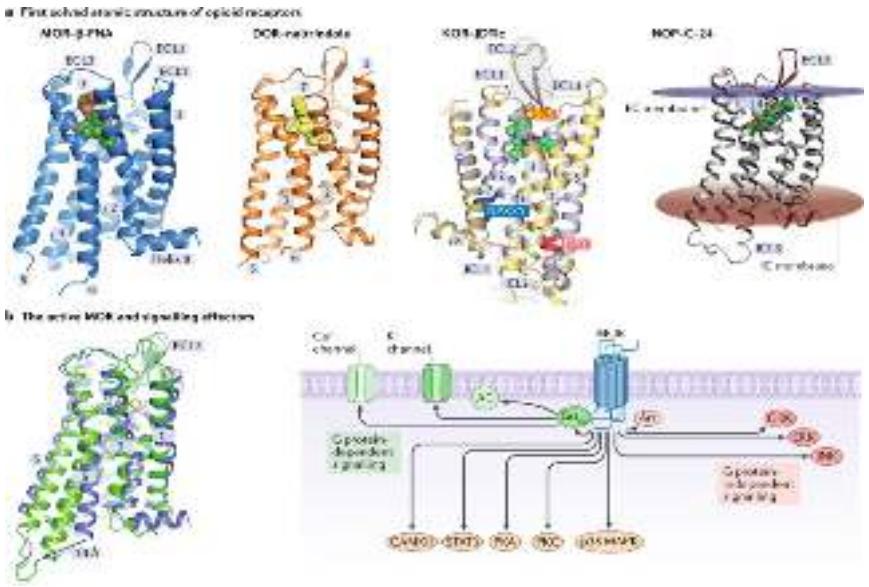
- **Analgesic receptors for Opiates:**
- **There are four different GPCR receptors which are associated with morphine's analgesic and side effects.**
- **They are –**
  - **μ (mu)**
  - **κ (kappa)**
  - **δ (delta)**
  - **σ (sigma)**





- **μ-receptor:**
- **Morphine binds strongly to this receptor and produces analgesia.**
- **Receptor binding also leads to the undesired side effects of respiratory depression, euphoria, and addiction.**
- **κ-receptor:**
- **Morphine binds less strongly to this receptor.**
- **The biological response is analgesia with sedation.**
- **No hazardous side effects are associated with this receptor.**

- **δ-receptor:**
- **The δ-receptor is where the brain's natural pain killers (enkephalins) interact.**
- **Morphine can also bind quite strongly to this receptor.**
- **This receptor is responsible only for analgesia effect.**
- **No side effects are associated with this receptor.**



- **σ-receptor:**
- **Morphine shows little or none affinity to this receptor.**
- **Activation of this receptor leads to hallucinations.**
- **For example, nalorphine and pentazocine shows affinity to this receptor and cause hallucinations.**
- **There is now a search going on for orally active opiate structures which can act as antagonists at μ and σ receptors and agonists at κ and δ receptors.**

- **Important binding groups for each receptor are-**

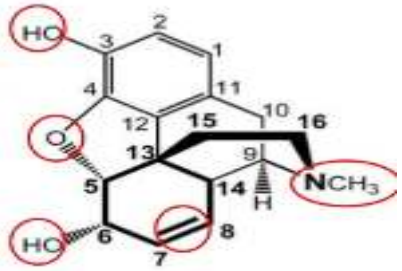
➢ **Phenolic hydroxyl group (hydrogen bonding)**

➢ **Aromatic ring (van der waals forces/hydrophobic interaction)**

➢ **Ionized nitrogen (ionic bonding)**

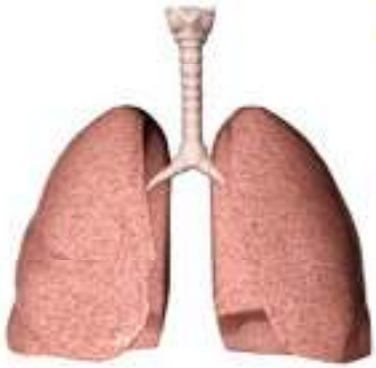
Biological action of opiods

- depends on
  1. **Phenolic hydroxyl group**
  2. **6 hydroxyl**
  3. Double bond between 7 & 8 c
  4. **N-methyl group**
  5. Ether (E) bridge
  6. Aromatic ring



Morphine therapy-Side effects-Withdrawal symptoms

- Side effects of morphine therapy are –
- Depression of respiratory centre (suffocation)
- Constipation
- Excitation
- Euphoria
- Nausea
- Pupil constriction
- Tolerance
- Dependence



Opioid Overdose

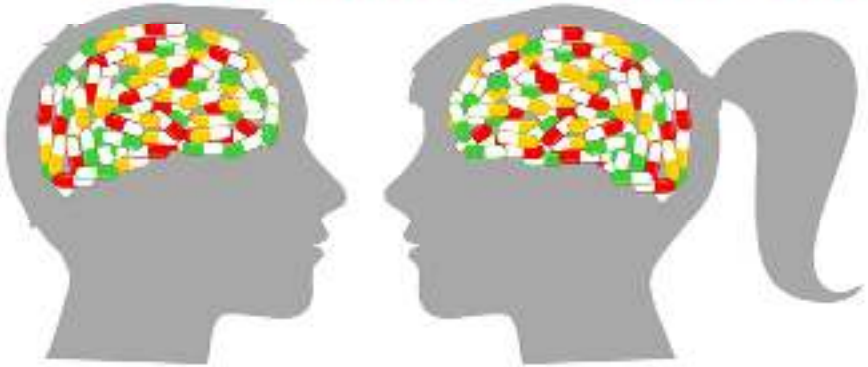
Hypoventilation and Respiratory Depression

Treatment goal is to support the airway and provide supplemental oxygen before administering naloxone

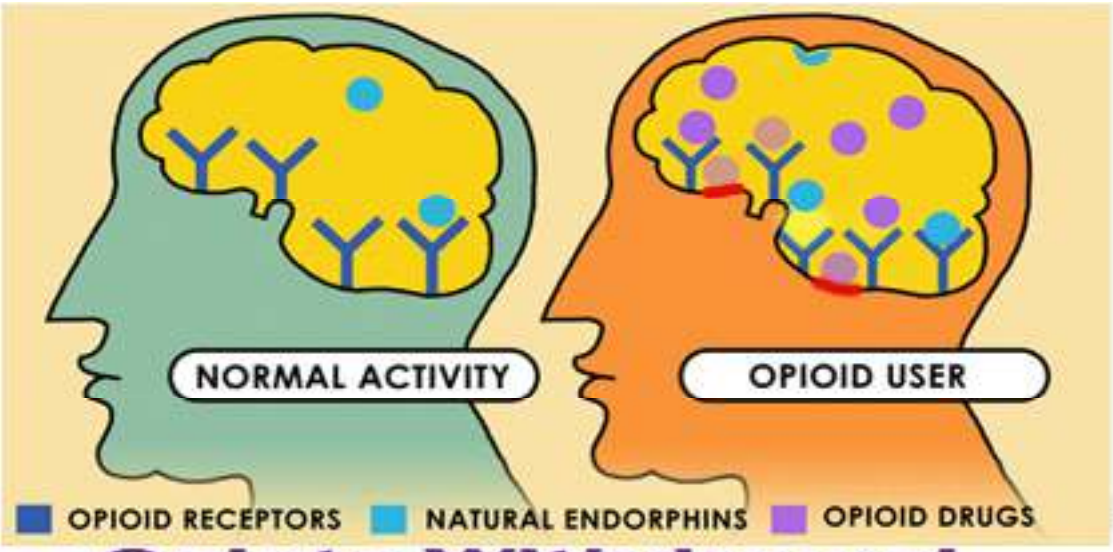
Miosis

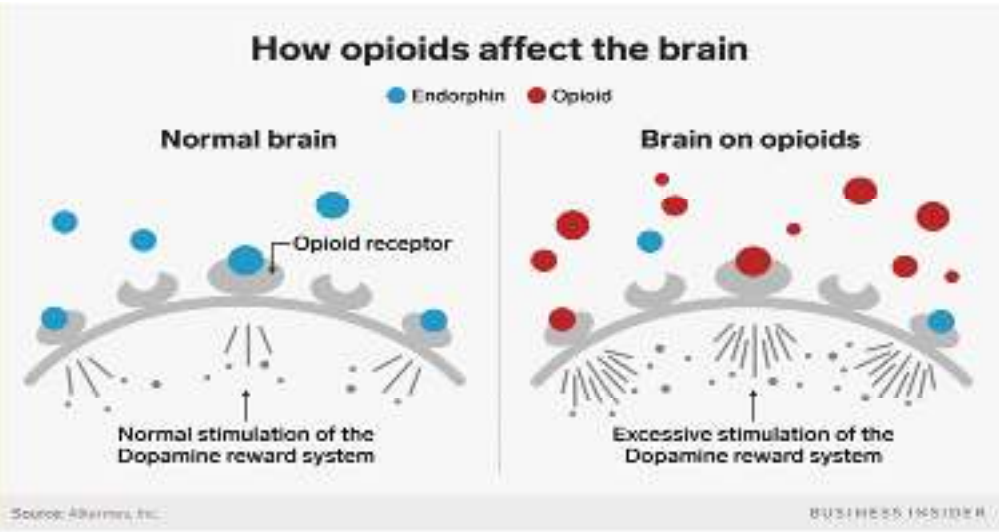
CNS depression

- **Some side effects can be advantageous ☹?**
- **Euphoria, for example, is a useful side effect when treating pain in terminally ill patients.**
- **Others, such as constipation are uncomfortable but can give clues to other possible uses for opiate structures. For example, opiate structures are widely used in cough medicines and treatment of diarrhoea.**



- The dangerous side effects of morphine are those of respiratory depression, tolerance and dependence.
- In fact, the most common cause of death from morphine overdose is suffocation.
- Tolerance and dependence in the one drug are particularly dangerous, and lead to severe withdrawal symptoms when the drug is no longer taken.





Opiate Withdrawal

Adrenergic Hyperactivity
CNS excitation
Tachypnea
Tachycardia
Hypertension

GI Symptoms
Abdominal cramping
Nausea
Vomiting
Diarrhea

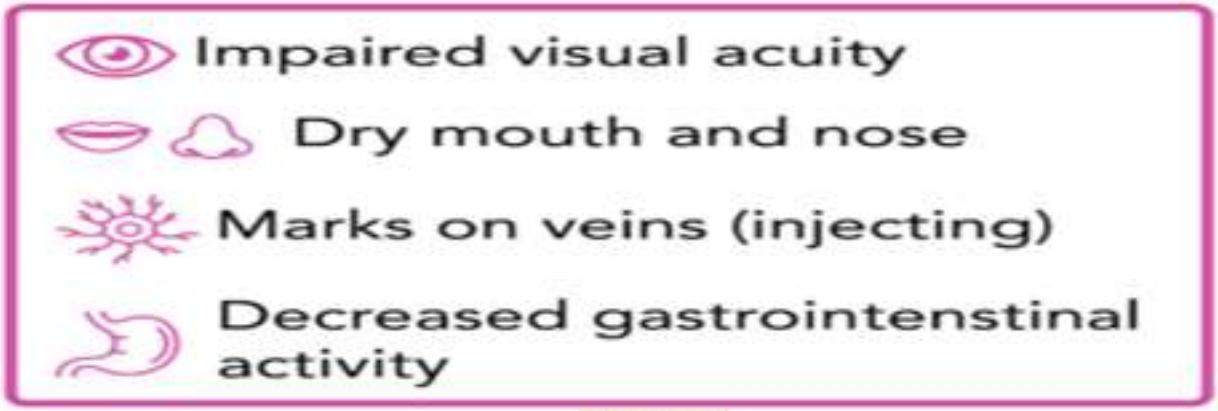
Mydriasis

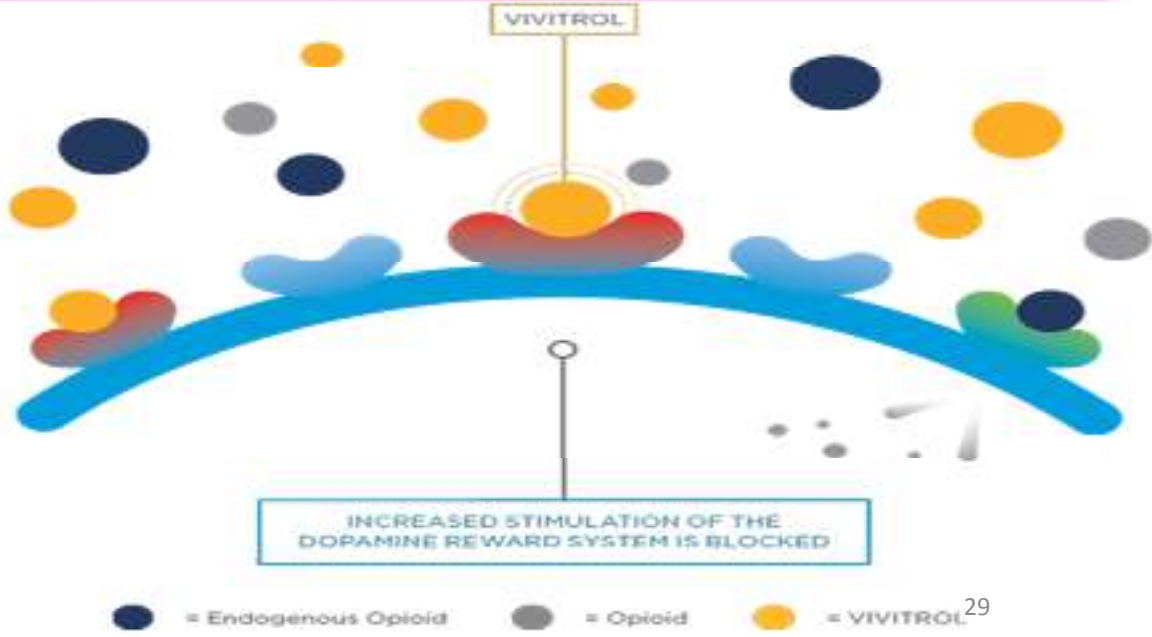
Yawning
Lacrimation

OPIATE ADDICTION INFLUENCES ON MENTAL HEALTH CONDITIONS

***Withdrawal symptoms often include:**

- Irritability
- Agitation
- Depression
- Insomnia
- Suicidal thoughts
- Anxiety
- Diarrhea
- Sweating
- Body aches
- Runny nose
- Headaches
- High blood pressure
- Irregular heartbeat

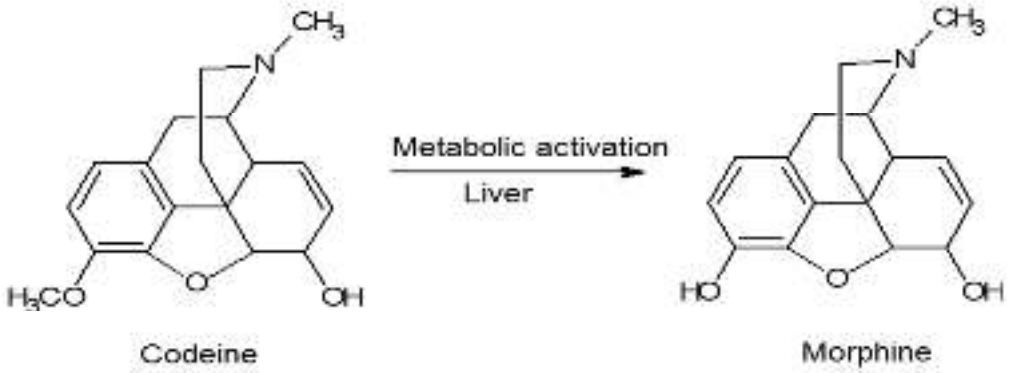




Development of Morphine Analogues and SAR

- Morphine has several functional groups, and a study of structure-activity relationships (SAR) is important in identifying those groups that are important for activity and those that are not.
- This will definitely help us to find a more delta and kappa selective agonists that are free from severe side effects of morphine.

- **The phenolic group:**
- **Codeine is the 3- methyl ether of morphine and is also present in opium.**
- **It is used for treating moderate pain, cough, and diarrhoea.**
- **Codeine undergoes hepatic metabolic O-demethylation to give Morphine.**

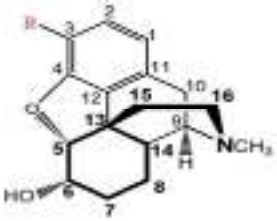


Codeine Morphine

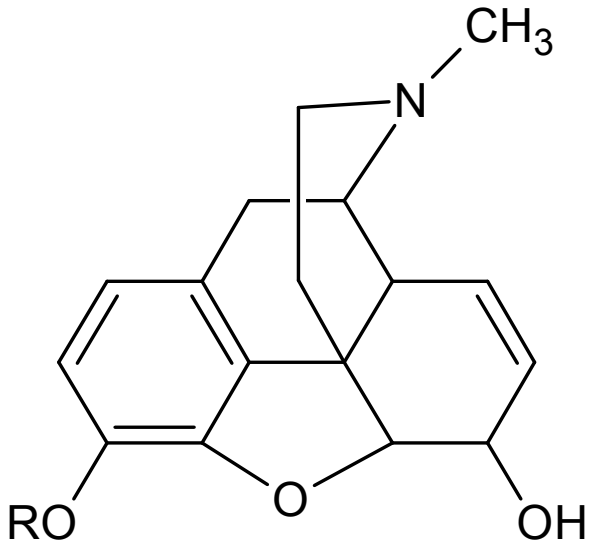
Phenolic hydroxyl group

- is needed for binding of μ & κ receptors;
- seen in all potent μ agonist.
- Changing -OH to just –H or -OCH3 lowers activity.

R= C3 substituent	Activity effect
-H	Decrease
-OH	Morphine
-OCH3 (codeine)	Decrease (1/3)



- **Methylating phenolic hydroxyl group causes a drop in receptor binding, and binding affinity for codeine is only 0.1% that of morphine.**
- **This indicates that a free phenolic group is crucial for analgesic effect.**
- **Thus, codeine can be viewed as a prodrug for morphine. Further evidence comes from the fact that codeine has no analgesic effect when it is injected directly in to brain.**

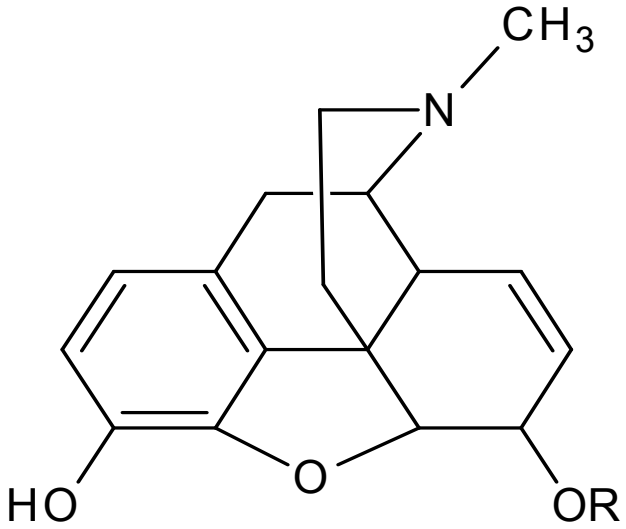


R = CH_3 , Codeine with decreased analgesic effect.

R = C_2H_5 , 3 - Ethylmorphine with decreased analgesic effect.

R = $CH_3.CO$, 3 -Acetylmorphine with decreased analgesic effect.

- **The alcohol group:**
- **Masking or losing the alcohol group does not decrease analgesic activity.**
- **In fact, it often improves activity as a result of improved pharmacokinetic properties.**
- **In other words, the drugs concerned reach the target receptor more easily.**



R = CH_3, Heterocodeine, increased activity.

R = C_2H_5, 6 - Ethylmorphine,increased activity.

R = $CH_3.CO$, 6 - Acetylmorphine, increased activity.

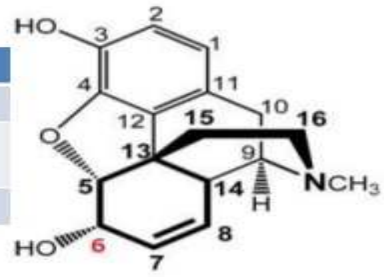
- **In this case, the morphine analogues shown are less polar than morphine because a polar alcohol group has been masked or lost.**
- **As a result they cross BBB more efficiently and accumulate at the target receptors in greater concentrations leading to better analgesic activity.**

Hydroxyl at 6

- Modifications at 6 OH which increases activity

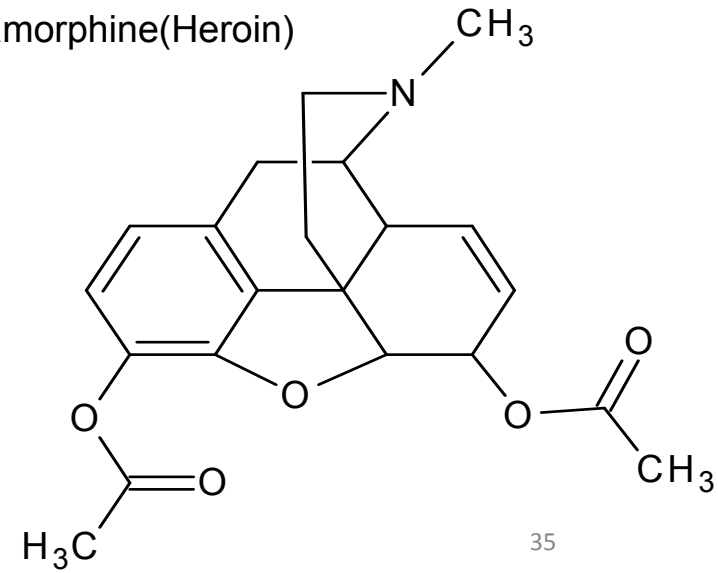
1. Removal of Hydroxyl at 6→ increases lipophylicity
2. Oxidation of Hydroxyl to keto group at 6 + reduction of 7,8 double bond eg Hydrocodone
3. Acetylation of Hydroxyl at 6 (eg. Heroin)

R= C6 substituent	Effect in activity
H	Increase 10X
=O (keto) =O (keto) with 7,8 reduction	decrease (1/3) Increases (6X)
$H_3CC=O$ (acetyl)	Increase

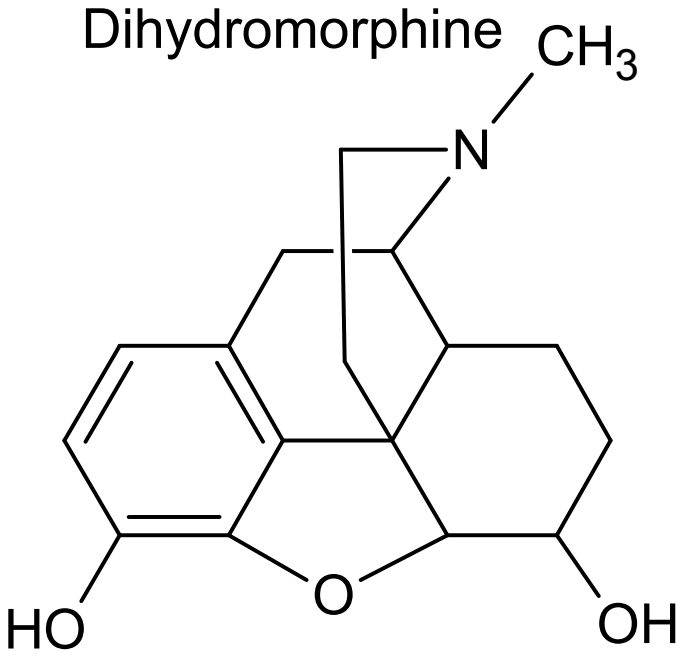


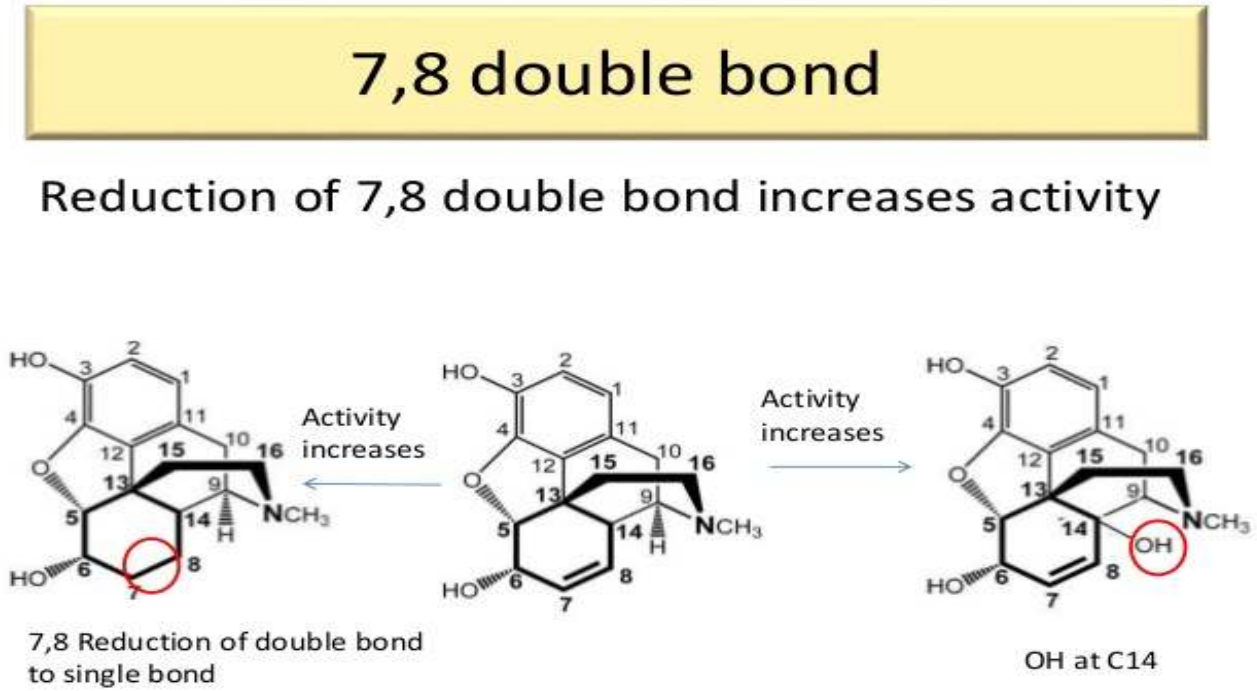
- **Both 6-acetylmorphine and heroin (diamorphine) are more active than morphine due to easy entry in to CNS.**
- **Unfortunately, they also have greater side effects as well as severe tolerance and dependence characteristics.**
- **Heroin is still used to treat terminally ill patients suffering chronic pain, but 6-acetylmorphine is banned due to dangerous side effects.**
- **To conclude, the 6-hydroxyl group is not required for analgesic activity and its removal can be beneficial to analgesic activity.**

Diamorphine(Heroin)



- **The double bond at 7th - 8th positions:**
- **Several analogues including dihydromorphine have shown that the double bond is not necessary for analgesic activity.**

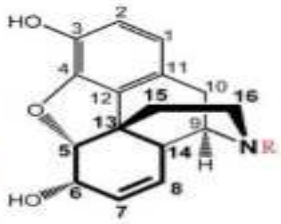




- **The N-methyl group:**
- **N-Demethylation to give normorphine reduces activity but does not eliminate it.**
- **The secondary NH group is more polar than the original tertiary group and so normorphine is less efficient at crossing BBB, leading to a drop in activity.**

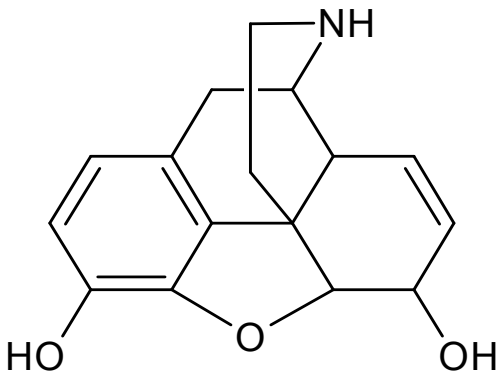
N-methyl group

- Interacts hydrophobically with μ receptor.
- Size of substituent on Nitrogen dictates potency and agonist/antagonist activity.

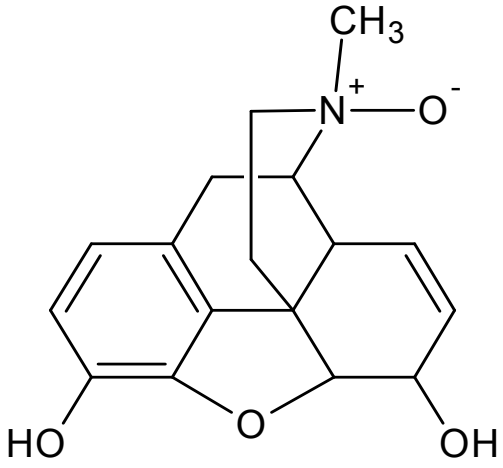


R= Nitrogen substituent	Effect
3-5 Carbons (with double bond/ small cyclic or aromatic rings) eg. $CH_2CH{=}CH_2$	**μ antagonist**
>5c (in chain or ring)	**μ agonist**
Aralkyl CH_2CH_2Ph (Total 8 C)	**μ agonist (10X** morphine)

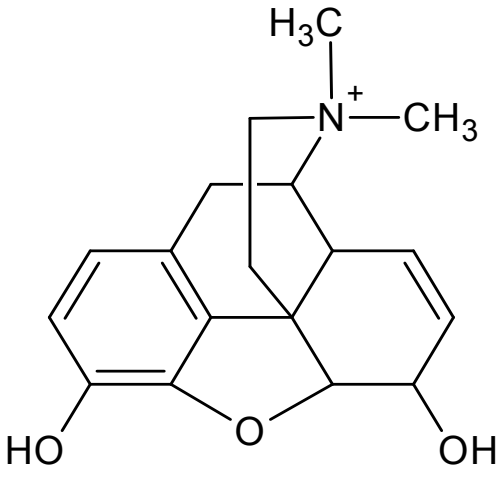
- **The fact that significant activity is retained shows that methyl substituent is not essential to activity.**
- **The nitrogen is crucial, however. If it is replaced by carbon, all analgesic activity is lost.**
- **The N-oxide and the N-methyl quaternary salt of morphine are both inactive when tested in vivo.**



Normorphine



N - Oxide analogue



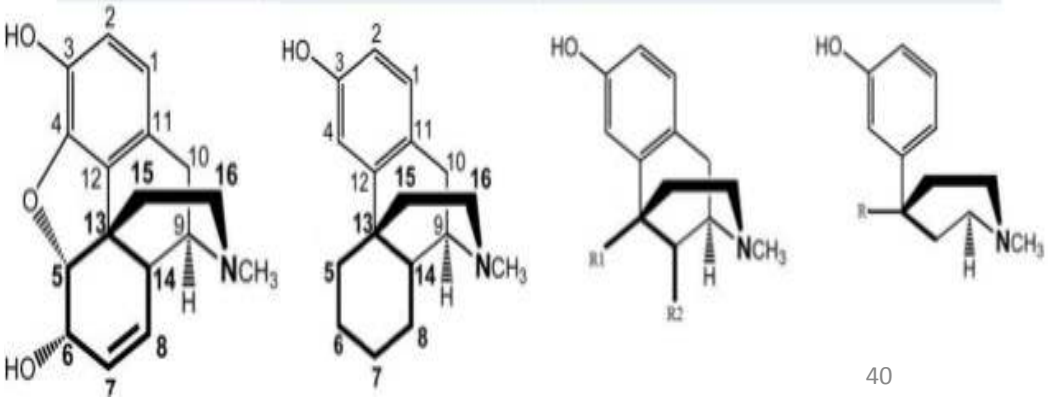
N - Methyl quaternary analogue

- **If these same compounds are injected directly in to the brain, both compounds actually have a similar analgesic activity to morphine.**
- **The fact that neither compound can lose its charge shows that the nitrogen atom of morphine must be ionized when it binds to the receptor.**
- **To conclude, the nitrogen atom is essential to analgesic activity and interacts with the analgesic receptor in the ionized form.**

- **The aromatic ring:**
- **The aromatic ring is essential.**
- **Compounds lacking it show no analgesic activity.**
- **The ether bridge:**
- **The ether bridge is not required for analgesic activity.**

Classification of opiods based on structure

		Eg.
Pentacyclic	Morphines	Codeine ,Buprenorphine, Oxycodone, Diacetylmorphine (Heroin)
Tetracyclic	Morphinan	Levorphanol, butorphanol
Tricyclic	Benzazocine	Pentazocine, Phenazocine
Bicyclic	Phenylpiperidine	Meperidine



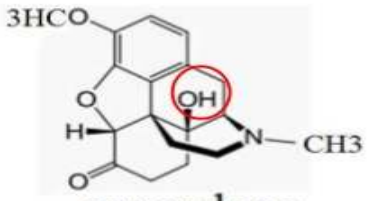
- **Drug extension:**
- **The strategy of drug extension involves the addition of extra functional groups to a lead compound in order to probe for extra binding regions in a binding site.**
- **Many analogues of morphine containing extra functional groups have been prepared. These have rarely shown any improvement.**
- **There are two exceptions, however.**

➢ **1st Exception- is introduction of a hydroxyl group at 14th position increases activity.**

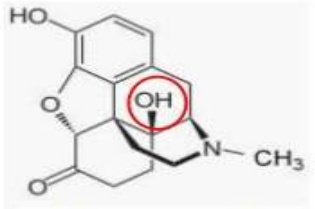
This suggests that there might be an extra hydrogen bond interaction taking place with the binding site.

14 β H/OH moiety

- Addition of OH at 14 β position
  1. Increases activity (2-3X)
  2. Increases penetration of BBB
  3. Decrease in antitussive action



oxycodone

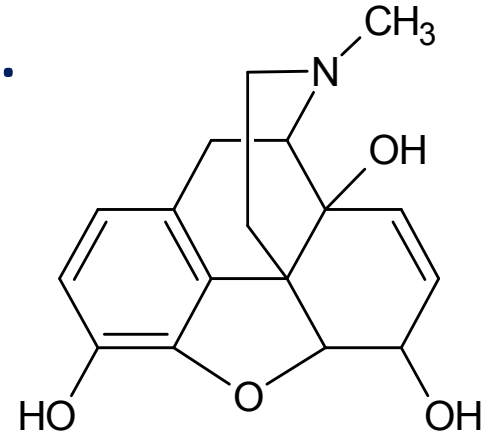


Oxy morphone

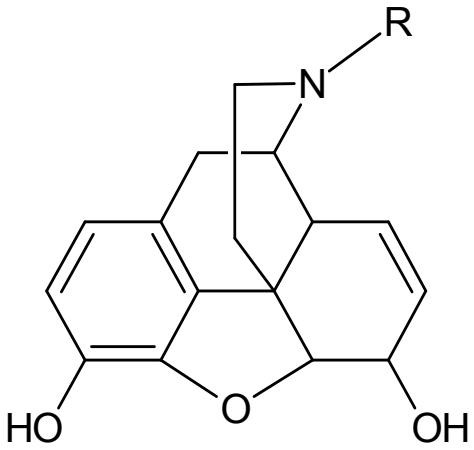
➢ **2nd Exception- involves the variation of alkyl substituents on the nitrogen atom.**

- **As the alkyl group is increased in size from methyl to a butyl group, the activity drops to zero.**
- **With a larger group such as a pentyl or a hexyl group, activity recovers slightly.**
- **But when a phenethyl group is attached, the activity increases 14-fold relative to morphine.**
- **What does this indicate?**

- **This strongly indicates that a hydrophobic binding region has been located which interacts favourably with the new aromatic ring.**
- **To conclude, the size and nature of the group on the nitrogen is important to activity spectrum.**
- **Drug extension can lead to better binding by making use of additional binding interactions.**



Oxymorphine



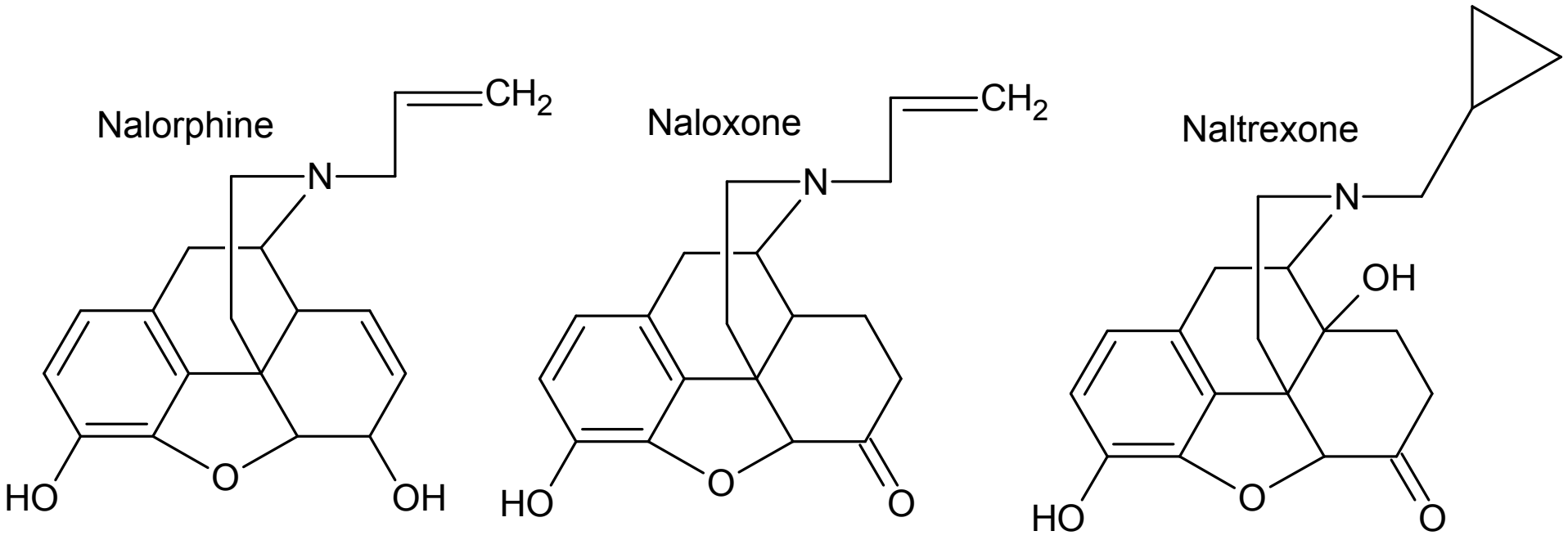
R = Ethyl, propyl,butyl. No activity.

R = Pentyl or hexyl. Slight increase in activity

R = Phenethyl. 14 times increase in activity.

- **N-Allyl substitution-Antagonist development:**
- **When an allyl or a cyclopropylmethylene group is attached to nitrogen, morphine antagonist activity is observed.**
- **Naloxone and naltrexone have no analgesic activity at all, and nalorphine retains only weak analgesic activity.**
- **They act as antagonists to morphine that is they bind to the analgesic receptors and block morphine from binding.**
- **As a result, morphine can no longer act as analgesic.**

- **Naltrexone is 8 times more active than naloxone as an antagonist and is given to drug addicts who have been weaned off morphine or heroin.**

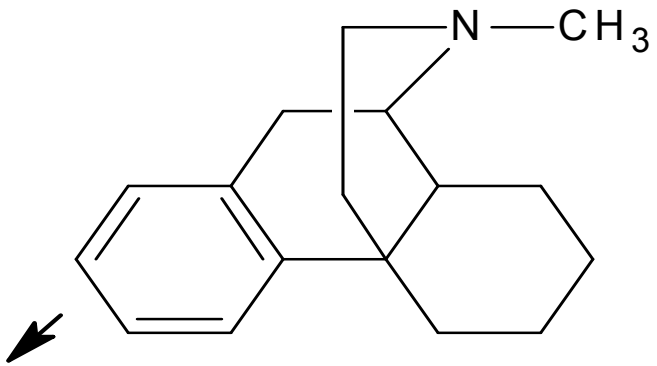


- **Nalorphine is a weak analgesic.**
- **It acts as a true antagonist at μ and δ receptors but partial agonist at κ and σ receptors (weak activation of these two receptors).**
- **Unfortunately, nalorphine has hallucinogenic side effects resulting from the activation of σ receptor, and it is therefore unsuitable as an analgesic.**

- **Drug dissection/ drug simplification:**
- **If the morphine molecule could be simplified, it would be easier to synthesize analogues.**
- **The structure of morphine has 5 rings (A, B, C, D and E) and analogues were made to see which rings could be removed.**
- **Removing ring D:**
- **Removing ring D leads to complete loss of activity.**
- **This indicates the importance of basic nitrogen to analgesic activity.**

- **Removing ring E (Morphinans):**
- **Removing the ether bridge gives a series of compounds called the morphinans, which have useful analgesic activity.**
- **This demonstrates that the ether bridge is not essential.**
- **N-Methylmorphinan is only 20% as active as morphine, but since the phenolic group is missing, this is not surprising.**

N - Methylmorphinan

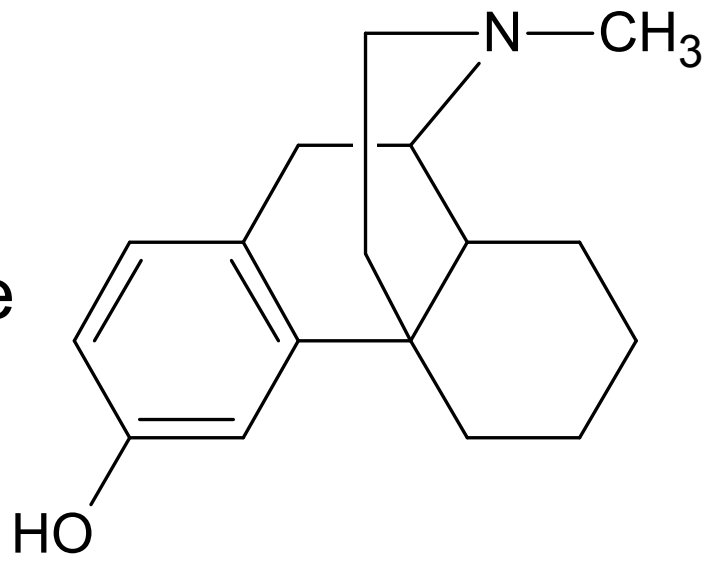


20% activity of morphine

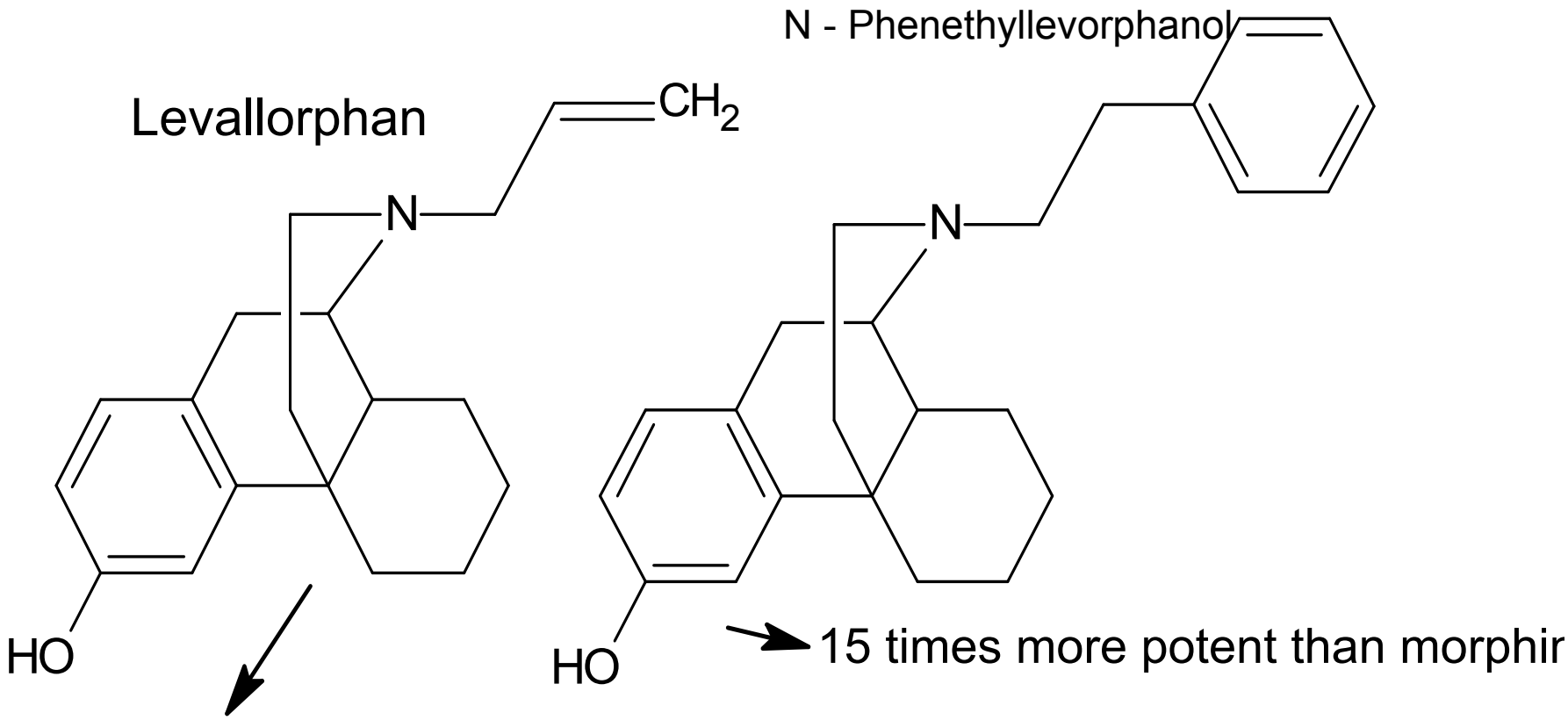
- **The more relevant levorphanol structure is 5 times more active than morphine and, although side effects are also increased, levorphanol has a massive advantage over morphine in that it can be taken orally and lasts much longer in the body.**

5 times more potent than morphine

Levorphanol



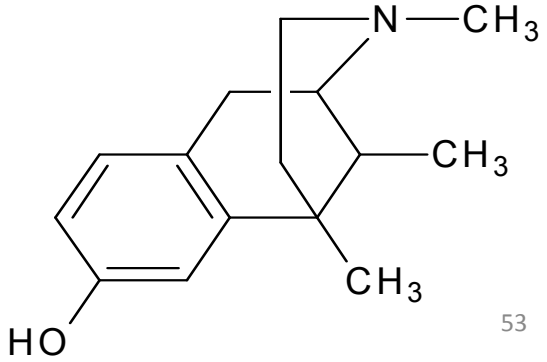
- **Drug extension-Morphinan Antagonists:**
- **The same strategy of drug extension already described for the morphine structures was tried on the morphinans with similar results.**
- **For example, adding an allyl substituent on the nitrogen gives antagonists.**
- **Adding a phenethyl group to the nitrogen greatly increases potency.**
- **Adding a 14-hydroxyl group also increases activity.**



5 times more potent than nalorphine as an atagonist

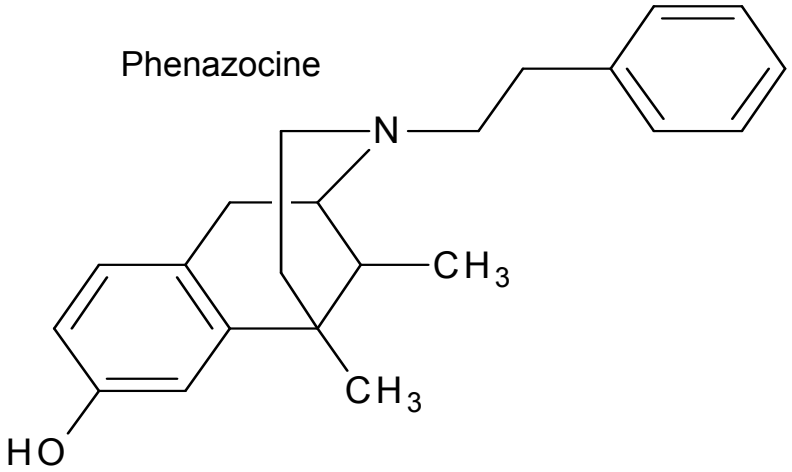
- **Removing rings C and E (Benzomorphans):**
- **Opening both rings C and E in morphine gives benzomorphans which retain analgesic activity.**
- **One of the simplest of these structures is metazocine which has the same analgesic activity as morphine.**
- **The two methyl groups in metazocine are *cis* with respect to each other and represent the remnants of ring C.**

Metazocine

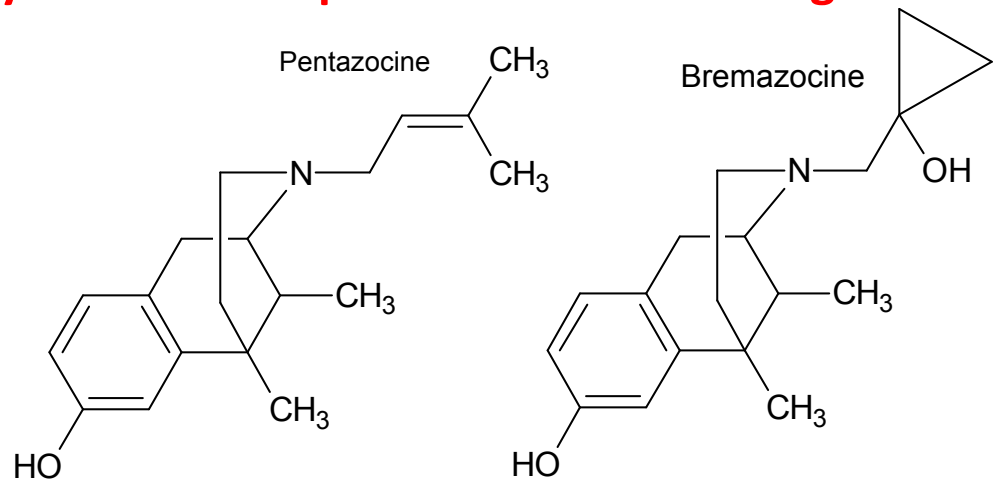


- **The same chemical modifications carried out on the benzomorphans as described for the morphinans and morphine, produce the same biological effects.**
- **For example, replacing the N-methyl group of metazocine with a phenethyl group gives phenazocine which is 4 times more active than morphine and is the first compound to have a useful level of analgesia without dependence properties.**

Phenazocine

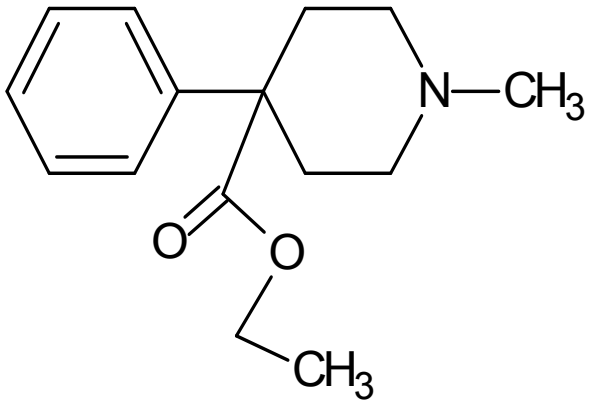


- **Further developments led to pentazocine (μ and κ antagonist but act as strong agonist at δ receptor) which has proved to be a useful long-term analgesic with a very low risk of addiction.**
- **A newer compound bremazocine (μ and κ antagonist but act as strong agonist at δ receptor) has a longer duration, 200 times the activity of morphine and does not depress breathing.**
- **Unfortunately, many of these compounds have hallucinogenic side effects.**

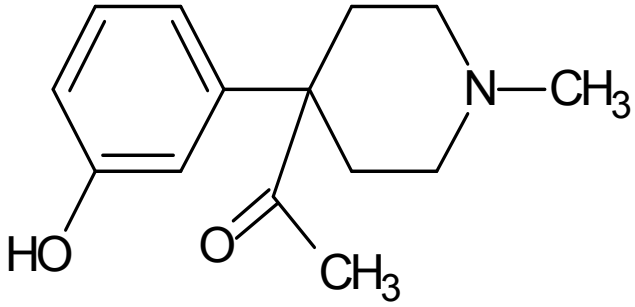


- **Removing rings B, C, and E:**
- **Removing rings B, C, and E gives a series of compounds known as 4-phenylpiperidines.**
- **Activity can be increased 6 fold by introducing the phenolic group and altering the ester to a ketone to give ketobemidone.**

Pethidine



Ketobemidone

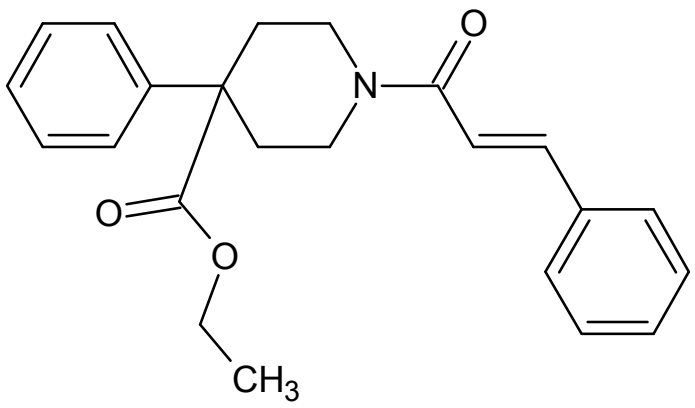


- **Pethidine (meperidine) is a weaker analgesic than morphine, but shares the same undesirable side effects.**
- **On the plus side, it has a rapid onset and shorter duration of action.**
- **As a result, it has been used as an analgesic in childbirth.**
- **The rapid onset and shorter duration of action mean that there is less chance of the drug depressing the baby's breathing once it is born.**

- **There is some doubt as to whether they act in the same way as morphine at analgesic receptors, since some of the chemical modifications we have already discussed do not lead to comparable biological results.**
- **For example, adding allyl or cyclopropyl groups does not give antagonists.**

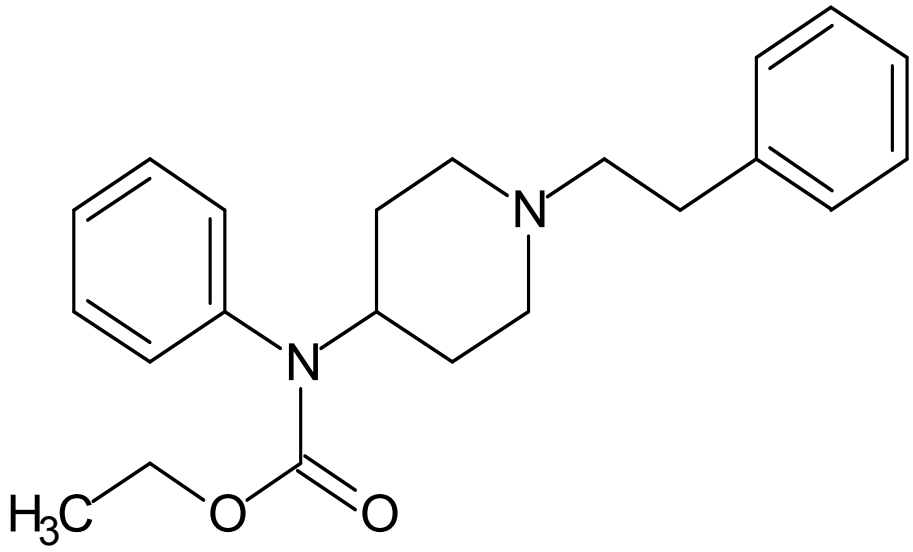
- **The replacement of the methyl group of pethidine with a cinnamic acid residue increases the activity by 30 times, whereas putting the same group on morphine eliminates activity.**
- **These unexpected results may be due to the fact that piperidines are more flexible than previous structures and are likely to bind with receptors in different ways.**

Cinnamic acid derivative of Pethidine



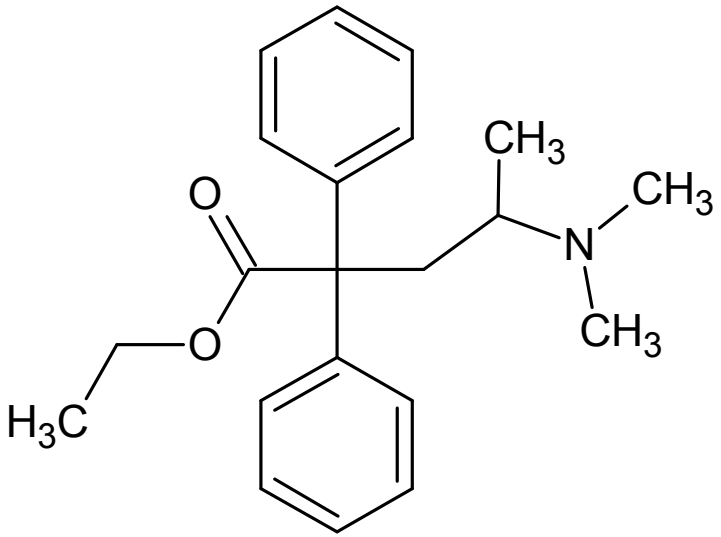
- One of the most successful piperidine derivatives is fentanyl, which is up to 100 times more active than morphine.
- The drug lacks a phenolic group, but is very lipophilic.
- As a result, it can cross BBB (blood-brain barrier) efficiently.
- All these results suggest that piperidine analgesics bind to receptors in a different manner.
- Aromatic ring and tertiary nitrogen in ionized form are essential for analgesic activity.

Fentanyl



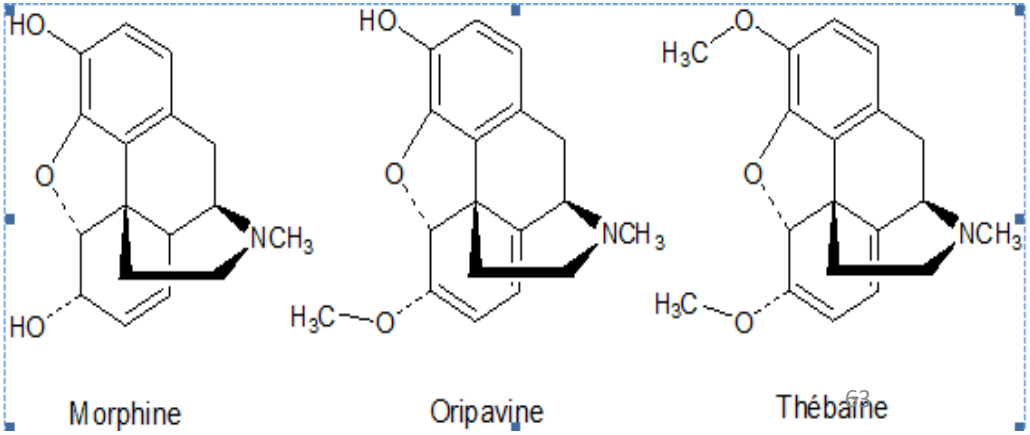
- **Removing rings B, C, D and E:**
- **The analgesic methadone has proved to be a useful agent, comparable in activity to morphine.**
- **It has a single asymmetric centre and therefore exists in R and S enantiomeric forms.**
- **R enantiomer is twice as powerful as morphine, whereas the S enantiomer is inactive.**

Methadone

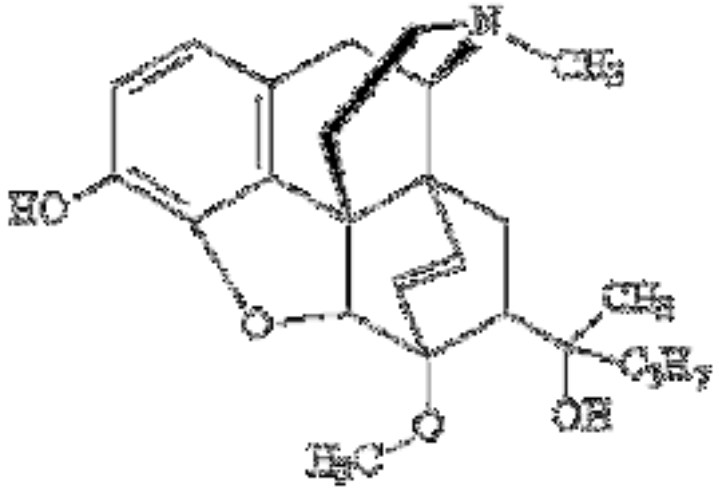


- **Methadone** is orally active and has less severe emetic and constipation side effects.
- Other side effects such as sedation, euphoria, and withdrawal symptoms are also less severe and therefore the compound has been given to drug addicts as a substitute for morphine or heroin in order to wean them off these drugs.

- **Rigidification- ORIPAVINES :**
- The strategy of rigidification is used to limit the number of conformations that a molecule can adopt.
- The aim is to retain the active conformation for the desired target and eliminate alternative conformations to avoid or minimize side effects.
- This should increase activity, improve selectivity and decrease side effects.
- The best examples of this tactic in analgesic field are the oripavines, which often show remarkably high activity.

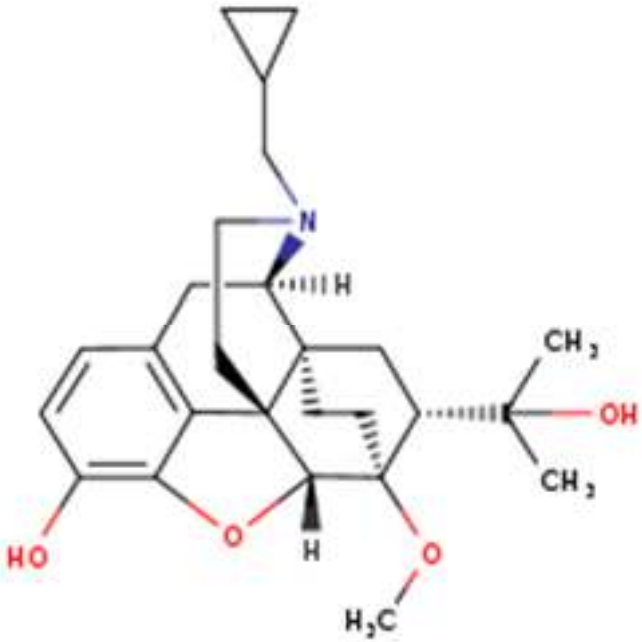


- **Etorphine is 10,000 times more potent than morphine.**
- **This is a combination of the fact that it is a very hydrophobic molecule and can cross BBB 300 times more easily than morphine, as well as having 20 times more affinity for the analgesic receptor site due to better binding interactions.**
- **It has a considerable margin of safety and is used to immobilize large animals such as elephants.**

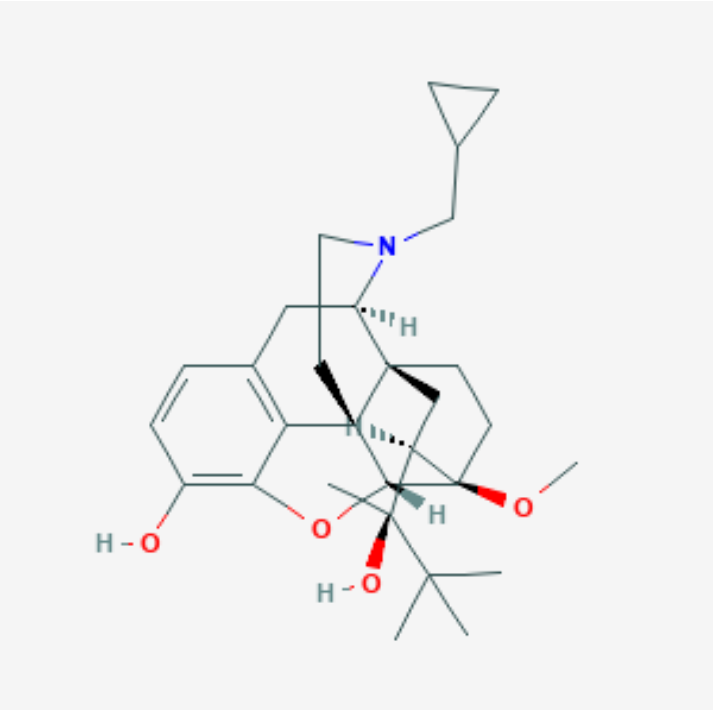


- **Diprenorphine** is 100 times more potent than nalorphine and can be used to reverse the immobilizing effects of etorphine.
- It has no analgesic activity.

DIPRENORPHINE

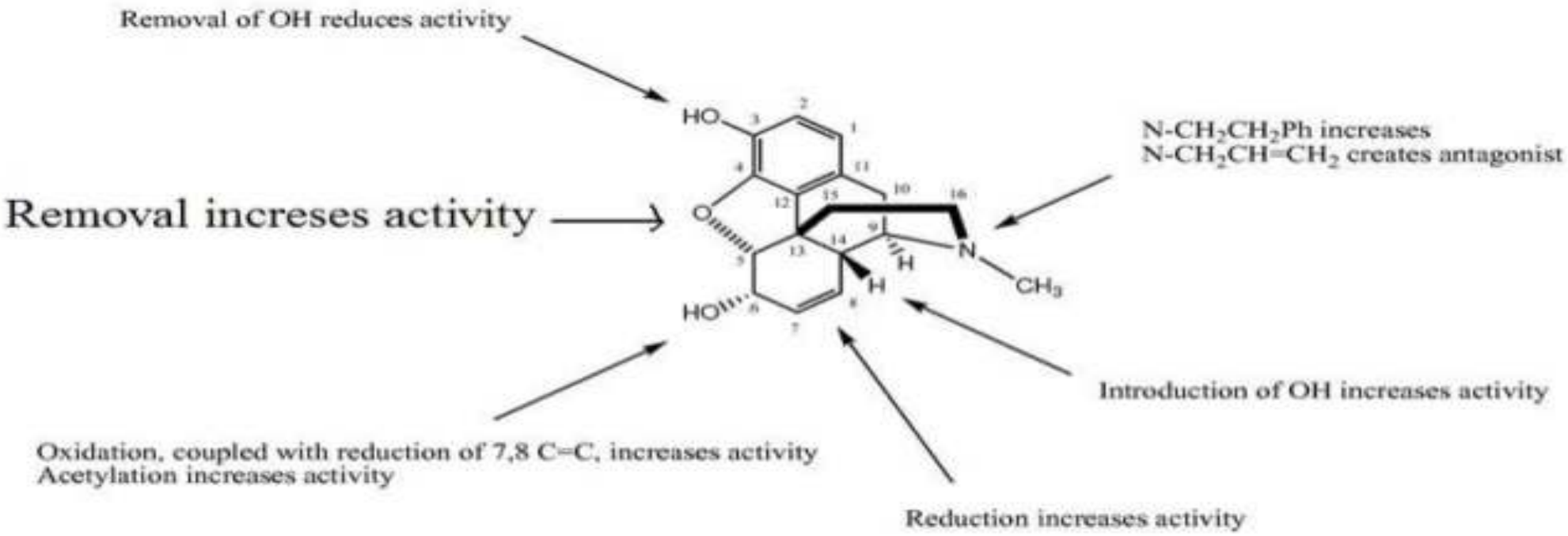


BUPRENORPHINE



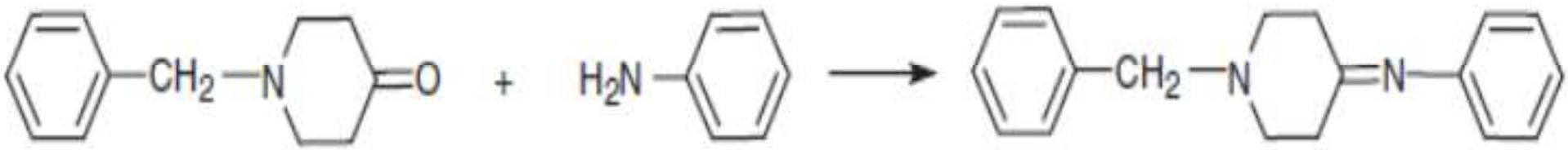
- **A similar compound is buprenorphine which has similar properties to drugs nalorphine and pentazocine, in that it has analgesic activity with a very low risk of addiction.**
- **It is 100 times more active than morphine as an agonist and 4 times more active than nalorphine as an antagonist.**
- **It has been used in hospitals to treat patients suffering from cancer and also after surgery.**
- **Its drawbacks include side effects such as nausea and vomiting, as well as the fact that it cannot be taken orally.**

Summary of structure-activity relationships (SAR's)

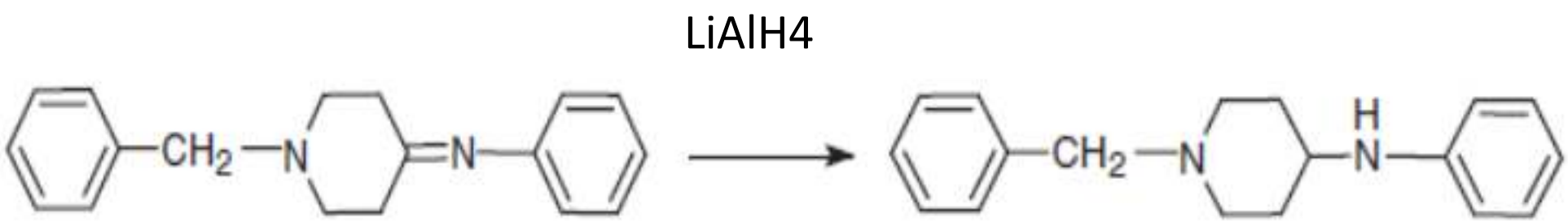


Synthesis of Fentanyl:

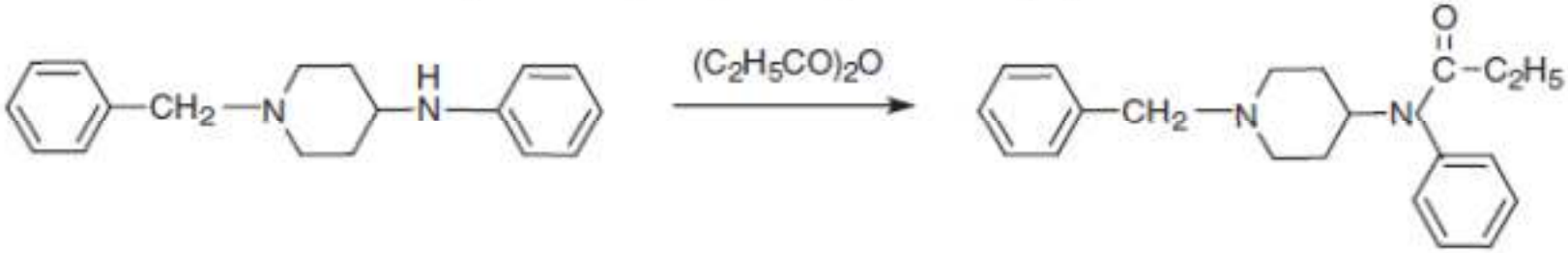
- Condensation of 1-benzylpiperidin-4-one with aniline form Schiff base.



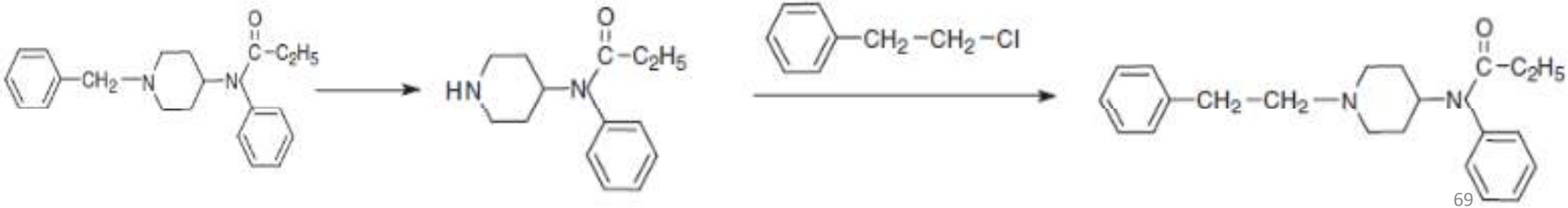
- The double bond in Schiff's base is reduced by lithium aluminum hydride to form 1-benzyl-4-anilinopiperidine.



- 1-benzyl-4-anilinopiperidine is acylated using propionic acid anhydride resulting in the formation of 1-benzyl-4-*N*-propinoylanilinopiperidine.

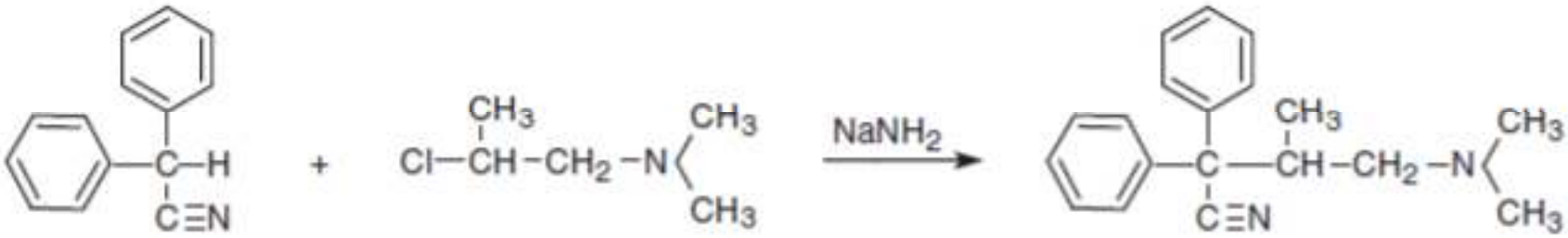


- Debenzylation of 1-benzyl-4-*N*-propinoylanilinopiperidine using hydrogen and a palladium on carbon catalyst gives 4-*N*propanoylanilinopiperidine. This is N-alkylated by 2-phenylethylchloride, to give fentanyl.

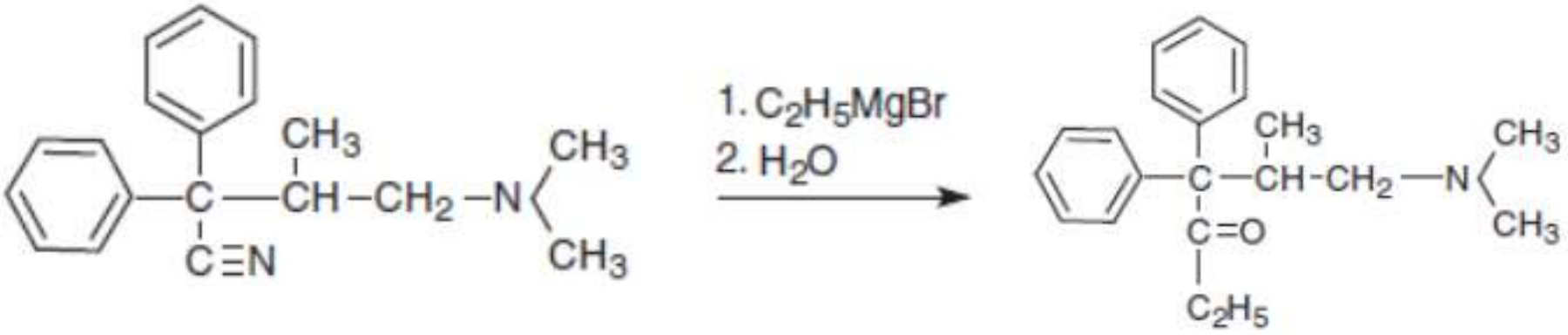


Synthesis of Methadone

- Methadone is synthesized by alkylation of diphenylacetonitrile using 1-dimethylamino-2-propylchloride in the presence of sodium amide.

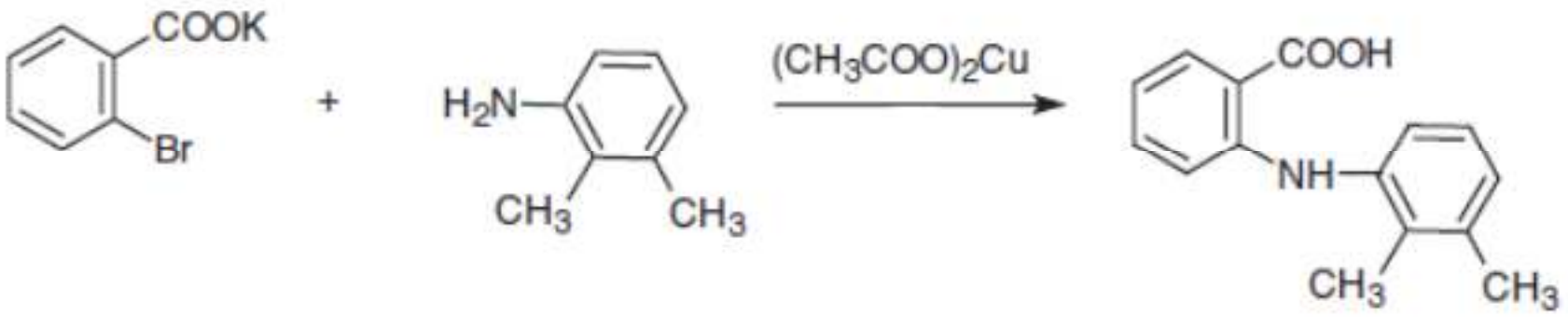


- The resulting 4-dimethylamino-2,2-dephenylvaleronitrile is reacted with the ethylmagnesiumbromide and then hydrolyzed. This resulting racemate is separated using (+)-tartaric acid, thus isolating (-)-methadone.

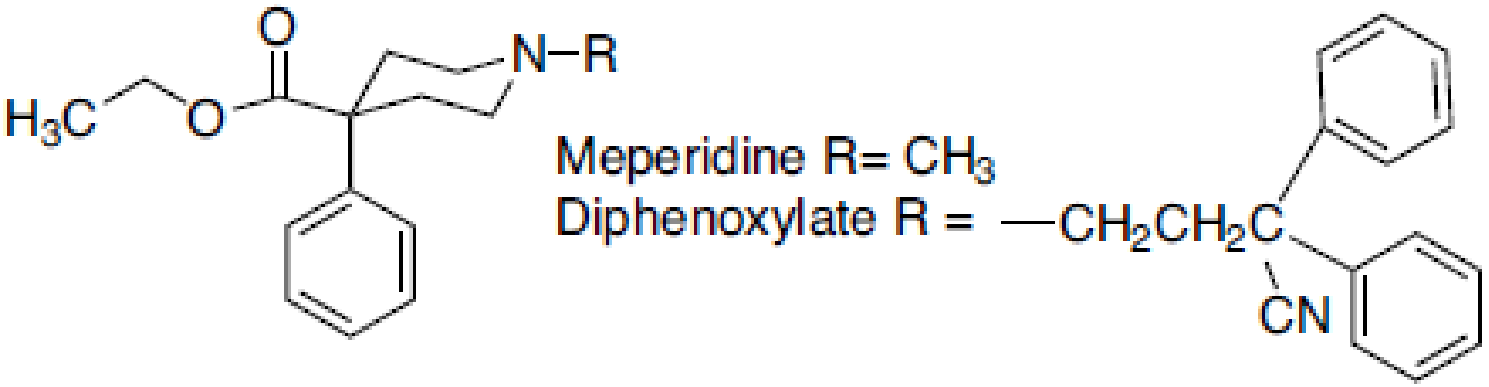


Synthesis of Mefenamic acid:

- Mefenamic acid is synthesized by the reaction of the potassium salt of 2-bromobenzoic acid with 2,3-dimethylaniline in the presence of copper (II) acetate.



- **MEPERIDINE: (4-Phenylpiperidine derivative)**
- **Meperidine produced the Straub tail reaction (tails in an erect position) in mice, which was indicative of narcotic analgesia.**
- **It is an agonist at the μ-receptor and a 300-mg oral or 75-mg IV dose is reported to be equianalgesic with morphine 30-mg oral or 10-mg IV dose.**



- **Chemistry and SAR (4-Phenylpiperidines):**
- **The 4-ethyl ester was found to be the optimal length for analgesic potency.**
- **Increasing or decreasing the chain length decreased activity.**
- **Structural changes that increase the potency of meperidine include**

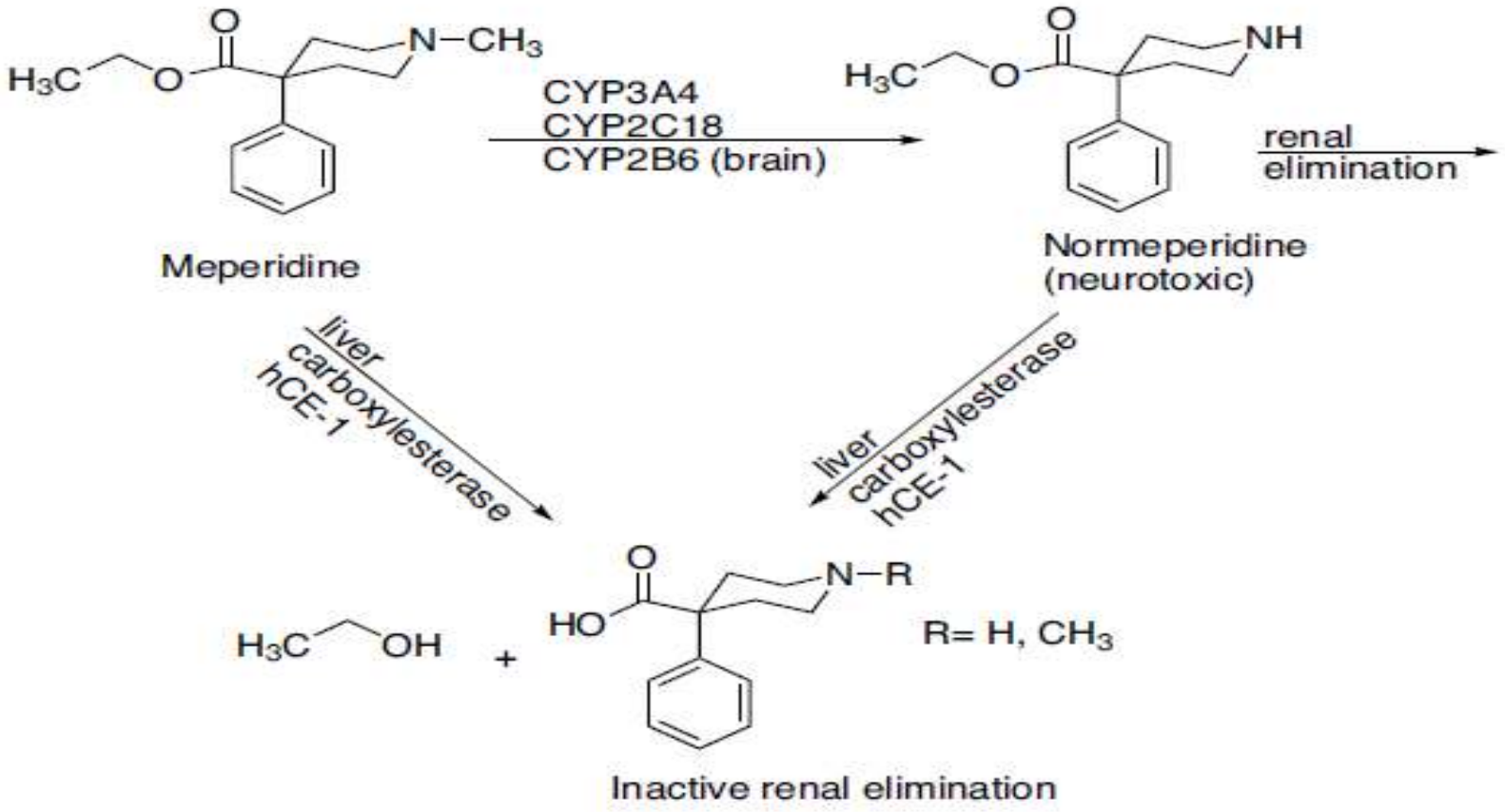
➢ **the introduction of an m-hydroxyl on the phenyl ring,**

➢ **substituting the methyl on the N for a phenylethyl or a *p-aminophenylethyl.***

- ***Replacing* the *N-methyl with an N-allyl or N-cyclopropylmethyl group* does not generate an antagonist.**

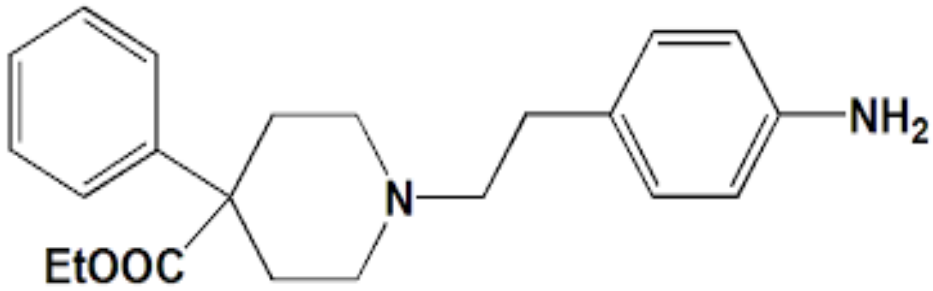
- **Pharmacokinetics:**
- **Meperidine quickly penetrates the blood-brain barrier and thus has a quick onset of activity and a high abuse potential.**
- **The duration of action is less than 3hrs.**
- **3- to 4-hrs half-life.**
- **Meperidine is metabolized to normeperidine by the liver enzymes (Hepatic CYP3A4 and CYP2C18 and in the brain by CYP2B6).**
- **Meperidine and normeperidine are also metabolized by liver carboxylesterases.**

- **Normeperidine shows CNS excitation resulting in tremors, twitches, "shaky feelings," and multifocal myoclonus potentially followed by grand mal seizures.**



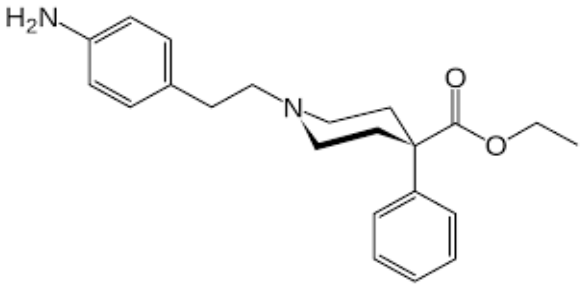
- **In addition to the CNS toxicity of normeperidine, meperidine has also been found to be a weak serotonin reuptake inhibitor and has been involved in serotonin toxicity reactions when used with monoamine oxidase inhibitors or serotonin reuptake inhibitors.**
- **Meperidine is contraindicated with MAO inhibitors or serotonin reuptake inhibitors.**

- **ANILERIDINE**
- **It is a synthetic analgesic drug.**
- **It is a piperidine derivative.**



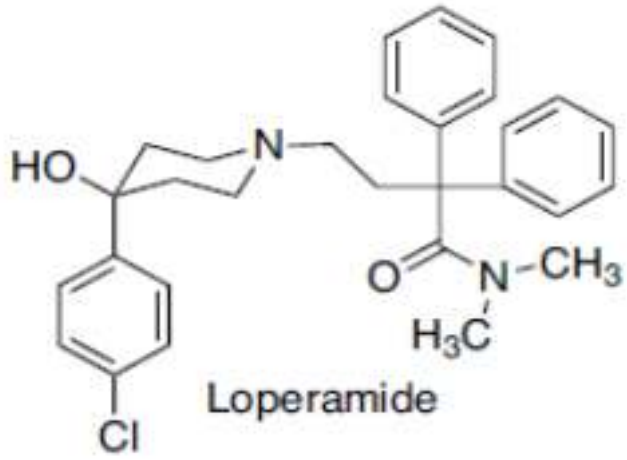
Anileridine

- **It differs from pethidine in that the N-methyl group of meperidine is replaced by an N-aminophenethyl group.**
- **This structural modification increases its analgesic activity.**



- **DIPHENOXYLATE**
- Diphenoxylate is a weak opioid agonist and is available combined with atropine for use as an antidiarrheal agent.
- At low doses, the opioid effect is minimal, and the atropine is added to dissuade/restrict abuse.
- Both codeine and loperamide are superior to diphenoxylate for treating chronic diarrhea.
- The manufacturer has strict dosing guidelines for pediatric use because opioid intoxication and deaths from diphenoxylate have been reported.

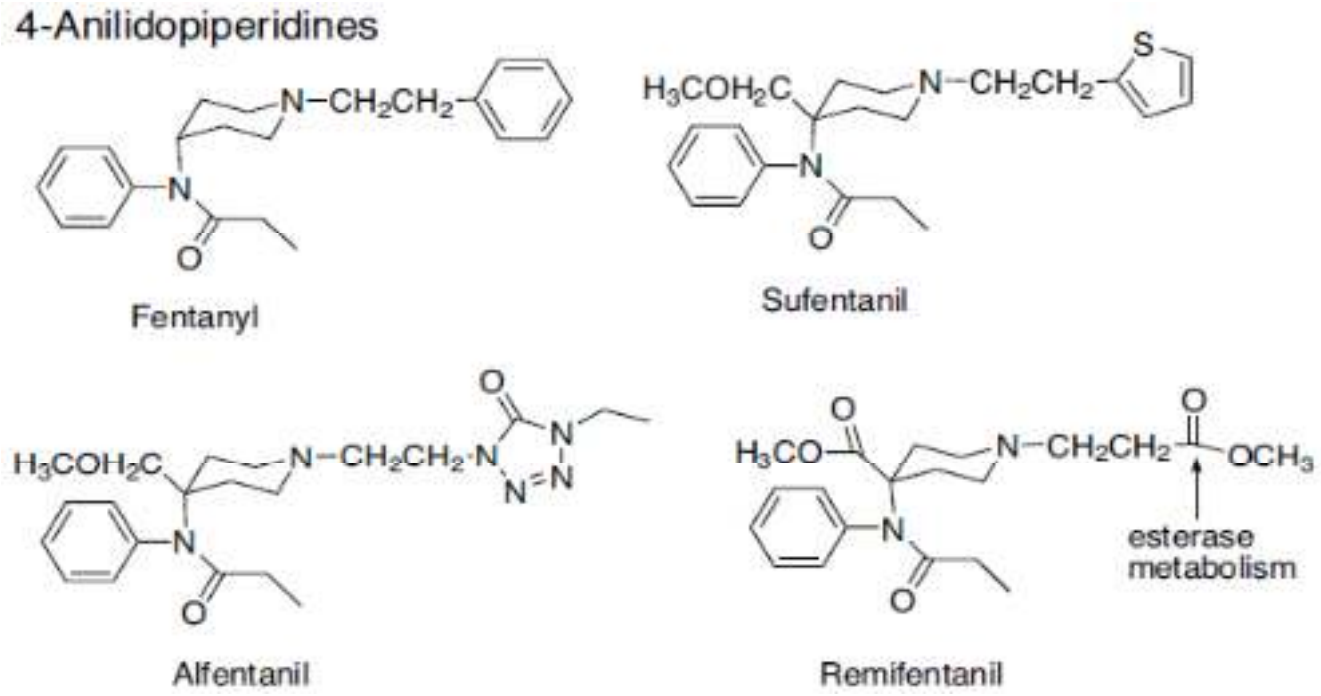
- **LOPERAMIDE**
- It is a 4-phenylypiperidine with a methadone-like structure attached to the piperidine nitrogen.
- It acts as an antidiarrheal by directly binding to the opiate receptors in the gut wall.
- It inhibits acetylcholine and prostaglandin release, decreasing peristalsis and fluid secretion.



Loperamide

- It is sufficiently lipophilic to cross the BBB, yet it displays no CNS-opioid effects.
- The reason for this is that it is actively pumped out of the brain via the P-glycoprotein pump (MDR1).
- Loperamide is available as 2-mg capsules for treatment of acute and chronic diarrhea.
- Recommended dosage is 4 mg initially, with 2 mg after each loose stool for a maximum of 16 mg/d.

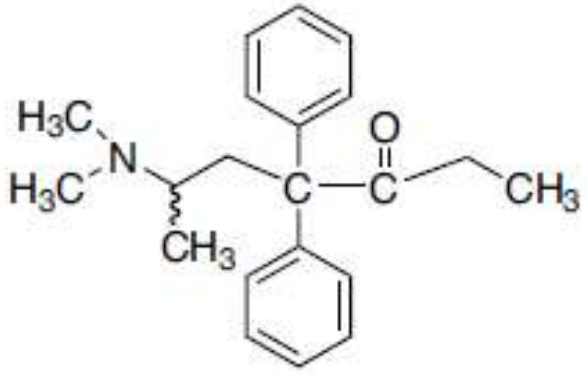
- **FENTANYL**
- When the 4-phenyl substituent of meperidine was replaced with a 4-aniline with a nitrogen connection, the potency increased.
- This led to the development of the 4-anilidopiperidine series of compounds.



- It is almost 500 times more potent than meperidine.
- The high lipophilicity of fentanyl gave it a quick onset, and the quick metabolism led to a short duration of action.
- The combination of potency, quick onset, and quick recovery led to the use of fentanyl as an adjunct anesthetic.
- In addition to the injectable formulation, fentanyl is available in a unique transdermal system.

- The SAR studies of the 4-phenylpiperidine analgesics found that the propionamide is the optimal chain length.
- Adding polar groups to the 4-piperidine carbon (CH2OCH3 in sufentanil and alfentanil, COOCH3 in remifentanil) increases potency.
- The piperidine nitrogen of fentanyl contains a phenethyl substituent that appears to be the correct chain length for optimal potency.

- **METHADONE: (Diphenylheptane derivative)**
- **Methadone is a synthetic opioid approved for analgesic therapy and for the maintenance and treatment of opioid addiction.**
- **It is marketed as a racemate, although the opioid activity resides in the R-enantiomer (7–50 times more potent than the S-enantiomer).**

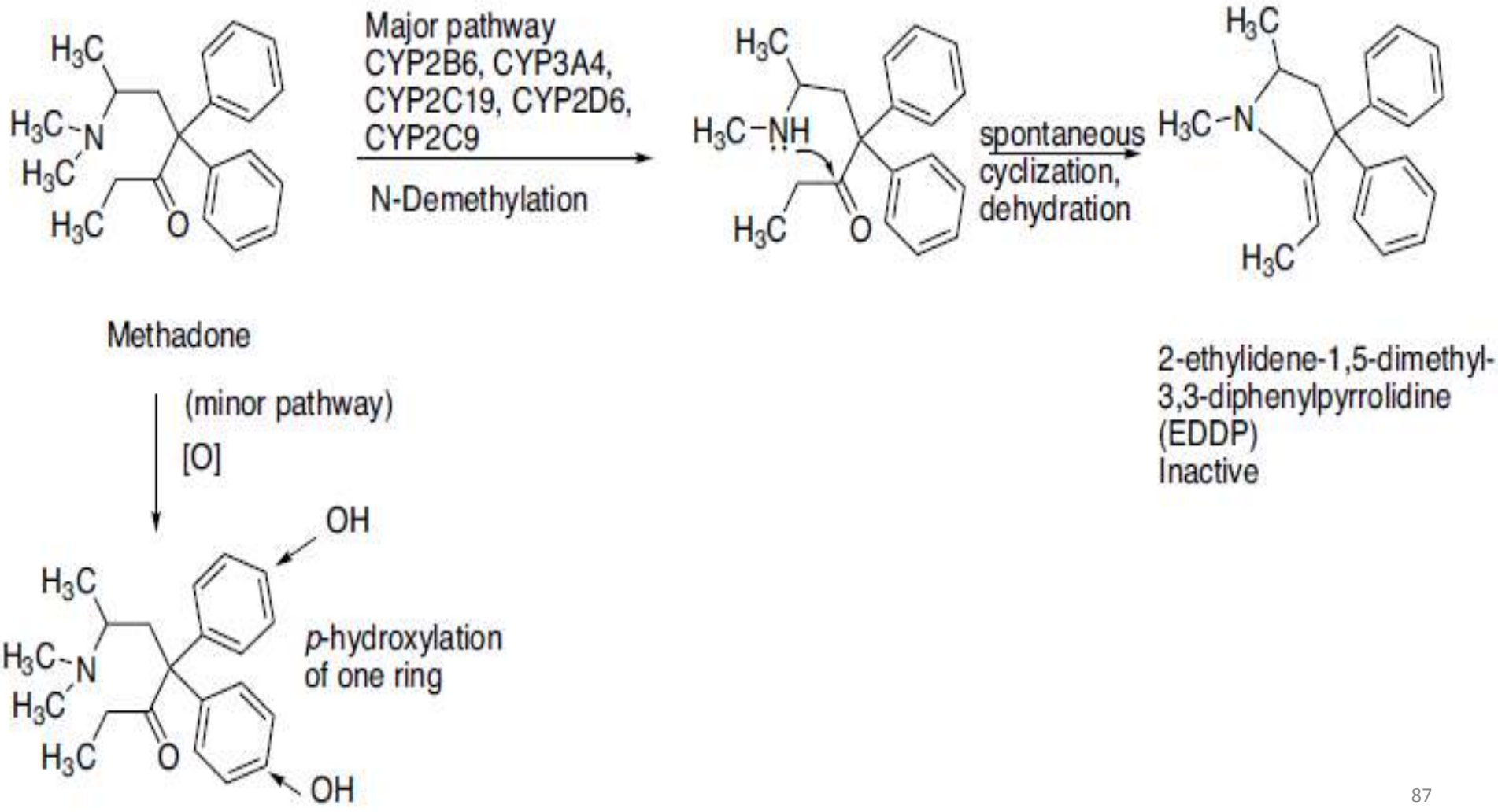


Methadone

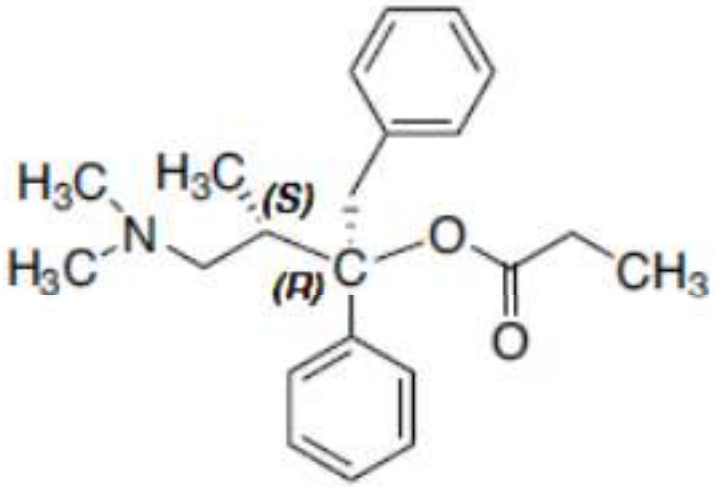
- **Methadone is a μ -receptor agonist with complex and highly variable pharmacokinetic parameters.**
- **Bioavailability following oral administration ranges from 36% to 100%.**
- **Volume of distribution ranges between 1.0 to 8.0 L/kg.**
- **Highly bound to plasma α 1-acid glycoprotein (85%–90%).**
- ***t1/2 elimination ranges between* 8 and 59 hours.**
- **Adverse effects of methadone include all of the standard opioid effects.**

- **The metabolism and elimination of methadone also lead to much interpatient variability and can be effected by genetic CYP levels, drug–drug interactions, and the pH of the urine.**
- **The major metabolic pathway of methadone metabolism is via *N-demethylation* to an unstable product that spontaneously cyclizes to form the inactive 2-ethylidene-1,5-dimethyl-3,3- diphenylpyrrolidine (EDDP).**

Metabolism of Methadone



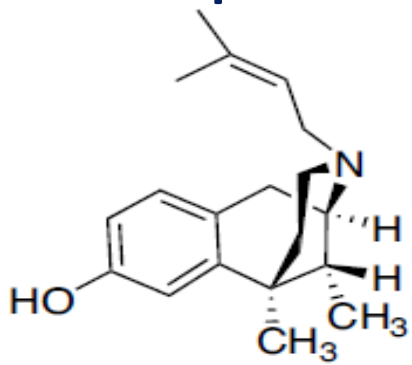
- **PROPOXYPHENE**
- Most of the structural changes to the methadone skeleton resulted in compounds with decreased opioid potencies.
- Propoxyphene is a derivative of methadone marketed as the enantiomerically pure (2S, 3R)- 4-(Dimethylamino)-3-methyl-1,2,-diphenyl-2-butanol propionate (ester).



Propoxyphene

- It is only about 1/10th as potent as morphine as an analgesic yet retains all the same opioid adverse effects.
- The metabolism of propoxyphene also contributes to the potential dangers of the drug.
- Propoxyphene is metabolized via *N*-demethylation to form norpropoxyphene.
- Norpropoxyphene has been shown to build up in cardiac tissues and result in naloxone-insensitive cardiotoxicity.

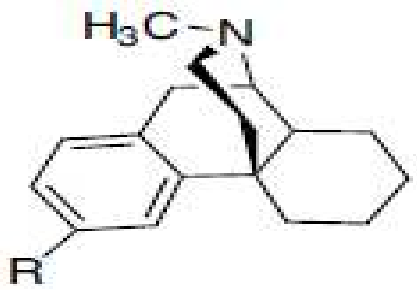
- **PENTAZOCINE:**
- **The benzomorphans are prepared synthetically and thus result in several stereoisomers.**
- ***Pentazocine* is a mixed agonist/antagonist displaying differing intrinsic activity at the opioid receptor subtypes.**
- **At the μ–receptor, pentazocine is a partial agonist and a weak antagonist.**



Pentazocine

- **A 50-mg dose of pentazocine has about the same analgesic potency as 60 mg of codeine and about 1/50th the antagonistic activity of nalorphine.**
- **Pentazocine is also an agonist at the κ-receptor, and this may be responsible for the higher dysphoria with pentazocine versus morphine.**
- **Some evidence also exists that women respond better to κ- agonists than men.**

- **LEVORPHANOL:**
- **Levorphanol is the levorotatory form of methorphan.**
- **It is 7.5 times more potent than morphine orally.**
- **The loss of the 4,5-epoxide and the 7,8-double bond allows levorphanol greater flexibility.**
- **Flexibility leads to the increased binding affinity at all opioid receptor subtypes compared with morphine.**

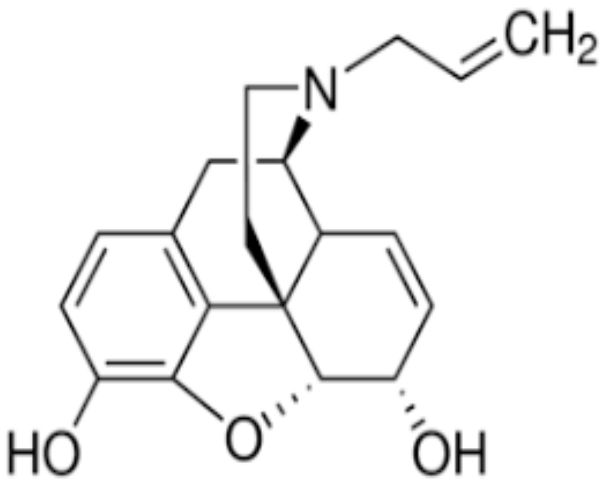


Morphinan
R= OH (-) Levorphanol oral = 2 mg
R= OCH_3 (+) Dextromethorphan

- **The plasma half-life of levorphanol is about 6 to 8 hours.**
- **But displays great interperson variability and may increase upon repeated dosing.**
- **The excretion of levorphanol is dependent on the kidneys, so caution must be used in renally compromised patients.**
- **The analgesic effect of levorphanol may not match the long plasma half-life, and patients must be closely monitored for drug accumulation and respiratory depression.**

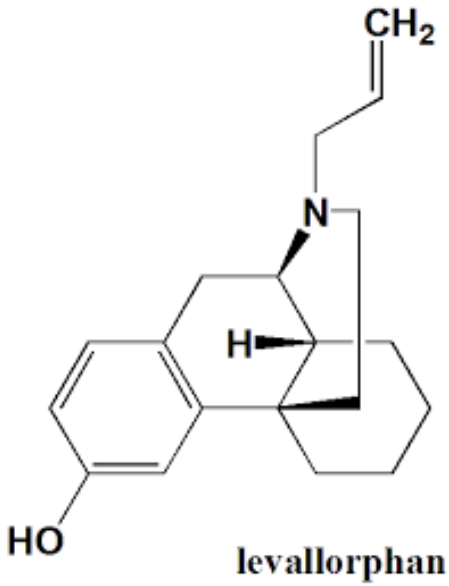
- **Levorphanol has strong agonist activity at the μ-,κ-,and δ-opioid receptors and has also been shown to be a noncompetitive *N-methyl-* D-aspartate (NMDA)-receptor antagonist.**
- **Levorphanol is available as a 2-mg oral tablet and a 2-mg/mL solution for injection.**

- **Narcotic/Opioid Antagonists**
- **Nalorphine**
- It has less of an analgesic effect than morphine;
- It does not have much value as an independent analgesic.
- It is used as an antagonist to narcotic analgesics.



- It eliminates suppression of the respiratory center, bradycardia, and vomiting caused by opiate receptor agonists.
- Nalorphine was the first compound used for narcotic (heroin in particular) overdose treatment; however, it exhibits a number of side effects such as visual hallucinations, and therefore its use is prohibited in some countries.

- **LEVALLORPHAN**



levallorphan

- It is an opioid modulator of the morphinan family.
- It is used as an opioid analgesic and opioid antagonist/antidote.
- Its properties are similar to those of naloxone.
- It also possesses some agonist property.
- It reverses severe opioid-induced respiratory depression.
- But it may exacerbate respiratory depression such as that induced by alcohol or other non-opioid CNS depressants.

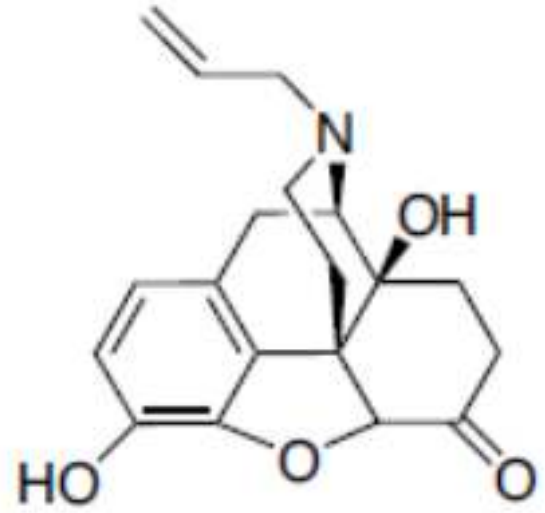
- **NALOXONE**

- It is a pure antagonist at all opioid receptor subtypes.

- Structurally, it resembles oxymorphone

except that the methyl group on the nitrogen

is replaced by an allyl group.



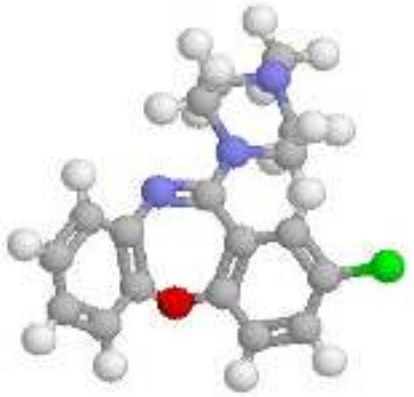
Naloxone

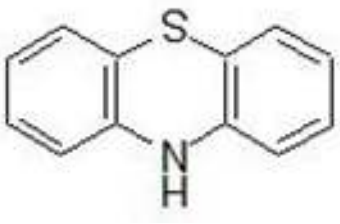
- This minor structural change retains high binding affinity to the receptor, but no intrinsic activity.

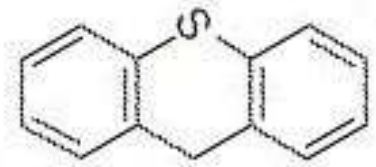
- It is used to reverse the respiratory depressant effects of opioid overdoses.

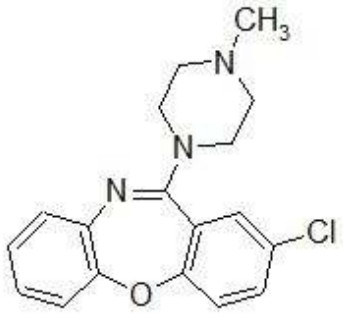
- Naloxone is administered intravenously with an onset of action within 2 minutes.
- Because it is competing with the opioid for the receptor sites, the dose and frequency of administration will depend on the amount and type of narcotic being antagonized.
- Overdoses of long-acting opioids (methadone) may require multiple IV doses of naloxone or continuous infusions.
- Neonates born to opioid-exposed mothers may be given IV naloxone at birth to reverse the effects of opiates.
- Major metabolite found in the urine is naloxone-3-glucuronide.

ANTIPSYCHOTICS (NON-PHENOTHIAZINES)



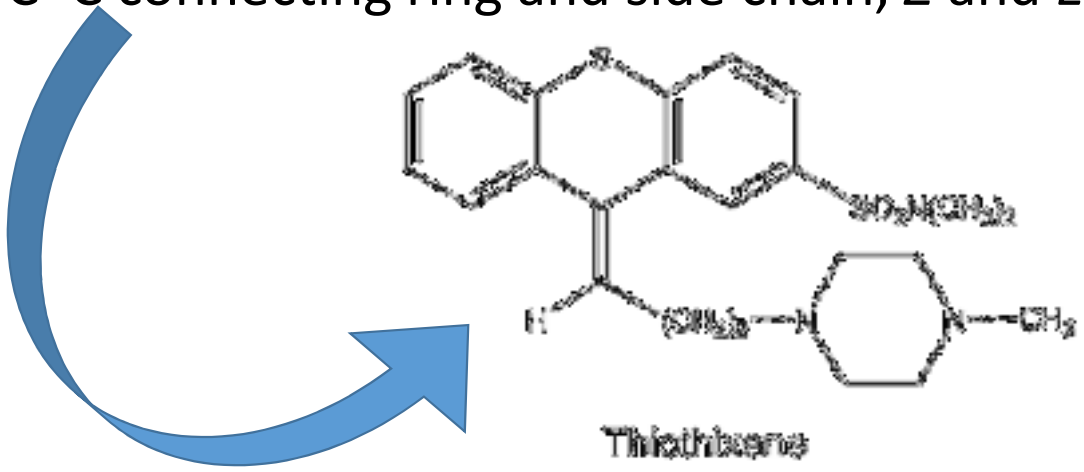


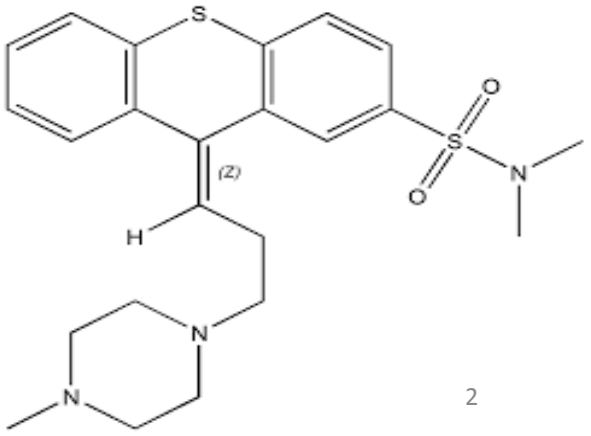




Ring Analogues of Phenothiazines

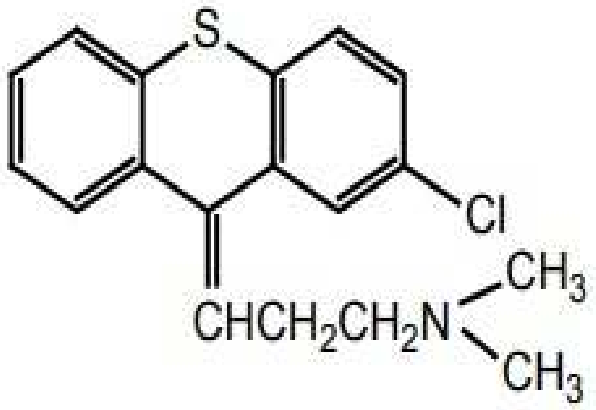
- ***THIOXANTHINE Derivatives***
- ***Thiothixene:***
- (*Z*-*N*-dimethyl-9-[3-(4-methyl-1-piperazinyl) propylidene]thioxanthene-2-sulphonamide
- The thioxanthene differs from the phenothiazine by replacement of the N-H moiety with a carbon atom doubly bonded to the propylidene side chain.
- With the C=C connecting ring and side chain, *Z* and *E*-isomers are produced.





- In accordance with the concept that the presently useful antipsychotics can be superimposed on DA, the *Z*-isomers are the more active antipsychotic isomers.
- The compounds of the group are very similar in pharmacological properties to the corresponding phenothiazines.
- Thus, thiothixene, displays properties similar to those of the piperazine subgroup of the phenothiazines.

- **Chlorprothixene:** **http://www.pharmacy180.com/article/thioxanthines-2131/**
- Chlorprothixene is a typical antipsychotic drug of the thioxanthene (tricyclic) class.
- Chlorprothixene exerts strong blocking effects by blocking the 5-HT2 D1, D2, D3, histamine H1, muscarinic and α1 adrenergic receptors.



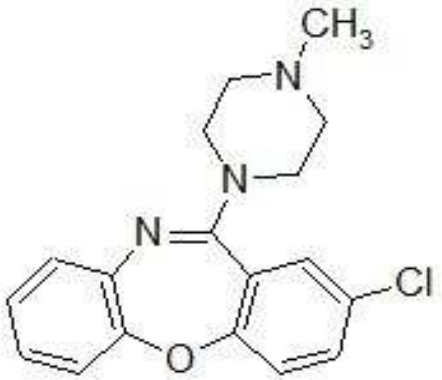
3-(2-Chloro-thioxanthen-9-ylidin)-N,N'-dimethyl-1-propenamine

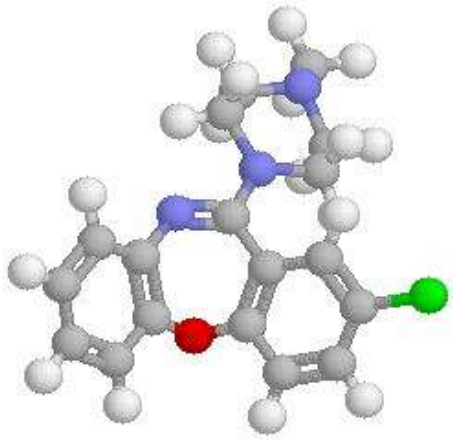
sychotic potency (1/2 to 2/3 of chlorpromazine).

ughly demonstrated an antidepressant or analgesic effect but it has demonstrated antiemetic effects.

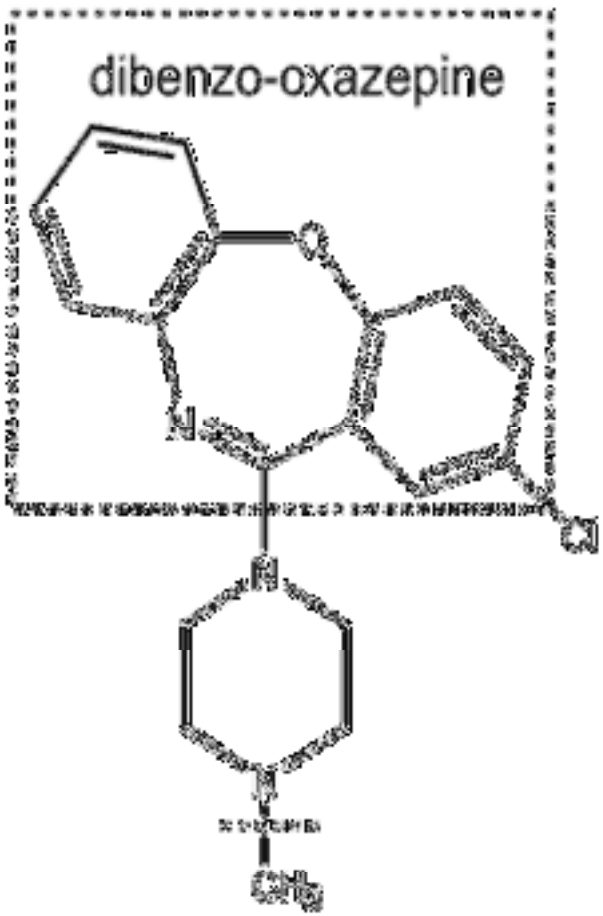
- It is used in the treatment of nervous, mental, and emotional conditions.
- Chlorprothixene has a similar side effect profile to thiothixene and chlorpromazine, though allergic side effects and liver damage are less frequent.

- ***Loxapine:***
- 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine succinate.
- A dibenzoxazepine derivative.
- The structural relationship to the phenothiazine antipsychotics is apparent.
- Examples in this group are clothiapine, metiapine, zotepine, and others.
- They have electron-withdrawing groups at position 2, relatively close to the side-chain nitrogen atoms.



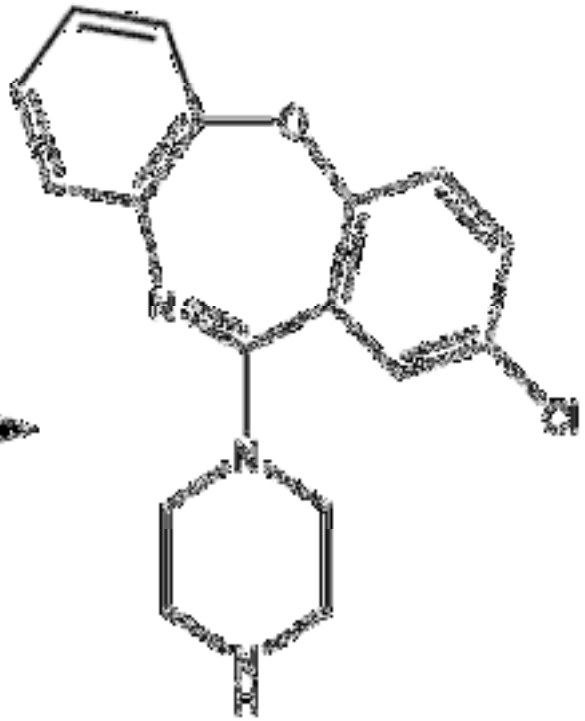


- It blocks D2-receptors and has side effects similar to those reported for the phenothiazines.
- Its metabolism involves aromatic hydroxylation to give several phenolic metabolites that have higher affinity for D2 receptors than the parent.
- It is also *N*-demethylated to yield amoxapine (an antidepressant drug), which inhibits norepinephrine (NE) neurotransporter to block neuronal NE reuptake.



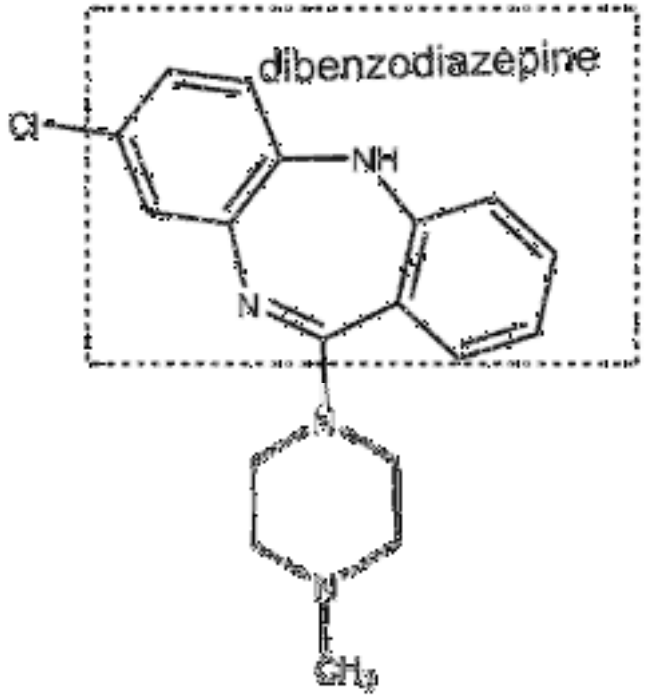
Loxapine
an antipsychotic

N-demethylation in vivo



Amoxapine
an antidepressant

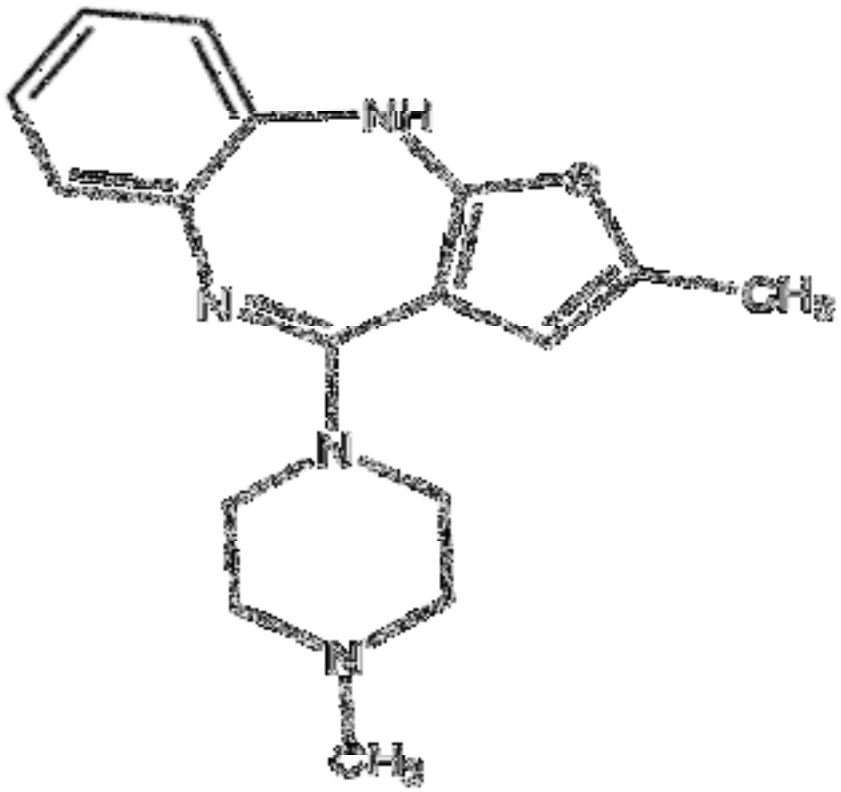
- **Clozapine:**
- It is a dibenzodiazepine derivative.
- It is not a potent antipsychotic on a milligram basis (note the orientation of the *N*-methyl piperazino group relative to the chlorine atom).
- In addition to their moderate potencies at DA receptors (mainly D4), clozapine interact with varying affinities at several other classes of receptors (α1 and α2 adrenergic, 5-HT1A, 5-HT2A, 5-HT2C, muscarinic cholinergic, histamine H1, and others).



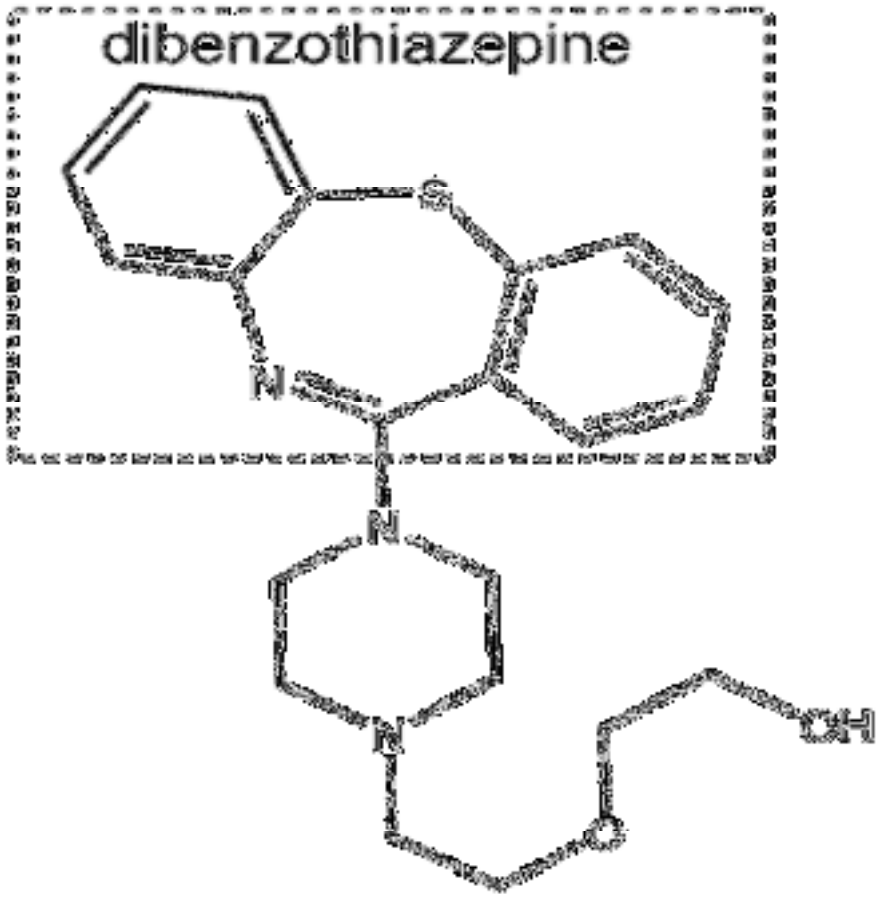
Clozapine

- It is effective against both positive and negative symptoms of schizophrenia and has a low tendency to produce EPS.
- Clozapine has proved effective even in chronically ill patients who respond poorly to standard neuroleptics.
- However, there are legal restrictions on its use because of a relatively high frequency of agranulocytosis.
- As a rule, two other antipsychotics are tried before recourse to therapy with clozapine.

- Clozapine is metabolized into demethylated, hydroxylated, and *N*-oxide derivatives that are excreted in urine and feces.
- Elimination half-life averages about 12 hours.
- Other clozapine- like atypical antipsychotics may lack a 2-Cl substituent on the aromatic ring (e.g., olanzapine and quetiapine).

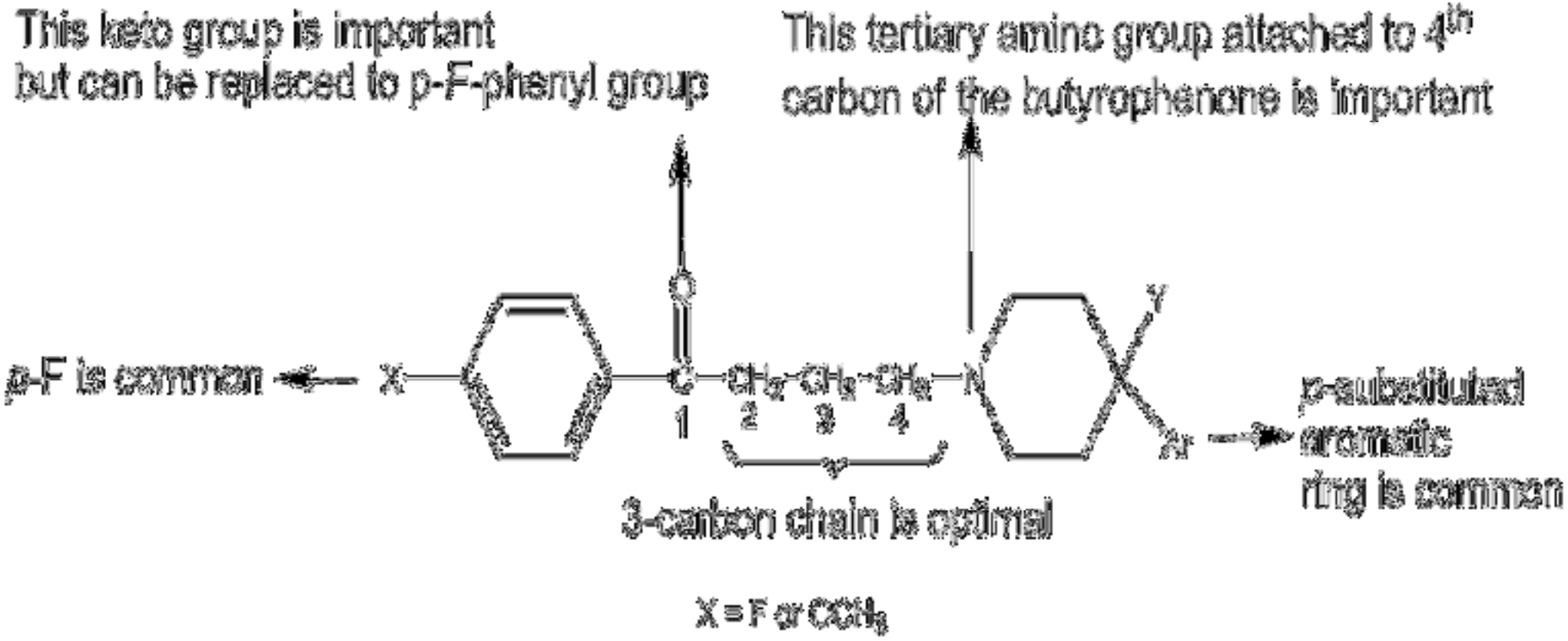


Olanzapine

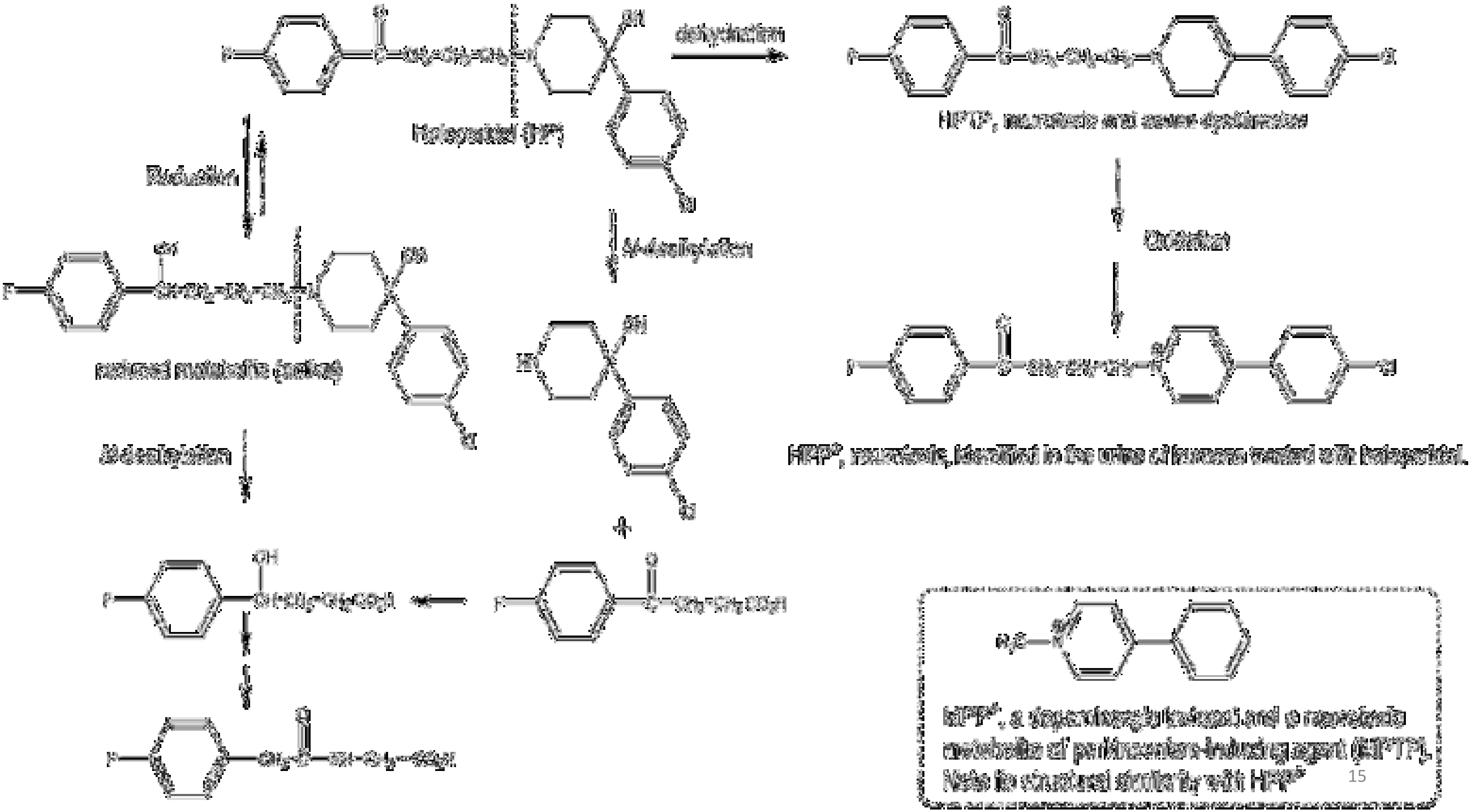


Quetiapine

- **FLURO BUTYROPHENONES:**
- They possess high antipsychotic potency.

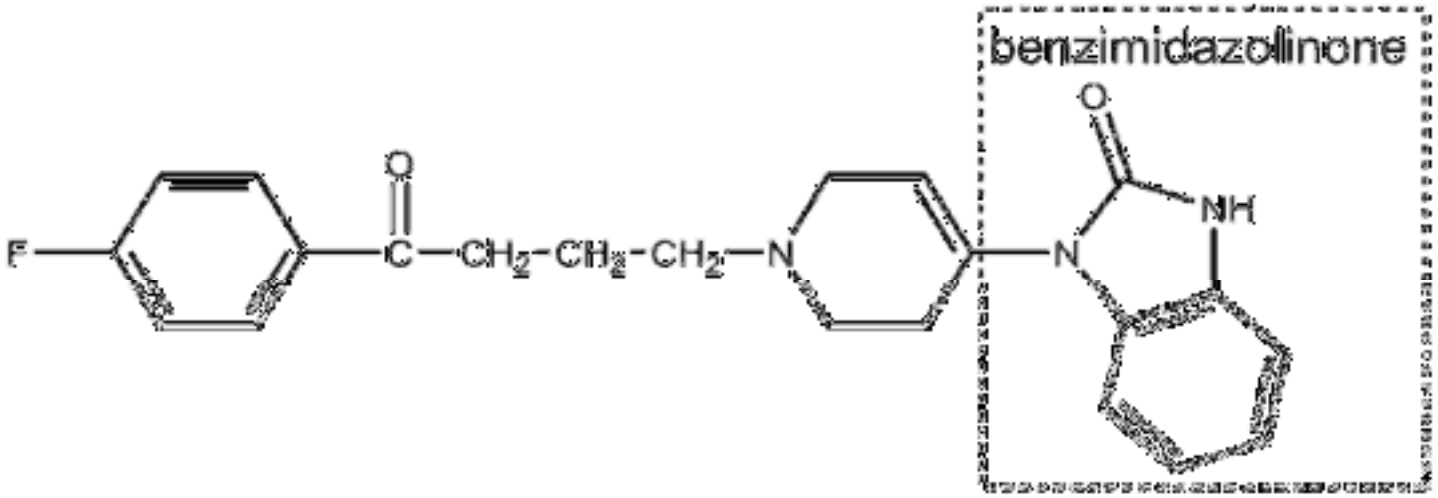


- **Haloperidol:**
- 4[4-(*p*-chlorophenyl)-4-hydroxypiperidone]-4-*n*-fluorobutyrophenone.
- It is a representative of aromatic butylpiperidine derivatives.
- It is a potent antipsychotic useful in schizophrenia and in psychoses associated with brain damage.
- It is frequently chosen as the agent to terminate mania and often used in therapy for **Gilles de la Tourette syndrome**.
- Haloperidol-induced dyskinesias may involve neurotoxicological metabolites similar to dopaminergic toxicant MPP+.


Haloperidol (HP)
dehydration
HPTP, neurotoxic and cause dyskinesias
Reduction
N-dealkylation
reduced metabolite (active)
Oxidation
N-dealkylation
HPP+, neurotoxic, identified in the urine of humans treated with haloperidol.
MPP+, a dopaminergic toxicant and a neurotoxic metabolite of parkinsonism-inducing agent (MPTP). Note its structural similarity with HPP+

- ***Droperidol:***

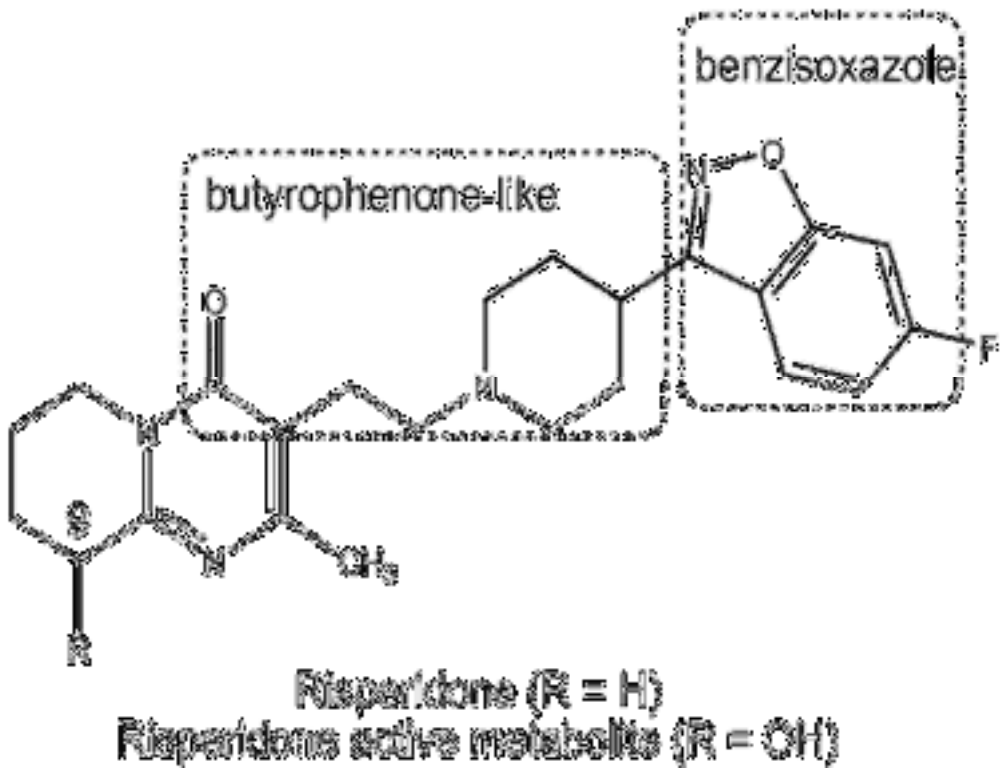
- 1-{1-[3-(*p*-fluorobenzoyl) propyl]-1,2, 3,6-tetrahydro-4-pyridyl}-2-benzimidazolinone.
- It may be used alone as a preanesthetic neuroleptic or as an antiemetic.
- Because of its very shortacting and highly sedating properties, its most frequent use is in combination with the narcotic agent fentanyl pre-anesthetically.



Droperidol

- ***Risperidone:***

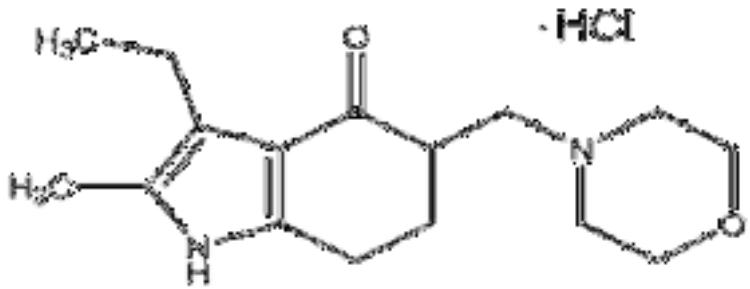
- It is a benzisoxazole derivative with the structural features of a butyrophenone antipsychotic.
- Few side effects (compared with haloperidol) at dosage of 6 mg/d or less and the lower risk of tardive dyskinesia have contributed to its very widespread use.



Risperidone (R = H)
Risperidone active metabolite (R = OH)

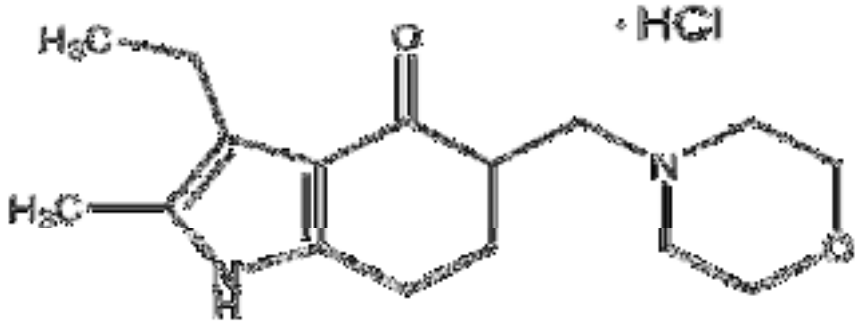
- It is reported to decrease the negative (e.g., withdrawal, apathy) as well as the positive (e.g., delusions, hallucinations) symptoms of schizophrenia.
- This is a consequence of the compound's combination 5-HT2–D2 receptor antagonistic properties.
- It is an important atypical antipsychotic.
- Risperidone is metabolized to an active metabolite, 9-hydroxyrisperidone.
- Because this metabolite and risperidone are nearly equipotent, the clinical efficacy of the drug reflects both compounds.

- **β-AMINOKETONES**
- Several β -aminoketones have been examined as antipsychotics.
- They evolved out of research on the alkaloid lobeline.
- The overall structural features associated with activity can be seen in the structure of **molindone**.
- In addition to the β-aminoketone group, there must be an aryl group positioned as in molindone.



Molindone Hydrochloride

- The proton on the protonated amino group in these compounds H-bonds with the electrons of the carbonyl oxygen atom.
- This would produce a cationic center, two-atom distance, and an aryl group that could be superimposed on the analogous features of protonated DA.
- Molindone(3-ethyl-6,7-dihydro-2-methyl-5-morpholinomethyl)indole-4(5*H*)-one) is about as potent an antipsychotic as trifluoperazine.
- Overall, side effects resemble those of the phenothiazines.



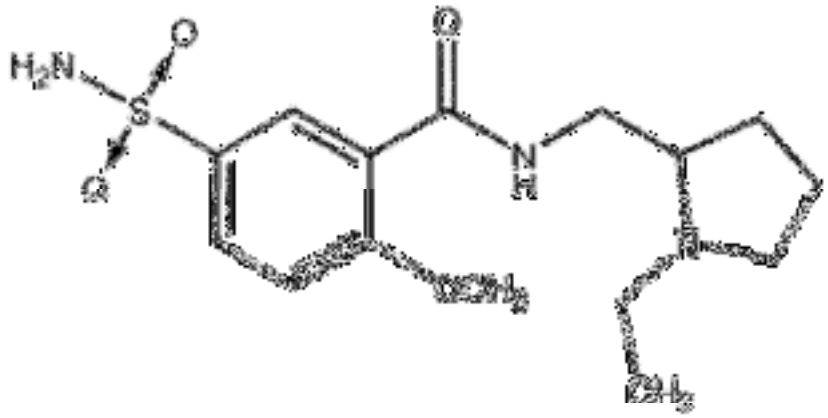
Molindone Hydrochloride

- **BENZAMIDES**

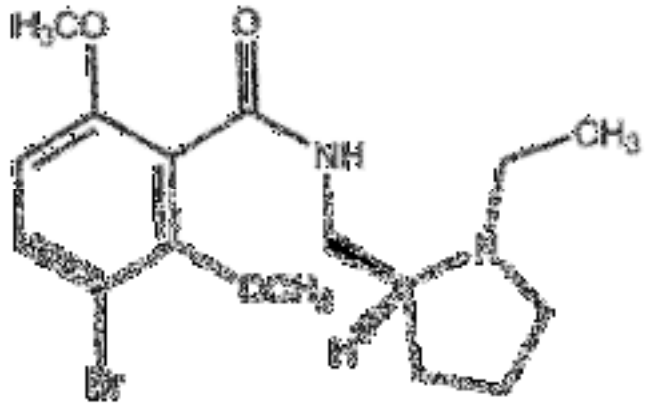
- The benzamides evolved from observations that the gastroprokinetic and antiemetic agent, metoclopramide, has antipsychotic activity related to D2 receptor block.
- These compounds show diminished EPS side effects.
- An H-bond between the amido H and the unshared electrons of the methoxyl group to generate a pseudo ring is considered important for antipsychotic activity in these compounds.
- Presumably, when the protonated amine is superimposed on that of protonated DA, this pseudo ring would superimpose on DA's aromatic ring.
- These features can be seen in sulpiride and remoxipride.

- **Sulpiride:**
- It is an atypical antipsychotic medication of the benzamide class.
- It is a selective dopamine D2 and D3 receptor antagonist.
- It is used mainly in the treatment of psychosis associated with schizophrenia and major depressive disorder, and sometimes used in low dosage to treat anxiety and mild depression.
- Clinical studies show a greater effect on treating the negative symptoms of schizophrenia rather than positive symptoms at low doses, though the effects are more equal at higher doses.
- **Sulpiride is not approved by the FDA, Health Canada, or the EMA; though it is approved in individual European countries.**

- It has a short duration of action as it is given twice daily, and a wide therapeutic window as patients have survived single doses as high as 16g.
- Patients should be counselled regarding increased motor agitation, extrapyramidal reactions, and neuroleptic malignant syndrome.

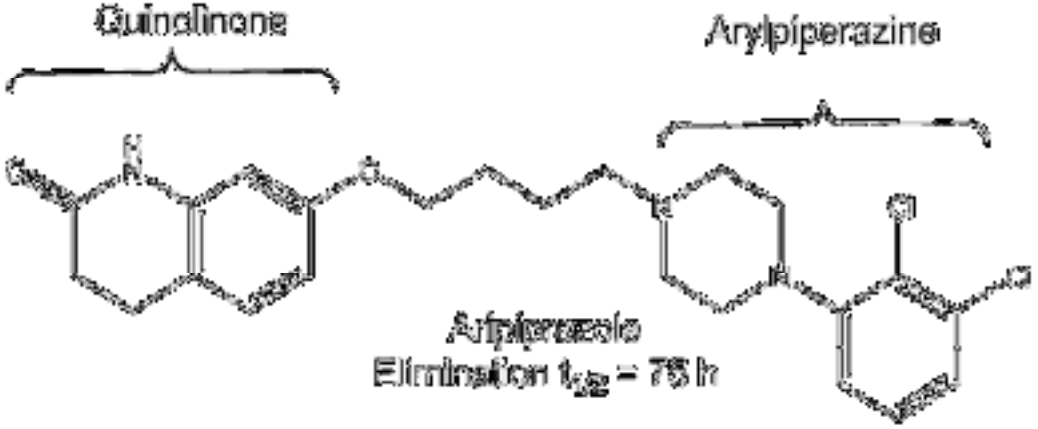


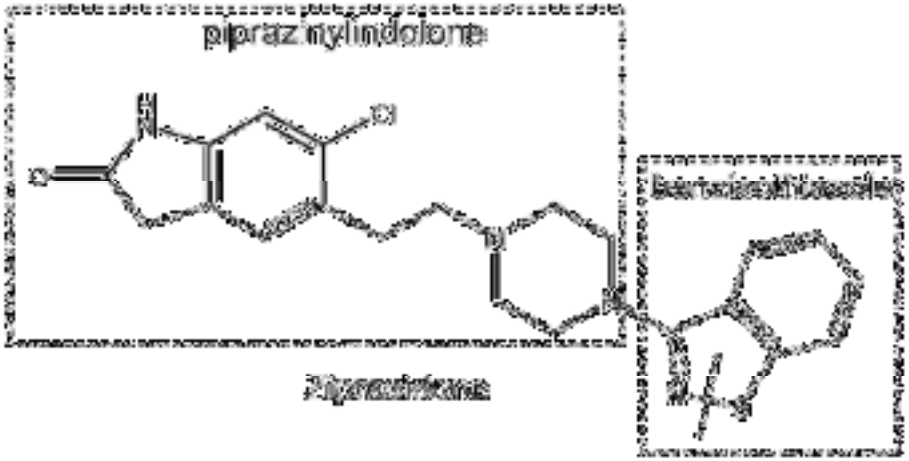
Sulpiride

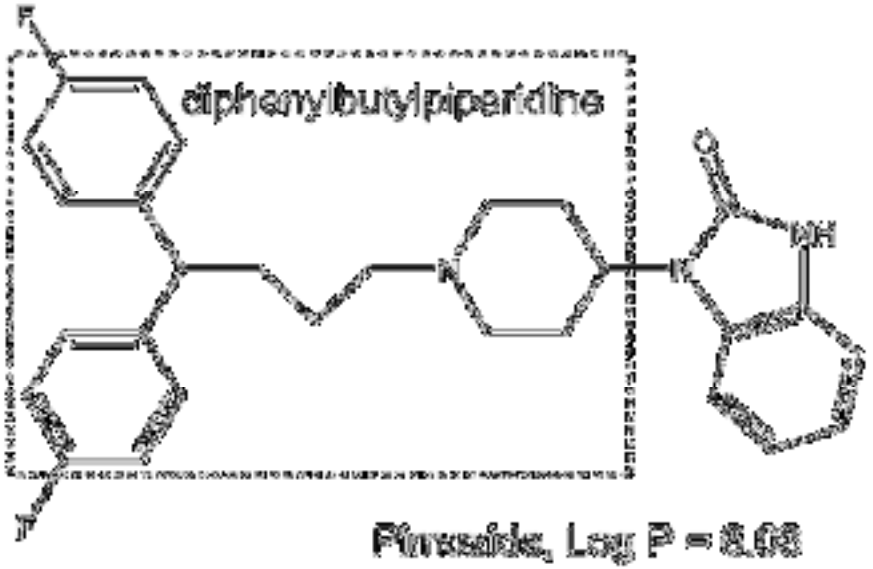


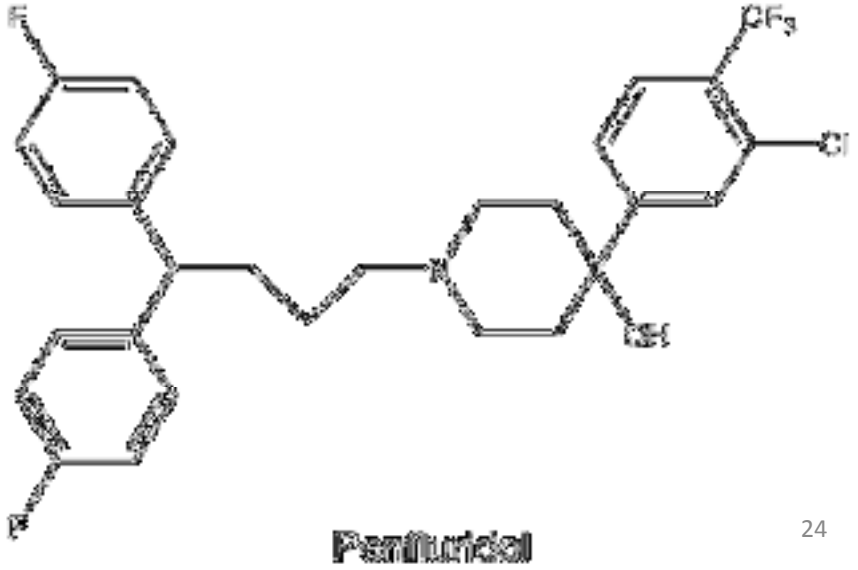
Remoxipride

- **Miscellaneous Antipsychotics**





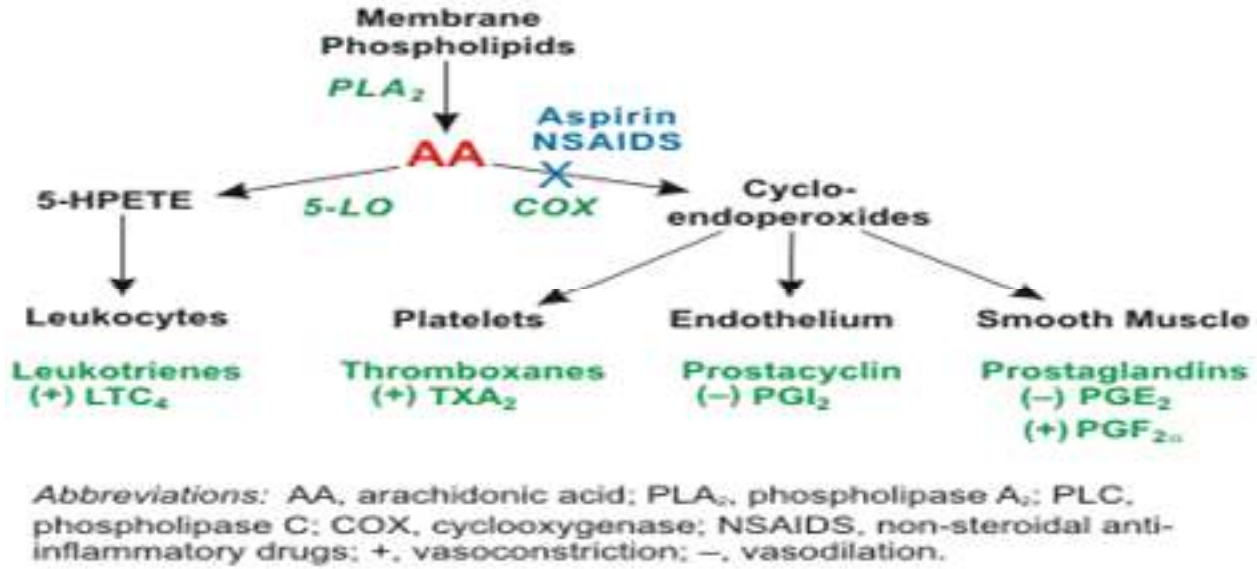




NSAIDs

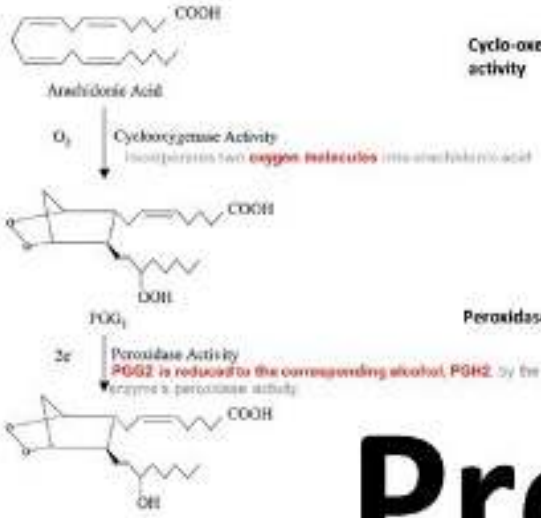
Inflammation and NSAIDs

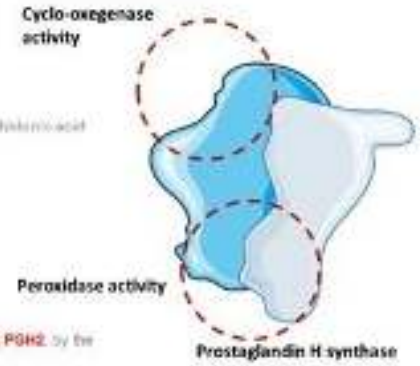
- Eicosanoids are a diverse group of inflammatory mediators including -
  - ➢ Prostaglandins (PG).
  - ➢ Thromboxanes (TX).
  - ➢ Leukotrienes.

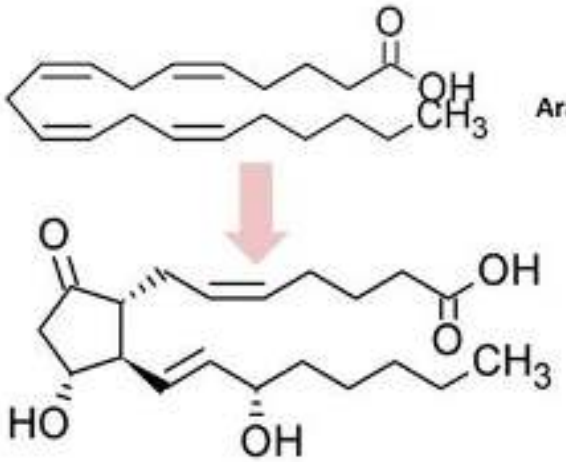


Abbreviations: AA, arachidonic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; –, vasodilation.

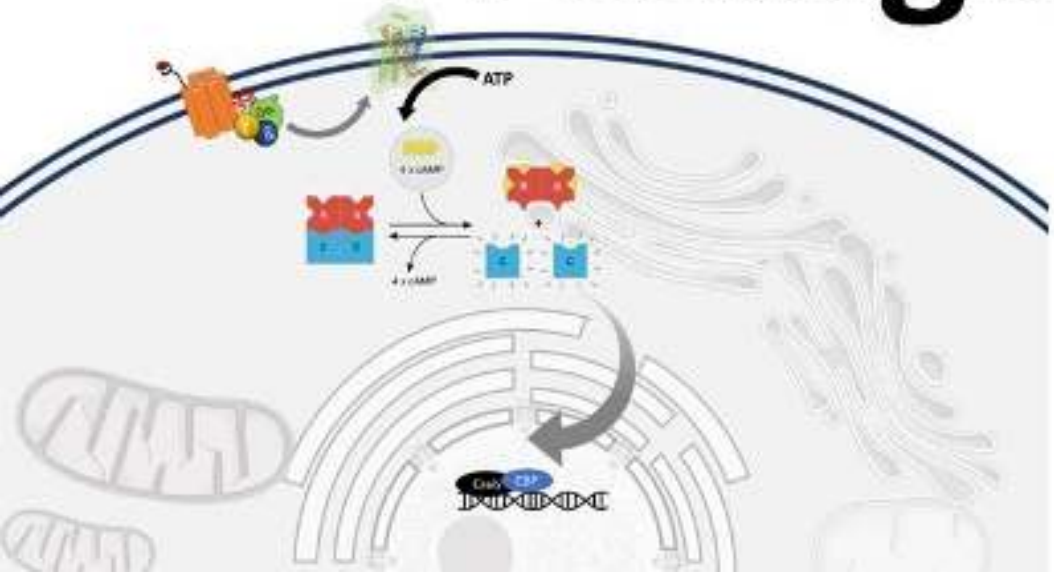
- They are derived from the fatty phospholipid bilayer that forms the cell membrane and act locally at the site of production for a short duration.

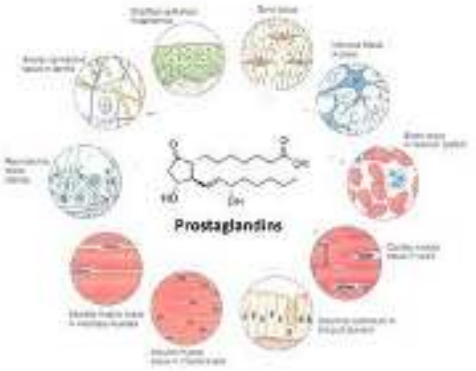




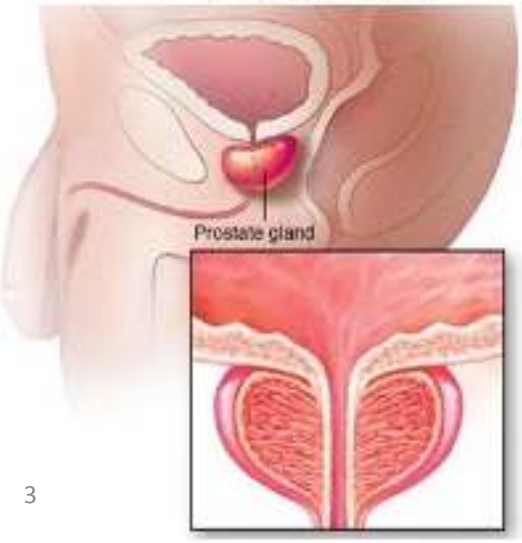


Prostaglandıns



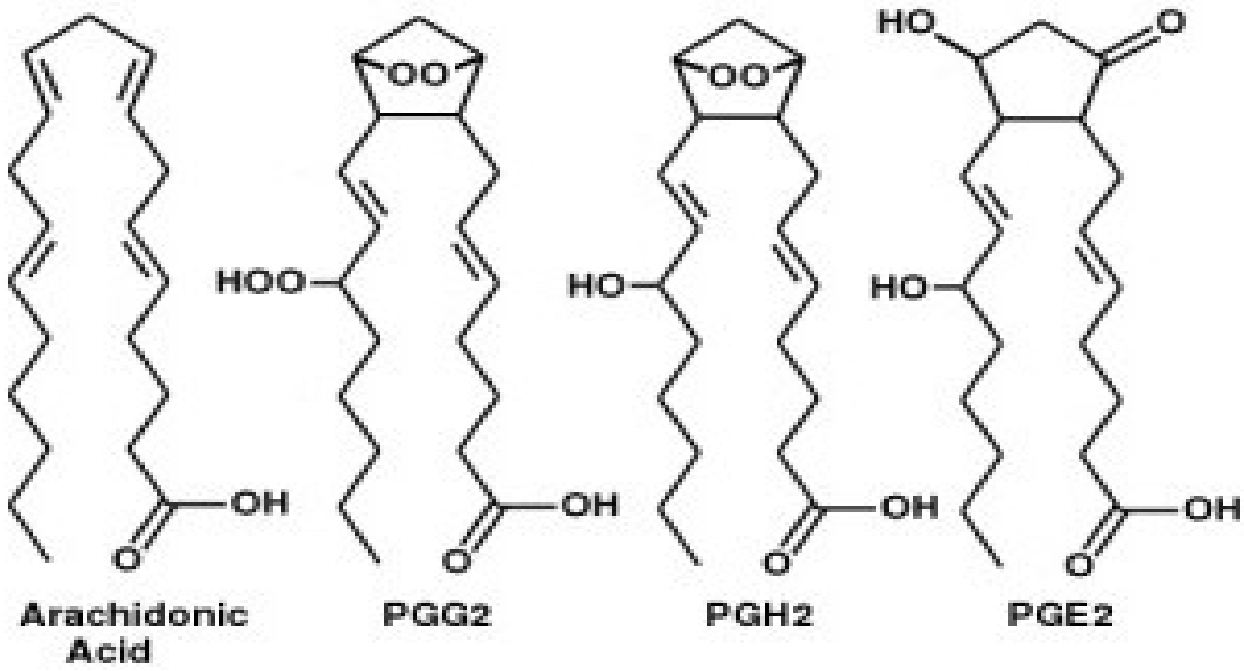


Prostrate Gland

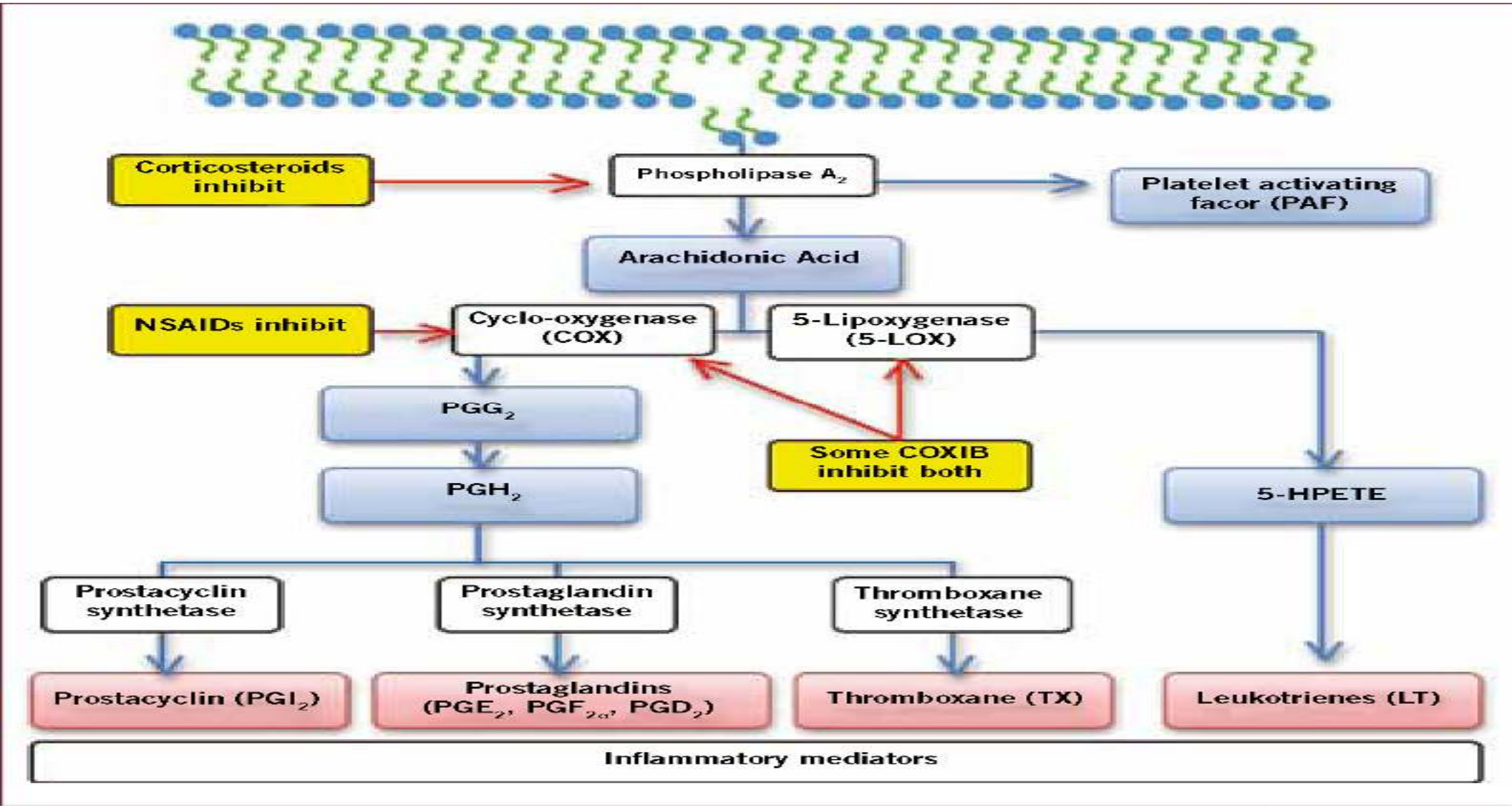


- A cascade of eicosanoids are produced playing roles in health and disease through complex interplay between host factors and intracellular responses.
- The most important enzymes in this cascade process are cyclo-oxygenase (COX) and lipoxygenase (LOX).
- The initial step in the cascade to PG and thromboxane production is the oxidation and cyclization of arachidonic acid to PGG2 through the action of COX.

- **PGG2 is relatively unstable and is rapidly transformed into different PGs depending on the presence or lack of certain enzymes.**
- **The cascade results in multiple eicosanoids production and the presence of COX is essential for the production of other products.**



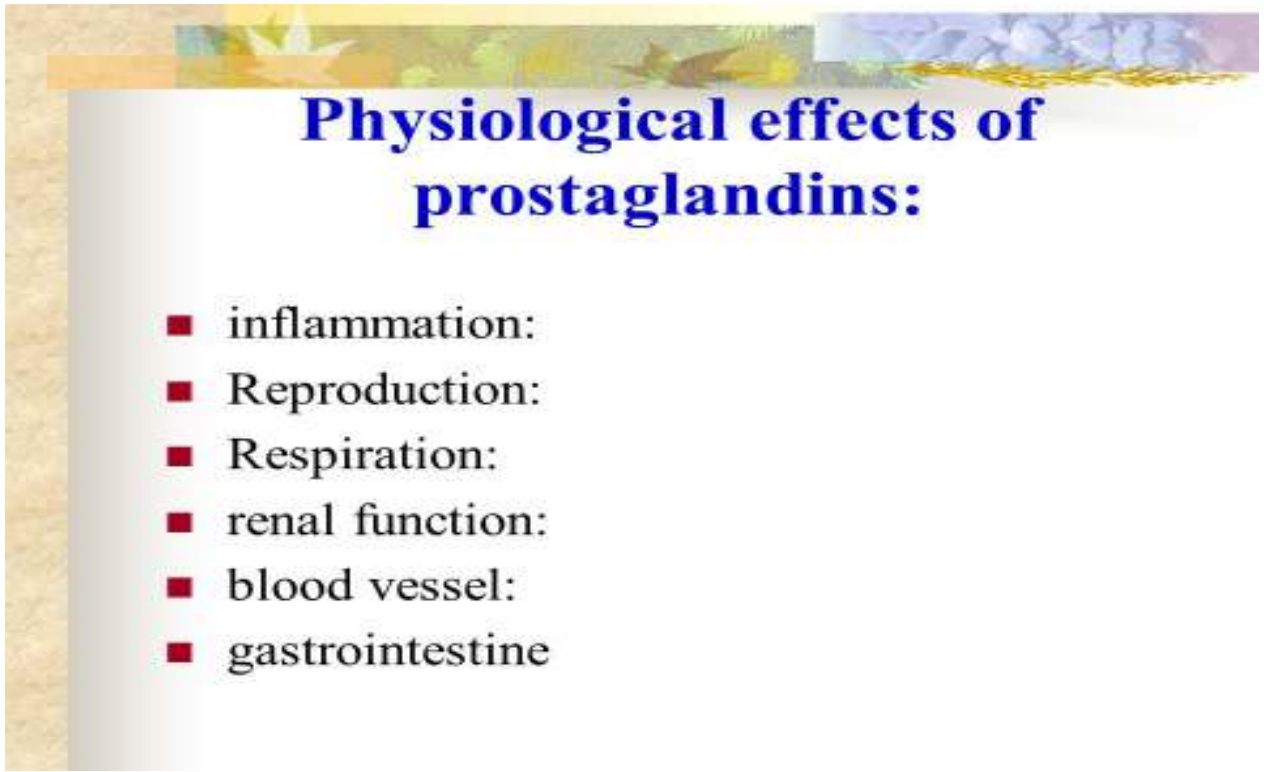
- **Targeting this step would be an effective method to prevent the production of the unwanted PGs and TXs.**
- **This is exactly what the NSAIDs do.**
- **LOX also acts on arachidonic acid but results in the production of leukotrienes through a metabolic pathway separate to the COX enzymes.**
- **Some of the newer NSAIDs have activity on both LOX and COX.**



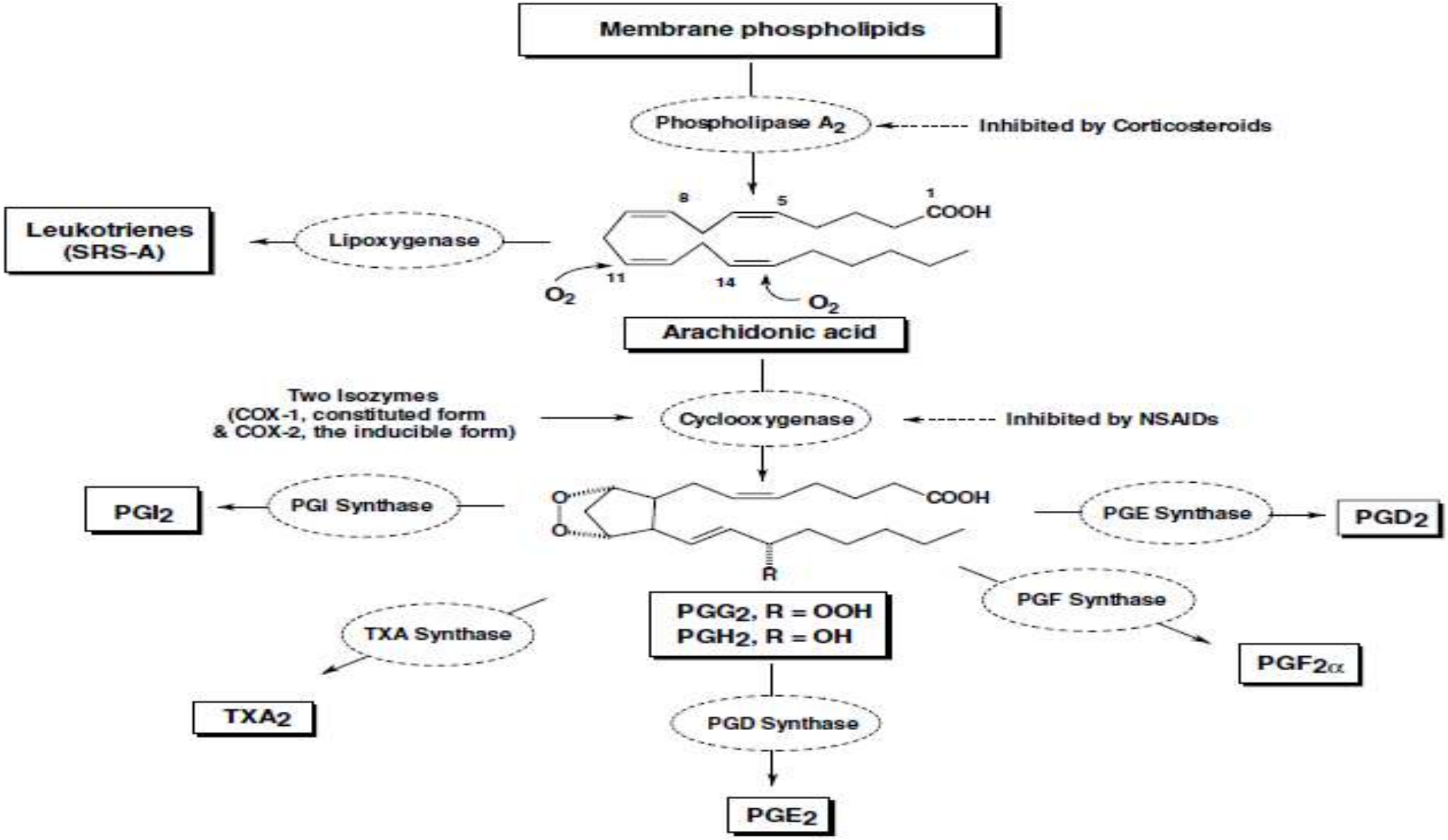
- **5-HPETE = Arachidonic acid 5-hydroperoxide (6,8,11,14-Eicosatetraenoic acid 5-hydroperoxide).**

- **PGs are short-lived, lipidlike molecules that play a vital role in modulating many important physiological and pathophysiological functions including -**

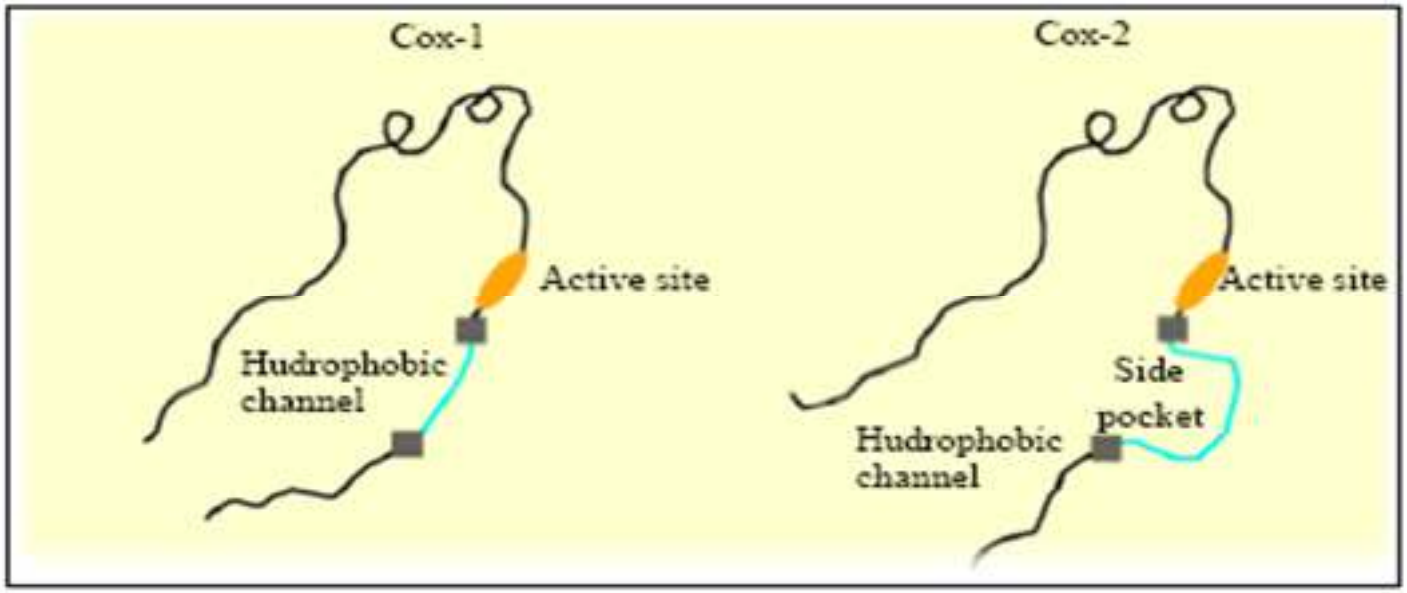
- **Pain**
- **Inflammation**
- **Gastric acid secretion**
- **Wound healing**
- **Renal function**



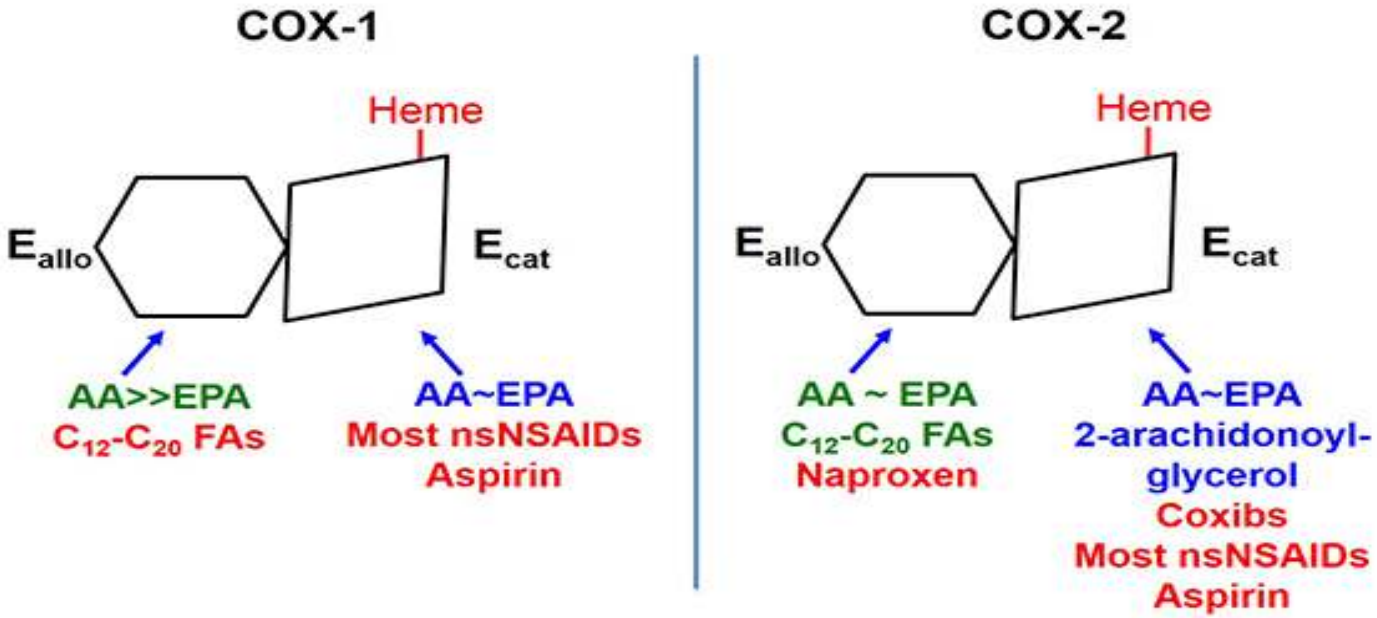
- They are biosynthesized via a tissue-specific cyclooxygenase pathway (COX-1 or COX-2) either on an as-needed basis (mostly via the COX-1 isozyme) or via the induced and overexpressed COX-2 isozyme because of an injury, inflammation, or infection.
- Arachidonic acid (AA) (5,8,11,14-eicosatetraenoic acid), a polyunsaturated fatty acid released from membrane phospholipids by the action of phospholipase A2.


Membrane phospholipids
Phospholipase A2
Inhibited by Corticosteroids
Leukotrienes (SRS-A)
Lipoxygenase
8
5
1
COOH
11
14
O2
O2
Arachidonic acid
Two Isozymes (COX-1, constituted form & COX-2, the inducible form)
Cyclooxygenase
Inhibited by NSAIDs
PGI2
PGI Synthase
COOH
PGE Synthase
PGD2
R
PGG2, R = OOH
PGH2, R = OH
PGF Synthase
TXA Synthase
PGF2α
TXA2
PGD Synthase
PGE2

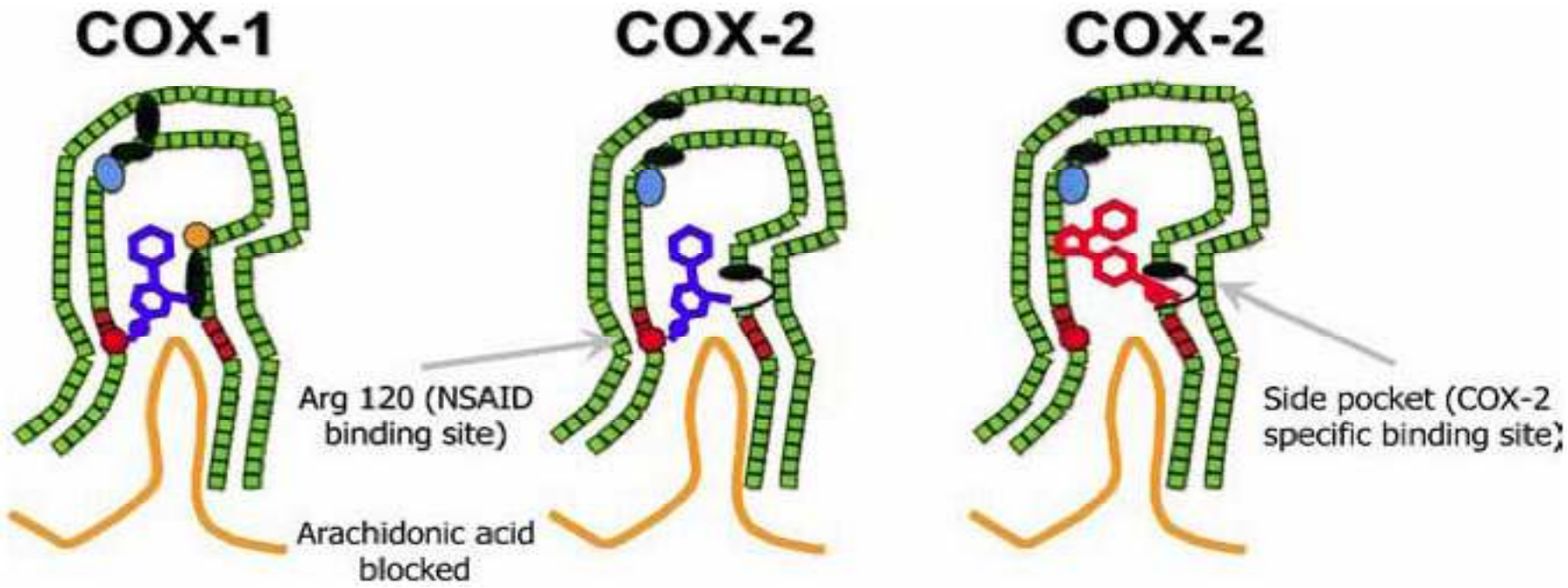
- **Cyclo-oxygenase (COX):**
- **COX exists as two major isoforms, one induced in inflammation and one continually present.**
- **COX-1 is considered the 'house-keeping' form of COX and is continually expressed in cells, producing PG used in the maintenance of homeostasis.**



- The two COX isoforms are sequence homodimers that function as conformational heterodimers.
- Both enzymes appear as structurally symmetric homodimers in crystal structures but function in solution as conformational heterodimers composed of an allosteric (E_{allo}) and a catalytic (E_{cat}) subunit.
- The subunits of COX-1 and COX-2 differ in their affinities for ligands and in their responses to ligands.
- Substrates are in blue.
- Ligands shown in green stimulate COX activity, and those shown in red inhibit activity.
- **The term "homodimer" — shorthand for "sequence homodimer" — connotes a protein molecule composed of two monomers with identical primary structures. It often is assumed these proteins function as pairs of independently operating monomers, but there are other scenarios. Many homodimers show a substrate or cofactor binding with high affinity to only half of the seemingly available sites and behave as conformational heterodimers. This permits allosteric regulation that is not possible with true conformational homodimers.**



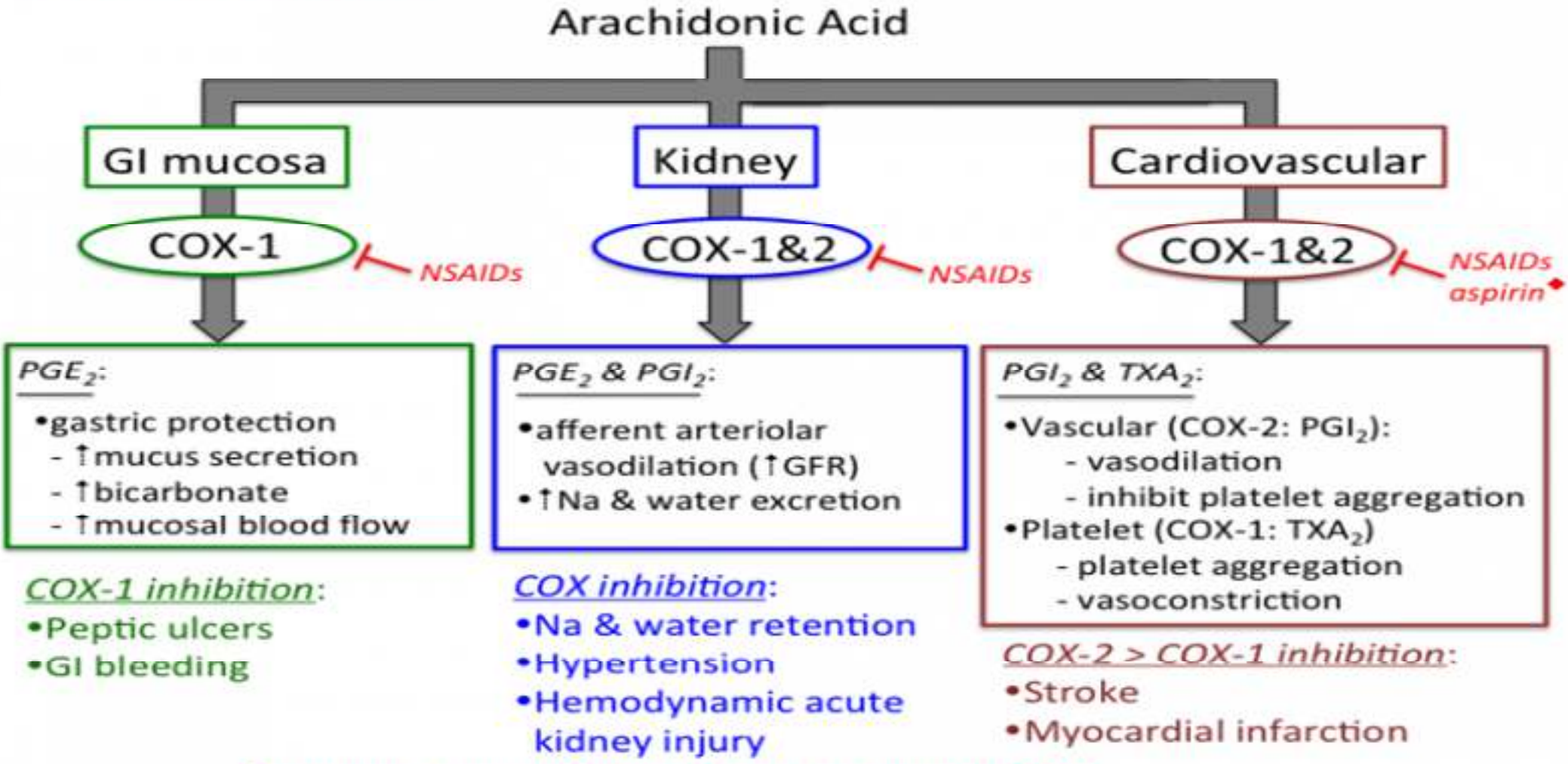
- **Left: schematic representation of the inhibition of COX-1 (large green figure) by a nonselective NSAID (central blue figure). The entrance channel to COX-1 is blocked by the NSAID. Binding and transformation of arachidonic acid (bottom yellow figure) within COX-1 is prevented.**
- **Middle: inhibition of COX-2 by a nonselective NSAID (central blue figure).**
- **Right: inhibition of COX-2 by COX-2 selective NSAID (central red figure). The COX-2 side pocket allows specific binding of the COX-2 selective NSAID's rigid side extension. The entrance channel to COX-2 is blocked. The bulkier COX-2-selective NSAID will not fit into the narrower COX-1 entrance channel, allowing uninhibited access of arachidonic acid into COX-1.**



- **Inflammatory PGs play an important role in inflammation, often working synergistically with other inflammatory mediators.**
- **For instance, PGE2 has a synergistic effect with histamine by increasing the pain response's intensity and duration: this is termed hyperalgesia.**
- **PGs act both peripherally and centrally in the pain pathways.**

- It was thought that the adverse effects of NSAIDs occur through inhibition of COX-1.
- However, it is now thought that COX-1 may play a role in inflammation as well, although COX-2 is still the principle enzyme involved in the inflammatory response.
- COX-3 is sometimes mentioned but is thought to be a subtype of COX-1.
- COX-3 is found in the brain and was thought to be a central mediator of pain, but is now generally grouped with COX-1.

NSAID Side Effects:



◆ Low dose aspirin irreversibly inhibits platelet COX-1

- **COX-2 is induced in inflammation and results in the production of the inflammatory PGs and TXs.**
- **COX-2 specific NSAIDs were once thought to be very hard to find, however, it is now recognized that COX-2 plays a role in angiogenesis and healing, and can even have anti-inflammatory effects in the late stages of inflammation.**
- **The COX-2 active sites are larger then COX-1 and the newer NSAIDs have larger, different structures to the 'classical' NSAIDS allowing them to limit their inhibition of COX-1 by steric hindrance.**

NSAIDs

- NSAIDs are the drugs with analgesic, antipyretic and anti-inflammatory effects so they reduce pain, fever and inflammation.
- The term "non-steroidal" is used to distinguish these drugs from steroids, which have a similar eicosanoid-depressing, anti-inflammatory action.
- As analgesics, NSAIDs are unusual in that they are non-narcotic.

Chemical Classification of NSAIDs

Chemical Group	Drugs
Alkanones	Nabumetone
Anthranilic acids (fenamates)	Meclofenamic acid, mefenamic acid
Arylpropionic acids	Fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin
Enolic acids	Oxicams (piroxicam, tenoxicam), pyrazolidinediones (oxyphenthatrazone, phenylbutazone)
Heteroaryl acetic acids	Diclofenac, ketorolac, tolmetin
Indole and indene acetic acids	Etodolac, indomethacin, sulindac
Para-aminophenol derivatives	Acetaminophen (paracetamol)
Pyrazol derivatives	Aminopyrine, antipyrine, dipyrone
Salicylic acid derivatives	Aspirin, choline magnesium trisalicylate, diflunisal, olsalazine, salicylsalicylic acid, salsalate, sodium salicylate, sulfasalazine

NSAIDs

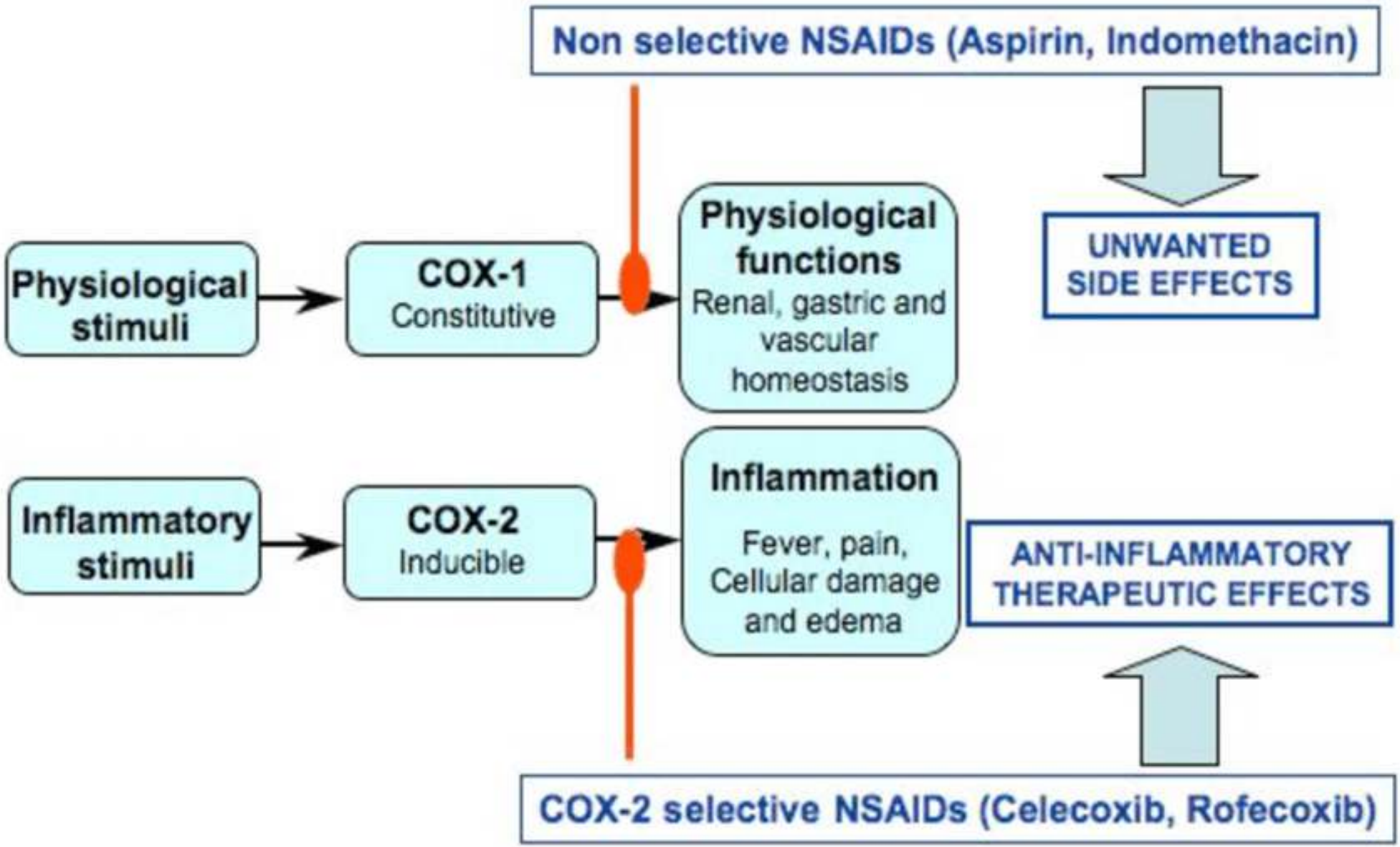
- **Mechanism of Action**

- Inhibits cyclo-oxygenase enzyme = ↓↓ Prostaglandin synthesis

COX-I	Most cells in the body
COX-II	Inflammatory and immune cells
COX-III	Hypothalamic temperature control center

NSAIDs that act on COX-I, COX-II & COX-III, more side effects

Selective COX-II NSAIDs, less side effects


Non selective NSAIDs (Aspirin, Indomethacin)
UNWANTED SIDE EFFECTS
Physiological stimuli
COX-1
Constitutive
Physiological functions
Renal, gastric and vascular homeostasis
Inflammatory stimuli
COX-2
Inducible
Inflammation
Fever, pain, Cellular damage and edema
ANTI-INFLAMMATORY THERAPEUTIC EFFECTS
COX-2 selective NSAIDs (Celecoxib, Rofecoxib)

NSAIDs

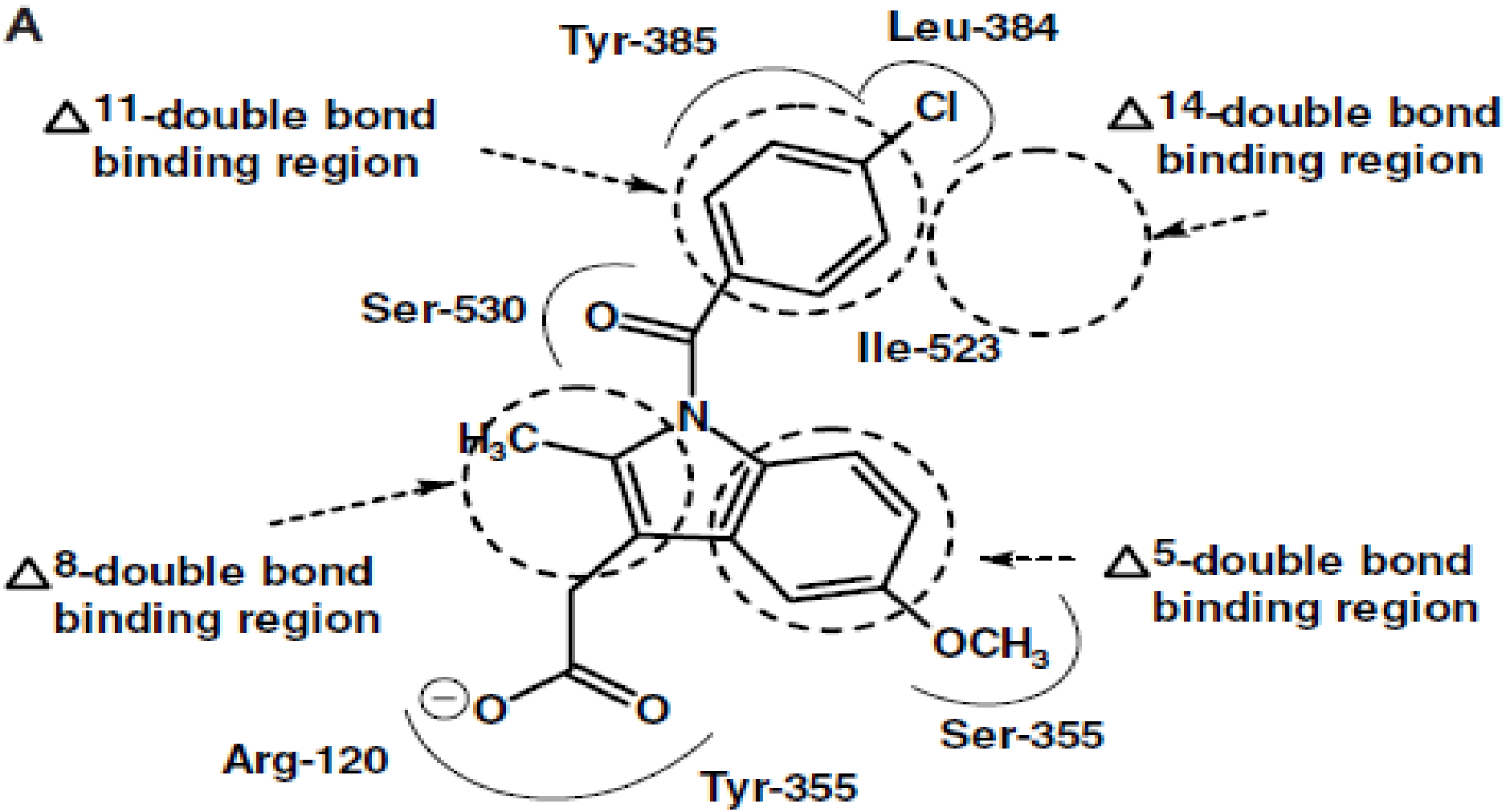
Common Pharmacological Effects

- Analgesic (CNS and peripheral effect)
- Antipyretic (CNS effect)
- Anti-inflammatory (except Paracetamol)
- Antiplatelet effect:
  - prevents platelet aggregation. (Aspirin low dose)

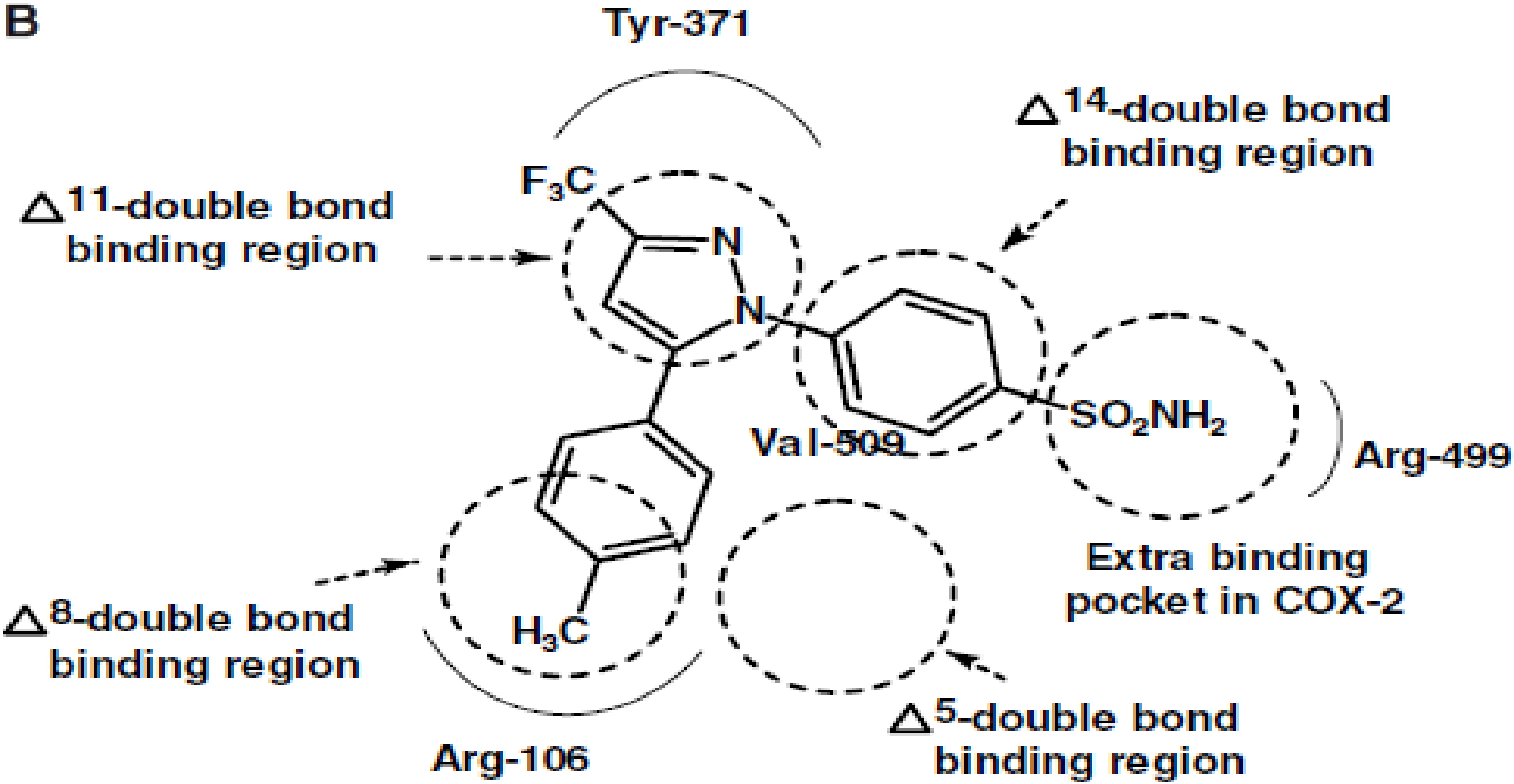
Common Adverse Effects

- Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)
- Platelet Dysfunction
- Acute Renal Failure in susceptible persons
- Sodium+ water retention and edema
- Analgesic nephropathy

HYPOTHETICAL BINDING MODEL OF INDOMETHACIN TO COX-1



HYPOTHETICAL BINDING MODEL OF CELECOXIB TO COX-2



Aspirin and Salicylic Acid Derivatives

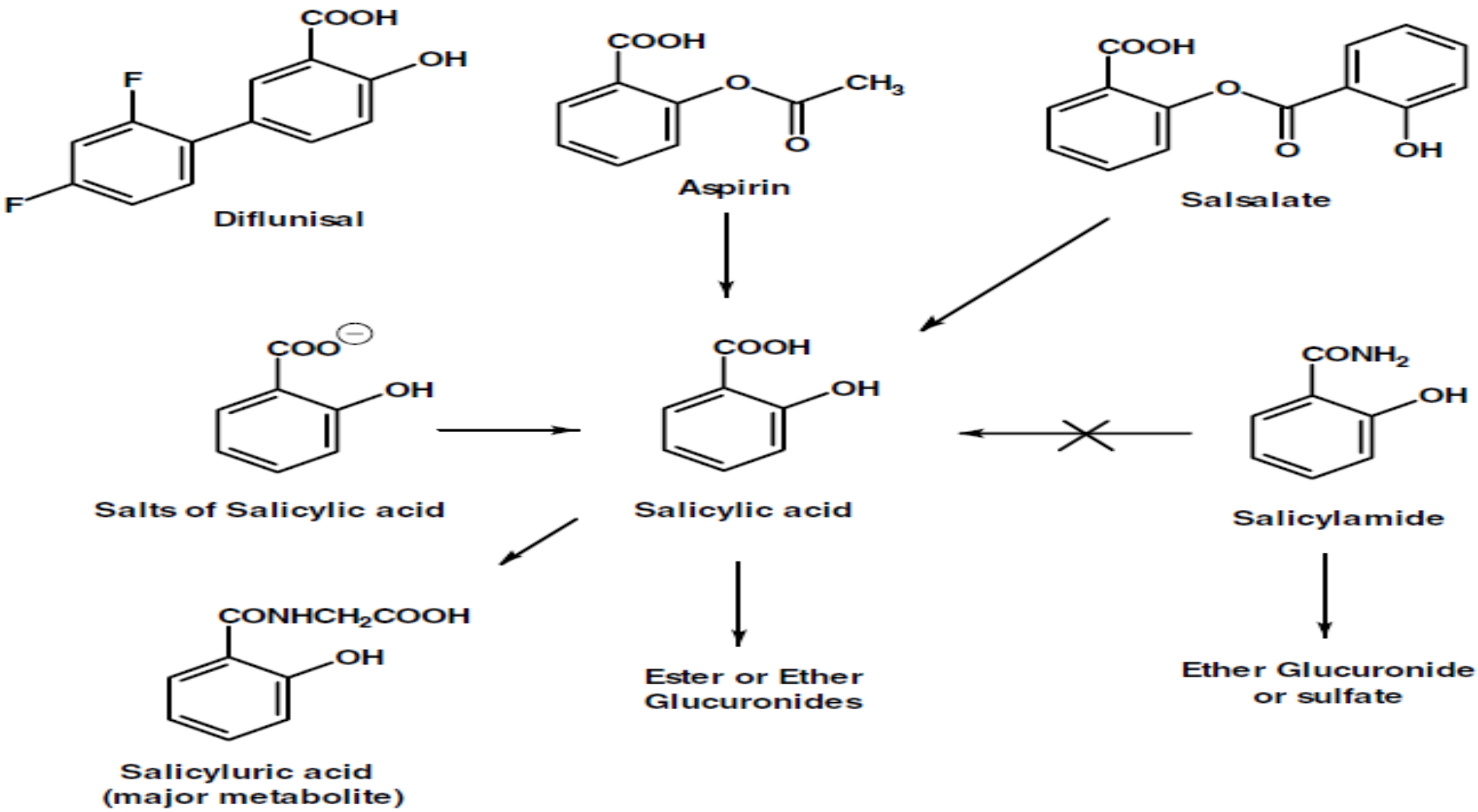
- Aspirin and the salicylates are the first group of NSAIDs.
- Most of the salicylates are marketed as-

➢ Salts of salicylic acid (sodium, magnesium, bismuth, choline, or triethanolamine)

➢ Ester or amide derivatives (aspirin, salsalate, salicylamide).

- 3 to 12 years Children recovering from flu or chicken pox should not take aspirin or any salicylates due to risk of developing a rare disease known as Reye syndrome.

Salicylates and their metabolites



- **ASPIRIN AND ITS COX-1 SELECTIVITY:**
- **Aspirin covalently binds to COX-1 and hCOX-2 isozymes by acetylating the OH group of Ser-530 in COX-1 and Ser- 516 in hCOX-2 isozymes.**
- **Ionic interaction occurs between the carboxylate anion and the cation of Arg-120 in COX-1 (or Arg-106 in hCOX-2).**
- **This interaction positions the acetyl group of aspirin for acetylating the COX isozymes.**

- **Even though both COX isozymes are irreversibly acetylated by aspirin, acetylation of Ser-530 totally blocks the accessibility of substrate arachidonic acid from entering into the active site, whereas an acetylated hCOX-2 is still able to form a significant amount of PGG2.**
- **Thus, aspirin, among all conventional NSAIDs, exhibits the highest selectivity toward the COX-1 isozyme, especially the COX-1 isozyme present in the platelets.**

- **Mechanism of Salicylates :**

Increasing heat elimination of the body

↓

Mobilization of water

↓

Dilution of the blood

↓

Perspiration

↓

Cutaneous dilatation

- **This does not occur with normal temperatures.**
- **The antipyretic and analgesic actions work by inhibiting cyclooxygenase and reducing the levels of PGE2.**

- **Pharmacokinetics of salicylates:**
- **Salicylates are acidic and so readily absorbed from the stomach and the small intestine.**
- **Absorption depends on the pH of the environment, thus co-administration of an antacid or buffering agents should be avoided.**
- **Highly bound to plasma proteins.**

- **Salicylates undergoes extensive phase-II metabolism.**
- **Excreted via the kidneys as-**
  - **Glycine conjugate (water soluble)**
  - **Salicyluric acid (major metabolite)**
  - **Acyl glucuronides (ester type, via the COOH)**
  - ***O-glucuronides* (ether type, via the phenolic OH)**
- **Alkalinization of the urine increases the rate of excretion of the free salicylates.**

- **Uses and Side effects of aspirin:**

- **Analgesic for minor aches and pains.**

- **Antipyretic to reduce fever.**

- **Higher doses can also be used to treat inflammation.**

- **It's use is often associated with many unwanted side effects including-**

➢ **Ulcers**

➢ **Stomach bleeding**

➢ **Tinnitus**

➢ **Salicylism**

Conventional Nonselective COX Inhibitors

- These NSAIDs once again become the drug of choice for the treatment of Rheumatoid Arthritis and other inflammatory diseases due to –

➢ More potency than aspirin and related salicylates.

➢ Cardiovascular risk associated with celecoxib.

➢ Removal of rofecoxib from the market.

Major drawback:

- Several drugs in this class are available OTC, but they are no safer than prescription medications with regard to their drug-induced GI liability.

- **These conventional nonselective COX inhibitors are classified in to –**
- **Aryl/Heteroaryl acetic acid derivatives:**

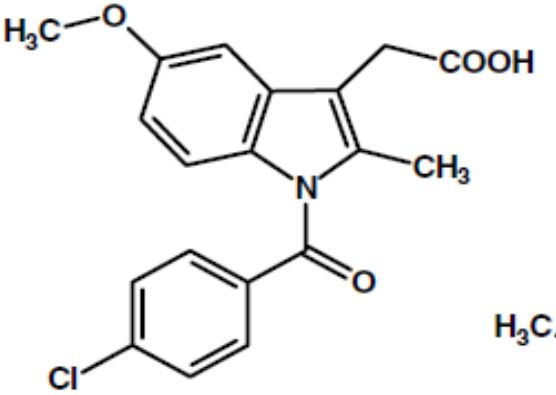
  i) Indomethacin ii) Sulindac iii) Ketorolac
- **Aryl/Heteroaryl propanoic acid derivatives:**

  i) Ibuprofen ii) Naproxen
- **N-Arylanthranilic acid derivatives (fenamates) and related drugs:**

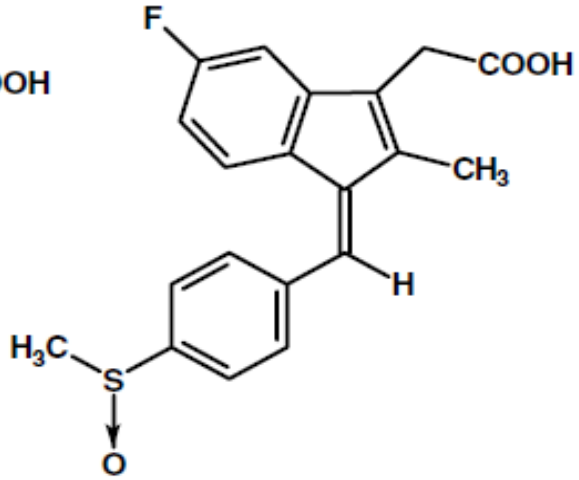
  i) Mefenamic acid ii) Diclofenac
- **Oxicams:**

  i) Piroxicam

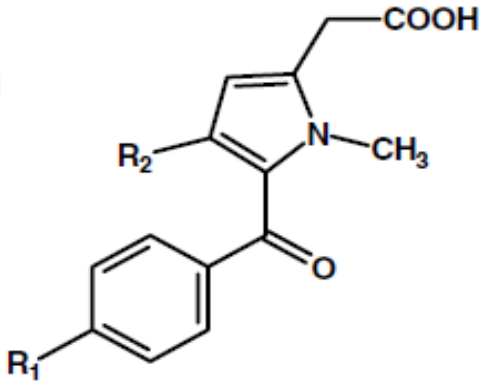
Aryl/Heteroaryl acetic acid derivatives



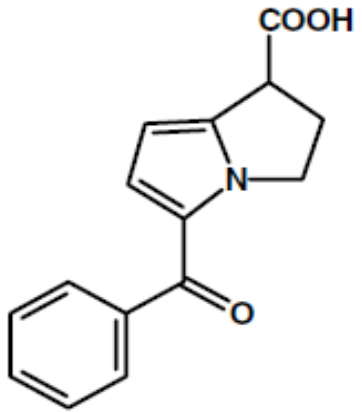
Indomethacin



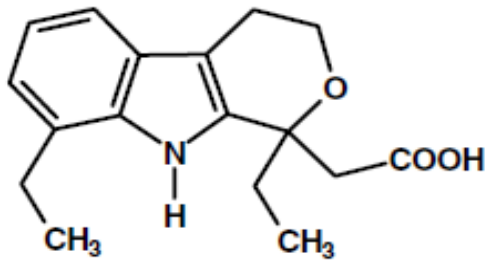
Sulindac



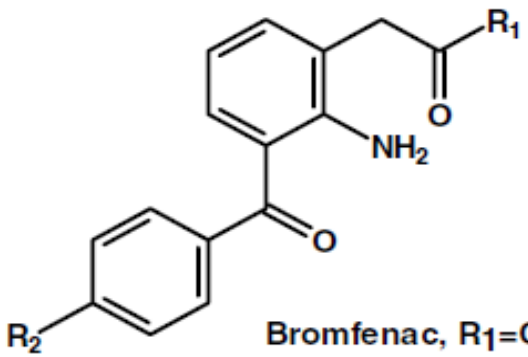
Tolmetin, R_1=CH_3, R_2=H
Zomipirac, R_1=Cl, R_2=CH_3



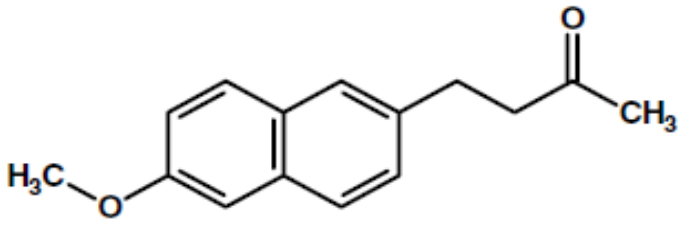
Ketorolac



Etodolac



Bromfenac, R_1=OH, R_2=Br
Amfenac, R_1=OH, R_2=H
Nepafenac, R_1=NH2, R_2=H



Nabumetone

- As a group, they show high analgesic potency in addition to their potent anti-inflammatory activity.
- Ketorolac, indomethacin, and tolmetin have the highest risk of GI irritation because of their higher affinity for the COX-1 isozyme.
- Etodolac has the lowest risk because of its COX-2 selective inhibitory action.
- Both sulindac and nabumetone are prodrugs that require activation, and therefore have lower risk of causing GI irritation than indomethacin.

- ***Indomethacin:***
- **It has been widely used as an analgesic to relieve inflammatory pain associated with-**

➢ **Rheumatoid arthritis**

➢ **Osteoarthritis**

➢ **Ankylosing spondylitis**

➢ **Gout**

- **It's use is often limited because of-**

➢ **Frequent GI distress**

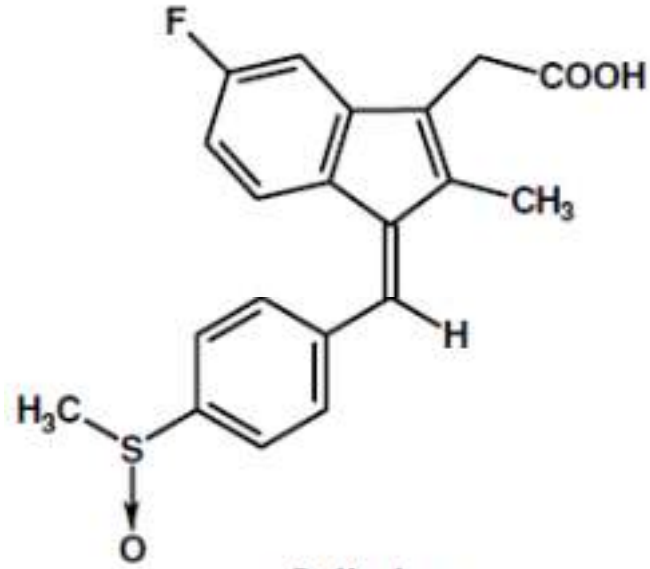
➢ **Potential drug interactions (especially with warfarin furosemide, and lithium)**

- **It elevates blood levels of lithium as a result of reducing renal blood flow and therefore increases lithium toxicities.**

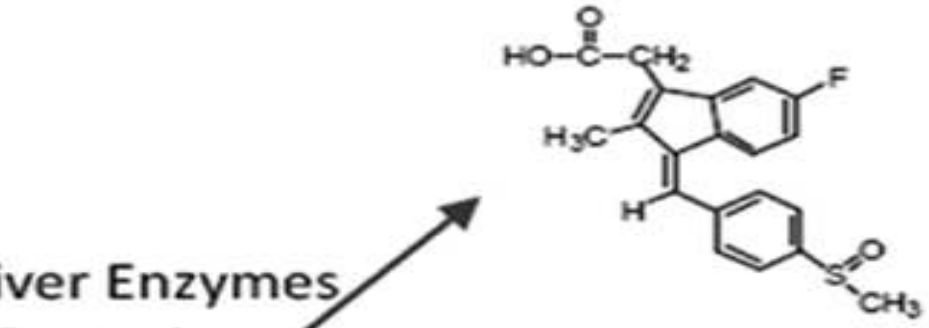
- **Pharmacokinetics:**
- **Oral administration.**
- **Rapidly absorbed.**
- **90% protein bound.**
- **Biological half-life of about 5 to 10 hours.**
- **Plasma clearance of 1 to 2.5 ml/kg per minute.**
- **It is metabolized to inactive metabolites *O-desmethyl, N-deschlorobenzoyl indomethacin metabolites (O-demethylation and Dechlorination).***

- ***Sulindac:***
- **It is an NSAID prodrug that contains a chiral sulfoxide moiety.**
- **But is marketed as the racemate.**
- **Because it undergoes *in vivo* reduction by the hepatic enzymes into its achiral, active metabolite, methyl sulfide.**
- **It exhibits potent and nonselective**

COX inhibition similar to indomethacin.



Sulindac

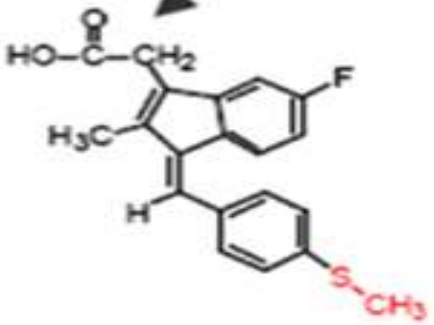


Liver Enzymes
Colonic Bacteria

Sulindac (sulfoxide)

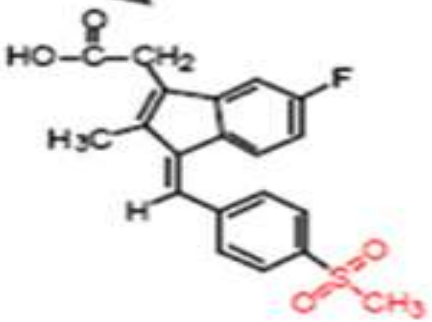
Lacks COX-1 and COX-2 inhibitory activity

Liver Enzymes



Sulindac Sulfide

Nonselective COX-1 and COX-2 inhibitor



Sulindac Sulfone

Lacks COX-1 and COX-2 inhibitory activity

- **Pharmacokinetics:**
- **Plasma half-life of 8 hours for parent and 16.4 hours for active metabolite.**
- **Sulindac is believed to have minimal nephrotoxicity associated with indomethacin.**
- **The long half-life of sulindac is caused by the extensive enterohepatic circulation and reactivation of the inactive sulfoxide.**

- **Coadministration of aspirin is contraindicated because it considerably reduces the sulfide blood levels.**
- **Gastric bleeding, nausea, diarrhea, dizziness, and other adverse effects have been noted with sulindac, but with a lower frequency than with aspirin.**
- **Sulindac is recommended for RA, OA, and ankylosing spondylitis.**

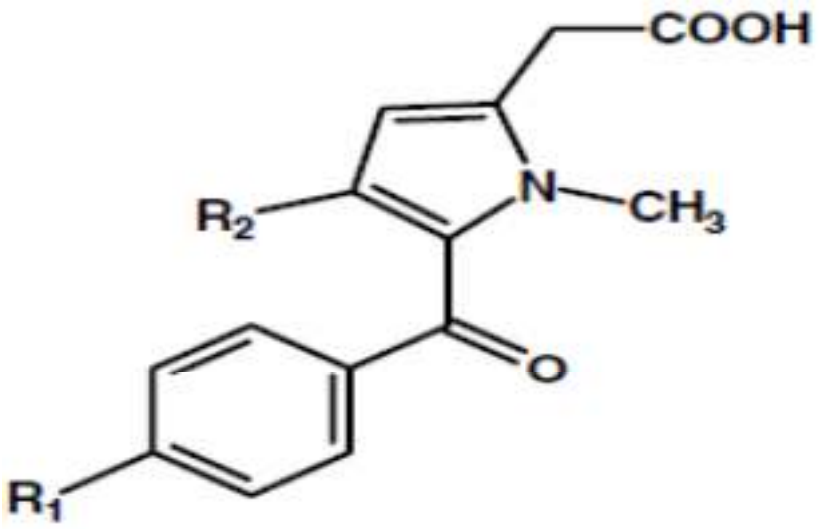
- ***Tolmetin and Zomepirac:***

- Both are arylacetic acid derivatives with a pyrrole as the aryl group.

- Tolmetin is well absorbed and has a relatively short plasma half-life (1 hour).

- It is recommended for use in the management of acute and chronic RA.

- Its efficacy is similar to aspirin and indomethacin, but with less frequency of the adverse effects.

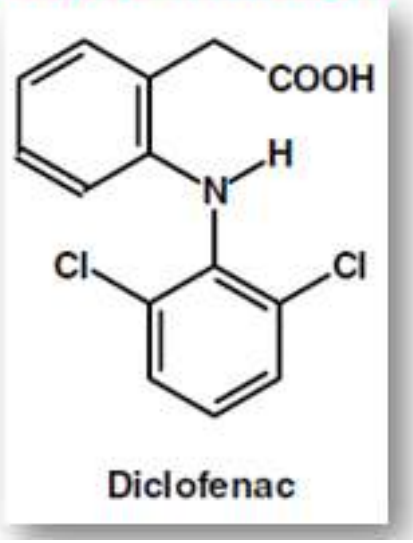


Tolmetin, $R_1=CH_3$, $R_2=H$
Zomipirac, $R_1=Cl$, $R_2=CH_3$

- It does not potentiate coumarin-like drugs nor alter the blood levels of sulfonylureas or insulin.
- However, tolmetin and especially zomepirac can produce a rare but fatal anaphylactic reaction because of irreversible binding of their unstable acyl glucuronides.
- Zomepirac contain a *p*-chlorobenzoyl group and an additional methyl group on the pyrrole ring.

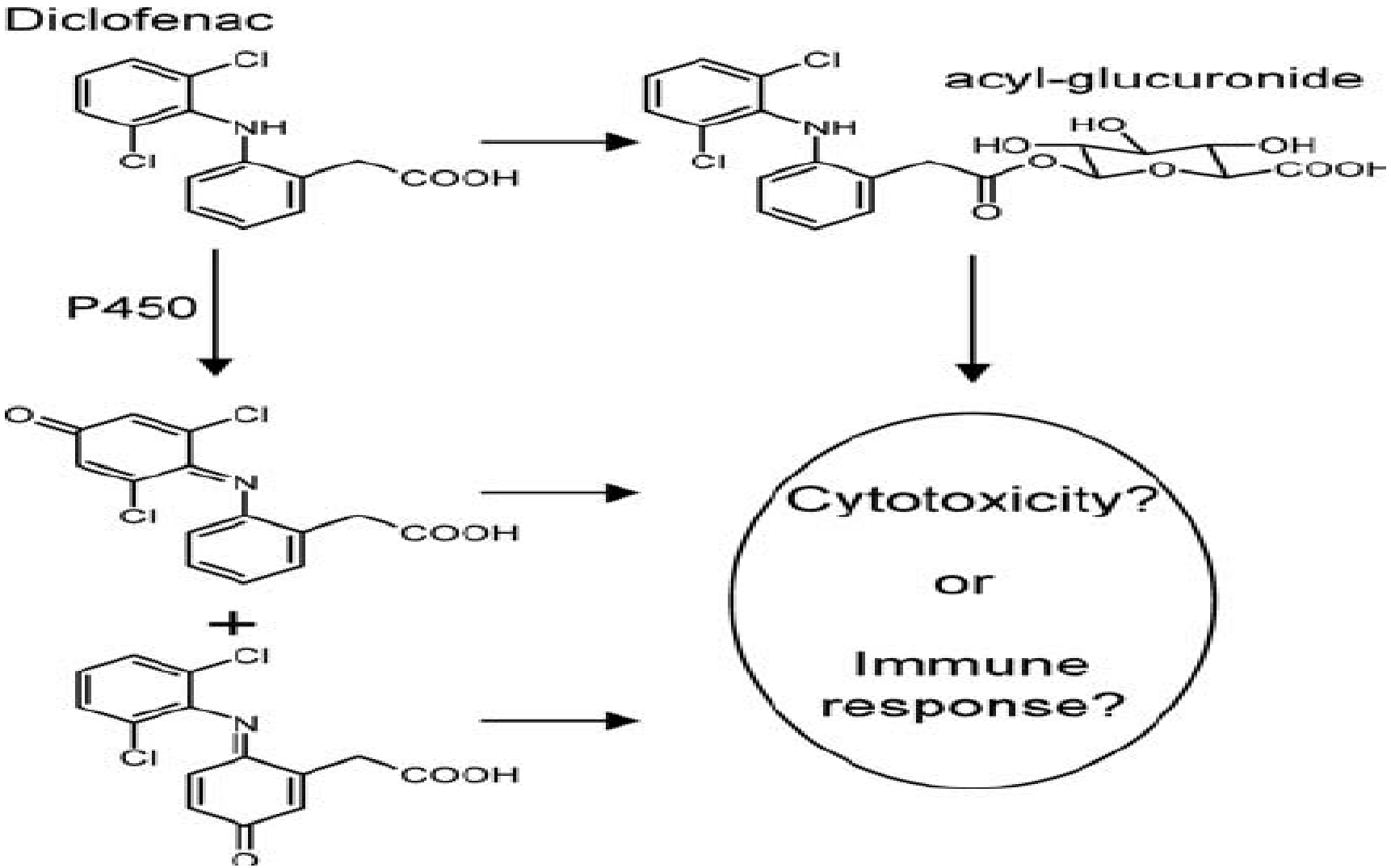
- Zomepirac was withdrawn from market because it is eliminated only via the ester-type, acyl glucuronide.
- Tolmetin is less toxic, because it undergoes additional hepatic benzylic hydroxylation via its *p*-methyl group and is excreted as its stable ether glucuronide.

- ***Diclofenac and Lumiracoxib:***
- Diclofenac sodium is indicated for short- and longterm treatment of RA, OA, and ankylosing spondylitis.
- The potassium salt is faster acting and indicated for acute pain and primary dysmenorrhea.
- Diclofenac is more hepatotoxic can cause severe liver damage.
- This idiosyncratic hepatotoxicity is due to the formation of reactive benzoquinone imines.



Diclofenac

Benzoquinone toxic metabolites and Metabolism of Diclofenac



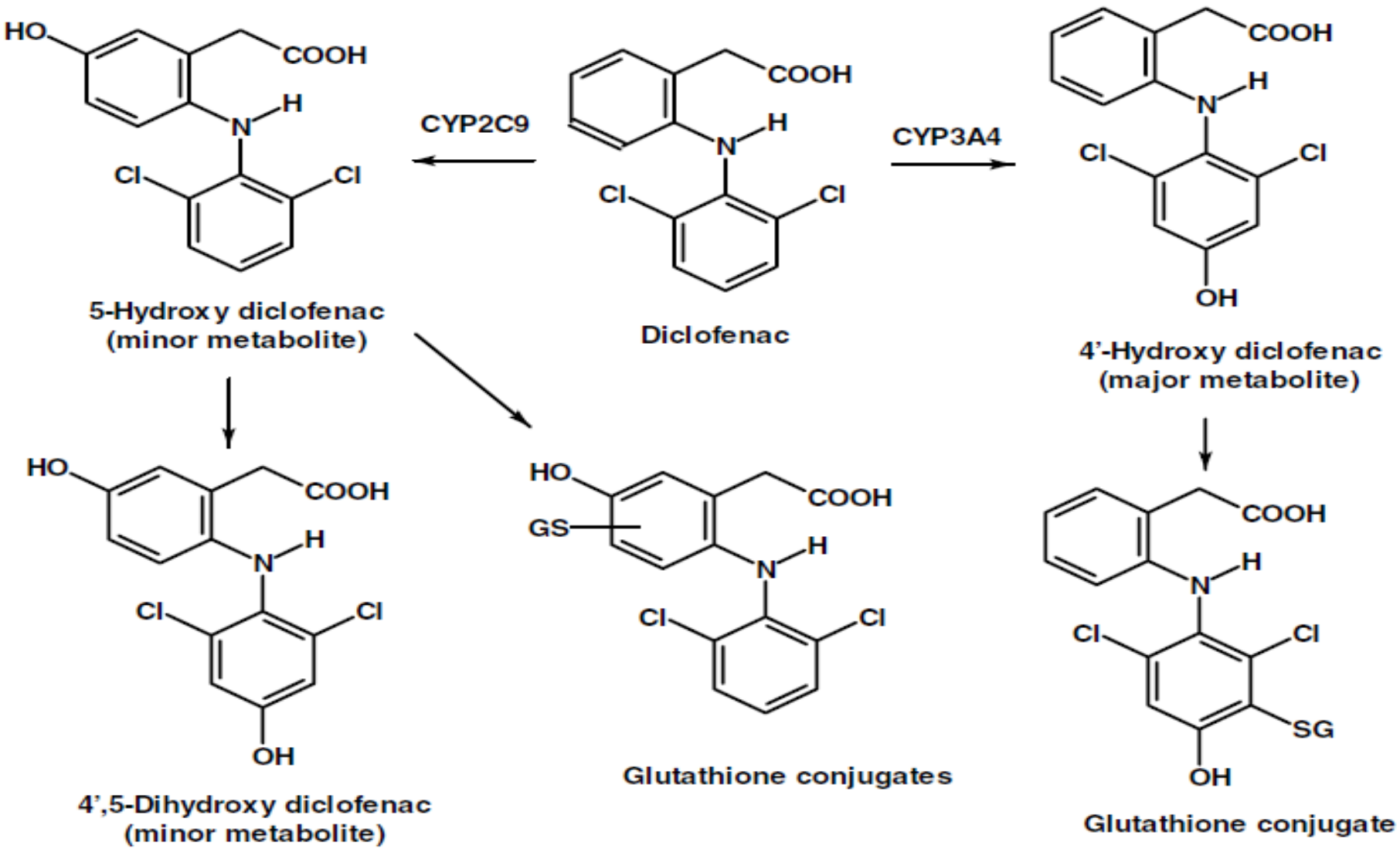
- **Diclofenac undergoes hepatic CYP2C9/3A4 catalyzed aromatic hydroxylations to give-**

➢ **4'-hydroxy-diclofenac(major inactive metabolite).**

➢ **5-hydroxy- diclofenac (minor metabolite).**

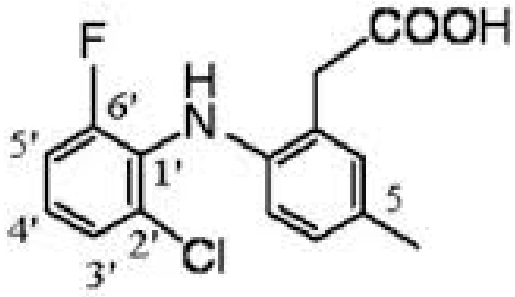
➢ **4',5-dihydroxy- diclofenac (minor metabolite).**

- **Both the 4' and 5-hydroxy metabolites are further activated to their reactive toxic quinone imines and finally deactivated by glutathione conjugation.**

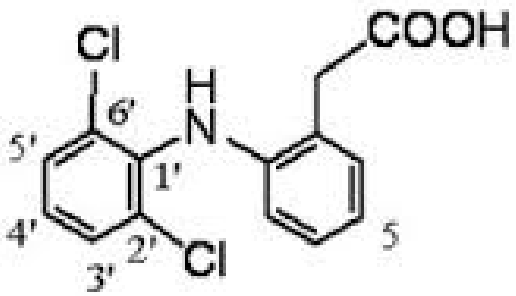

HO
COOH
H
N
Cl
Cl
5-Hydroxy diclofenac
(minor metabolite)
CYP2C9
COOH
H
N
Cl
Cl
Diclofenac
CYP3A4
COOH
H
N
Cl
Cl
OH
4'-Hydroxy diclofenac
(major metabolite)
HO
COOH
H
N
Cl
Cl
OH
4',5-Dihydroxy diclofenac
(minor metabolite)
HO
GS
COOH
H
N
Cl
Cl
Glutathione conjugates
COOH
H
N
Cl
Cl
SG
OH
Glutathione conjugate

- **Lumiracoxib differs from diclofenac with an additional methyl substituent on 5th position of phenylacetic acid ring.**
- **It is extensively metabolized by CYP2C9, just like diclofenac, into three major inactive metabolites-**

  - **5-carboxy**
  - **4'-hydroxy**
  - **4'-hydroxy-5-carboxy.**



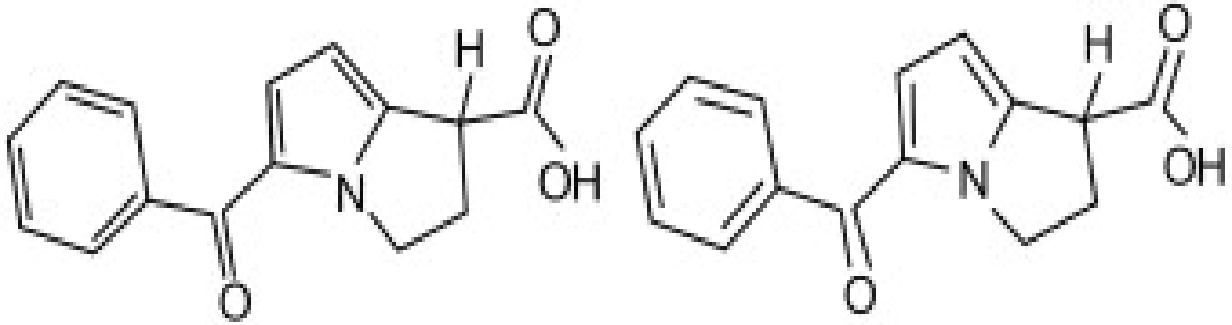
Lumiracoxib



Diclofenac

- **It was withdrawn from market in October, 2007 because of serious adverse hepatotoxicity.**

- ***Ketorolac:***
- **It is marketed as a mixture of R(+) and S(-) ketorolac enantiomers.**
- **It is a potent NSAID analgesic indicated for the treatment of moderately severe, acute pain.**
- **Pharmacokinetics of ketorolac depend on enantioselectivity.**
- **Highest risk of GI complications and therefore its administration should not exceed 5 days.**

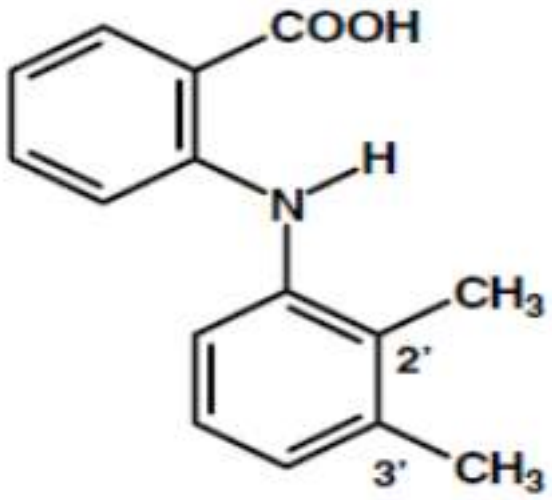


R-Ketorolac S-Ketorolac

- ***Mefenamic Acid:***
- It is a derivative of N-aryl anthranilic acid (fenamate).
- **The second aromatic ring in fenamates is connected to the main aromatic carboxylic acid containing ring through a secondary amine linkage (rather than carbonyl group or other nonbasic linker) and at the ortho position rather than at the meta or para position.**
- As a result of this structural feature,

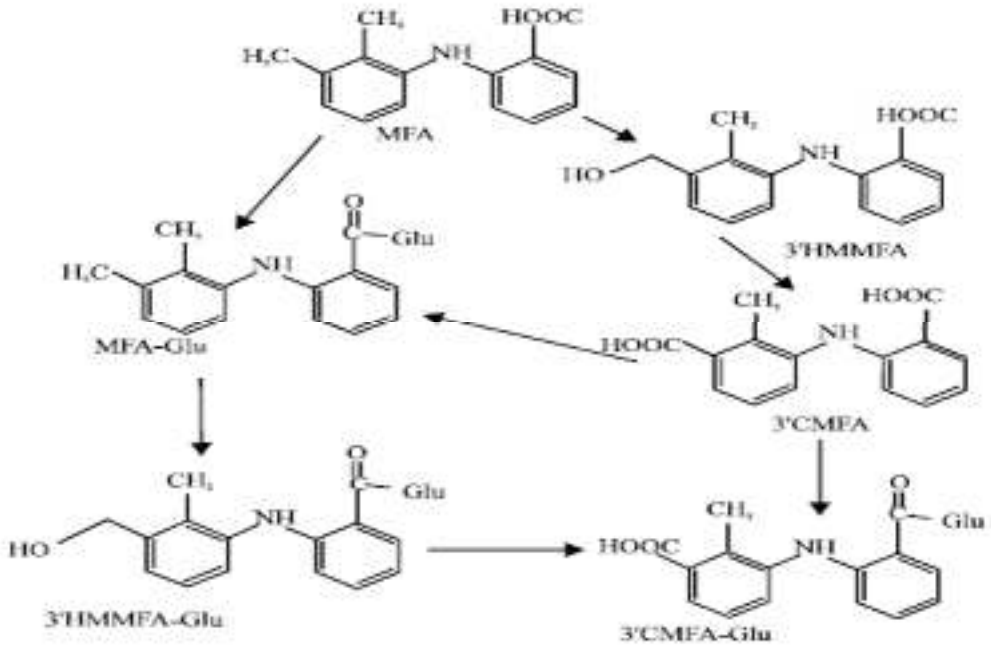
fenamates appears to have a lower risk

of causing GI irritation.



Mefenamic acid

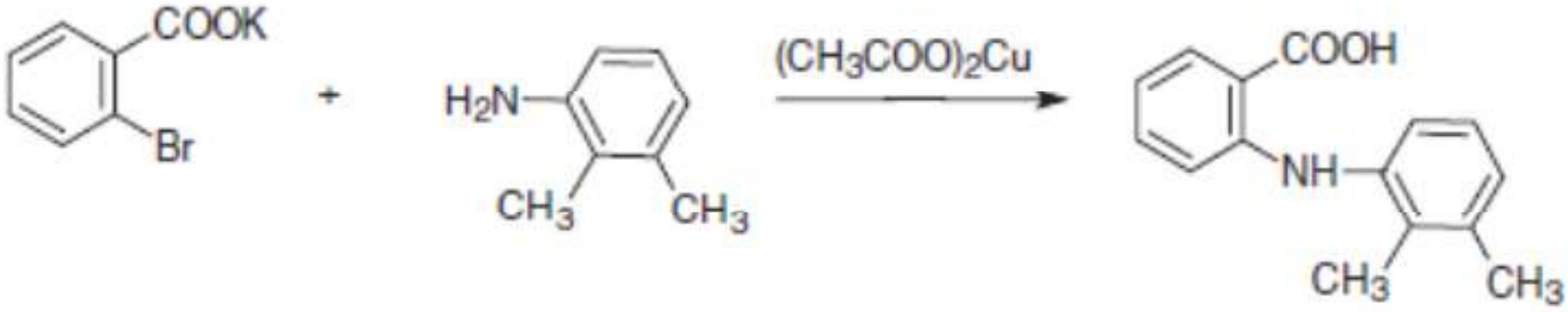
- Hepatic benzylic hydroxylation **of its 3-methyl group give inactive metabolites, 3-hydroxymethylmefenamic acid and the 3-carboxylate metabolite.**
- **Rapidly absorbed after oral administration.**
- **Peak plasma levels 2 to 4 hours.**



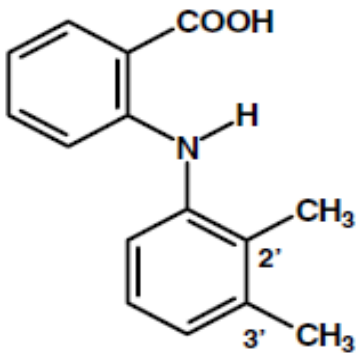
- **Used for mild to moderate pain and for primary dysmenorrhea.**
- **It is contraindicated in patients with pre-existing renal dysfunction.**
- **Common side effects include diarrhea, drowsiness, and headache.**
- **The possibility of blood disorders prompted limitation of its administration to 7 days.**
- **It is not recommended for children or during pregnancy.**

- **Synthesis of Mefenamic acid:**

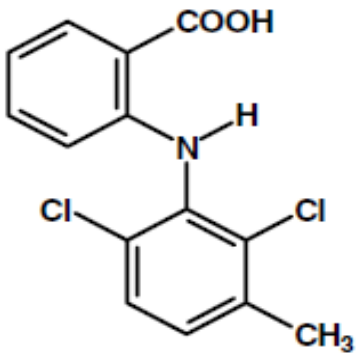
- It is synthesized by the reaction of the potassium salt of 2-bromobenzoic acid with 2,3-dimethylaniline in the presence of copper (II) acetate.



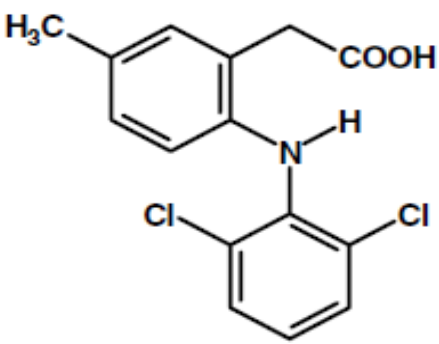
- ***Meclofenamate:***
- Meclofenamate sodium is available for use in the treatment of acute and chronic RA, OA, and primary dysmenorrhea.
- It is metabolized in a similar manner to mefenamic acid discussed above, thus a similar restriction is also applied to meclofenamate.
- The most significant side effects are GI, including diarrhea.



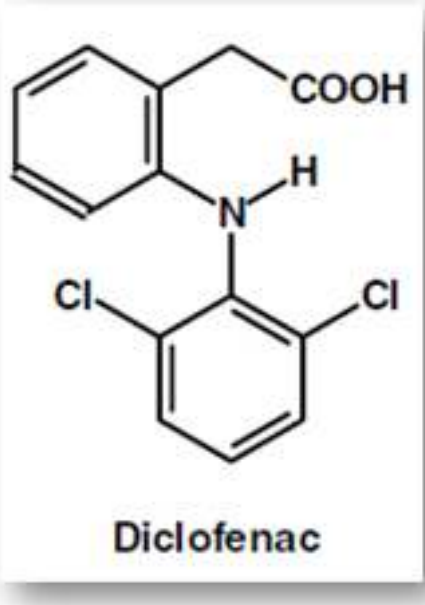
Mefenamic acid



Meclofenamic acid

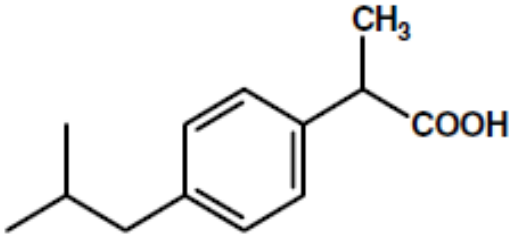


Lumiracoxib

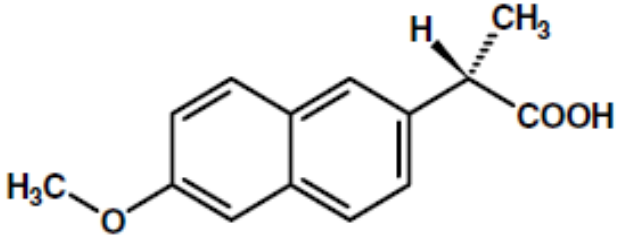


Diclofenac

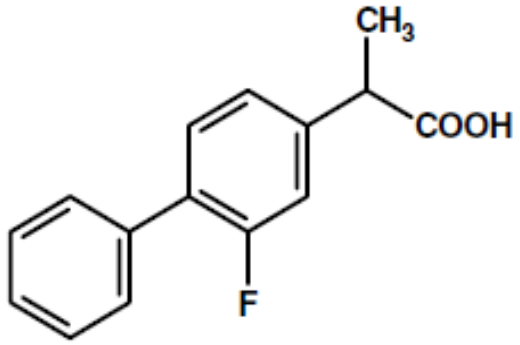
Aryl/Heteroaryl propanoic acid derivatives



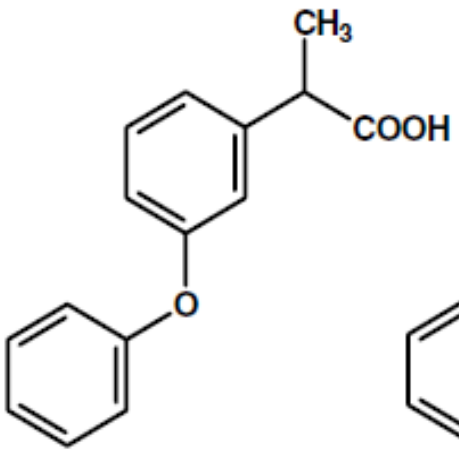
Ibuprofen



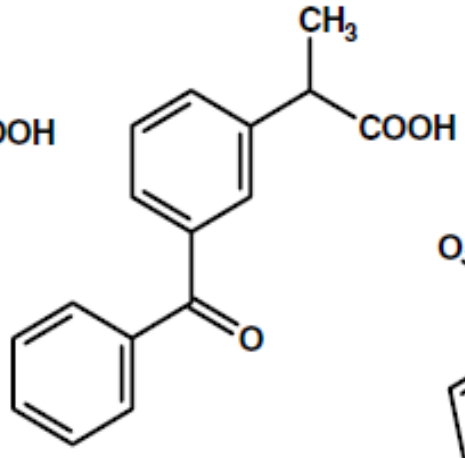
Naproxen



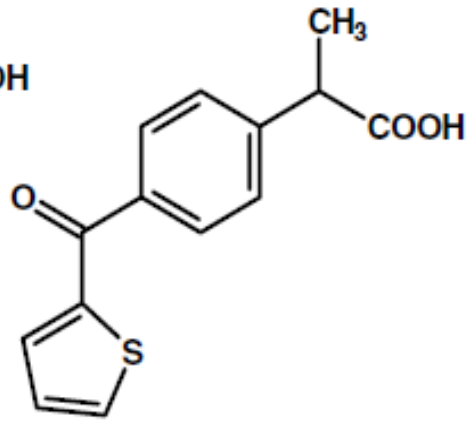
Flurbiprofen



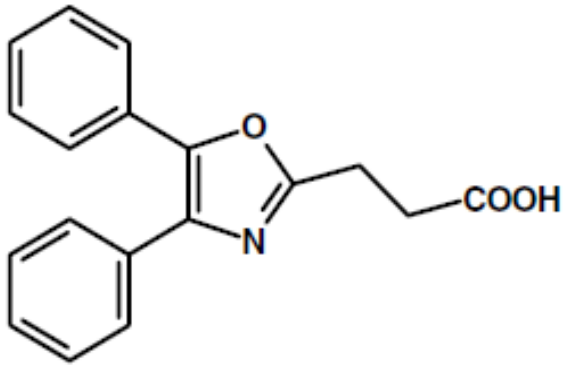
Fenoprofen



Ketoprofen



Suprofen



Oxaprozin

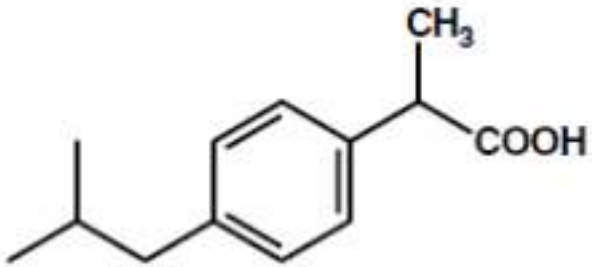
- All members of this class (except oxaprozin) contain a chiral carbon in the α-position of the acid side chain.
- Most are marketed as racemates.
- But only the S-enantiomer exhibit COX inhibitory activity.
- S-enantiomer is responsible for therapeutic action as well as drug-induced GI side effects and nephrotoxicity.
- *In vivo* Epimerization:
- In most cases, the inactive R-enantiomer is epimerized by 2-arylpropionyl coenzyme-A epimerase, to its active (S)-enantiomer.

- ***Ibuprofen:***

- **It's efficacy is comparable to aspirin in the treatment of RA, but with a lower incidence of side effects.**

- **Also used in the treatment of primary dysmenorrhea, which is caused by an excessive concentration of PGs and endoperoxides.**

- **Concurrent use of ibuprofen and aspirin may interfere with the cardioprotective effects of aspirin.**

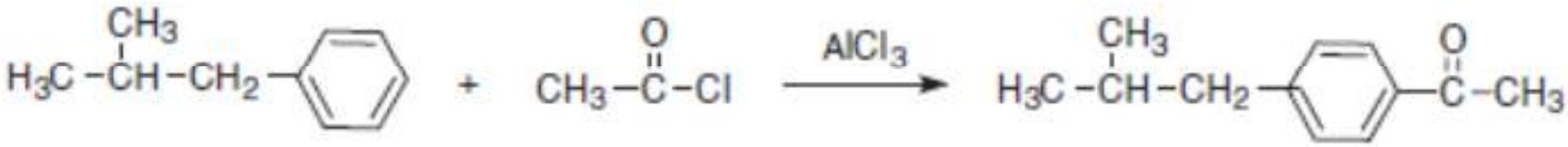


Ibuprofen

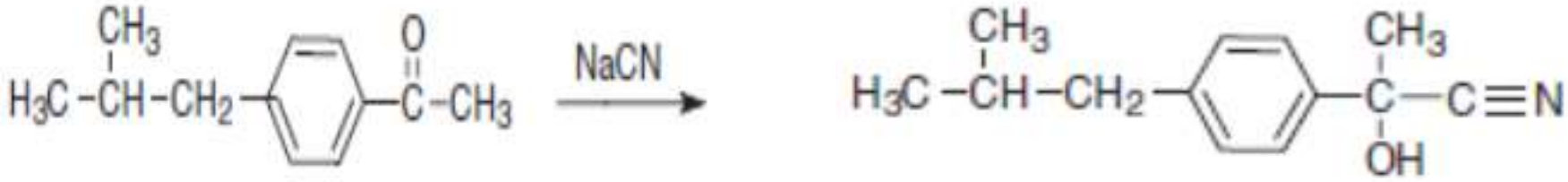
- **This is because ibuprofen can reversibly bind to the platelet COX-1 isozymes, thereby blocking aspirin's ability to inhibit TXA2 synthesis in platelets.**

- **Synthesis of Ibuprofen:**

- Fridel-Crafts acylation of *iso*-butylbenzene by acetyl chloride gives *iso*-butylbenzophenone .



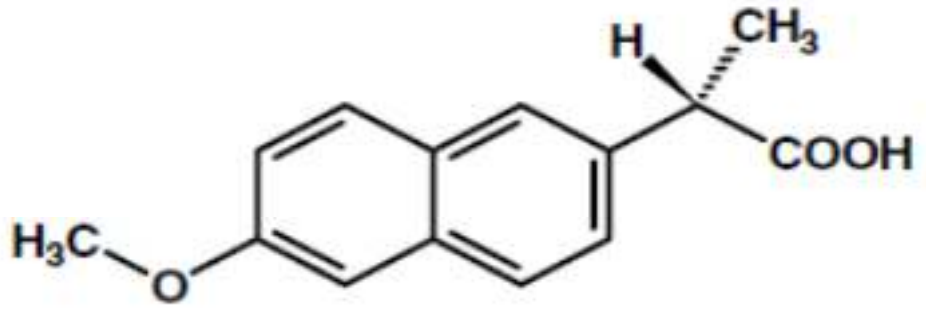
- This is reacted with sodium cyanide, giving oxynitrile (cyanohydrin).



- Oxynitrile upon reaction with hydroiodic acid in the presence of phosphorus is converted into 2-(4-*iso*-butylphenyl)propionic acid.
- This subsequently undergoes phases of dehydration, reduction, and hydrolysis to give ibuprofen.

- ***Naproxen:***

- It is marketed as the S-enantiomer.
- Well absorbed after oral administration.
- Peak plasma levels in 2 to 4 hours.
- Half-life of 13 hours.

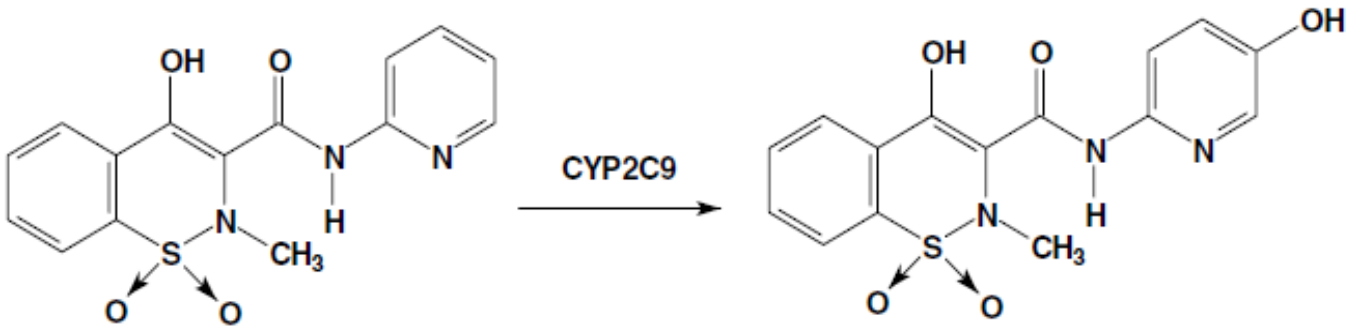


Naproxen

- Highly protein bound and displaces most protein- bound drugs.
- It is used in RA, OA, acute gouty inflammation, and in primary dysmenorrhea.
- It shows good analgesic activity (i.e., 400 mg is comparable to 75–150 mg of oral meperidine and superior to 65 mg of propoxyphene and 325 mg of aspirin plus 30 mg of codeine).
- It is also available OTC as 200-mg tablets.

OXICAMS

- **Oxicams lack a free carboxylic acid side chain but carry an acidic enolic 1,2-benzothiazine carboxamide ring.**
- **Only two members of this class, piroxicam and meloxicam, are available for the management of inflammatory arthritis.**



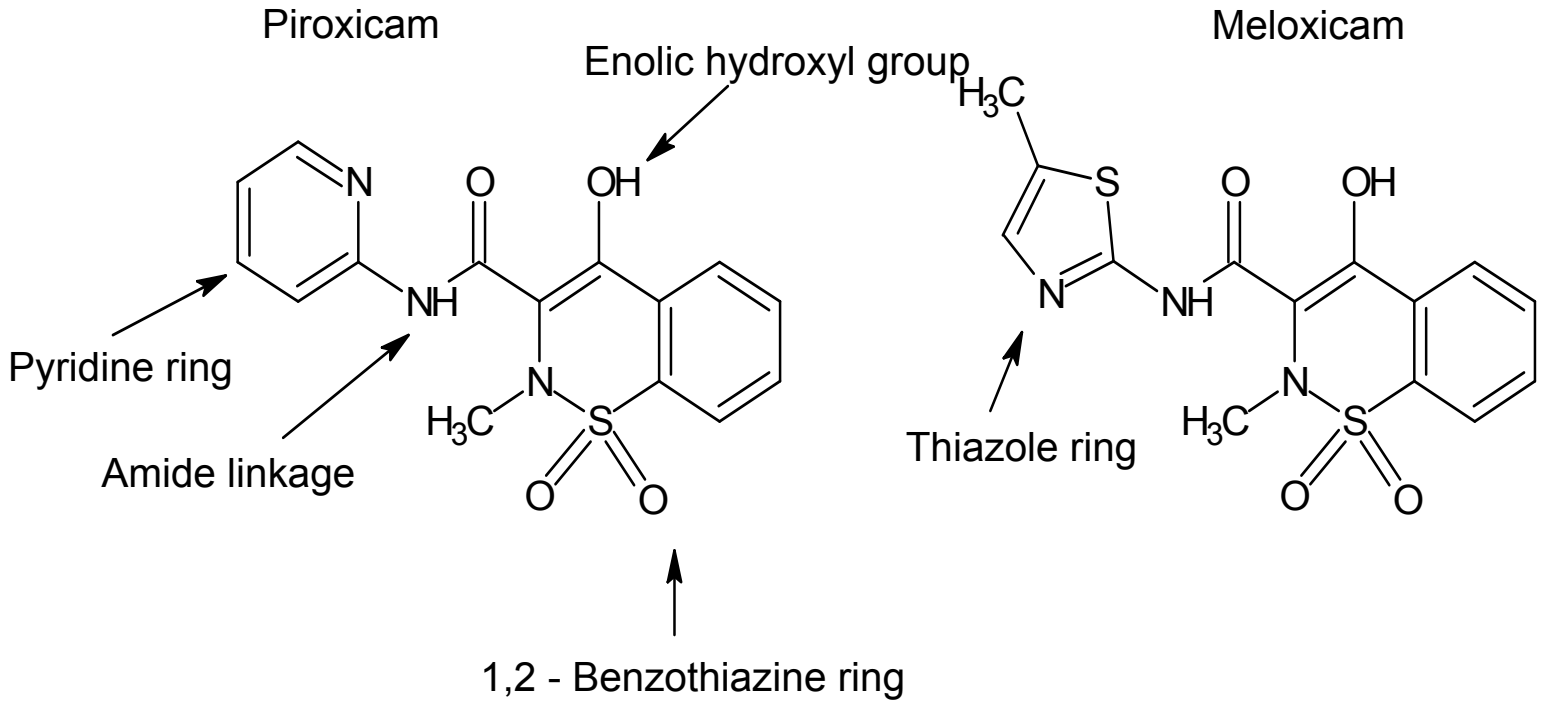
Piroxicam

5'-Hydroxypiroxicam

- **Tenoxicam is a close isosteric analog of piroxicam (i.e., with a 1,2-thiazole ring replacing the benzene ring fused to the thiazine ring), is available, but with a pharmacodynamic and pharmacokinetic profile similar to piroxicam.**
- **Both piroxicam and meloxicam have very different affinities for the COX isozymes, and therefore exhibit very different risks for GI complications.**

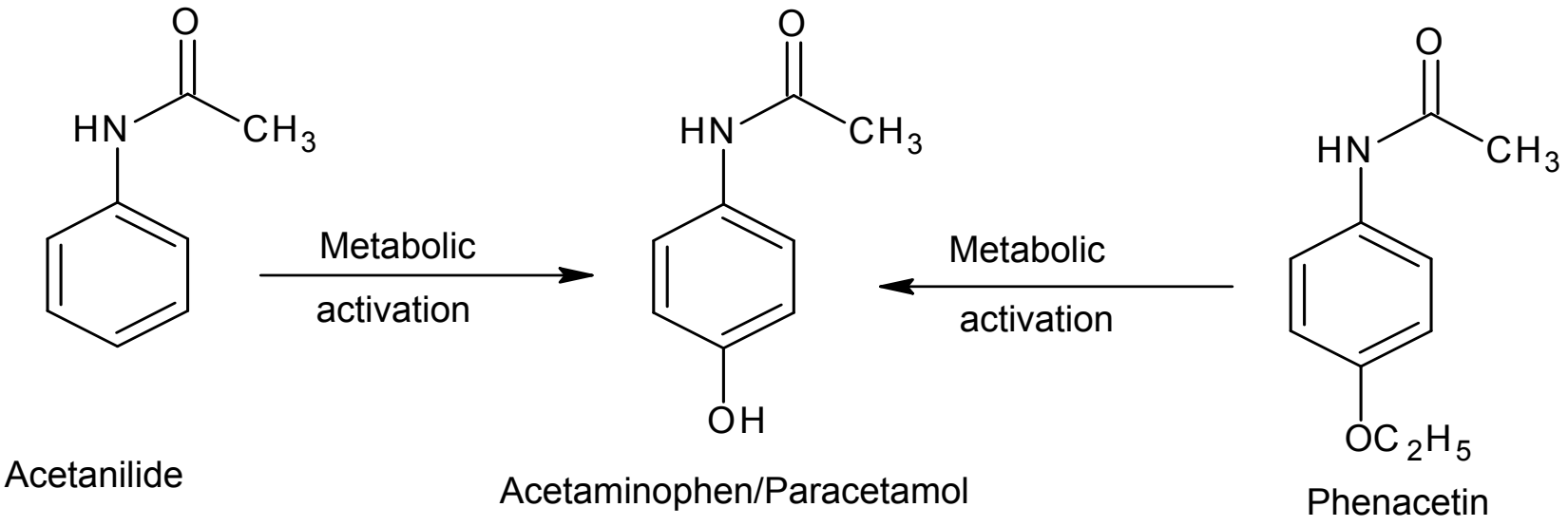
- ***Piroxicam:***
- **It is the most widely used oxicam because of its once-daily dosing schedule.**
- **It is well absorbed after oral administration.**
- **Plasma half-life of 50 hours.**
- **Require a dose of only 20 to 30 mg once daily.**
- **It undergoes extensive hepatic metabolism, catalyzed by CYP2C9 to give 5-hydroxypiroxicam as its major metabolite.**

- **Several piroxicam prodrugs have been synthesized via derivatization of the enol alcohol group (amipiroxicam, droxicam, and pivoxicam) to reduce piroxicam-induced GI irritation.**



The Analgesic Antipyretics: Paracetamol

- **Paracetamol (acetaminophen) and the related analgesic antipyretics (acetanilide, phenacetin) were introduced into therapy about the same time as aspirin and the other salicylates.**



- They were once the most widely used analgesic antipyretics for relieving pain and reducing fever because, unlike aspirin and salicylates, they do not cause ulceration or increase bleeding time.
- Because of the toxicity (methemoglobin formation, renal and urinary tract tumors), both acetanilide and phenacetin are now no longer available.
- Thus paracetamol is the only drug in this class that is still widely used worldwide because it is a safer and better tolerated pain medication.

- **Paracetamol shows similar analgesic and antipyretic efficacy to the conventional NSAIDs such as aspirin, ibuprofen, or diclofenac.**
- **However, unlike the conventional NSAIDs, it lack the antiplatelet effects of aspirin or the GI side effects associated with NSAIDs.**
- **Paracetamol also has little or no anti-inflammatory properties.**

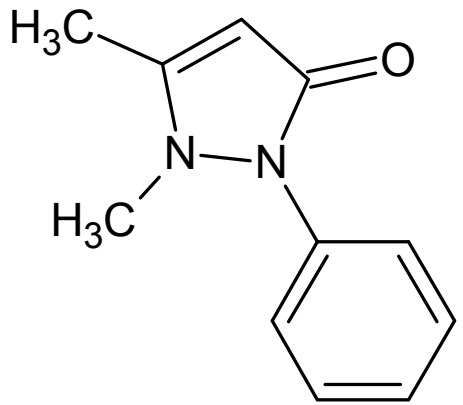
- The mechanism of action of paracetamol is unknown, but it is generally assumed that it work centrally by blocking a brain-specific enzyme, COX-3 isozyme, responsible for the biosynthesis of prostaglandin.
- Paracetamol produces analgesia and induces hypothermia centrally.
- Both of these actions are accompanied by a dose-dependent reduction of brain PGE2 levels that are not observed with diclofenac.
- The peripheral levels of PGE2/PGI2 levels were reduced only by diclofenac but not by acetaminophen.

- **Paracetamol is well tolerated with a low incidence of GI side effects.**
- **It also has good oral bioavailability, a fast onset and a plasma half-life of approximately 2 hours after dosing.**
- **Frequently used by itself OTC or in combination with codeine, hydrocodone, or oxycodone for the treatment of mild to moderate pain and to reduce fever.**
- **It is available in several non-prescription forms and is also marketed in combination with aspirin and caffeine.**

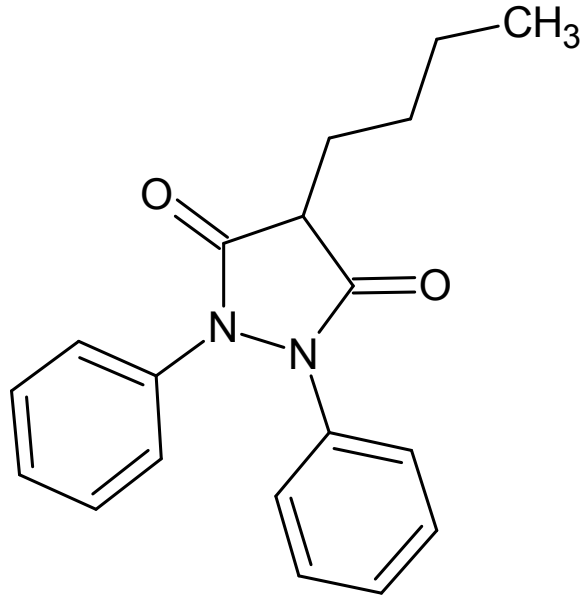
- **Phenacetin:**
- It was once a very popular analgesic antipyretic drug, more so than paracetamol/acetaminophen, because it was perceived to be safer than acetaminophen toward the stomach (i.e., less acidic in nature).
- Its use was continued until the late 1970s.
- It was already reported in 1949 that acetaminophen was the active metabolite of acetanilide and phenacetin.

- Phenacetin undergo mostly *O*-dealkylation to acetaminophen, whereas a small amount was converted by deacetylation to *p*-phenetidine, also responsible for methemoglobin formation.
- Phenacetin fell out of favor around 1980 when it was found to cause renal and urinary tract tumors in experimental animal models.
- Because of the toxicity, both acetanilide and phenacetin are now no longer available, thus acetaminophen is the only drug in this class that is still widely used worldwide because it is a safer and better tolerated pain medication.

- **Antipyrine / Phenazone:**
- It is an analgesic often used to test effects of other drugs on liver enzymes.
- In combination with benzocaine in otic solutions, antipyrine is indicated for the symptomatic relief of acute otitis media arising from various etiologies.

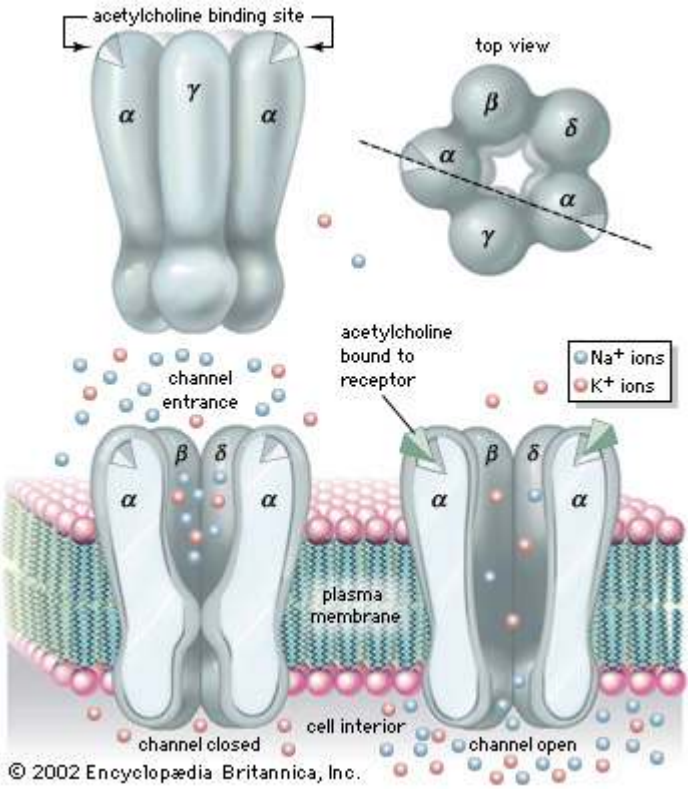


- **Phenylbutazone:**
- It is a derivative of 1,2-diphenylpyrazolidine-3,5-dione.
- It is a potent pain reliever, antipyretic, and anti-inflammatory.
- It was originally made available for use in humans for the treatment of rheumatoid arthritis and gout in 1949.
- It is no longer marketed for any human use.
- Currently it was used in veterinary practice.



Transport across the membrane

The chemical structure of the cell membrane makes it remarkably flexible, the ideal boundary for rapidly growing and dividing cells. Yet the membrane is also a formidable barrier, allowing some dissolved substances, or solutes, to pass while blocking others. Lipid-soluble molecules and some small molecules can permeate the membrane, but the lipid bilayer effectively repels the many large, water-soluble molecules and electrically charged ions that the cell must import or export in order to live. Transport of these vital substances is carried out by certain classes of intrinsic proteins that form a variety of transport systems: some are open channels, which allow ions to diffuse directly into the cell; others are "facilitators," which, through a little-understood chemical transformation, help solutes diffuse past the lipid screen; yet others are "pumps," which force solutes through the membrane when they are not concentrated enough to diffuse spontaneously. Particles too large to be diffused or pumped are often swallowed or disgorged whole by an opening and closing of the membrane.



[ligand-gated ion channel: nicotinic acetylcholine receptor

The nicotinic acetylcholine receptor is an example of a ligand-gated ion channel. It is composed of five subunits arranged symmetrically around a central conducting pore. Upon binding

acetylcholine, the channel opens and allows diffusion of sodium (Na^+) and potassium (K^+) ions through the conducting pore.]

Behind this movement of solutes across the cell membrane is the principle of diffusion. According to this principle, a dissolved substance diffuses down a concentration gradient; that is, given no energy from an outside source, it moves from a place where its concentration is high to a place where its concentration is low. Diffusion continues down this gradually decreasing gradient until a state of equilibrium is reached, at which point there is an equal concentration in both places and an equal, random diffusion in both directions.

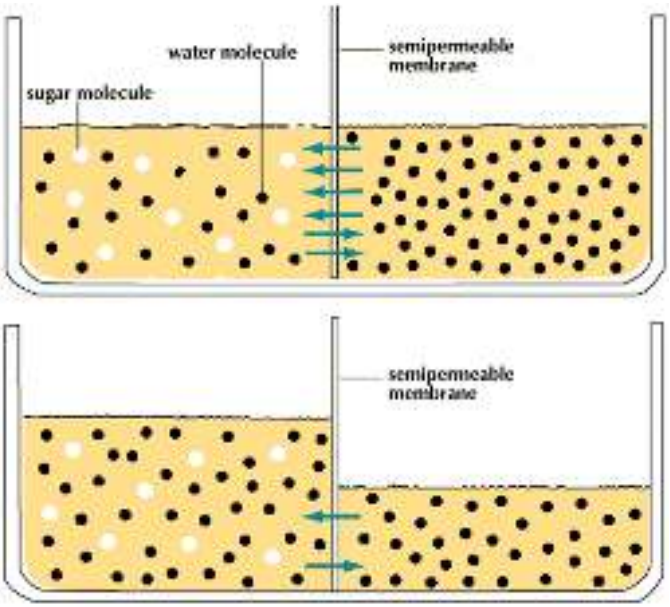
A solute at high concentration is at high free energy; that is, it is capable of doing more "work" (the work being that of diffusion) than a solute at low concentration. In performing the work of diffusion, the solute loses free energy, so that, when it reaches equilibrium at a lower concentration, it is unable to return spontaneously (under its own energy) to its former high concentration. However, by the addition of energy from an outside source (through the work of an ion pump, for example), the solute may be returned to its former concentration and state of high free energy. This "coupling" of work processes is, in effect, a transferal of free energy from the pump to the solute, which is then able to repeat the work of diffusion.

For most substances of biological interest, the concentrations inside and outside the cell are different, creating concentration gradients down which the solutes spontaneously diffuse, provided they can permeate the lipid bilayer. Membrane channels and diffusion facilitators bring them through the membrane by passive transport; that is, the changes that the proteins undergo in order to facilitate diffusion are powered by the diffusing solutes themselves. For the healthy functioning of the cell, certain solutes must remain at different concentrations on each side of the membrane; if through diffusion they approach equilibrium, they must be pumped back up their gradients by the process of active transport. Those membrane proteins serving as pumps accomplish this by coupling the energy required for transport to the energy produced by cell metabolism or by the diffusion of other solutes.

Permeation

Permeation is the diffusion, through a barrier, of a substance in solution. The rates at which biologically important molecules cross the cell membrane through permeation vary over an enormous range. Proteins and sugar polymers do not permeate at all; in contrast, water and

alcohols permeate most membranes in less than a second. This variation, caused by the lipid bilayer, gives the membrane its characteristic permeability. Permeability is measured as the rate at which a particular substance in solution crosses the membrane.



[**permeation; diffusion**

The principle of permeation can be illustrated by differences in the diffusion of sugar and water through a membrane. Large sugar molecules in the solution cannot pass through the membrane into the water (top). In contrast, small water molecules easily diffuse through the membrane (bottom). The ability of water to readily cross membranes is vital for establishing equilibrium.]

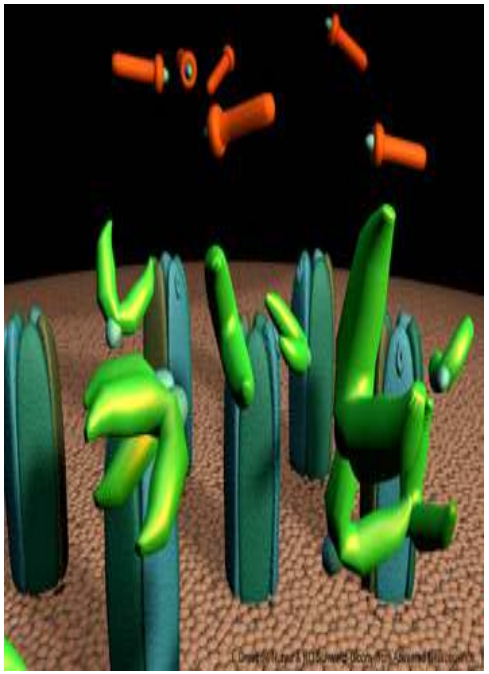
For all cell membranes that have been studied in the laboratory, permeability increases in parallel with the permeant's ability to dissolve in organic solvents. The consistency of this parallel has led researchers to conclude that permeability is a function of the fatty acid interior of the lipid bilayer, rather than its phosphoryl exterior**. This property of dissolving in organic solvents rather than water is given a unit of measure called the partition coefficient. The greater the solubility of a substance, the higher its partition coefficient, and the higher the partition coefficient, the higher the permeability of the membrane to that particular substance. For example, the water solubility of hydroxyl, carboxyl, and amino groups reduces their solubility in organic solvents and, hence, their partition coefficients. Cell membranes have been observed to have low permeability toward these groups. In contrast, lipid-soluble methyl residues and hydrocarbon rings, which have high partition**

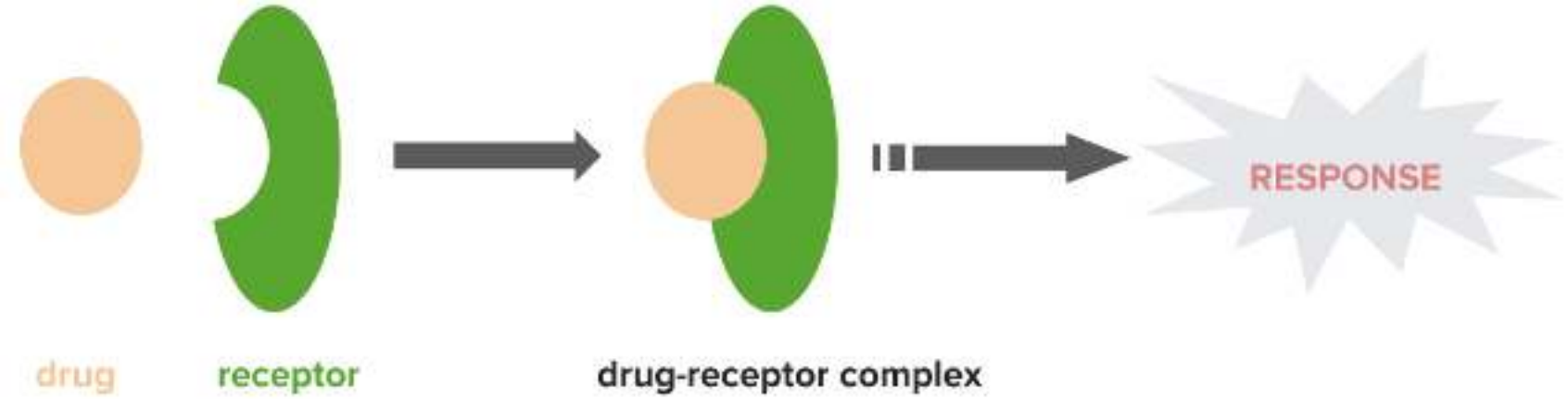
coefficients, penetrate cell membranes more easily—a property useful in designing chemotherapeutic and pharmacological drugs.

For two molecules of the same partition coefficient, the one of greater molecular weight, or size, will in general cross the membrane more slowly. In fact, even molecules with very low partition coefficients can penetrate the membrane if they are small enough. Water, for example, is insoluble in organic solvents, yet it permeates cell membranes because of the small size of its molecules. The size selectivity of the lipid bilayer is a result of its being not a simple fluid, the molecules of which move around and past a diffusing molecule, but an organized matrix, a kind of fixed grate, composed of the fatty acid chains of the phospholipids through which the diffusing molecule must fit.

Many substances do not actually cross the cell membrane through permeation of the lipid bilayer. Some electrically charged ions, for example, are repelled by organic solvents and therefore cross cell membranes with great difficulty, if at all. In these cases special holes in the membrane, called channels, allow specific ions and small molecules to diffuse directly through the bilayer.

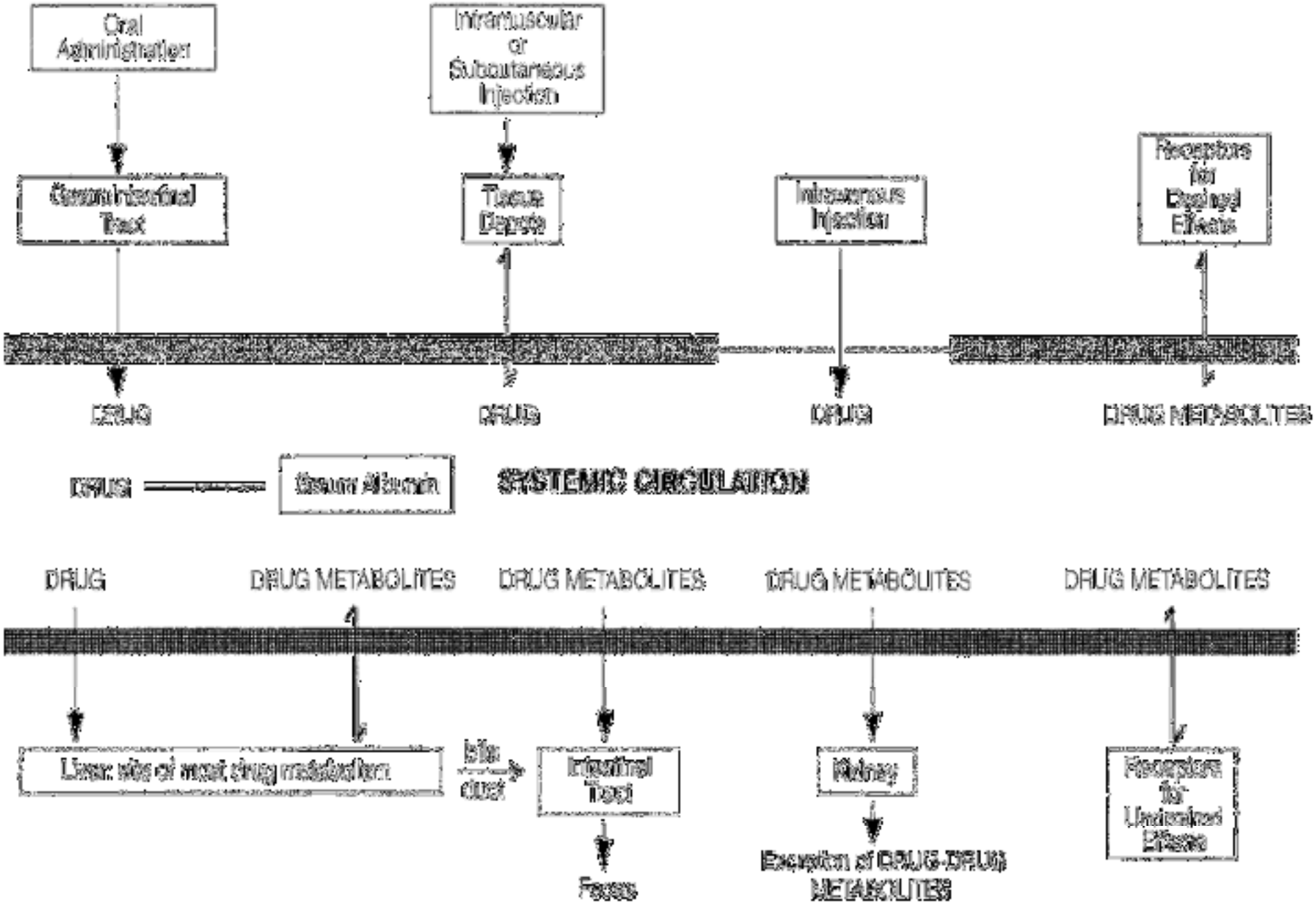
Partition Coefficient
Protein Binding
Hydrogen Bonding





- **Partition Coefficient**
- The most common physicochemical descriptor is the molecule's partition coefficient in an octanol/water system.

- The drug will go through a series of partitioning steps:
- (a) leaving the aqueous extracellular fluids
- (b) passing through lipid membranes
- (c) entering other aqueous environments before reaching the receptor


Oral Administration
Intramuscular or Subcutaneous Injection
Gastrointestinal Tract
Tissue Depots
Intravenous Injection
Receptors for Desired Effects
DRUG
DRUG
DRUG
DRUG METABOLITES
DRUG
Tissue Albumin
SYSTEMIC CIRCULATION
DRUG
DRUG METABOLITES
DRUG METABOLITES
DRUG METABOLITES
DRUG METABOLITES
Liver: site of most drug metabolism
bile duct
Intestinal Tract
Kidney
Receptors for Undesired Effects
Feces
Excretion of DRUG-DRUG METABOLITES
Drug must pass through membranes.
Drug administered directly into systemic circulation.

- 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.

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

- It is more common to use the logarithmic expression.

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

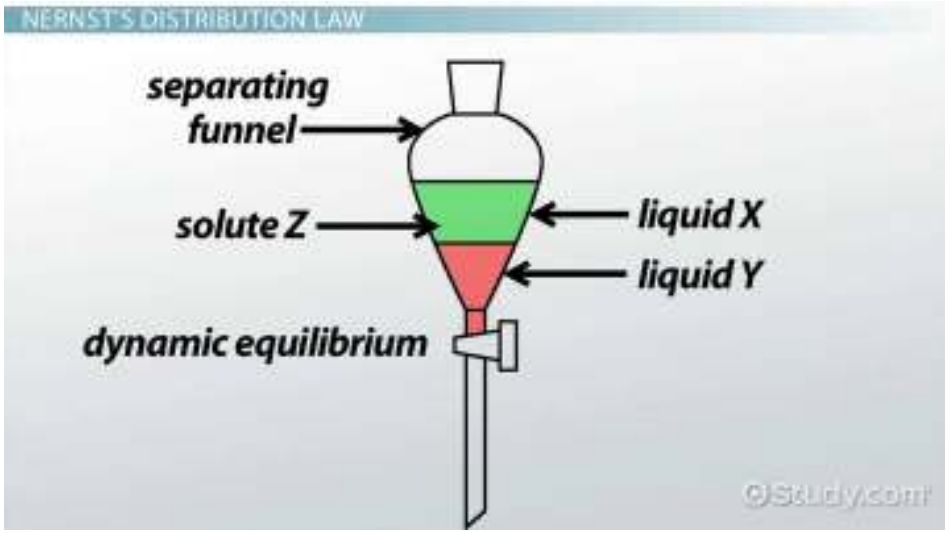
- There is large difference between the separatory funnel model and what actually occurs in the body.
- The partitioning in the funnel will reach an equilibrium at which the rate of chemical leaving the aqueous phase and entering the organic phase will equal the rate of the chemical moving from the organic phase to the aqueous phase.
- Inside body, dynamic changes occur to the drug-

➢ Metabolism

➢ Protein binding

➢ Excretion from the body

➢ Binding to receptors



- **The environment for the drug is not static.**

- A large percentage of drugs are amines and significant percentage of the drug will be in its protonated, ionized form at physiological pH 7.4.
- Similarly, HA acids (carboxyl, sulfonamide, imide) will be in their anionic forms at physiological pH.
- 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.

- The log D is defined as the equilibrium ratio of both the ionized and un-ionized species of the molecule in an octanol/water system.

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

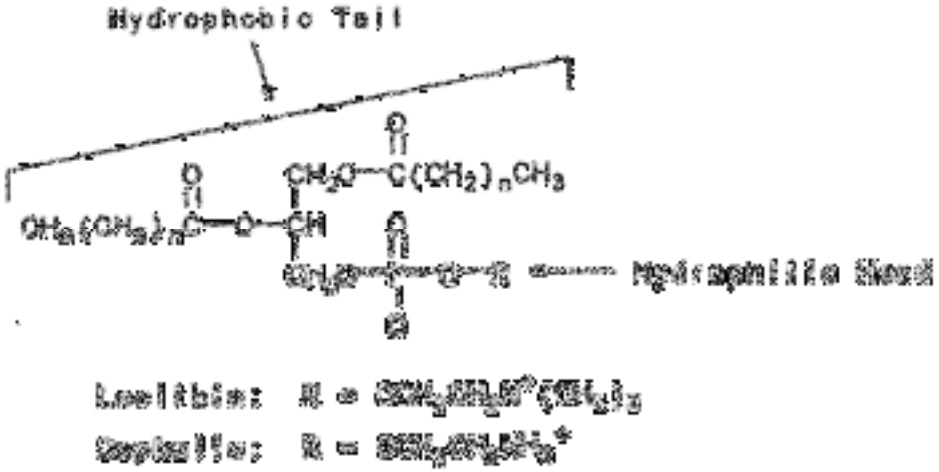
$$\log D_{acids} = \log P = \log\left[\frac{1}{(1 + 10^{(pH - pK_a)})}\right]$$

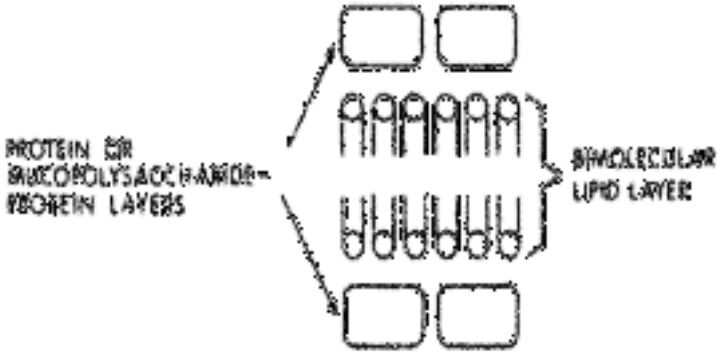
$$\log D_{bases} = \log P = \log\left[\frac{1}{(1 + 10^{(pK_a - pH)})}\right]$$

- The property of dissolving in organic solvents rather than water is given a unit of measure called the partition coefficient.
- The greater the solubility of a substance, the higher its partition coefficient, and the higher the partition coefficient, the higher the permeability of the membrane to that particular substance.
- For example, the water solubility of hydroxyl, carboxyl, and amino groups reduces their solubility in organic solvents and, hence, their partition coefficients.

- Cell membranes have been observed to have low permeability toward these groups.
- In contrast, lipid-soluble methyl residues and hydrocarbon rings, which have high partition coefficients, penetrate cell membranes more easily. This property is very much useful in designing chemotherapeutic and pharmacological drugs.
- For two molecules of the same partition coefficient, the one of greater molecular weight, or size, will in general cross the membrane more slowly.

- In fact, even molecules with very low partition coefficients can penetrate the membrane if they are small enough.
- Water, for example, is insoluble in organic solvents, yet it permeates cell membranes because of the small size of its molecules.
- The size and selectivity of the lipid bilayer is a result of its being not a simple fluid, the molecules of which move around and past a diffusing molecule, but an organized matrix, a kind of fixed grate, composed of the fatty acid chains of the phospholipids through which the diffusing molecule must fit.





- Experimental determination of octanol/water partition coefficients is tedious and time consuming.
- Today, most are calculated (clogP).
- The accuracy of these calculations is only as good as the assumptions made by the writers of the software.
- These include atomic fragment values, correction factors, spatial properties, effects of resonance and induction, internal secondary bonding forces, etc.
- There are over 30 different software packages for calculating a molecules partition coefficient, and their accuracy varies widely.

- **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.

- Depending on the equilibrium constant, 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.

- The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.
- Protein binding can have a profound effect on the-

➢ drug's effective solubility

➢ drug metabolism

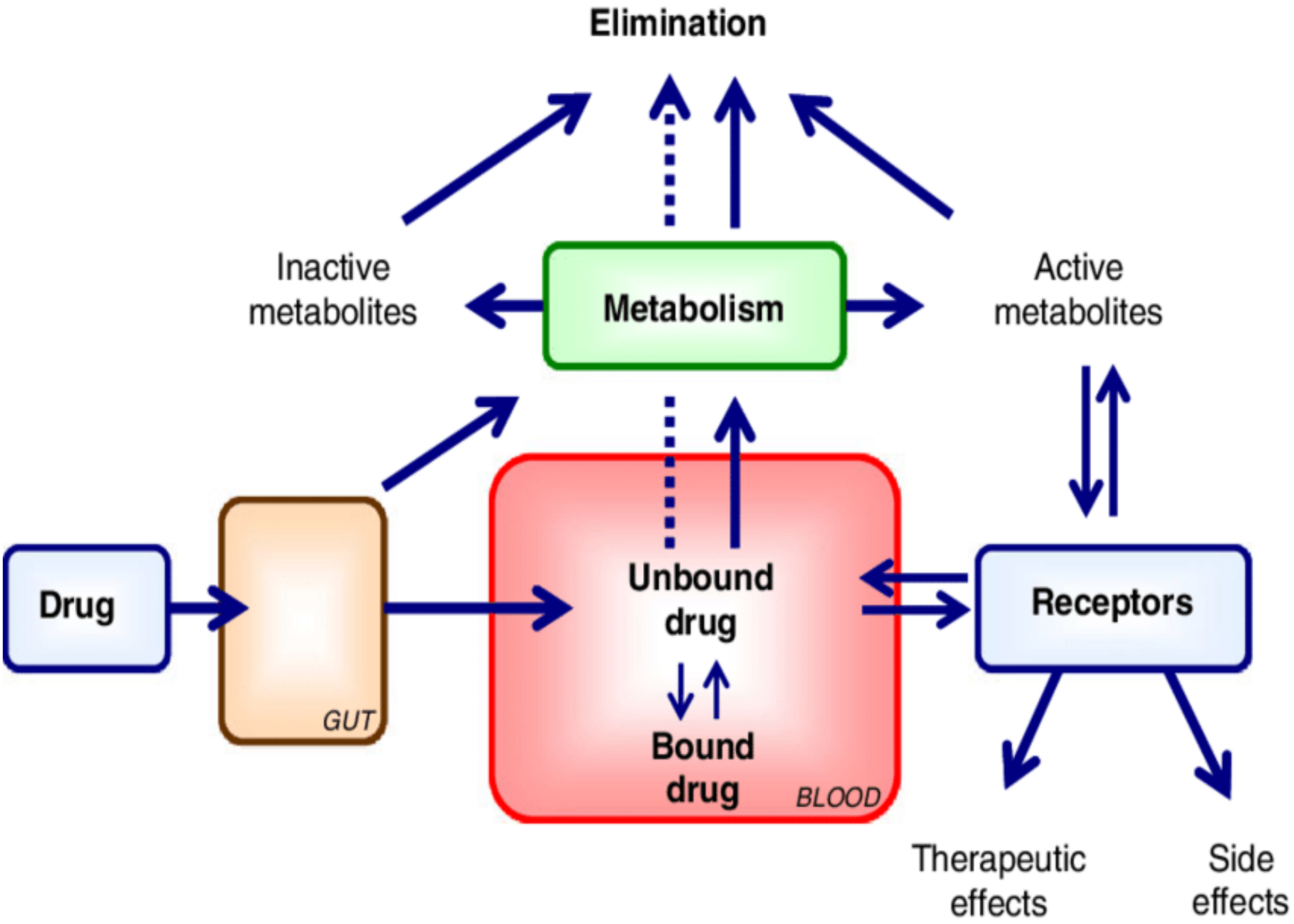
➢ biodistribution

➢ half-life in the body

➢ excretion

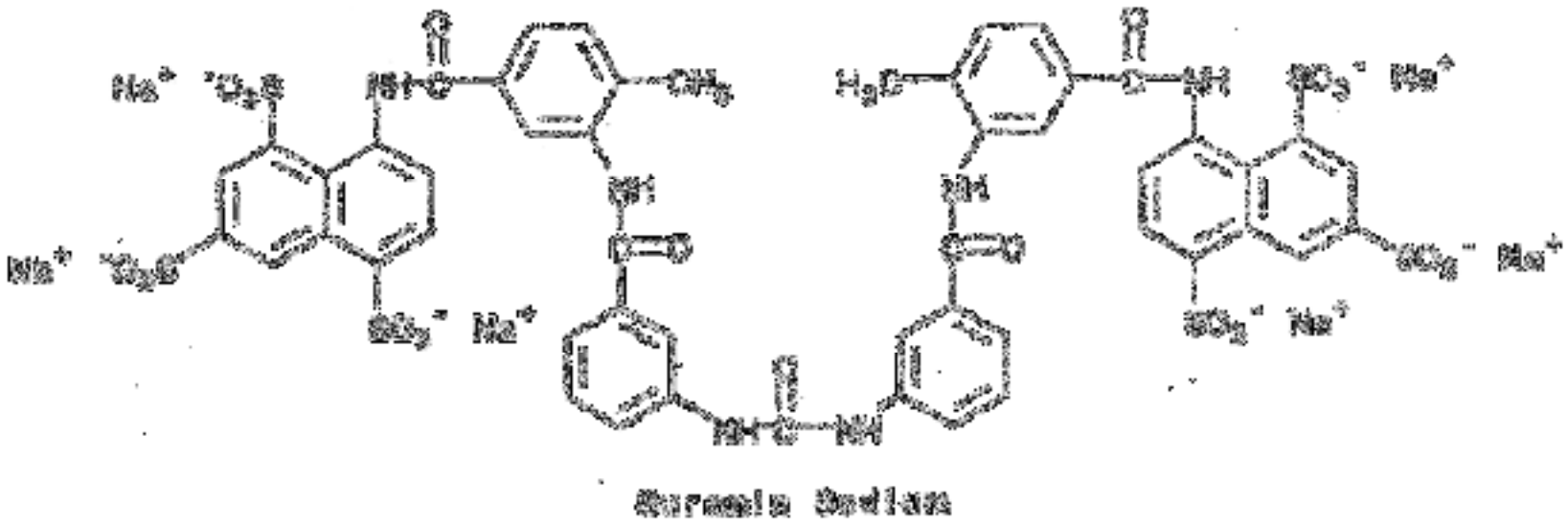
➢ Interaction with targets

➢ interaction with other drugs.

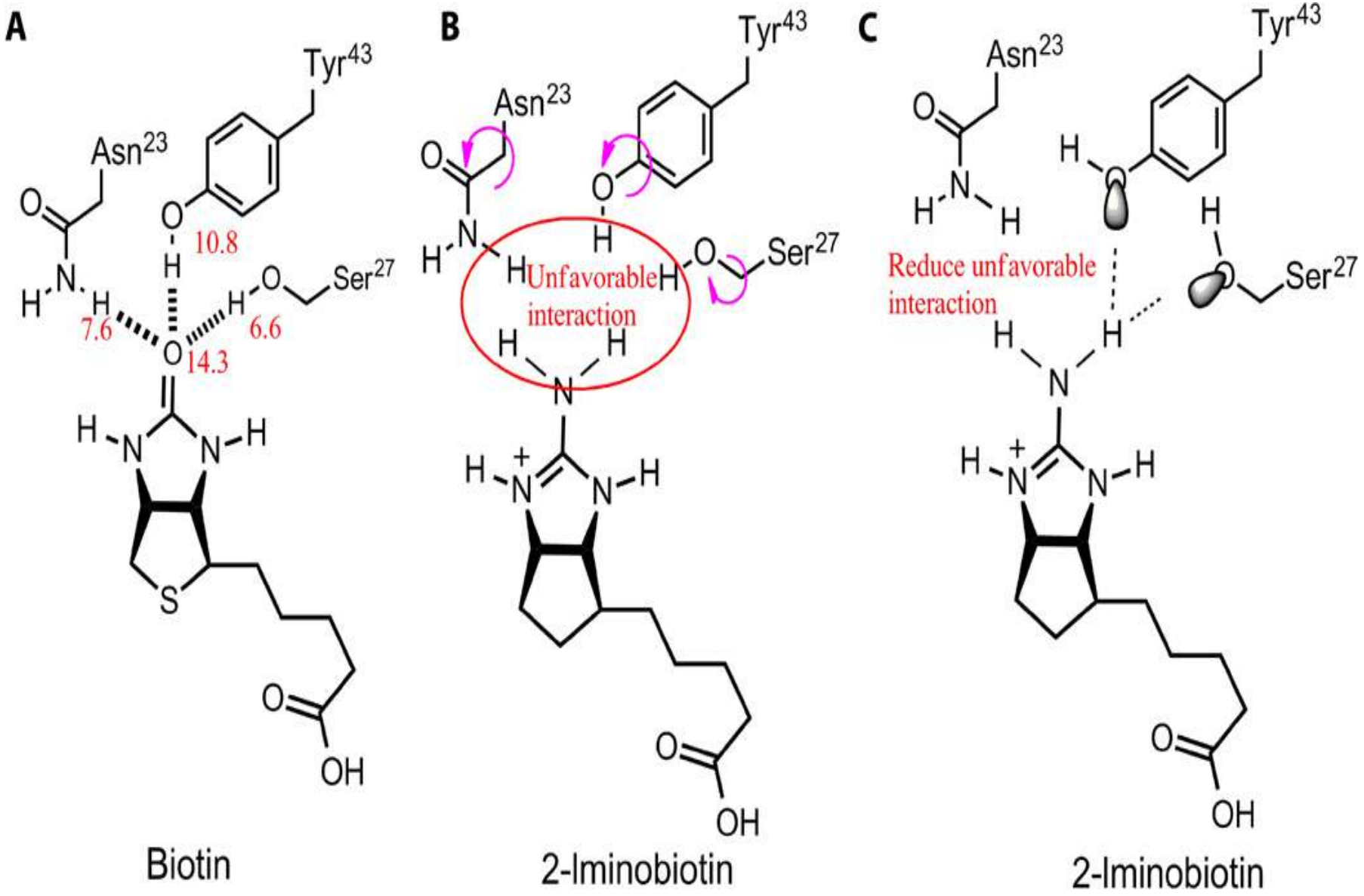

Elimination
Inactive metabolites
Metabolism
Active metabolites
Drug
GUT
Unbound drug
Bound drug
BLOOD
Receptors
Therapeutic effects
Side effects

- The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.
- 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.

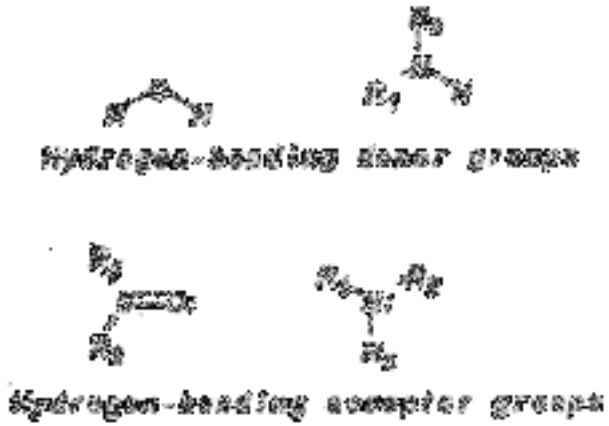
- Protein binding also can prolong the drug's duration of action.
- For example, the large, polar trypanocide suramin remains in the body in the protein-bound form for as long as 3 months (*t*1/2 = 50 days).



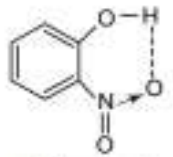
- The drug–protein binding phenomenon can lead to some clinically significant drug–drug interactions that result when one drug displaces another from the binding site on albumin.
- A large number of drugs can displace the anticoagulant warfarin from its albumin-binding sites.
- This increases the effective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


A
Tyr43
Asn23
O
10.8
H
N
H
H
7.6
O
14.3
H
6.6
O
Ser27
H
N
N
H
S
O
OH
Biotin
B
Tyr43
Asn23
O
H
N
H
H
Unfavorable
interaction
H
O
Ser27
H
H
N
H
+
N
N
H
O
OH
2-Iminobiotin
C
Tyr43
Asn23
O
H
N
H
H
Reduce unfavorable
interaction
H
O
H
Ser27
H
H
N
H
+
N
N
H
O
OH
2-Iminobiotin

- **Hydrogen Bond**
- Hydrogen bond is one of the important non-covalent interaction that occur between drug and it's target.
- 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.

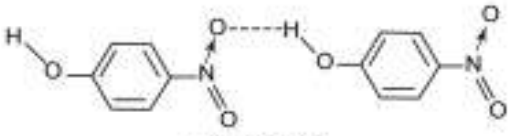


Intramolecular hydrogen bonding



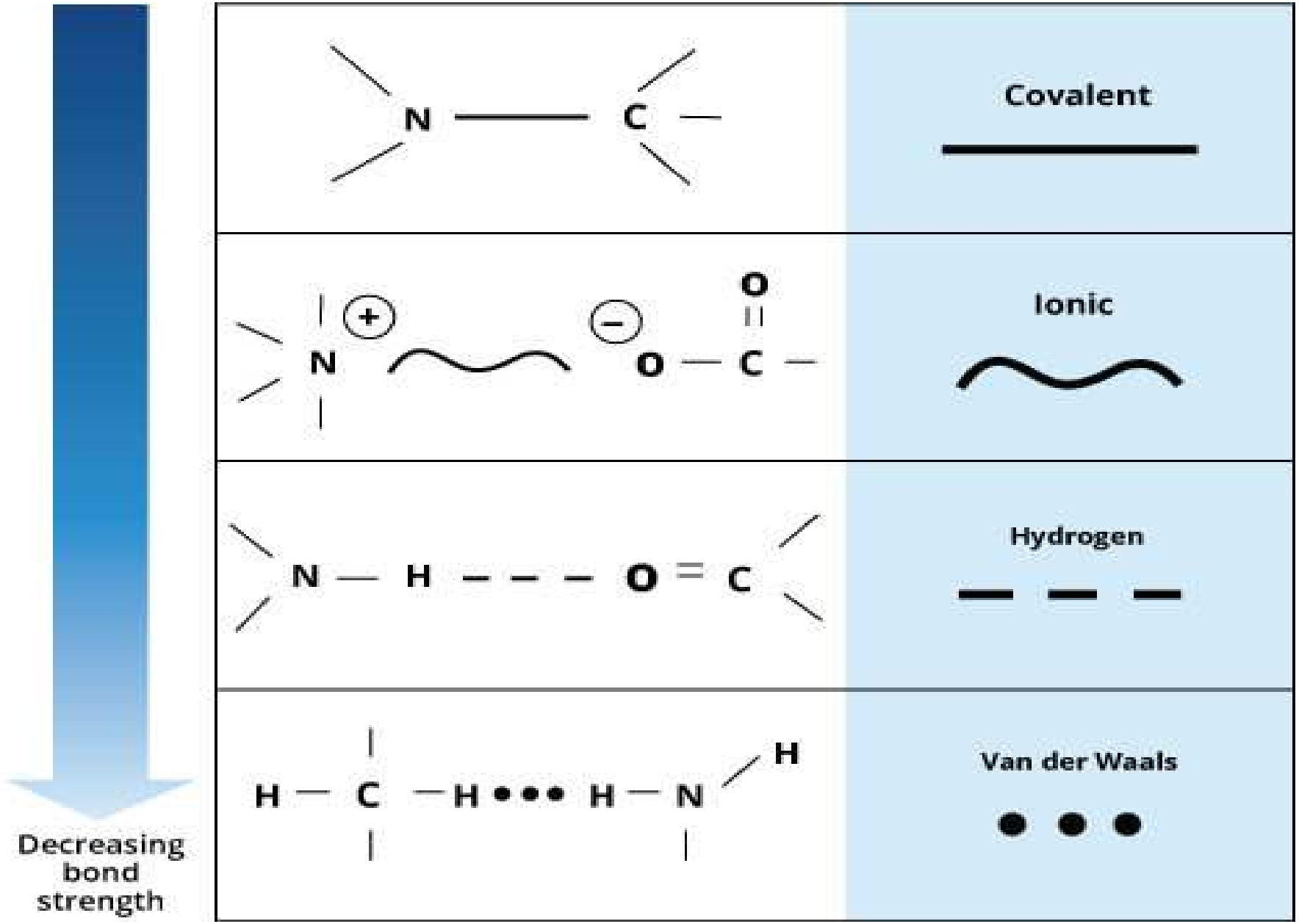
o-Nitrophenol

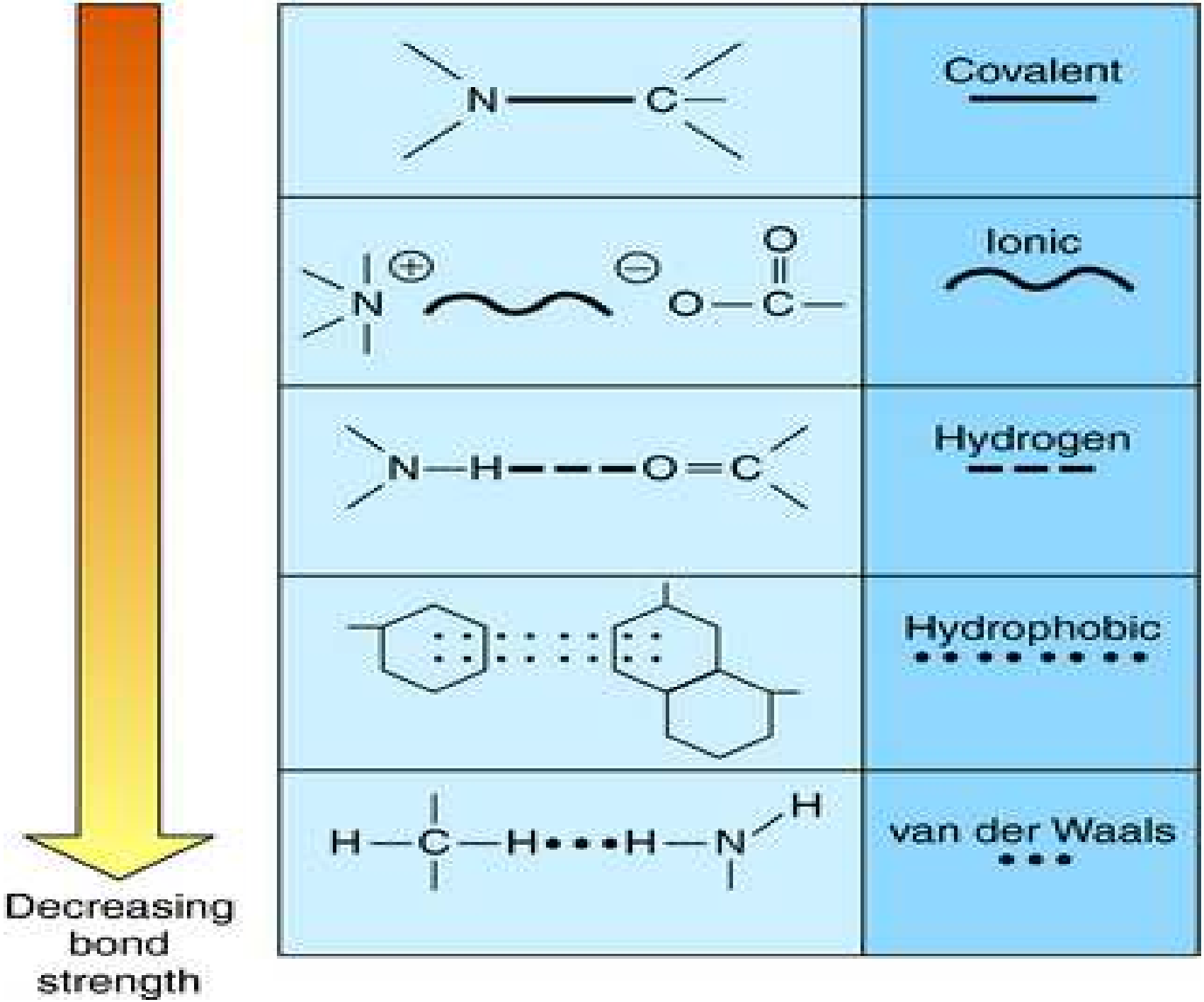
Intermolecular hydrogen bonding



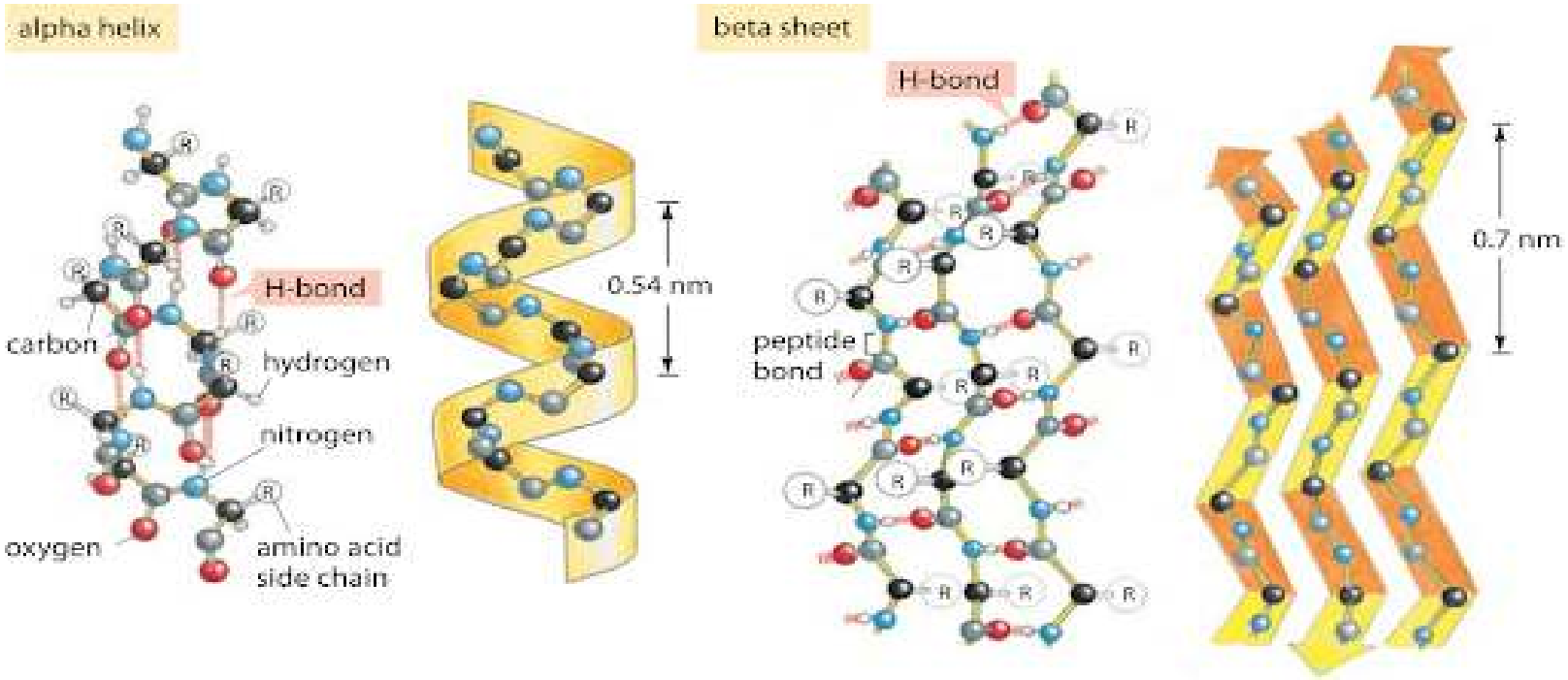
p-Nitrophenol

- Non-covalent interactions

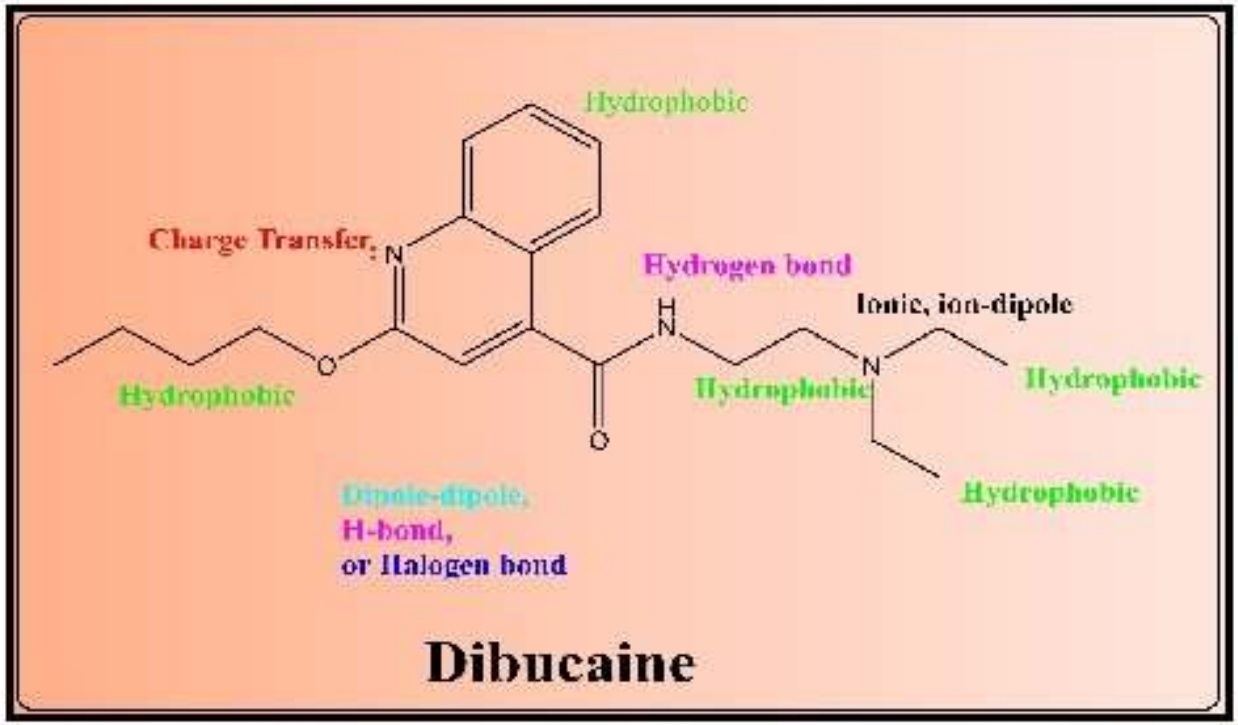



Covalent
Ionic
Hydrogen
Hydrophobic
van der Waals
Decreasing bond strength

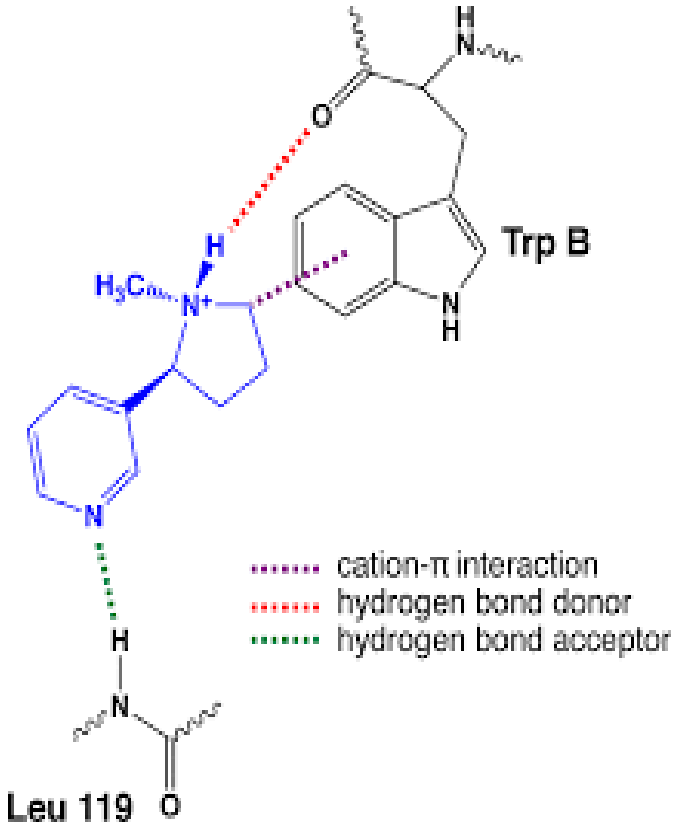
- Where multiple hydrogen bonds may be formed, the total effect may be sizable, such as that demonstrated by the stability of the protein α-helix and by the stabilizing influence of hydrogen bonds between specific base pairs in the double-helical structure of DNA.



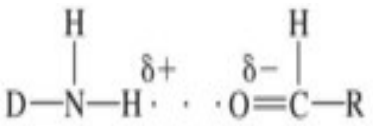
EXAMPLE OF POTENTIAL MULTIPLE DRUG–RECEPTOR INTERACTIONS

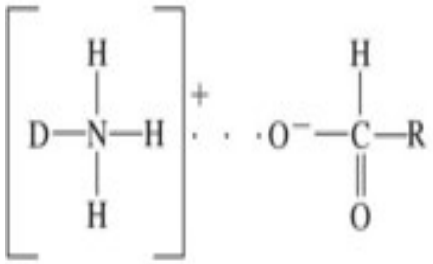


Dibucaine, the local anaesthetic drug exhibits variety of *interactions.*

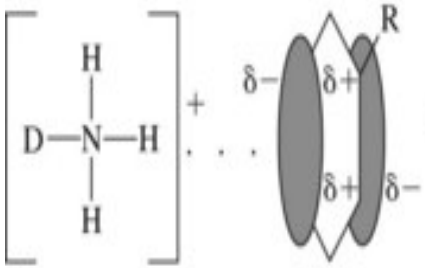

Trp B
Leu 119
cation-π interaction
hydrogen bond donor
hydrogen bond acceptor

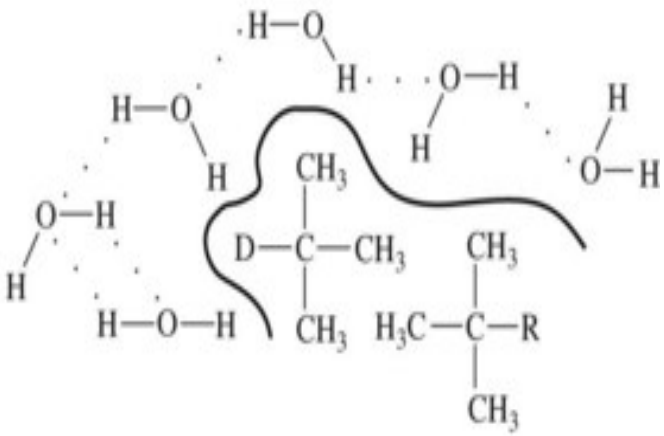

Covalent


Hydrogen

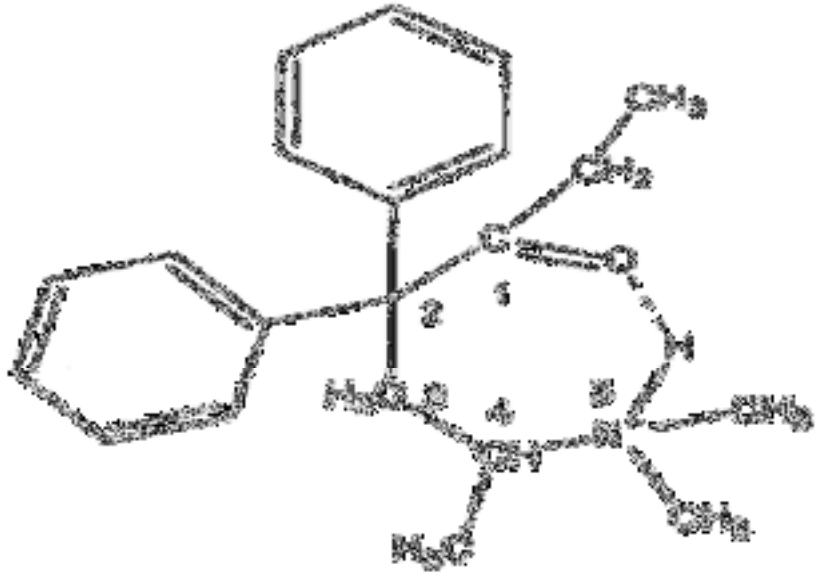

Ionic


Van der Waals


Cation–π

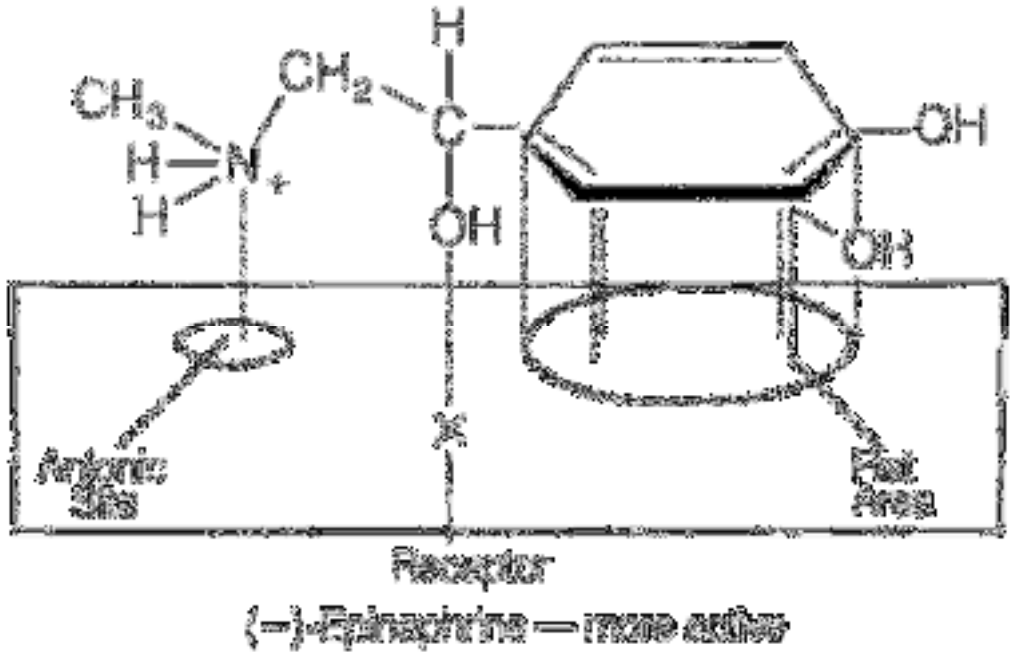

Hydrophobic

- Methadone may exist partially in a cyclic form in solution because of hydrogen bonding between the hydrogen on the nitrogen and the carbonyl oxygen or dipolar attractive forces .



Methadone stabilized by hydrogen bonding

- Classical three-point attachment model for epinephrine (adrenaline) receptor reveals that the benzene ring, benzylic hydroxyl, and protonated amine present in epinephrine are necessary to match up with the hydrophobic or aromatic region, a **hydrogen-bonding center** and an anionic site.

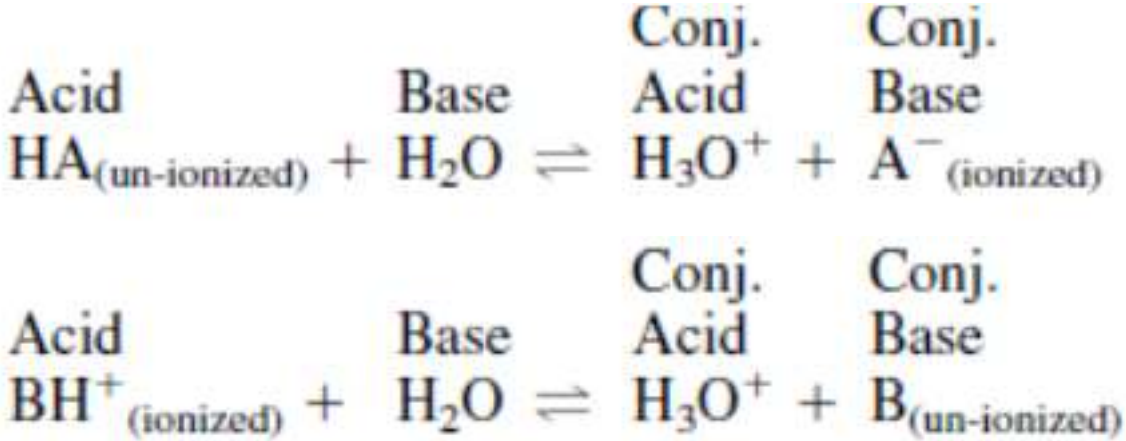


Physicochemical Properties in relation to Biological Action

- Physicochemical properties in relation to biological action:

- Ionization
- Solubility
- Partition Coefficient
- Hydrogen bonding
- Protein binding
- Chelation
- Bioisosterism
- Optical and Geometrical isomerism

- **Percent Ionization**
- Using the drug's pKa, the formulation or compounding pharmacist 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 where understanding the drug's acid–base chemistry becomes important.



- 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 –

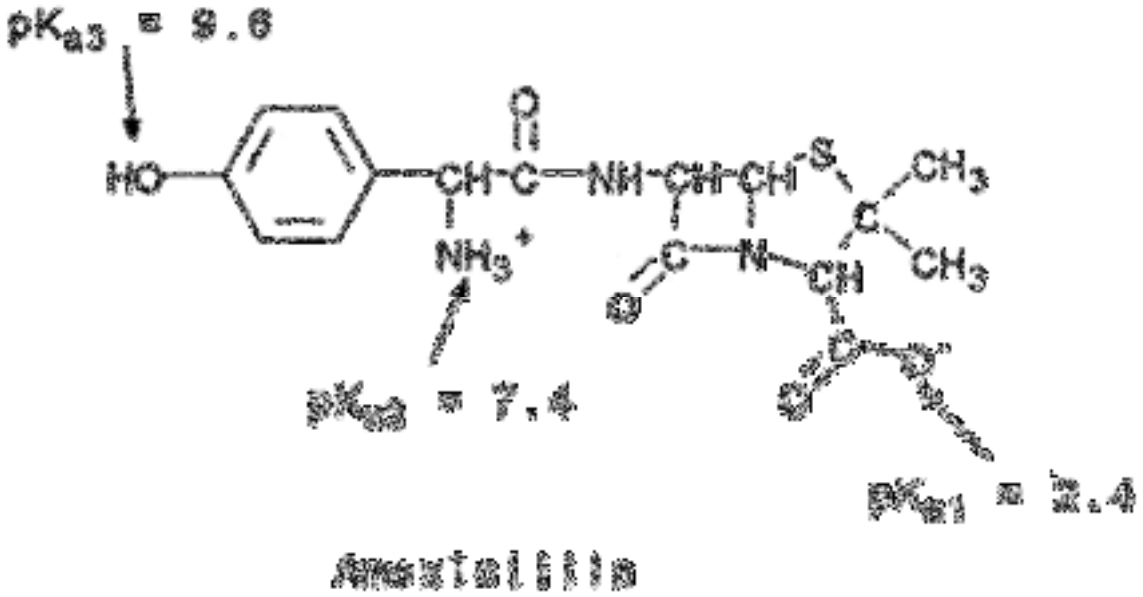
➢ the inorganic acids (e.g., HCl, H_2SO_4),

➢ enols (e.g., barbiturates, hydantoins),

➢ carboxylic acids (e.g.,arylacetic acids),

➢ amides and imides (e.g., sulphonamides and saccharin, respectively).

- The pharmaceutically important BH+ acids are all protonated amines.
- A polyfunctional drug can have several pKa's (e.g., amoxicillin).
- The latter's ionic state is based on amoxicillin's ionic state at physiological pH 7.4.



Amoxicillin

- The percent ionization of a drug is calculated by using Equation 2.3 for HA acids and Equation 2.4 for BH+ acids.

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pK_a - pH)}} \qquad \text{(Eq. 2.3)}$$

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pH - pK_a)}} \qquad \text{(Eq. 2.4)}$$

- Percent ionization relative to pKa:

	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

What is the percentage ionization of ephedrine HCl (pK_a 9.6) in an intestinal tract buffered at pH 8.0 (see example 1)? Use Equation 2.4 because this is a BH^+ acid.

$$\% \text{ ionization} = \frac{100}{1 + 10^{(8.0-9.6)}} = 97.6\%$$

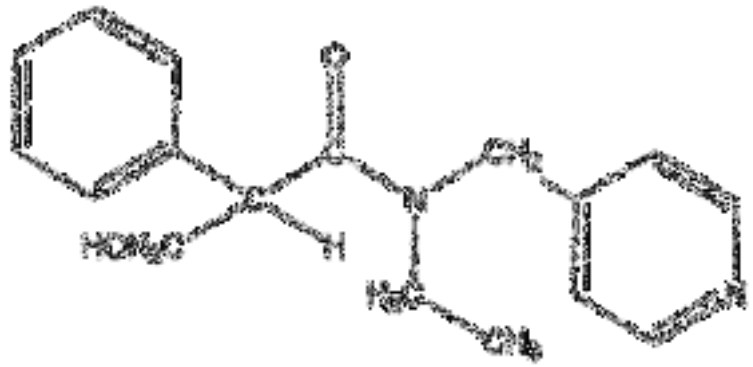
Only 2.4% of ephedrine is present as the un-ionized conjugate base.

What is the percentage ionization of indomethacin (pK_a 4.5) in an intestinal tract buffered at pH 8.0? Use Equation 2.3 because this is an HA acid.

$$\% \text{ ionization} = \frac{100}{1 + 10^{(4.5-8.0)}} = 99.97\%$$

For all practical purposes, indomethacin is present only as the anionic conjugate base in that region of the intestine buffered at pH 8.0.

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



Tropicamide

- In an acidic media, drugs that are un-ionized will be better able to diffuse through a lipid cellular membrane, cross a biologic barrier, and enter the bloodstream (e.g. be absorbed) compared to drugs that are ionized.
- A drug that is a weak acid will be best absorbed in an acidic environment (because it gains a proton and becomes un-ionized).
- The opposite is true for drugs that are weak bases.
- Consider, a weak base, NH_3.
- In an acidic environment, H^+, the drug gains a proton and becomes ionized.

- On the other hand, in an alkaline environment, a drug that is a weak base would remain un-ionized.
- Weakly basic drugs are more likely to absorbed in alkaline environments where they remain un-ionized.
- Ionized (or charged) drugs are not absorbed as efficiently as un-ionized drugs are.
- Practically speaking, this means that if taken orally, a drug that is a weak acid will be absorbed primarily in the acidic environment; whereas, a drug that is a weak base will be absorbed in the alkaline environment small intestines.

- Physiogically speaking, even though the stomach is acidic, it is not well-suited for drug absorption, even for drugs that are weak acids due to its thick mucus layer and relatively small surface area.
- The stomach is more of a “storage” organ than an absorptive one.
- In contrast, the small intestines have a large surface area available for absorption owing to extensive villi and microvilli.

- As a result, acidic drugs are most likely to be absorbed in the acidic areas of the proximal duodenum; whereas, basic drugs will be best absorbed in more alkaline areas of the distal ileum.
- In addition to a drug's ionization status, a drug is more likely to be absorbed if it contains lipophilic chemical groups, lacks bulky/oxygenated side chains, and is not too large in size.

- **Solubility:**
- **Oral ingestion** is the most convenient and commonly employed route of drug delivery due to its –

➢ ease of administration

➢ high patient compliance

➢ cost effectiveness

➢ least sterility constraints

➢ flexibility in the design of dosage form

- As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products

Lipinski Rule of Five

There are various guidelines to help, the most well-known of which is the

Lipinski Rule of Five

- molecular weight < 500
- logP < 5
- < 5 H-bond donors (sum of NH and OH)
- < 10 H-bond acceptors (sum of N and O)

Note that all numbers are multiples of five, which is the origin of the rule's name.

Otherwise absorption and bioavailability are likely to be poor.

NB This is for **oral** drugs only.

DRUG-LIKE PROPERTIES: CONCEPTS, STRUCTURE DESIGN AND METHODS FROM ADME TO TOXICITY OPTIMIZATION. EDWARD H. KERNS.

- **The major challenge with the design of oral dosage forms is their poor bioavailability.**
- The oral bioavailability depends on several factors including –

➢ Aqueous solubility

➢ Drug permeability

➢ Dissolution rate

➢ First-pass metabolism

➢ Pre-systemic metabolism

➢ Susceptibility to efflux mechanisms.

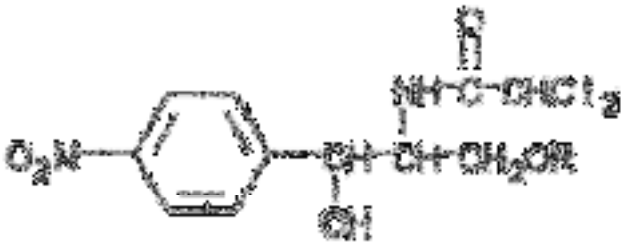
- The most frequent causes of low oral bioavailability are attributed to **poor solubility** and low permeability.
- Solubility also plays a major role for other dosage forms like parenteral formulations.
- Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.
- Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration.

- Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.
- Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.
- Water is the solvent of choice for liquid pharmaceutical formulations.
- Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility

- Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.
- For orally administered drugs solubility is the most important rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response.
- Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT.

- **Techniques for Solubility Enhancement:**
- Physical Modifications: Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.
- Chemical Modifications: Change of pH, use of buffer, derivatization, complexation, and salt formation.
- Miscellaneous Methods: Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

- **Solubility and patient compliance:**
- 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 chloramphenicol's primary alcohol.
- 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.
- Chloramphenicol succinate is freely soluble in water and is given IM.



Chloramphenicol: R = H

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

- **Solubility and Prodrugs:**
- The solubility of methylprednisolone can be altered from essentially water-insoluble methylprednisolone acetate to slightly water-insoluble methylprednisolone to water-soluble methylprednisolone sodium succinate.
- The water-soluble sodium hemisuccinate salt is used in oral, intravenous, and intramuscular dosage forms.
- Methylprednisolone itself is normally found in tablets. The acetate ester is found in topical ointments and sterile aqueous suspensions for intramuscular injection.
- Both the succinate and acetate esters are hydrolyzed to the active methylprednisolone by the patient's own systemic hydrolytic enzymes (esterases).

Ionization and Drug Absorption:

Absorption is the process of delivering a drug into the blood stream. Absorption can be accomplished by administering the drug in a variety of different ways (e.g. orally, rectally, intra-muscularly, subcutaneously, inhalation, topically, etc.). Note, that if a drug is administered intravenously (placed directly into the blood stream), the need for absorption is bypassed entirely.

For drug absorption to occur, a drug must cross biologic barriers (e.g. epithelial/endothelial cells, etc.). Only a few drugs move across cellular barriers in an "active" way; that is, a way that requires energy (ATP) and moves the drug from an area of low concentration to an area of higher concentration. On the other hand, most drugs cross cellular barriers via passive diffusion; that is, drugs simply move from an area of higher concentration to an area of lower concentration by diffusing through cell membranes. This type of drug movement does not require any energy expenditure, but will be influenced by the size of the drug and the solubility of the drug

For drug absorption to be most efficient, the properties of the drug itself and the pH of the environment where the drug is located must be considered. Most drugs are either weak acids or weak bases. Drugs that are weak acids will pick up a proton when placed in an acidic environment and will, thus, be un-ionized.

$H^+ + A^- <-> HA$

In the above example, when the weak acid, A^-, is placed into an acidic environment, H^+; the drug picks up a proton and is no longer ionized (it becomes protonated as HA). If the same acid, A^-, is placed into an alkaline environment, ^-OH, the drug will remain ionized, as A^-.

Drugs that are un-ionized will be better able to diffuse through a lipid cellular membrane, cross a biologic barrier, and enter the bloodstream (e.g. be absorbed) compared to drugs that are ionized. A drug that is a weak acid will be best absorbed in an acidic environment (because it gains a proton and becomes un-ionized).

The opposite is true for drugs that are weak bases. Consider, a weak base, NH_3. In an acidic environment, H^+, the drug gains a proton and becomes ionized.

$H^+ + NH_3 <-> NH_4^+$

On the other hand, in an alkaline environment, a drug that is a weak base would remain un-ionized.

Weakly basic drugs are more likely to absorbed in alkaline environments where they remain un-ionized compared to acidic environments where whey gain a proton and pick up a charge. Ionized (or charged) drugs are not absorbed as efficiently as un-ionized drugs are. Practically speaking, this means that if taken orally, a drug that is a weak acid will be absorbed primarily in the acidic environment; whereas, a drug that is a weak base will be absorbed in the alkaline environment small intestines.

Physiogically speaking, even though the stomach is acidic, it is not well-suited for drug absorption, even for drugs that are weak acids due to its thick mucus layer and relatively small surface area. The stomach is more of a "storage" organ than an absorptive one. In contrast, the small intestines have a large surface area available for absorption owing to extensive villi and microvilli. As a result, acidic drugs are most likely to be absorbed in the acidic areas of the proximal duodenum; whereas, basic drugs will be best absorbed in more alkaline areas of the distal ileum.

In addition to a drug's ionization status, a drug is more likely to be absorbed if it contains lipophilic chemical groups, lacks bulky/oxygenated side chains, and is not too large in size.

Other factors that also impact drug absorption include the following:

1. Physiologically, a drug's absorption is enhanced if there is a large surface area available for absorption (e.g. villi/microvilli of intestinal tract) and if there is a large blood supply for the drug to move down its concentration gradient.

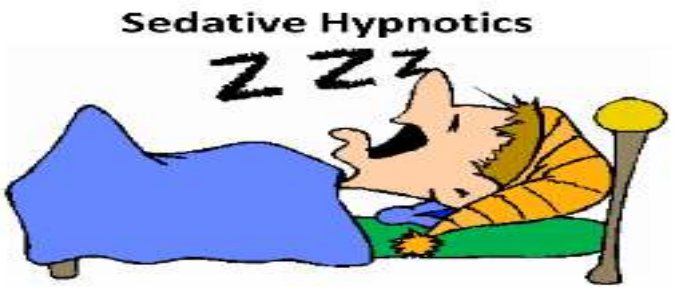
2. The presence of food/other medications in the stomach may impact drug absorption – sometimes enhancing absorption and other times forming insoluble complexes that are not absorbed (it depends on the specific drug).

3. Some drugs are inactivated before they can be absorbed by enzymes, acidity, bacteria, etc.

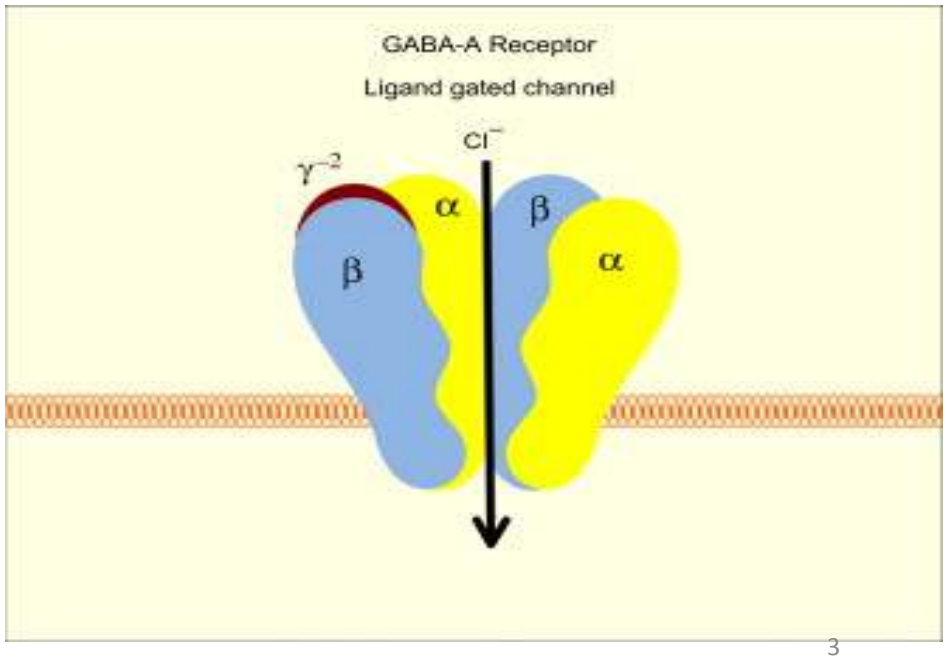
SEDATIVES AND HYPNOTICS

INTRODUCTION

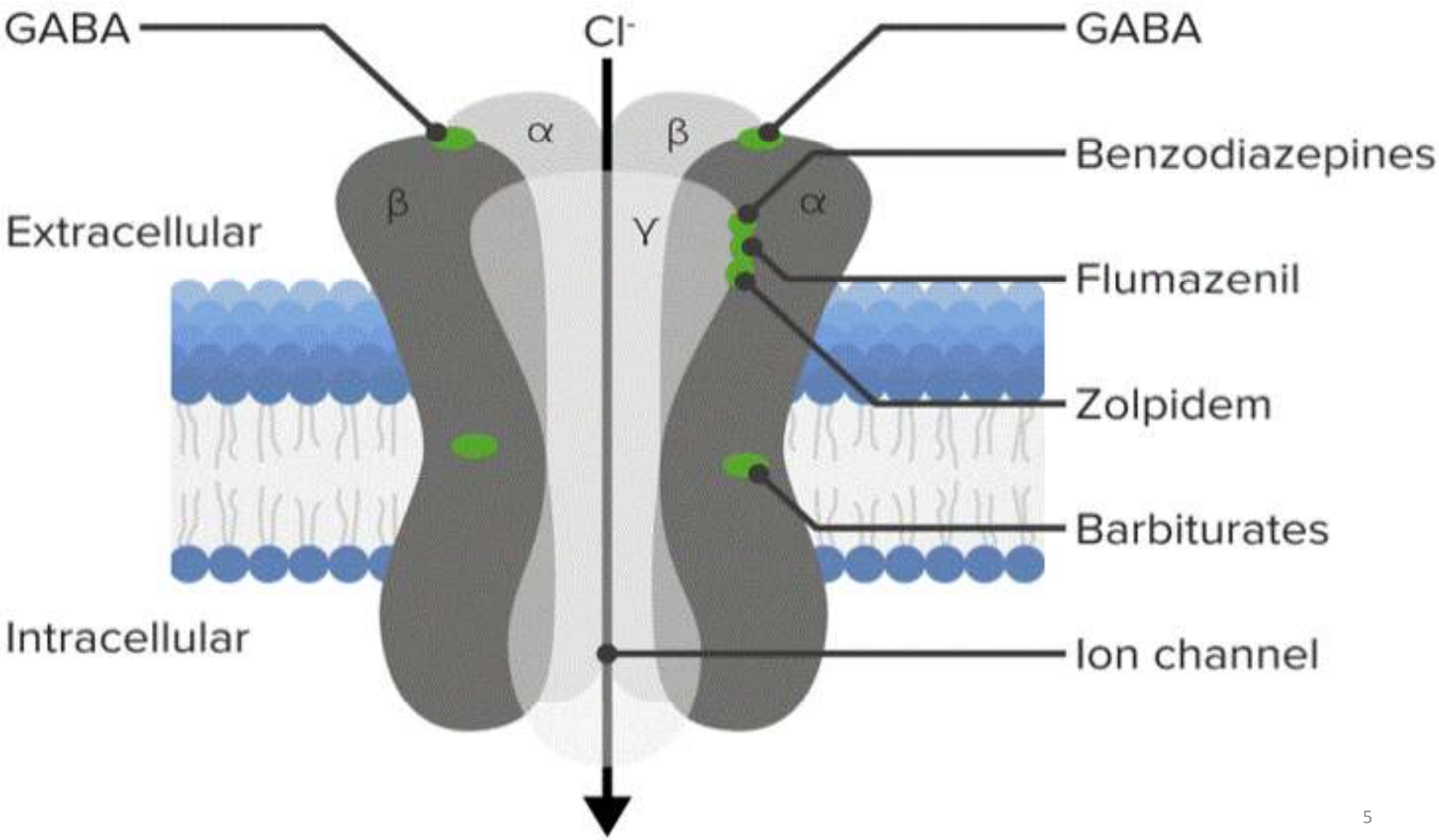
- Both sedatives and hypnotics are **central nervous system depressants.**
- They **induce sleep which resemble natural sleep**.
- **Sedative drug** produces **mild depression of central nervous system**.
- It decreases the activity and excitement of the affected person and calms down.

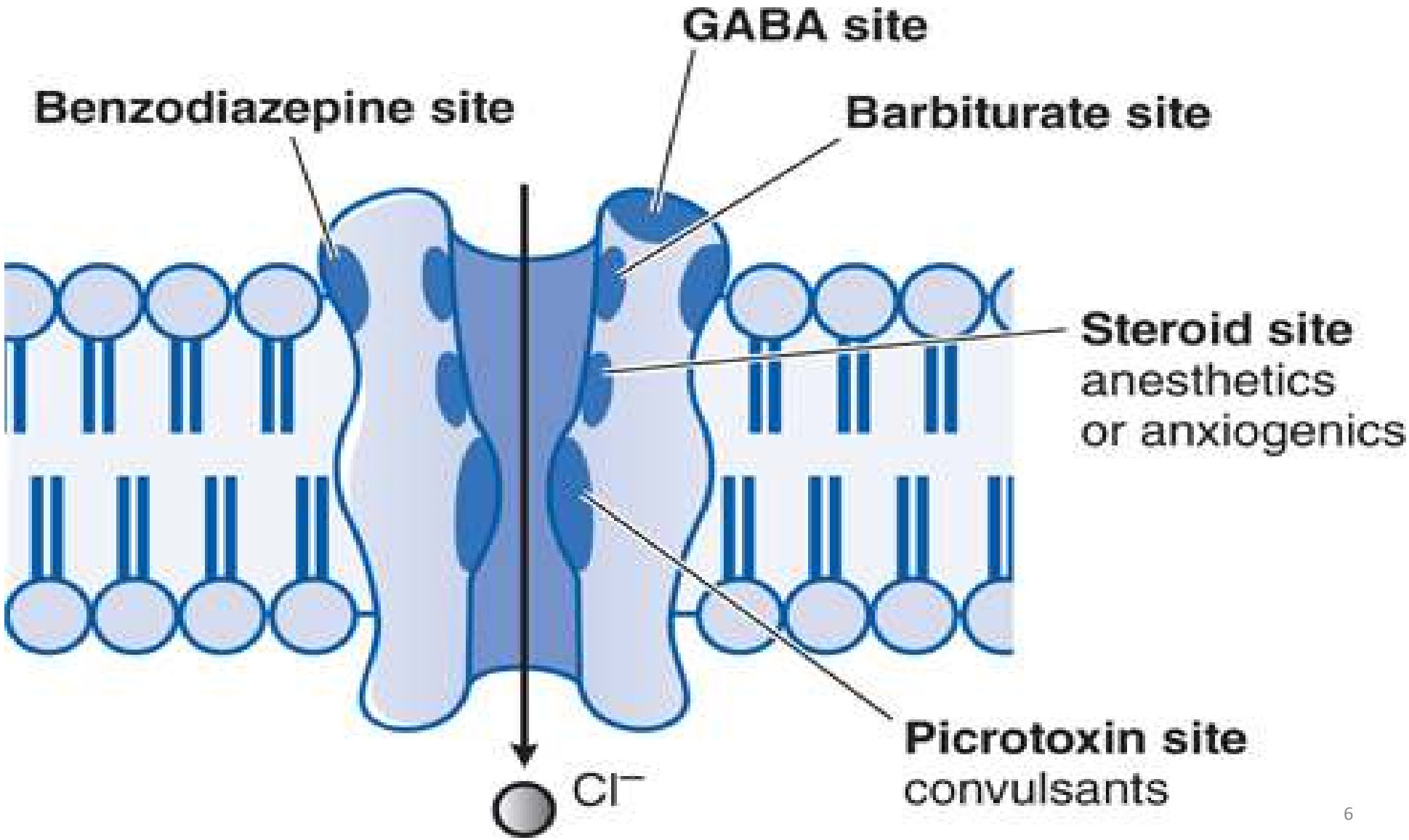


- **Hypnotic drug** produces **maximum depression of central nervous system** when compared with sedative.
- It produces drowsiness and makes the affected person to sleep which resemble natural sleep.
- Reticular activity is absent.



- **General mechanism of action:**
- Majority of sedatives and hypnotics interfere with the GABA receptors (inhibitory neurotransmitter) and induce opening of chloride ion channel.
- Some may interfere with glutamate receptors(excitatory) and inhibit the actions of glutamate(excitatory neurotransmitter).
- Drugs like barbiturates and benzodiazepines are known for their positive allosteric modulation of GABA receptors.


GABA
Cl-
GABA
α
β
Benzodiazepines
β
α
Extracellular
γ
Flumazenil
Zolpidem
Barbiturates
Intracellular
Ion channel


GABA site
Benzodiazepine site
Barbiturate site
Steroid site
anesthetics
or anxiogenics
Picrotoxin site
convulsants
Cl⁻

- **Therapeutic Uses:**

- Treatment of Insomnia (sleeplessness).
- Treatment of Convulsions.
- Induction of General anesthesia.
- Treatment of Psychiatric disorders.
- Treatment of anxiety.
- Some drugs like meprobamate are also used as skeletal muscle relaxant.

- **CLASSIFICATION:**
- **1. GABAA receptor modulators**
- **Benzodiazepines** are highly effective anxiolytic and hypnotic agents (e.g., diazepam, chlordiazepoxide, prazepam, clorazepate, oxazepam, alprazolam, flurazepam, lorazepam, triazolam, temazepam, estazolam, and quazepam).
- They bind to benzodiazepine-binding sites on GABA-A receptor (also known as benzodiazepine receptor [BzR]).
- They are sometimes called benzodiazepine receptor agonists (BzRAs).

- **Nonbenzodiazepine hypnotics (Z-drugs):**
- Imidazopyridine (zolpidem), pyrazolopyrimidine (zaleplon), and cyclopyrrolone (zopiclone and its [*S*]-[+]-enantiomer eszopiclone).
- **Barbiturates** including amobarbital, aprobarbital, butabarbital, pentobarbital, phenobarbital, and secobarbital are largely obsolete and superseded by benzodiazepines.
- Their use is now confined to anesthesia and treatment of epilepsy.
- **General anesthetics and ethanol.**

- **2. Melatonin-1 receptor (MT1) agonists.**
- A new drug in this area is **ramelteon**.
- It is one among 10 Food and Drug Administration (FDA)-approved drugs for insomnia.
- Five benzodiazepines, four non-benzodiazepines and ramelteon.
- **3. Atypical azaspirodecanediones:**
- **Buspirone** is a partial 5- HT1A receptor agonist and an anxiolytic.
- It is less sedative and has less abuse potential.

- **4. Miscellaneous drugs** such as **chloral hydrate**, **meprobamate**, and **glutethimide** are no longer recommended, but occasionally used.
- **5. Antipsychotics and anticonvulsants.**
- It has been proposed that **dopamine (DA)** has a facilitative and active role in the sleep–wakefulness cycle.
- Waking appears to be a state maintained by D2 receptor activation, whereas **blocking D2 receptor appears to cause sedation**.

- **6. Antidepressants:**

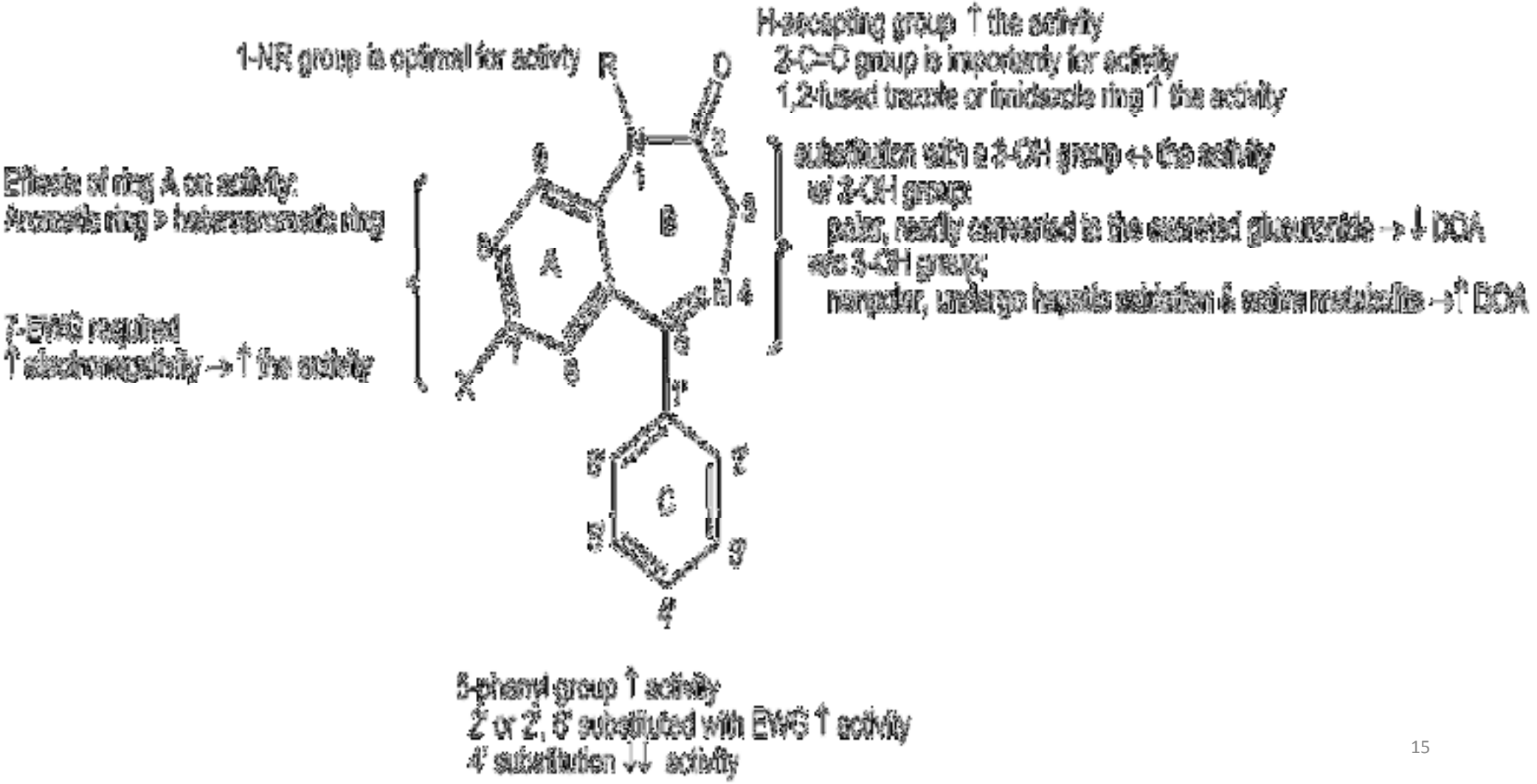
- Many antidepressants cause sedation, of which **trazodone**, **doxepin**, and **mirtazapine** have been shown to be effective in the treatment of insomnia in patients with depression.

- **Several selective serotonin reuptake inhibitors (SSRIs)**, including **escitalopram**, **fluoxetine**, **fluvoxamine**, **paroxetine**, and **sertraline**, became the first-line therapy for some anxiety disorders in 1990s because they are **not as addictive as benzodiazepines**.

- **7. Sedative H1-antihistamines:**
- **Diphenhydramine and Doxylamine:**
- Diphenhydramine is sometimes used as sleeping pills, particularly for wakeful children.
- It is proposed that histamine may have an involvement in wakefulness and rapid eye movement (REM) sleep.
- The H1 receptor agonists and the H3 receptor antagonists increase wakefulness, whereas the **H1 receptor antagonists** and **H3 receptor agonists** have the opposite effect.
- Another example of H1-antihistamines is doxylamine.

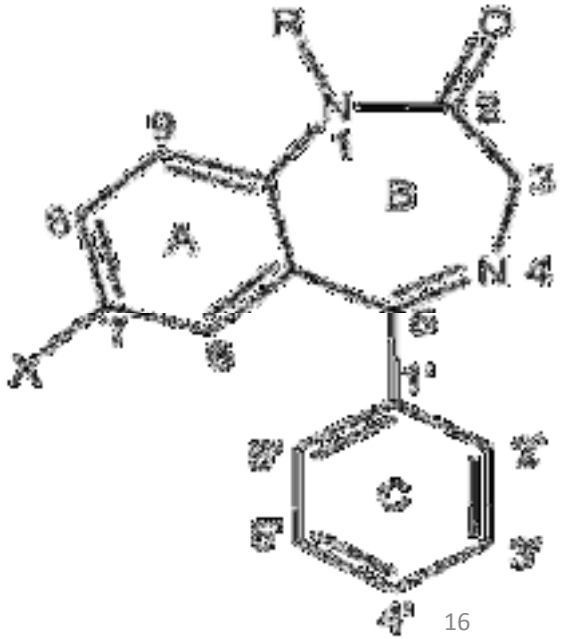
- **8. β-Adrenoceptor antagonists** (e.g., propranolol) are sometimes used by actors and musicians to reduce the symptoms of stage fright, but their use by snooker players to minimize tremor is banned as unsportsmanlike.
- **9. New areas explored for sleep-promoting agents:**
- **Adenosine-2A receptor (A2A) agonists** (adenosine is a possible endogenous sleep-producing agent).
- **Linoleamide** and **9,10-octadecenoamide** are possible endogenous sleep-producing agents and are positive modulators of GABA-A receptors.
- **Anandamide** is an endogenous cannabinoid that might be used as a lead to search for new hypnotics.

- **General Structure and SAR of Benzodiazepines:**

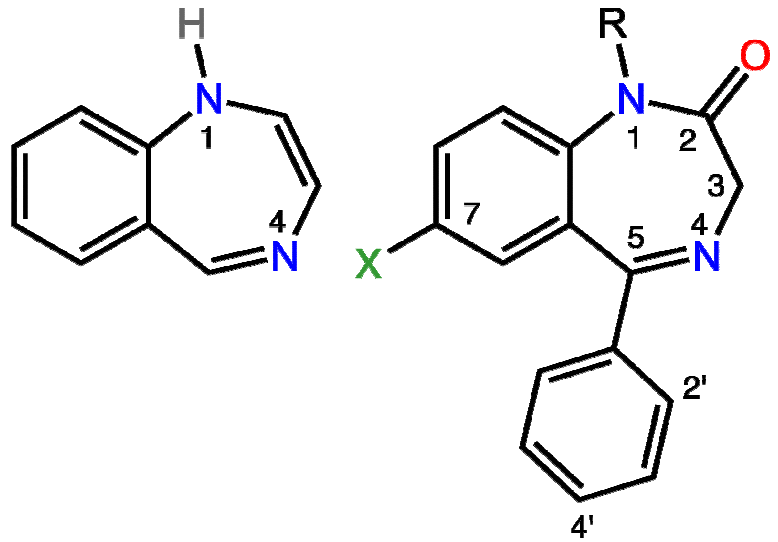


- Most benzodiazepines are **5-aryl-1,4-benzodiazepines** and contain a **carboxamide** group in the **seven-membered diazepine ring** structure.
- **Aromatic or heteroaromatic ring A is required for the activity.**
- This aromatic ring participate in **π-π interaction** with aromatic amino acid residues of the receptor.
- An **electronegative substituent at position 7**

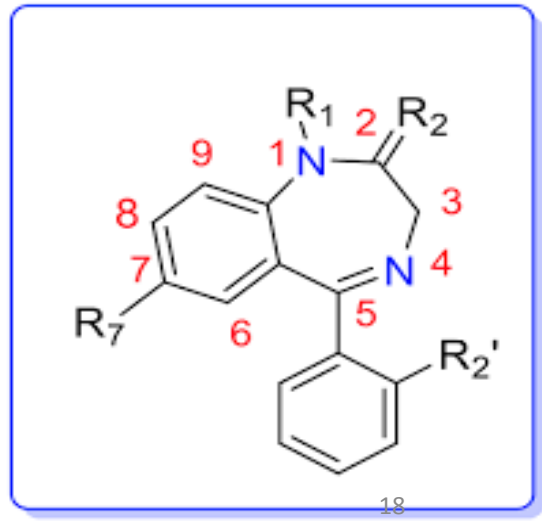
  is required for activity.
- The more electronegative it is, the higher the activity.



- Positions 6, 8, and 9 should not be substituted.
- A phenyl ring C at position 5 promotes activity.
- If this phenyl group is *ortho* (2) or di*ortho* (2,6) substituted with electron-withdrawing groups, activity is increased.
- On the other hand, *para* substitution decreases activity greatly.



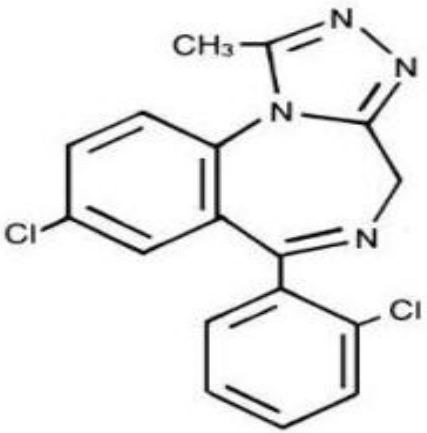
- In diazepine ring B, saturation of the 4,5-double bond or a shift of it to the 3,4-position decreases activity.
- Alkyl substitution at the 3-position decreases activity; substitution with a 3-hydroxyl does not decrease activity.
- The presence or absence of the 3-hydroxyl group is important pharmacokinetically.
- Compounds without the 3-hydroxyl group are nonpolar.
- They are 3-hydroxylated in liver slowly to active 3-hydroxyl metabolites, and have long overall half-lives.



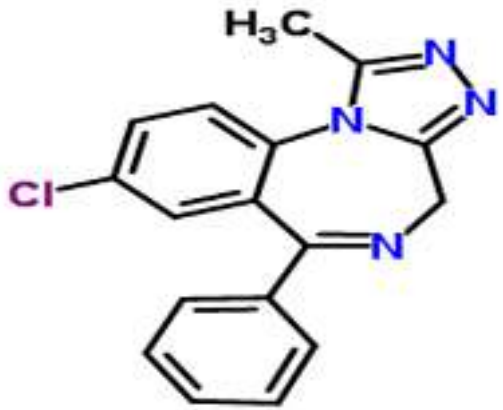
- In contrast , 3-hydroxyl compounds are much more polar, rapidly converted to inactive 3-glucuronides, which are excreted in urine and thus are short-lived.
- The 2- carbonyl function is important for activity, as is the nitrogen atom at position 1.
- The *N*1-alkyl side chains are tolerated.
- A proton-accepting group at C2 is required and may interact with histidine residue (as a proton donor) in benzodiazepine binding site of GABAA receptor.

- Other triazole or imidazole rings capable of H-bonding can be fused on positions 1 and 2 and increase the activity.
- Compounds with a fused triazolo ring(triazolam and alprazolam) and with a fused imidazolo ring(midazolam) are also active.

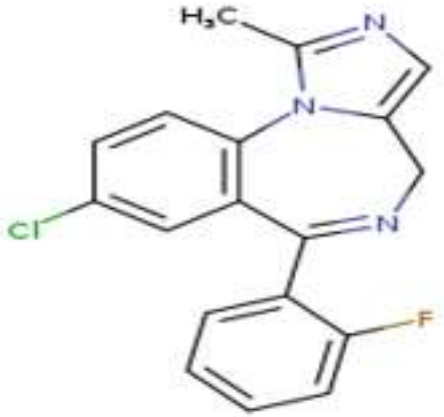
TRIAZOLAM



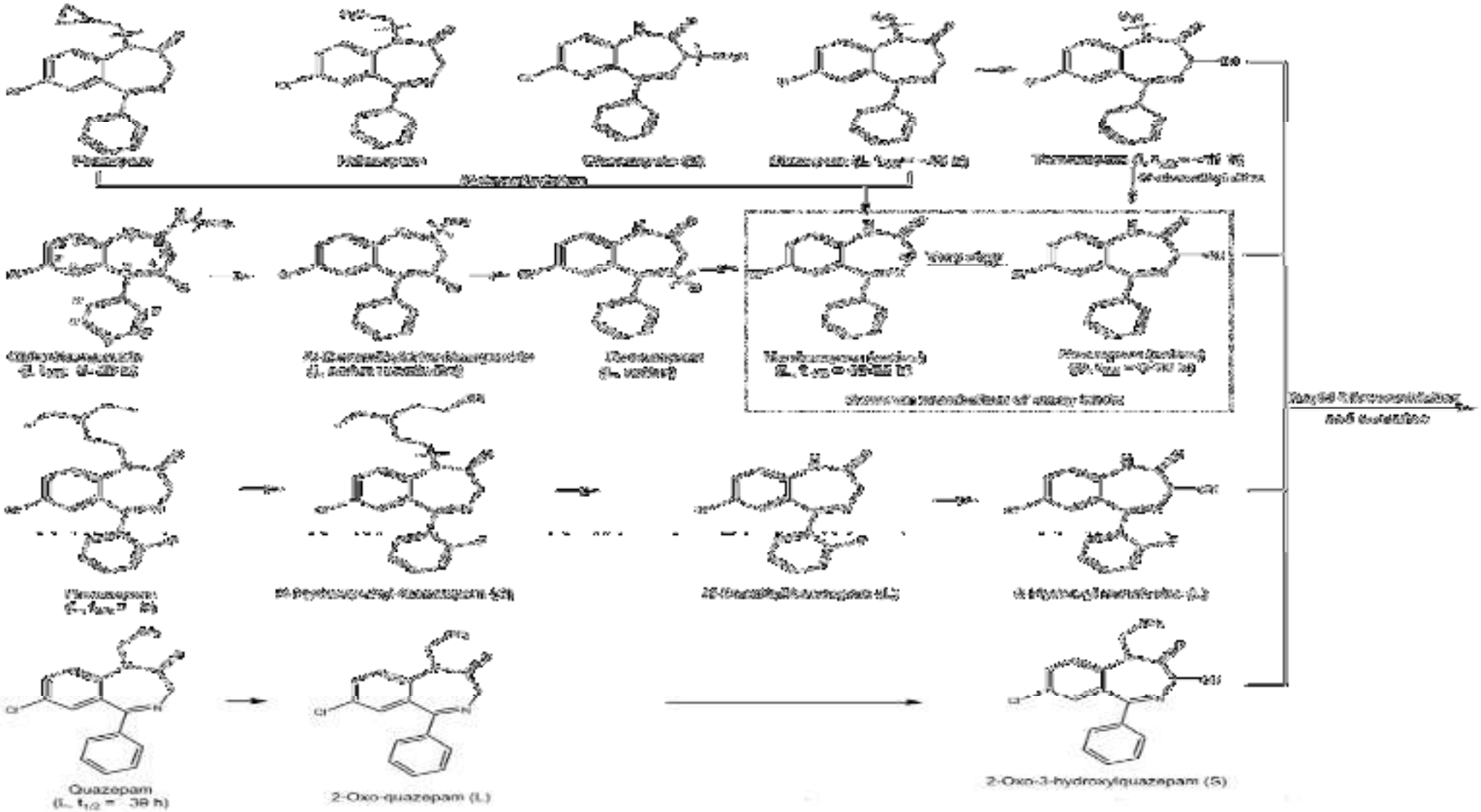
ALPRAZOLAM



MIDAZOLAM

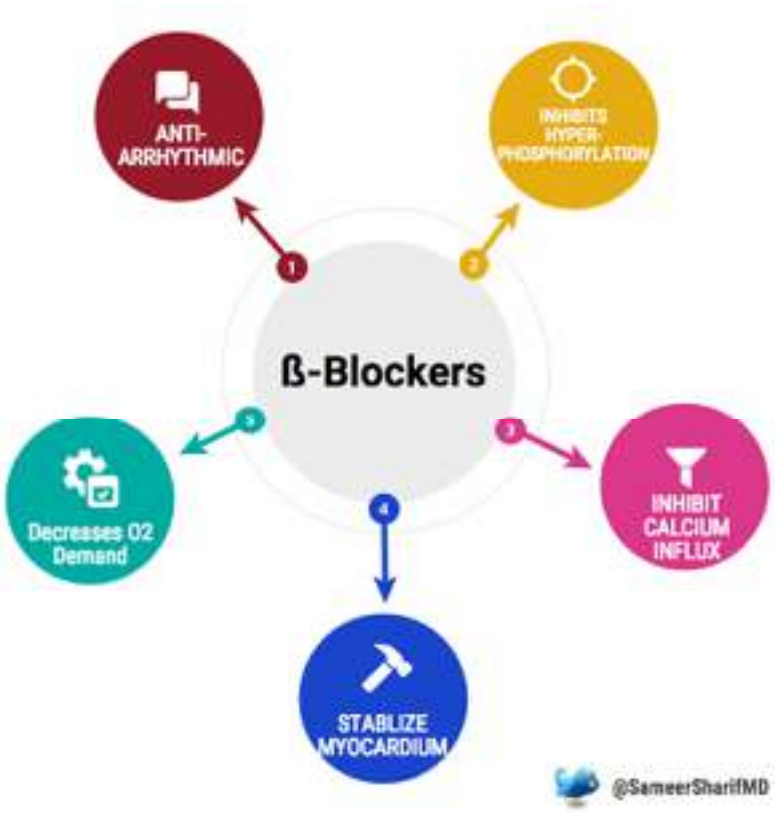


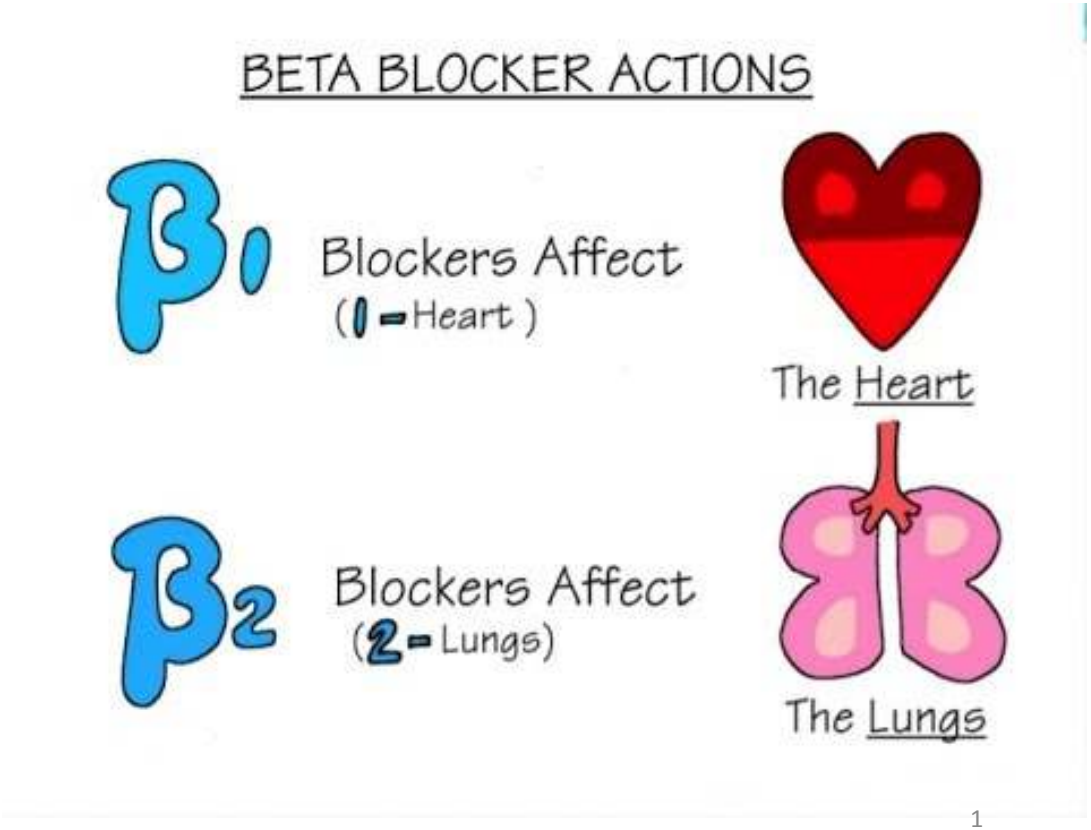
- These compounds are short acting because they are metabolized rapidly by α-hydroxylation of the methyl substituent on the triazolo or imidazolo ring (analogs to benzylic oxidation).
- The resulting active α-hydroxylated metabolite is quickly inactivated by glucuronidation.
- The compounds are also metabolized by 3-hydroxylation of the benzodiazepine ring.
- Interestingly, an electron-attracting group at position 7 is not required for activity in some of these compounds.



Metabolism of benzodiazepines and their duration of action.

SPECIFIC BETA-1 BLOCKERS





INTRODUCTION

- Cardioselective β1-blockers have a greater affinity for the β1-receptors of the heart than for β2-receptors in other tissues.
- Such cardioselective agents provide two important therapeutic advantages.
- The first advantage should be the **lack of a blocking effect on the β2-receptors in the bronchi**.
- This would make **β1-blockers safe for use in patients who have bronchitis or bronchial asthma**.

- The second advantage should be the **absence of the vascular β2-receptor blockade, which mediate vasodilation**.
- This would be expected to **reduce or eliminate the increase in peripheral resistance** that sometimes occurs after the administration of nonselective β-blockers.
- **Unfortunately, cardioselectivity is usually observed with β1-blockers at only relatively low doses.**
- **At normal therapeutic doses, much of the selectivity is lost.**

- At present, the following β1-selective blockers are used therapeutically:

➢ *Acebutolol*,

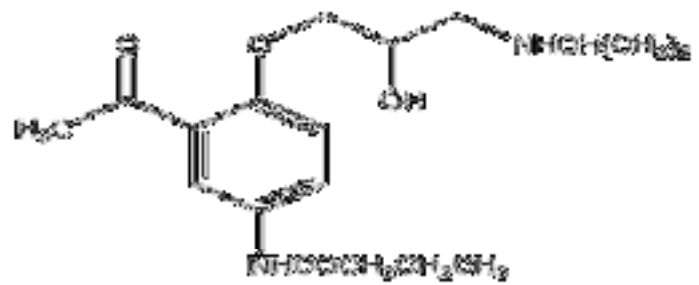
➢ *Atenolol*,

➢ *Betaxolol*,

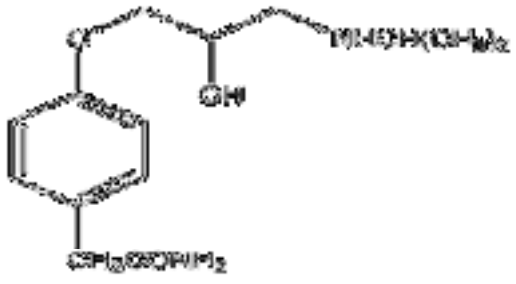
➢ *Bisoprolol*,

➢ *Esmolol*,

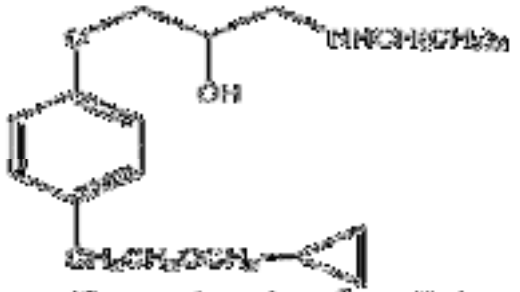
➢ *Metoprolol*.



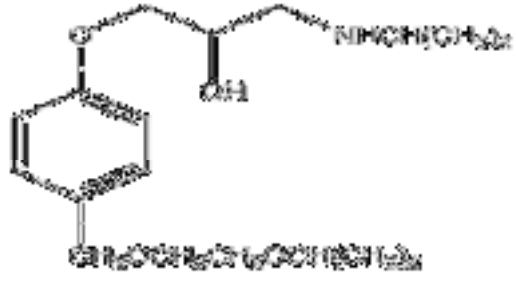
Acebutolol: antihypertensive



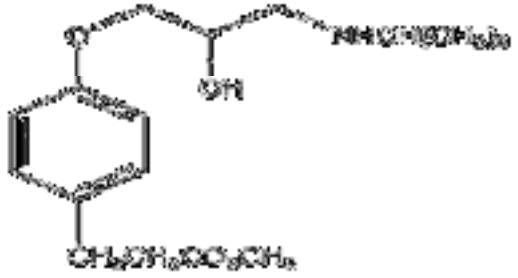
Atenolol: antihypertensive



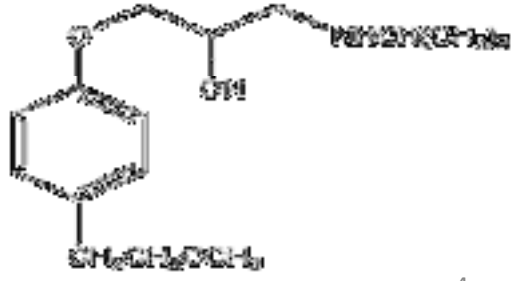
Betaxolol: antihypertensive & antiglaucoma



Bisoprolol: antihypertensive



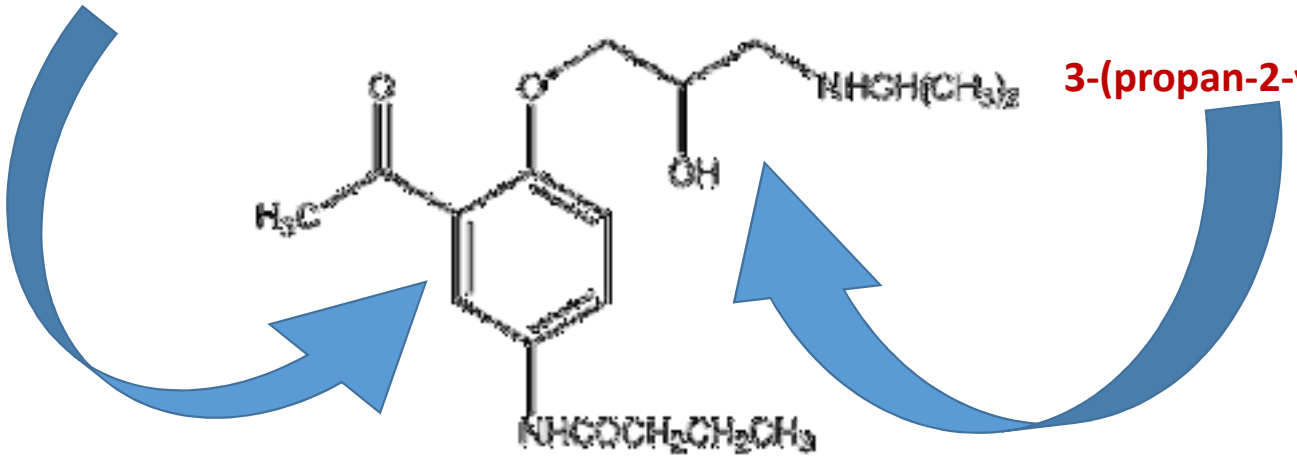
Esmolol: short-acting antihypertensive



Metoprolol: antihypertensive

- **ACEBUTOLOL:**
- ***N-[3-acetyl-4-[2-hydroxy-3-(propan-2-ylamino) propoxy] phenyl] butanamide.***
- Acebutolol is a synthetic butyranilide .
- It belongs to aryloxypropanolamine class.

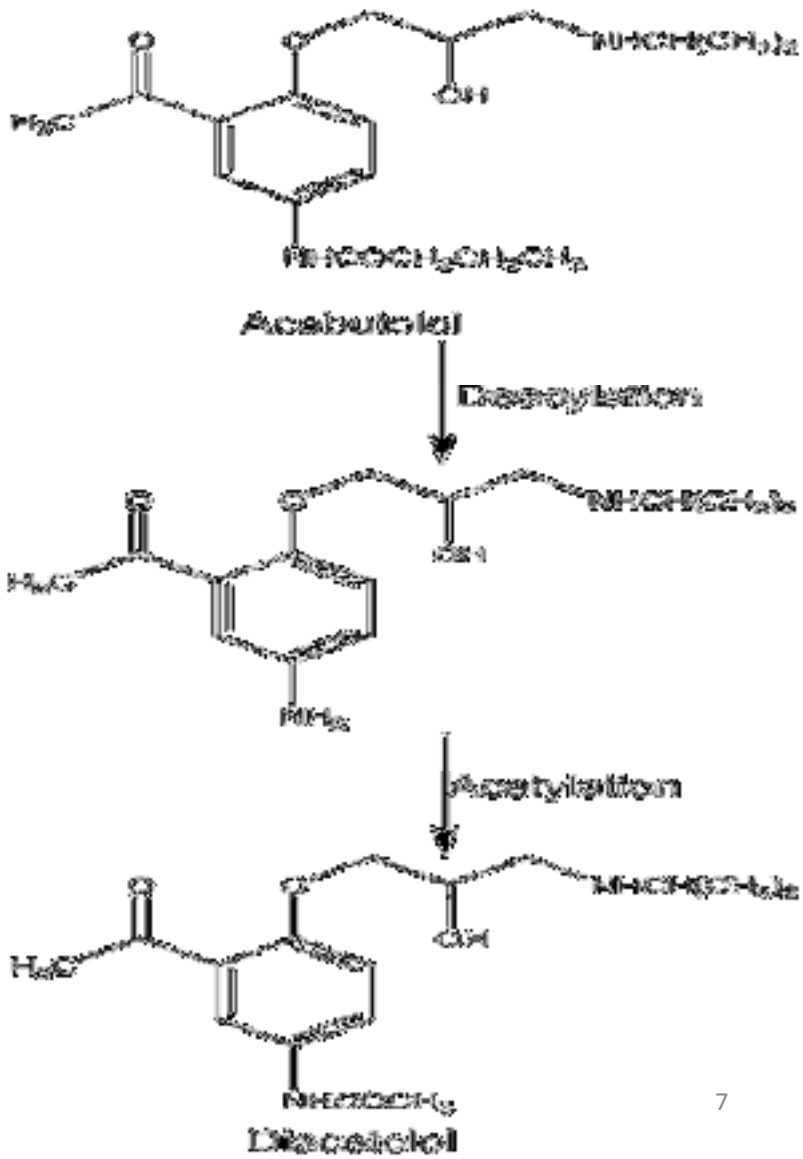
2-acetyl-4-(butanoylamino)phenyl



3-(propan-2-ylamino)propane-1,2-diol

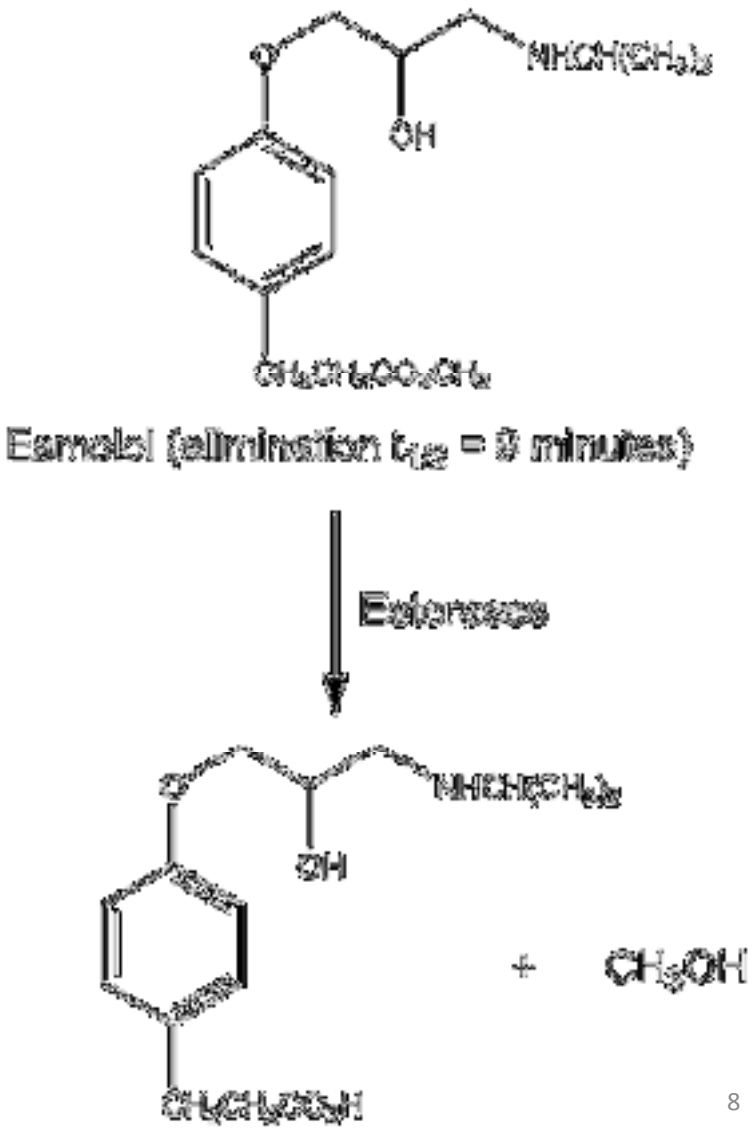
- Among all β1-selective blockers, only acebutolol possesses ISA.
- However, this activity is very weak.
- Acebutolol and betaxolol possess membrane-stabilizing activity, but the activity is much weaker than propranolol.
- Acebutolol and esmolol are also indicated for treating certain cardiac arrhythmias.

- Acebutolol is well absorbed from GIT.
- It undergoes extensive first-pass metabolic conversion to diacetolol metabolite.
- After oral administration, plasma levels of diacetolol are higher than those of acebutolol.
- Diacetolol is also a selective β1-blocker with partial agonistic activity.
- It has a longer half-life (8–12hours) than the parent drug and is excreted by the kidneys.



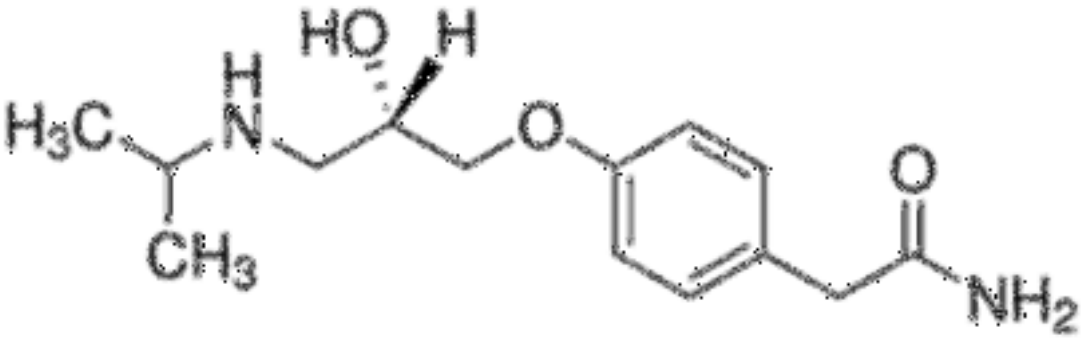
ESMOLOL

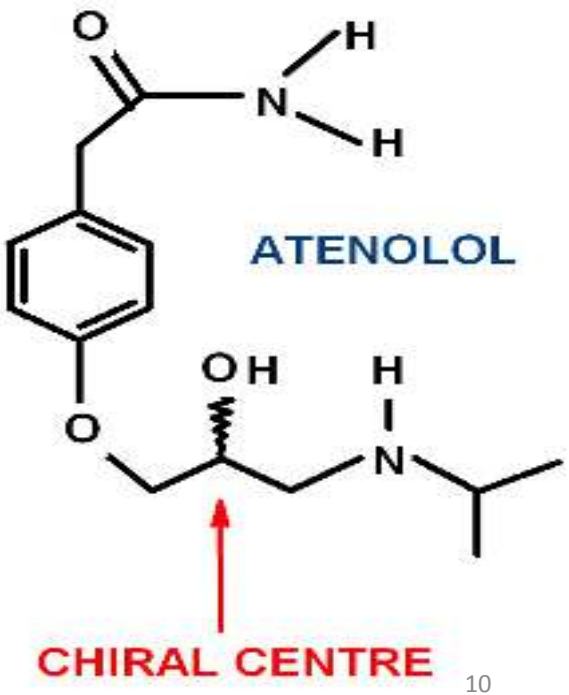
- Esmolol was designed specifically to possess a very short DOA.
- Its elimination half-life is 9 minutes.
- Its effects disappear within 20 to 30 minutes after the infusion is discontinued.
- The short DOA of esmolol is the result of rapid hydrolysis of its ester functionality by esterases present in erythrocytes.



- The carboxylic acid metabolite is a weak β-blocker.
- This acid metabolite has an elimination half-life of 3 to 4 hours and is excreted primarily by the kidneys.
- This agent is administered by continuous intravenous infusion for control of ventricular rate in patients with atrial flutter, atrial fibrillation, or sinus tachycardia.
- Its rapid onset and short DOA render it useful during surgery, after an operation, or during emergencies for short-term control of heart rates.

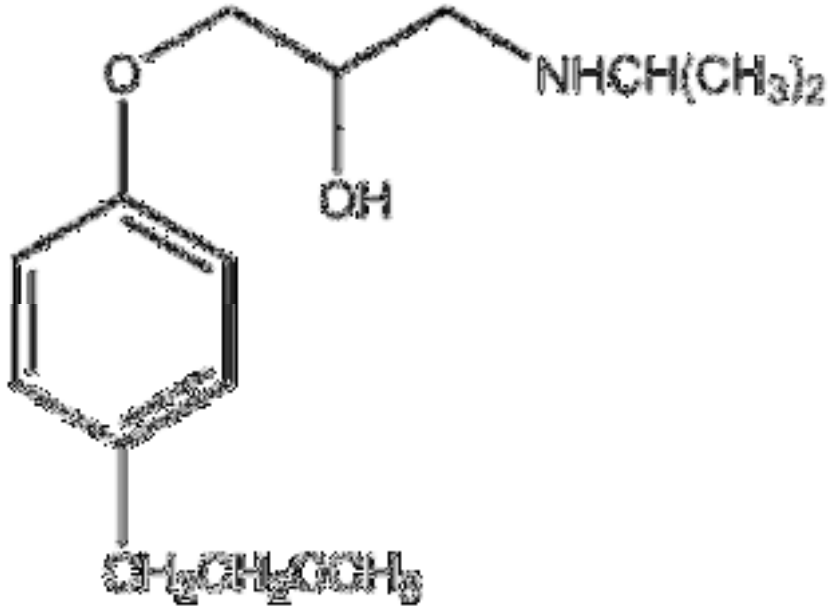
- **ATENOLOL: 2-[4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl]acetamide**
- It is a member of **aryloxypropanolamine** and a **monocarboxylic acid amide**.
- It act as a **beta-adrenergic antagonist**, an **anti-arrhythmia drug**, an **antihypertensive agent** and **sympatholytic agent**.
- **S(-) enantiomer is more active**.





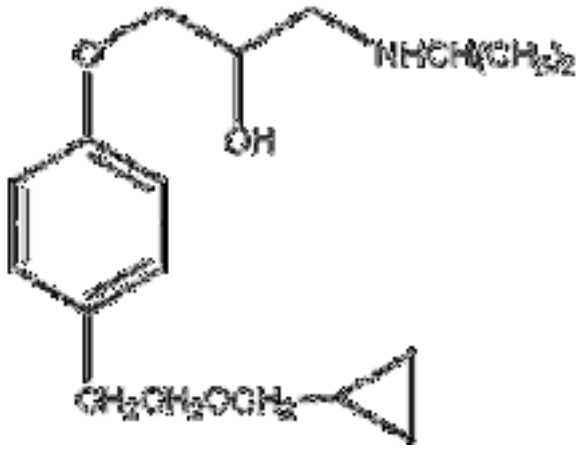
- Atenolol (log P 0.10) has low lipid solubility and does not cross the BBB.
- It is absorbed incompletely from the gastrointestinal tract.
- The oral bioavailability is approximately 50%.
- Atenolol and metoprolol are also approved for use in treating angina pectoris and in therapy following myocardial infarction.
- Atenolol has been linked to rare cases of drug induced liver injury, some of which have been fatal.
- It is reported as an **environmental contaminant**.

- **METOPROLOL:** **1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol**
- Metoprolol is a cardioselective competitive beta-1 adrenergic receptor antagonist.
- It is antihypertensive and devoid of intrinsic sympathomimetic activity.



- Metoprolol has low bioavailability because of significant first-pass metabolism.
- It reduces the rate and force of myocardial contraction leading to a reduction in cardiac output.
- It may also reduce the secretion of renin with subsequent reduction in levels of angiotensin II thereby preventing vasoconstriction and aldosterone secretion.

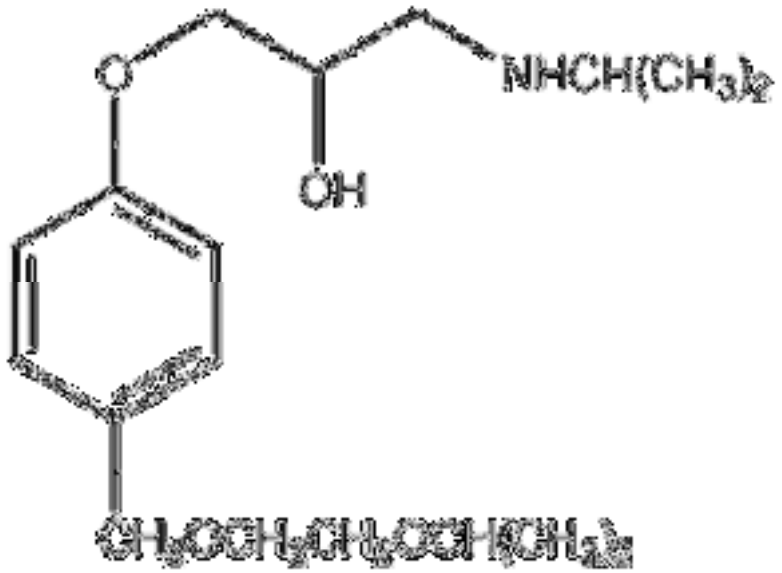
- **BETAXOLOL:** **1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(propan-2-ylamino)propan-2-ol**
- It is a racemic mixture and selective beta-1 adrenergic receptor antagonist.
- It is a propanolamine that is 3-aminopropane-1,2-diol in which the hydrogen of the primary hydoxy is substituted by a 4-[2-(cyclopropylmethoxy)ethyl]phenyl group and one of the hydrogens attached to the amino group is substituted by isopropyl.



- It has antihypertensive and anti-glaucoma activities and devoid of intrinsic sympathomimetic activity.
- It selectively and competitively binds to and blocks beta-1 adrenergic receptors in the heart.
- It decreases cardiac contractility and rate.
- This leads to a reduction in cardiac output and lowers blood pressure.

- When applied topically in the eye, this agent reduces aqueous humor secretion and lowers the intraocular pressure (IOP).
- In addition, betaxolol prevents the release of renin, a hormone secreted by the kidneys that causes constriction of blood vessels.
- Betaxolol is the only β1-selective blocker indicated for the treatment of glaucoma.

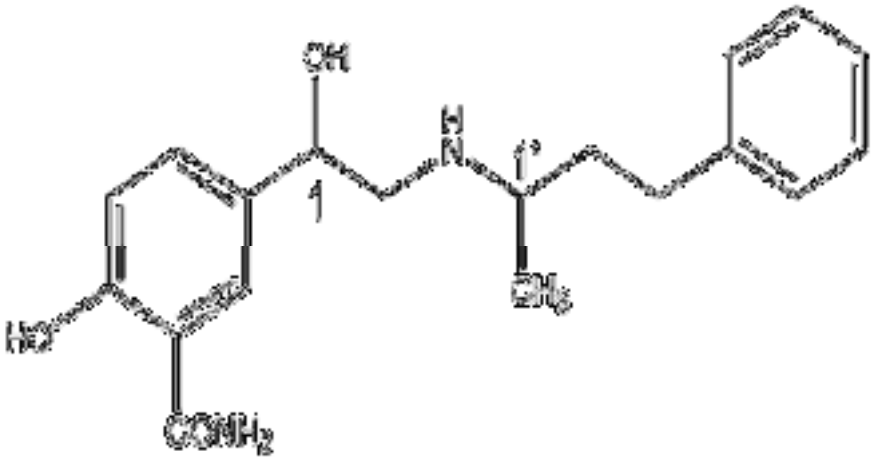
- **BISOPROLOL:** 1-(propan-2-ylamino)-3-[4-(2-propan-2-yloxyethoxymethyl)phenoxy]propan-2-ol
- Bisoprolol is a selective beta-1 adrenergic receptor antagonist with antihypertensive activity and devoid of intrinsic sympathomimetic activity.



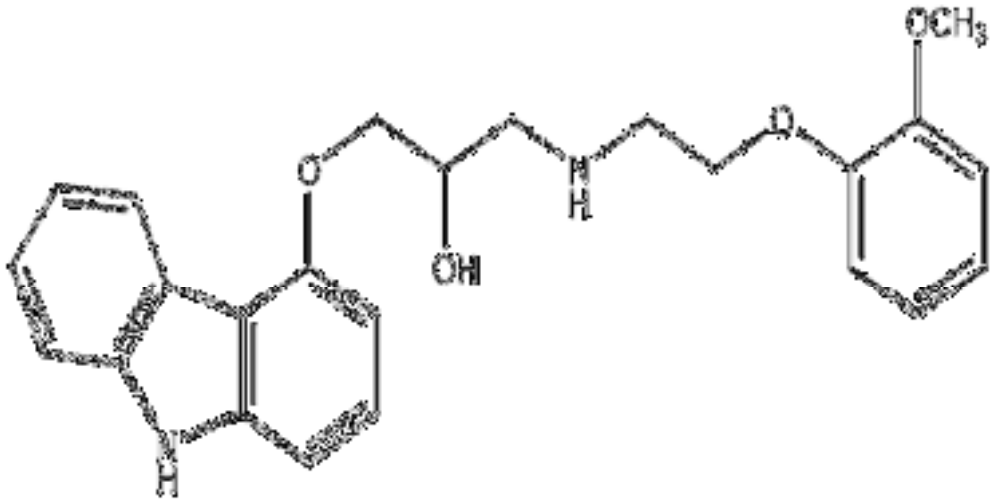
- Bisoprolol selectively and competitively binds to and blocks beta-1 adrenergic receptors in the heart, thereby decreasing cardiac contractility and rate.
- This leads to a reduction in cardiac output and lowers blood pressure.
- In addition, bisoprolol prevent the release of renin, a hormone secreted by the kidneys that causes constriction of blood vessels.

β-BLOCKERS WITH α1-ANTAGONIST ACTIVITY

- Several drugs have been developed that possess both β– and α-receptor blocking activities within the same molecule.
- Two examples of such molecules are **labetalol and carvedilol**.



Labetalol



Carvedilol

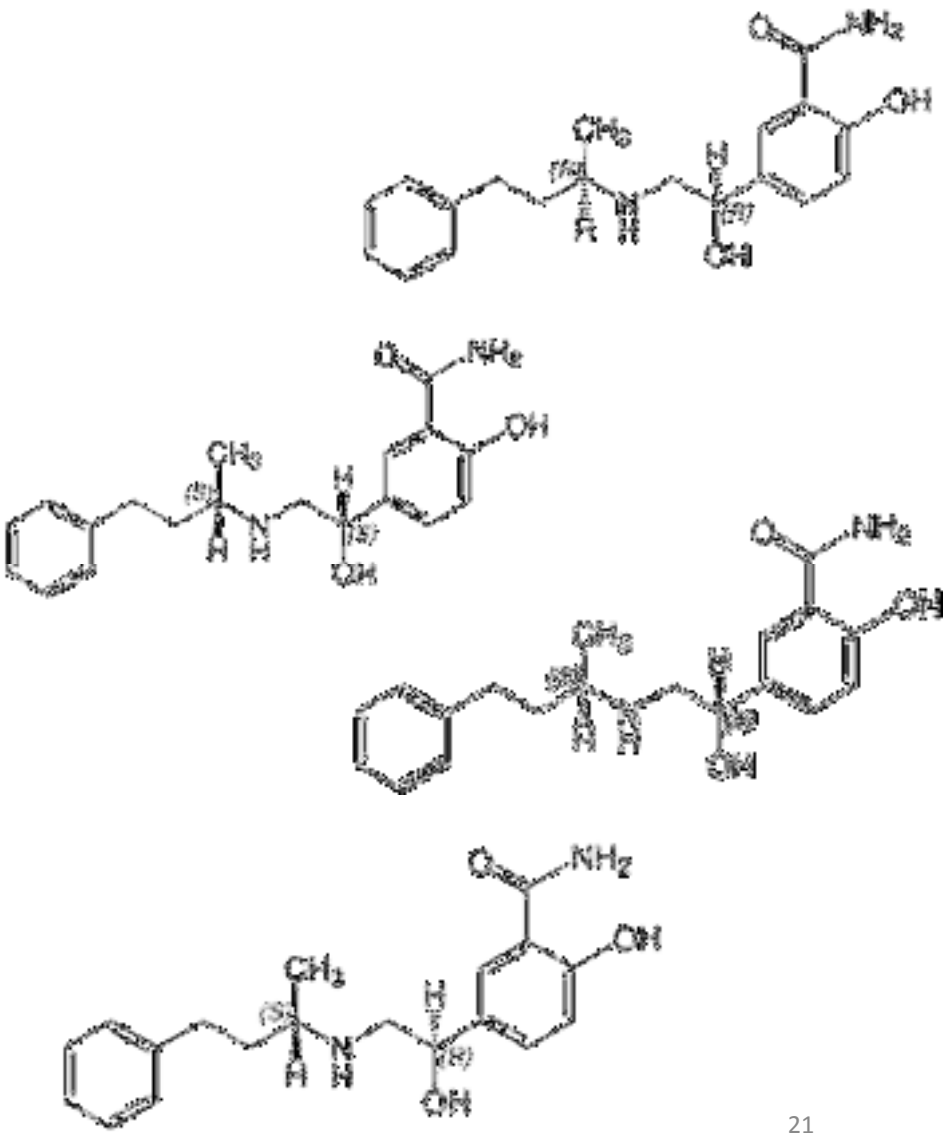
- As in the case of dobutamine, the arylalkyl group with nearby methyl group in these molecules is responsible for its α1-blocking activity.
- The bulky *N*-substituents and another substituted aromatic ring are responsible for its β-blocking activity.

Labetalol

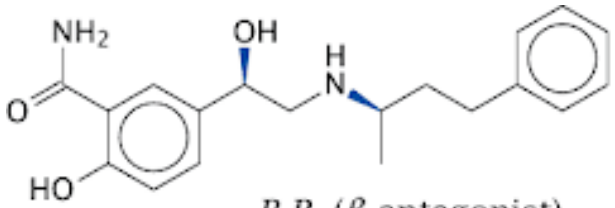
	R	R'	R''	R'''
RR- isomer:	OH	H	H	CH_3
SS- isomer:	H	OH	CH_3	H
SR-isomer:	H	OH	H	CH_3
RS-isomer:	OH	H	CH_3	H

LABETALOL

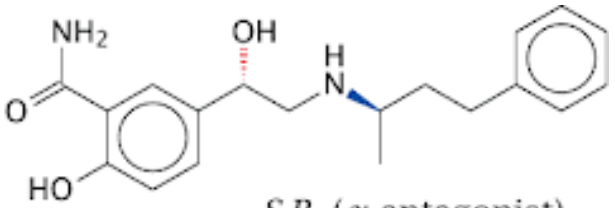
- Phenylethanolamine derivative.
- Competitive blocker at α1-, β1-, and β2-receptors.
- More potent β-blocker than α-blocker.
- 2 asymmetric carbon atoms (1 and 1').
- It exists as a mixture of four isomers.
- This mixture is used clinically in treating hypertension.



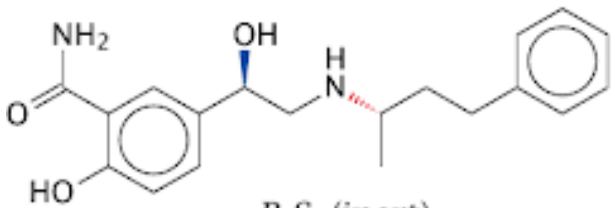
- The different isomers possess different α- and β-blocking activities.
- The **β-blocking activity** resides solely in the **(1*R*,1*R*)** isomer, whereas the **α1-blocking activity** is seen in the **(1*S*,1*R*).**
- **Isomers (1R,1S) and (1*S*,1*S*) are almost inactive.**



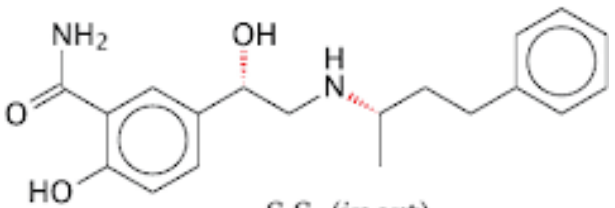
R,R (β-antagonist)



S,R (α-antagonist)

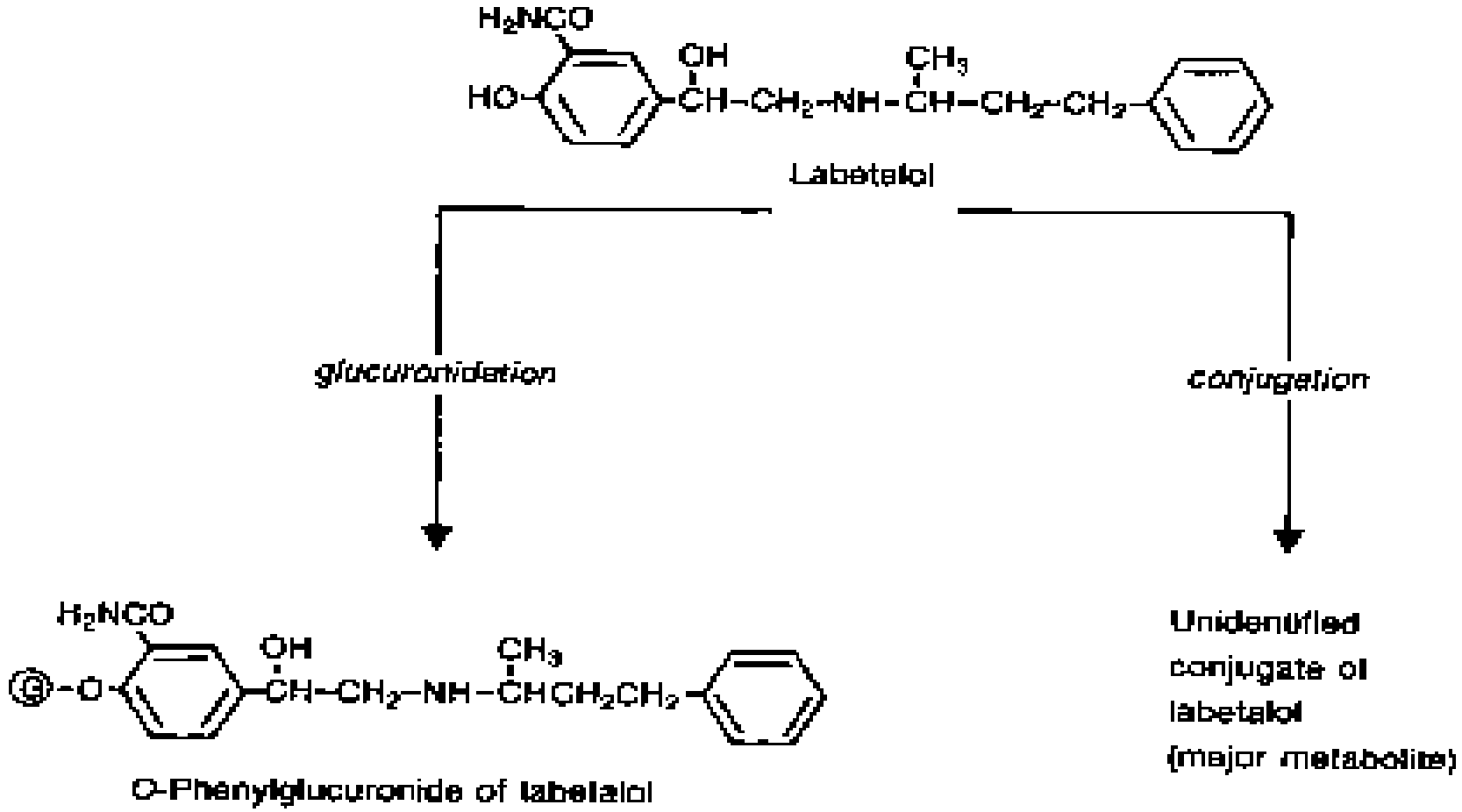


R,S (inert)



S,S (inert)

- Although labetalol is very well absorbed, it undergoes extensive first-pass metabolism.



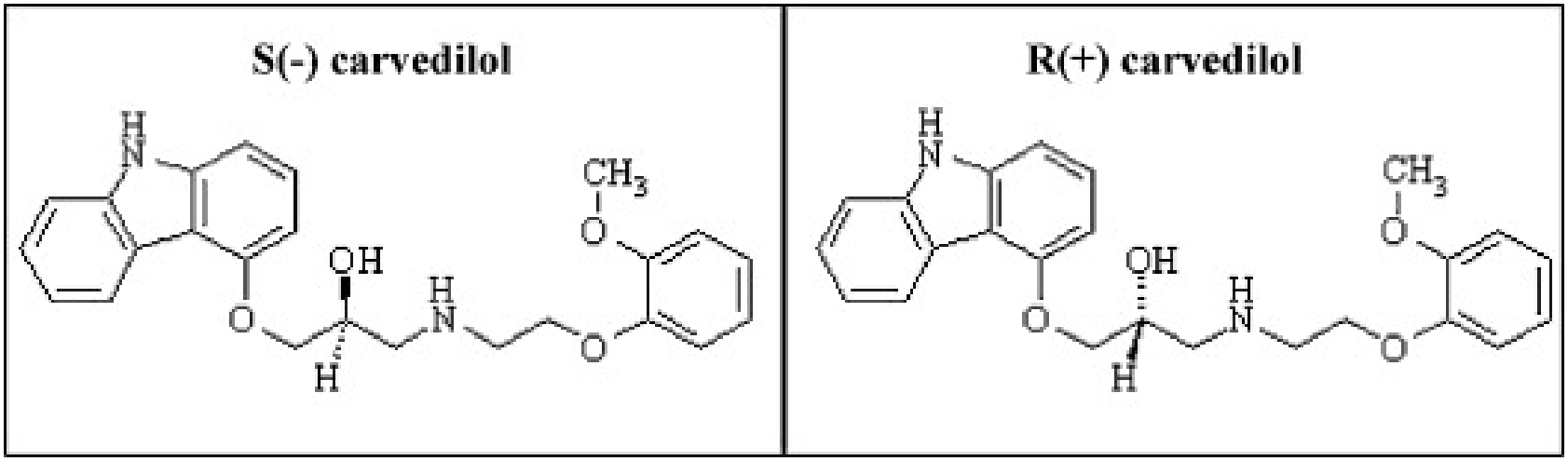
- **Therapeutic Uses:**
- Labetalol is a clinically useful **antihypertensive agent**.
- The rationale for its use in the management of hypertension is that-

➢ its α-receptor–blocking effects produce vasodilation

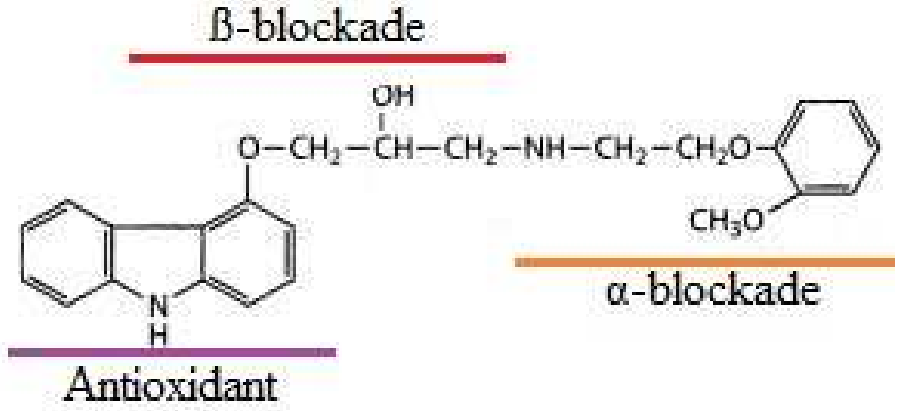
➢ its β-receptor–blocking effects prevent the reflex tachycardia usually associated with vasodilation.

CARVEDILOL

- Carbazole derivative.
- Like labetalol, it is a β-blocker that possesses α1-blocking activity.
- Only the S(-) enantiomer possesses the β-blocking activity, although both enantiomers are blockers of the α1-receptor.
- Overall, its β-blocking activity is 10- to 100-fold of its α-blocking activity.

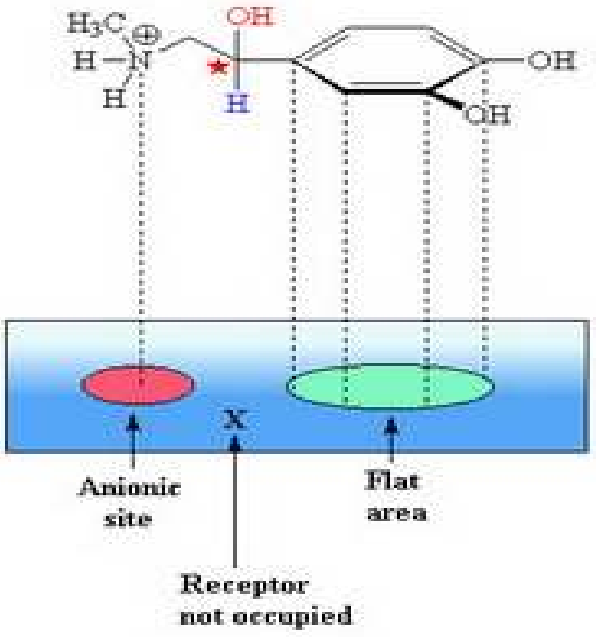


- This drug is also unique in that it possesses **antioxidant activity** and an **antiproliferative effect** on vascular smooth muscle cells.
- It thus has a **neuroprotective effect** and the ability to provide major cardiovascular organ protection.
- **It is used in treating hypertension and congestive heart failure**.

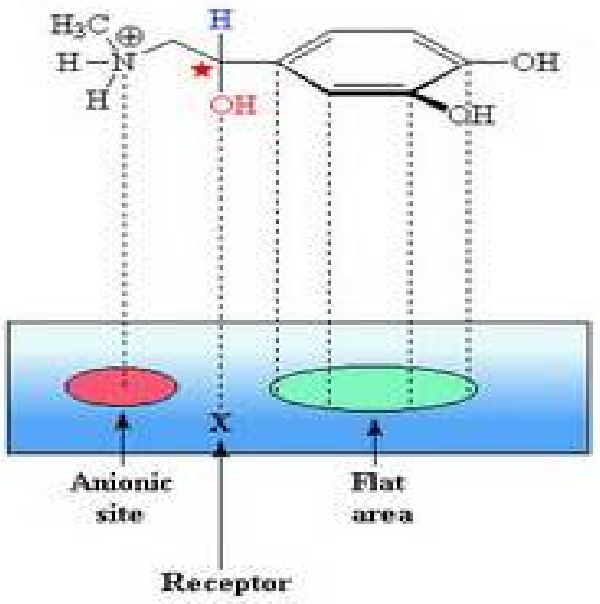


Unit 2

Drugs acting on Autonomic Nervous System



(+) Epinephrine - less active



(-) Epinephrine - more active

- Drugs acting on Autonomic Nervous System- Adrenergic Neurotransmitters:
- Biosynthesis and catabolism of catecholamine.
- Adrenergic receptors (Alpha & Beta) and their distribution.
- Sympathomimetic agents: SAR of Sympathomimetic agents
- Direct acting: Nor-epinephrine, Epinephrine, **Phenylephrine***, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, **Salbutamol***, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.
- Indirect acting agents: Hydroxyamphetamine, Pseudoephedrine, Propylhexedrine.
- Agents with mixed mechanism: Ephedrine, Metaraminol.
- Adrenergic Antagonists:
- Alpha adrenergic blockers: **Tolazoline***, Phentolamine, Phenoxybenzamine, Prazosin, Dihydroergotamine, Methysergide.
- Beta adrenergic blockers: SAR of beta blockers, **Propranolol***, Metibranolol, Atenolol, Betazolol, Bisoprolol, Esmolol, Metoprolol, Labetolol, Carvedilol.

Adrenergic Neurotransmitters

- Adrenergic neurotransmitters (NTs) include norepinephrine (NE, noradrenaline), epinephrine (E, adrenaline), and dopamine (DA).
- These NTs modulate many vital functions, such as -

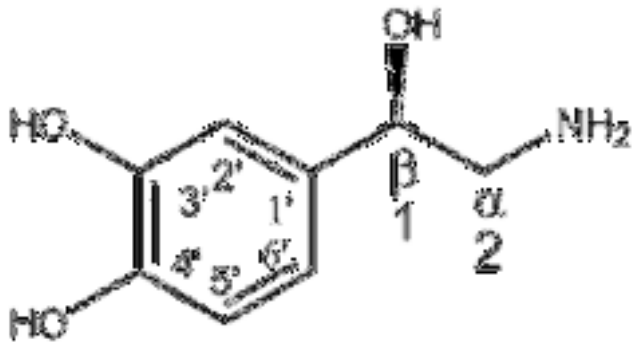
➢ rate and force of cardiac contraction,

➢ constriction & dilation of blood vessels,

➢ constriction & dilation of bronchioles,

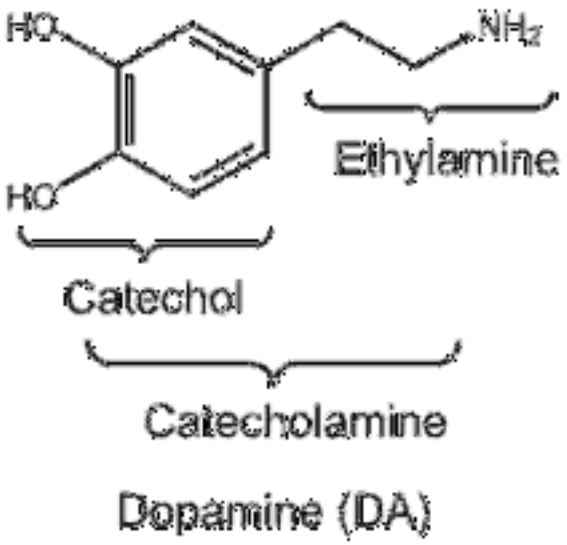
➢ release of insulin,

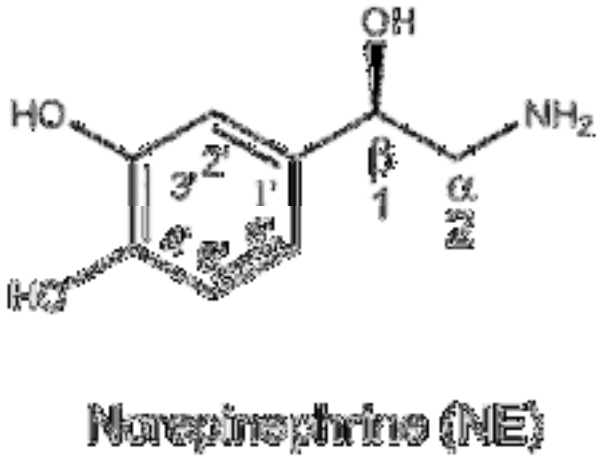
➢ breakdown of fat.

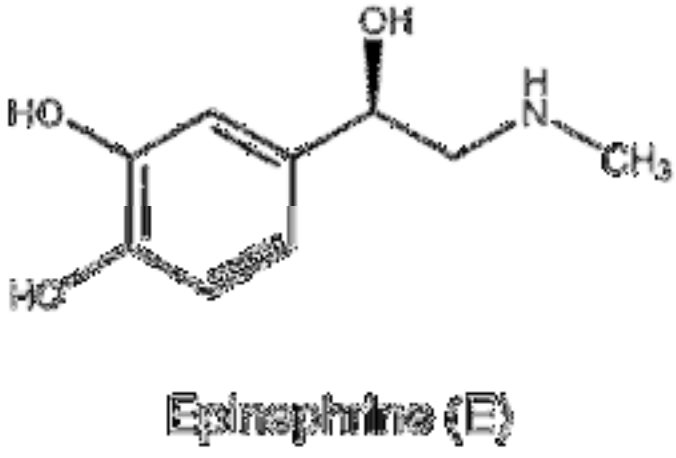


Norepinephrine (NE)

- **Chemistry of NTs:**
- NE, E, and DA are chemically catecholamines (CAs).
- CA s are organic compounds that contain a catechol nucleus (ortho-dihydroxybenzene) and an ethylamine group.

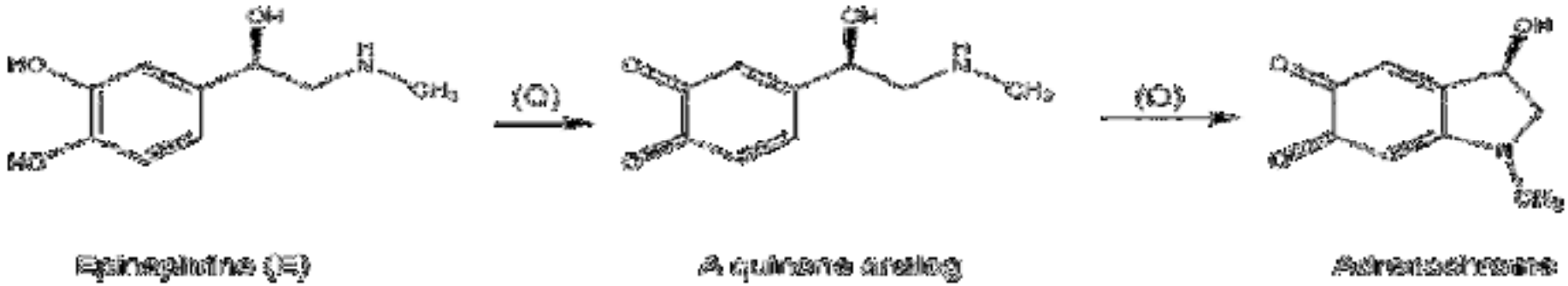




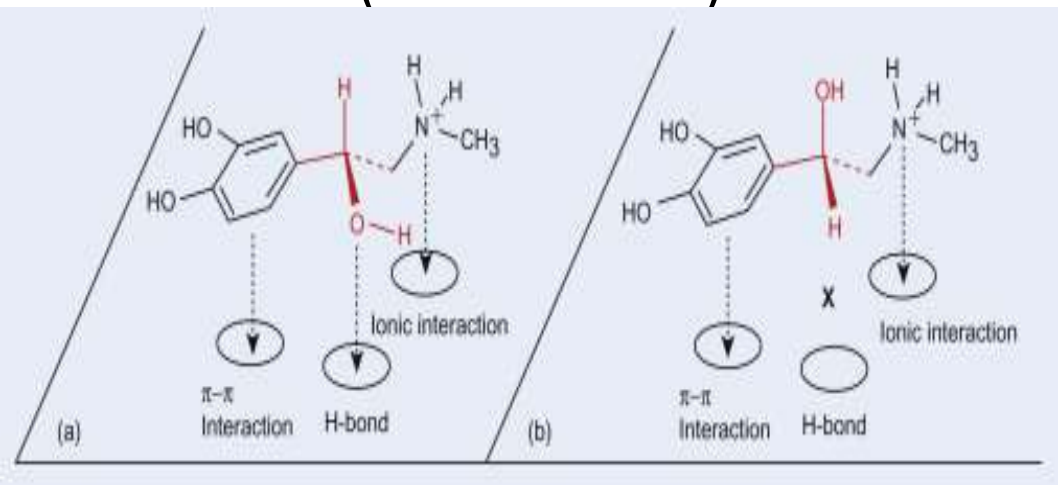


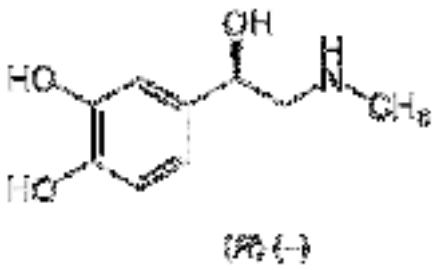
- **Physicochemical properties and Pharmacokinetics:**
- Epinephrine contains one secondary amino group and three hydroxyl groups.
- It is a weak base (pKa =9.9) because of its aliphatic amino group.
- It is also a weak acid (pKa = 8.7) because of its phenolic hydroxyl group.
- At physiological pH it exists in ionized form.
- All catecholamines are freely soluble in water.
- Epinephrine and other catecholamines has poor oral absorption and poor central nervous system (CNS) penetration.

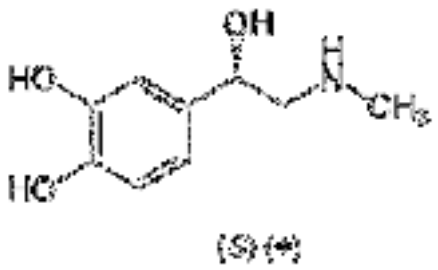
- Like most phenols, the catechol functional groups in CAs are highly susceptible to facile oxidation.
- E and NE undergo oxidation to produce a quinone analog, which undergoes further reactions to give mixtures of colored products, one of which is adrenochrome.
- Hence, solutions of these drugs often are stabilized by the addition of an antioxidant (reducing agent) such as ascorbic acid or sodium bisulfite.



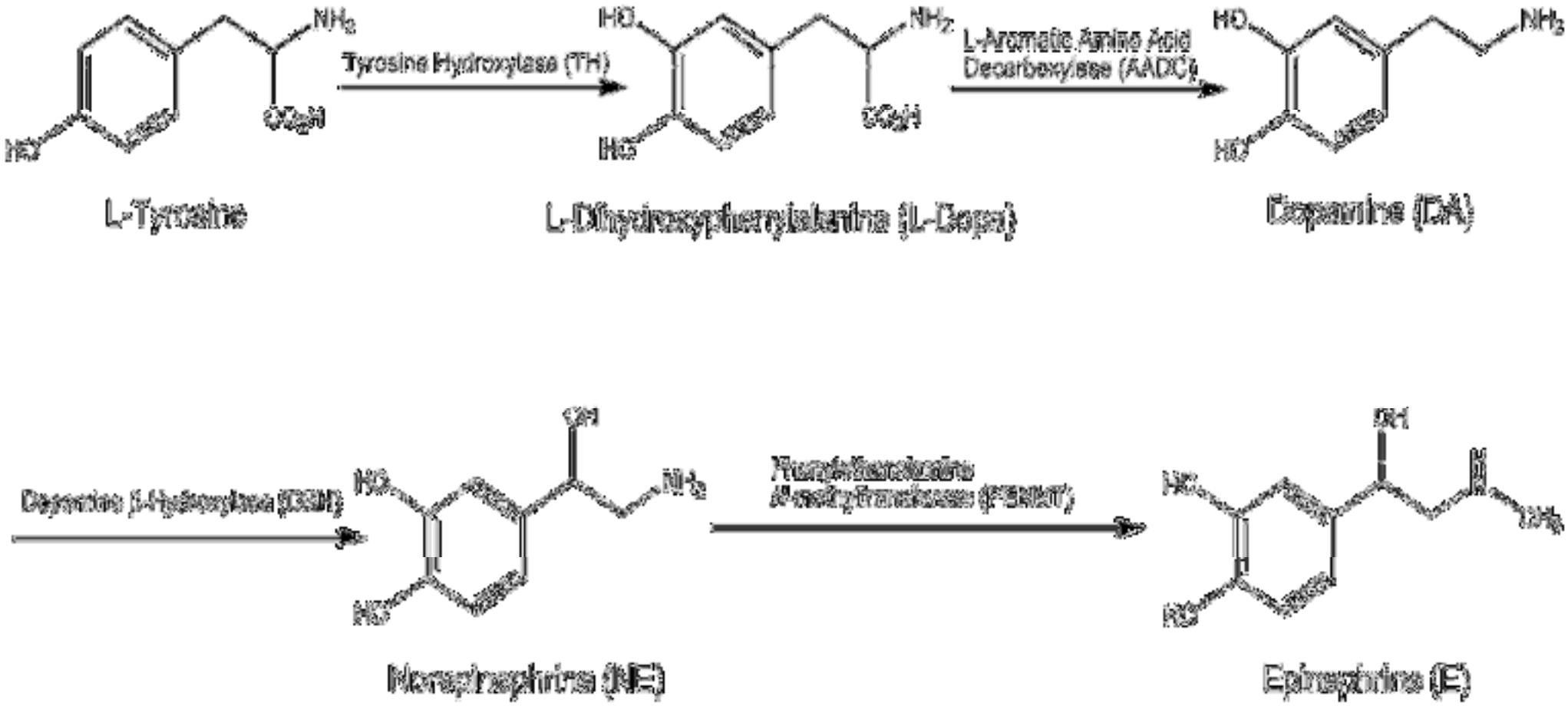
- **Stereochemistry and Biological activity:**
- E and NE each possess a chiral carbon atom; thus, each can exist as an enantiomeric pair of isomers.
- The enantiomer with the (*R*) configuration is biosynthesized by the body and possesses the biological activity.
- This (*R*) configuration of many other adrenergic agents also contributes to their high affinity to the corresponding adrenoceptors.
- **R-Epinephrine** is approx. 15 to 40 times more pharmacologically active than its **S**-enantiomer (D-Adrenaline).



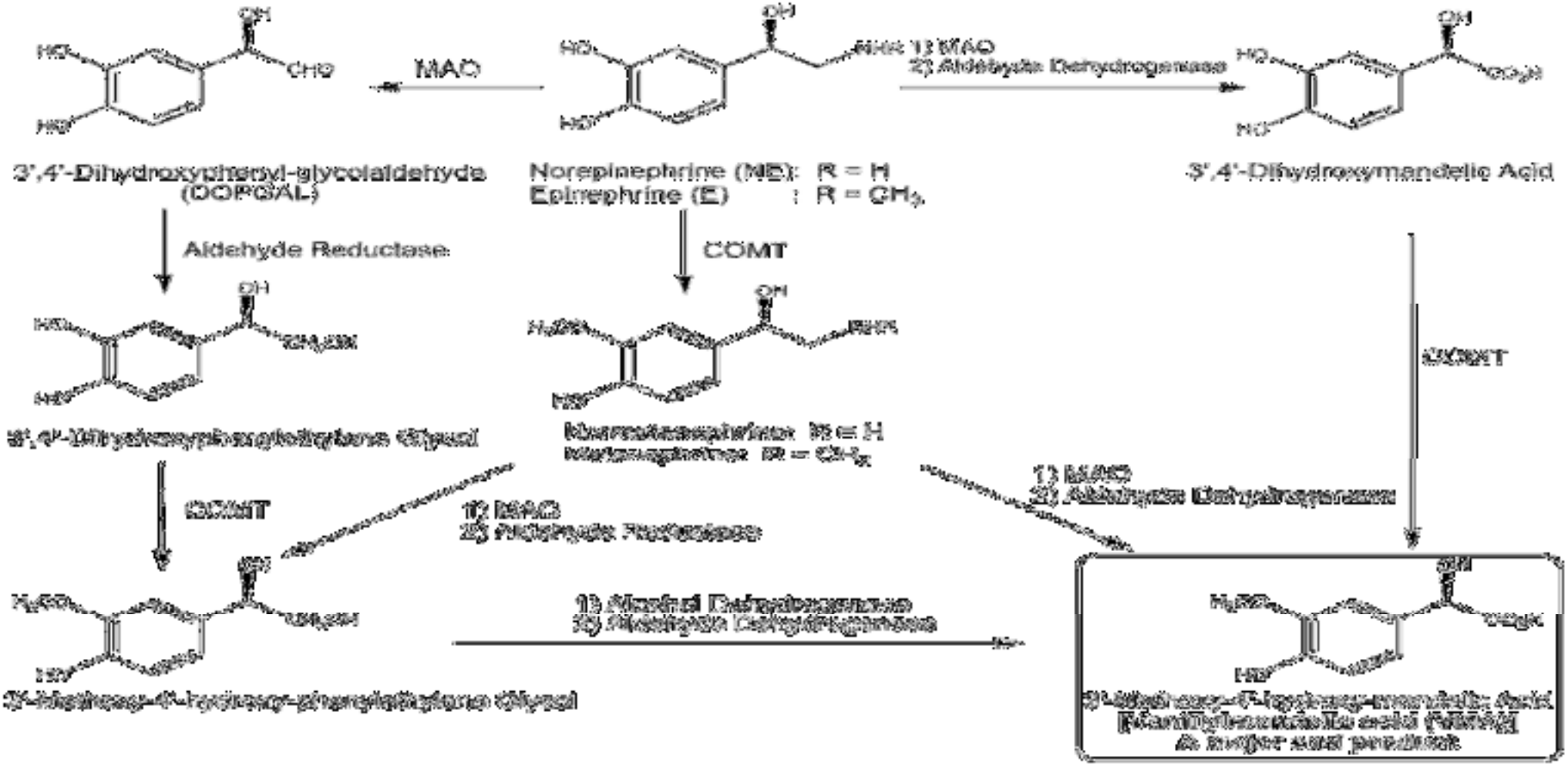




Biosynthesis of Catecholamines



Metabolism of Catecholamines



Adrenergic Receptors

- The diverse physiological responses of CAs are mediated via α1-, α2-, and β-adrenoceptors.
- They are further divided into α 1A, α 1B, α 1D, α 2A, α 2B, α 2C, β 1, β 2, and β 3.
- They all belong to the superfamily of guanine nucleotide (G)-regulatory proteins (G-protein)–coupled receptors (GPCR).
- An important factor in the response of any cell or organ to adrenergic drugs is the density and proportion of α- and β-adrenoceptors.
- For example, NE has relatively little capacity to increase bronchial airflow, because the receptors in bronchial smooth muscle are largely of the β2-subtype.
- In contrast, isoproterenol (ISO) and E are potent bronchodilators.

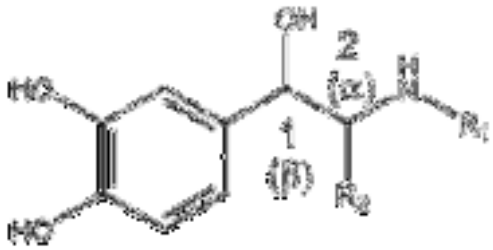
Organ or Tissue	Predominant Adrenoceptors	Effect of Activation	Physiological Effect	Drugs	Therapeutic Uses
Blood vessels and skin	α_1	Vasoconstriction	↑ Blood pressure	α_1-Agonists	Shock, hypotension
Mucous membranes	α_1	Vasoconstriction		α_1-Agonists α_1-Antagonists	Nasal congestion Hypertension
Prostatic gland muscle	α_{1A}	Contraction	Prostatic hyperplasia	α_{1A}-Antagonists	BPH
CNS	α_2	↓ NE release	↓ Blood pressure	α_2-Agonists	Hypertension
Heart muscle	β_1 (minor β_2, β_3)	Muscle contraction	↑ Heart rate & force	β_1-Antagonists	Hypertension Arrhythmias
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways		
	β_2 (Bronchodilation)	Smooth muscle relaxation	Dilates & opens airways	β_2-Agonists	Asthma and COPD
Uterus (pregnant)	α_1	Muscle contraction			
	β_2	Smooth muscle relaxation	(–) Uterine contractions	β_2-Antagonists	Premature labor
Kidney	β_1	Increases rennin secretion	↑ Blood pressure		

Sympathomimetic Agents

- Sympathomimetic agents produce effects resembling those produced by stimulation of the sympathetic nervous system.
- They may be classified as agents that produce effects by a direct, indirect, or mixed mechanism of action.
- **Direct-acting agents** elicit a sympathomimetic response by interacting directly with adrenergic receptors.

- **Indirect-acting agents** produce effects primarily by causing the release of NE from adrenergic nerve terminals; the NE that is released by the indirect- acting agent activates the receptors to produce the response.
- **Compounds with a mixed mechanism of action** interact directly with adrenergic receptors and indirectly cause the release of NE.
- The mechanism by which an agent produces its sympathomimetic effect is related to its chemical structure.

- **Direct-Acting Sympathomimetics - SAR:**
- The parent structure with common features for many of the adrenergic drugs is **β- phenylethylamine.**



- **Available sites for structural modification-**

➢ the *meta*- and *para*-positions of the aromatic ring,

➢ on the amino (R1),

➢ on α-, (R2)-, and β -positions of the ethylamine side chain.

Aromatic substituents

3', 4'-diOH for both α & β agonist activity
metabolized by COMT→
poor oral activity and short DOA
hydrophilic → poor CNS activity

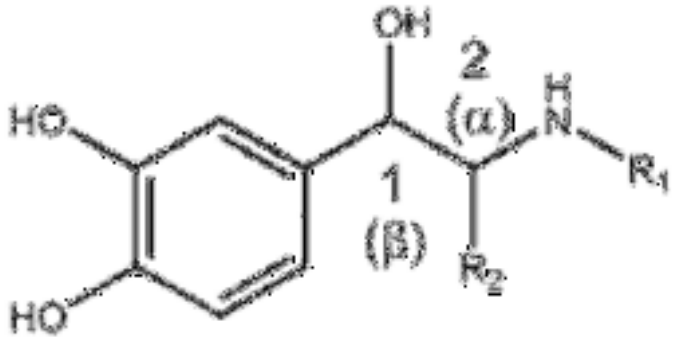
3', 5'-diOH (e.g., metaproterenol)
3'-CH_2OH, 4'-OH (e.g., albuterol)
↑ β_2 activity
↓ degradation by COMT →
↑ absorption, oral activity, & DOA

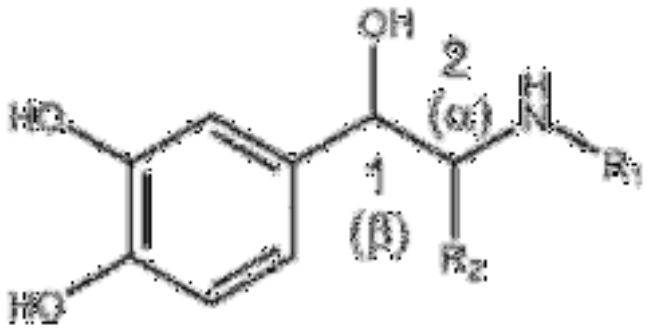
4'-OH is more important for β activity
3'-OH is more important for α activity
(e.g., phenylephrine: α-agonist)

No phenolic substitution:
↓both α and β activity
direct or indirect activity

Structure required for activity:

1. β-Phenylethylamine
2. Catechol ring
3. (1R)-OH





R_1-Substitution on N

↑ the size of R_1 →

↑ β activity

↓ α activity

t-butyl: ↑ β_2 activity

↓ degradation by MAO

R_2-Substitution on C_2

small alkyl groups (Me, Et) tolerated

⇓ degration by MAO

still substrates for PNMT → little effect on DOA

Et group:

↓ α >> β (more β–selective, eg., ethylnorepinephrine)

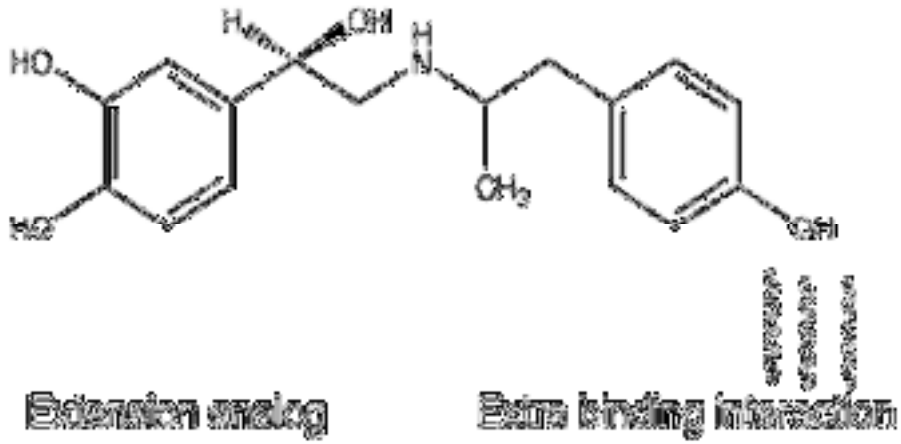
↑ CNS activity

↑ oral activity & DOA

(2S) methyl group: ↑ α_2 activity

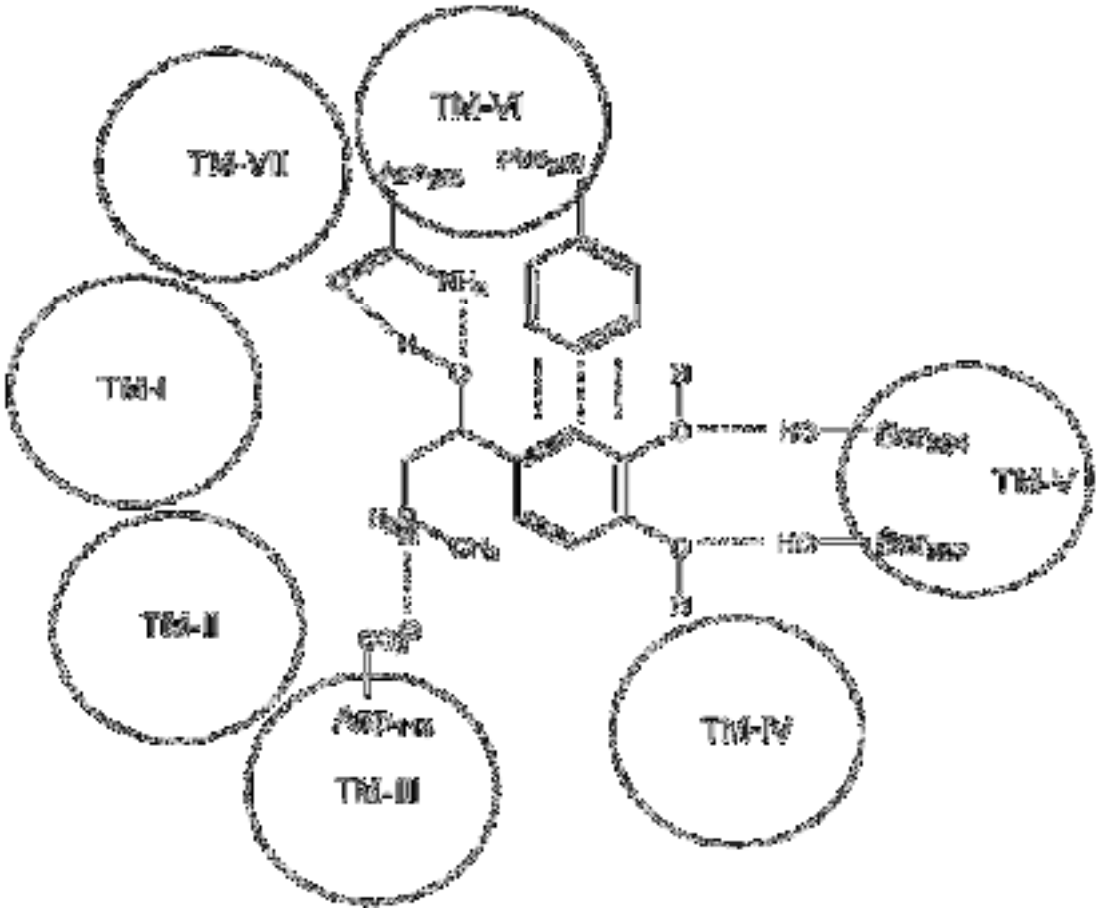
- **Structural modification leads to changes in the following properties -**

- mechanism of action
- receptor selectivity
- absorption and oral activity
- metabolism and degradation
- duration of action (DOA)



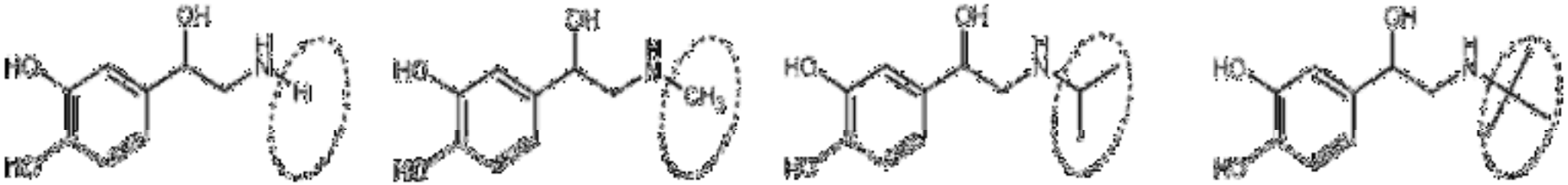
- ***Optical Isomerism-Stereoselectivity:***
- (1*R*,2*S*) isomers seem correct configuration for direct-acting activity.
- For CAs, the more potent enantiomer has the (1*R*) configuration.
- This enantiomer is typically several 100-fold more potent than the enantiomer with the (1*S*) configuration.
- The more potent enantiomer of all phenylethylamine agonists is structurally similar to NE.
- It is capable of assuming a conformation that results in the spatial arrangement of the catechol group, the amino group, and the (1*R*)-OH group resembling (1*R*)-NE.

- This explanation of stereoselectivity is based on the interaction of these 3 pharmacophoric groups with three complementary binding areas on the receptor and is known as the **Easson-Stedman hypothesis**. This three-point interaction is supported by site-directed mutagenesis studies on the adrenergic receptor.
- * TM= Transmembrane region.



- ***Separation of Aromatic Ring and Amino Group.***
- The greatest adrenergic activity occurs when two carbon atoms separate the aromatic ring from the amino group. This rule applies with few exceptions to all types of activities.
- ***R1, Substitution on the Amino Nitrogen Determines α- or β-Receptor Selectivity.***
- The amine is normally ionized at physiological pH.
- This is important for direct agonist activity.
- Replacing nitrogen with carbon results in a large decline in activity.
- The activity is also affected by the number of substituents on the nitrogen.

- Primary and secondary amines have good adrenergic activity, whereas tertiary amines and quaternary ammonium salts do not.
- The nature of the amino substituent also affects the **receptor selectivity** of the compound.
- As the size of the nitrogen substituent increases, α -receptor agonist activity generally decreases and β -receptor agonist activity increases.



Norepinephrine (NE)
α_1, α_2, β_1 agonist
α agonist

Epinephrine (E)
α_1, β_1 and β_2 agonist
nonselective α and β agonist

Isoproterenol (ISO)
β_1 and β_2 agonists
nonselective β agonist

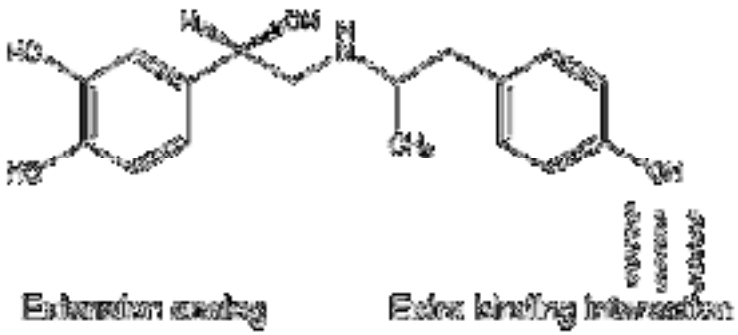
Metaproterenol (Alupent)
selective β_2 agonist

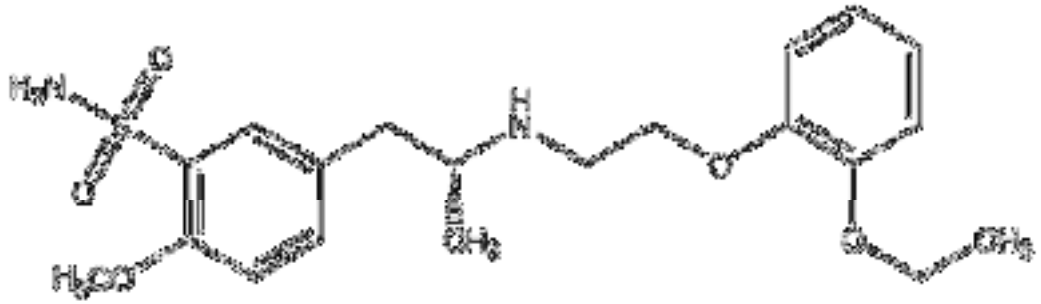
- The nature of the substituents can also affect β1- and β2- receptor selectivity.
- *N-tert*-butyl group is a β2-directing group. It enhances β2-selectivity.
- For example, *N-tert*-butylnorepinephrine (Colterol) is 9 to 10 times more potent as an agonist at tracheal β2-receptors than at cardiac β1-receptors.

***The β–receptor has a larger lipophilic binding pocket than do the α-receptors.**

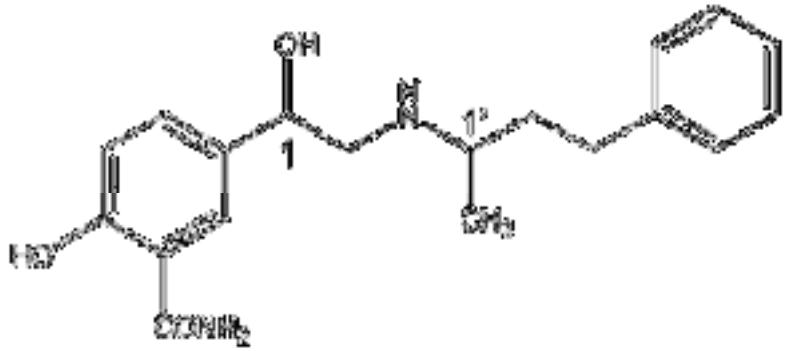
- Increasing the length of the alkyl chain offers no advantage.
- Adding a phenol group to the end of a C2 alkyl chain rises activity.
- This indicates that an extra polar-binding region responsible for H-bonding is present.

- As R1 becomes larger than butyl group, it can provide compounds with α1-blocking activity (e.g., tamsulosin and labetalol).
- Large substituents on the amino group also protect the amino group from undergoing oxidative deamination by MAO.





Tamsulosin



Labetalol