



UNIT-II

AUTONOMIC NERVOUS SYSTEM

The peripheral nervous system, or PNS, consists of the cranial nerves, spinal nerves and ganglia. The peripheral nervous system subdivided into:

1. Autonomic nervous system:

- a) sympathetic nervous system
- b) parasympathetic nervous system

2. Somatic nervous system.

The autonomic nervous system (ANS or visceral nervous system) is the part of the peripheral nervous system that acts as a control system functioning largely below the level of consciousness, and controls function. It is also Responsible for control of “involuntary” or visceral body function: like Cardiovascular, Respiratory, Digestive, Urinary, Reproductive functions and also play the key role in the bodies response to stress. The autonomic nervous system (ANS) regulates the activities of cardiac muscle, smooth muscle, and glands. It is classically divided into two subsystems:

1. SYMPATHETIC NERVOUS SYSTEM:

- Allow body to function under stress
- Fight or flight
- Primes body for intense skeletal muscle activity

2. PARASYMPATHETIC NERVOUS SYSTEM

- Maintenance functions
- Rest-and-digest
- Counterbalances sympathetic function



In general nerve impulses from one division of the ANS stimulate the organ to increase its activity (excitation), and another part inhibit the organs activity (inhibition). Structurally, ANS includes:

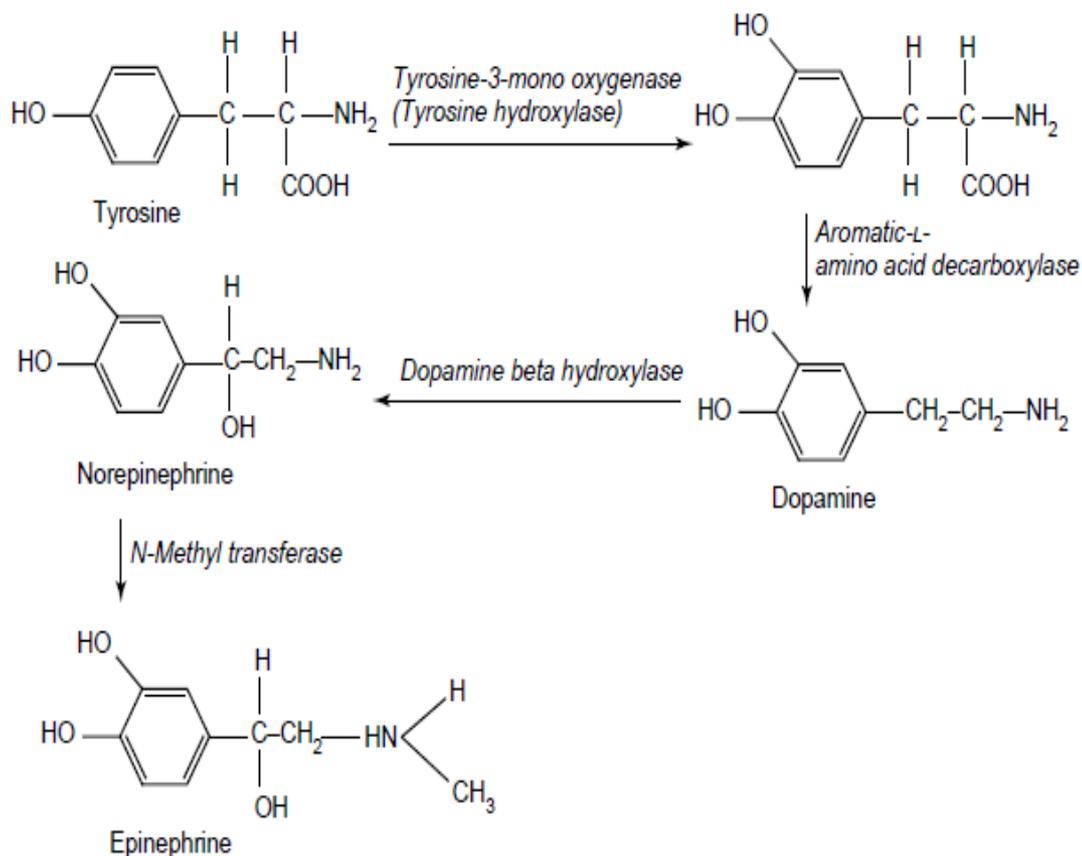
- a. autonomic sensory neurons (afferent)
- b. integrating centers in the CNS
- c. autonomic motor neurons (efferent)

ADRENERGIC NEUROTRANSMITTERS

The sympathetic system activates and prepares the body for vigorous muscular activity, stress, and emergencies. Adrenergic drugs stimulate the adrenergic nerves directly by mimicking the action of norepinephrine or indirectly by stimulating the release of norepinephrine. Therapeutically, these drugs are used to combat life-threatening disorders, which include acute attacks of bronchial asthma, shock, cardiac arrest, and allergic reactions. In addition these drugs are used as nasal decongestants and appetite suppressants.

In adrenergic neurons (sympathetic postganglion), the neurotransmitter released is norepinephrine, which is also called noradrenaline. There are closely related catecholamines (CAs), that is, adrenaline and dopamine that has minor effects secreted by adrenal medulla and in limbic system basal ganglia, respectively. CAs are synthesized from amino acid phenylalanine. Tyrosine hydroxylase is the rate-limiting enzyme and its inhibition by α -methyl-p-tyrosine leads the CAs to dissipate. Other endogenous transmitter, that is, 5-HT produced by aromatic L-amino acid decarboxylase converts DOPA into dopamine and methyl dopamine, and then, it is converted by dopamine β -hydroxylase to α -methyl norepinephrine. The steps involved in the synthesis of epinephrine and norepinephrine are.

Biosynthesis of epinephrine and norepinephrine.



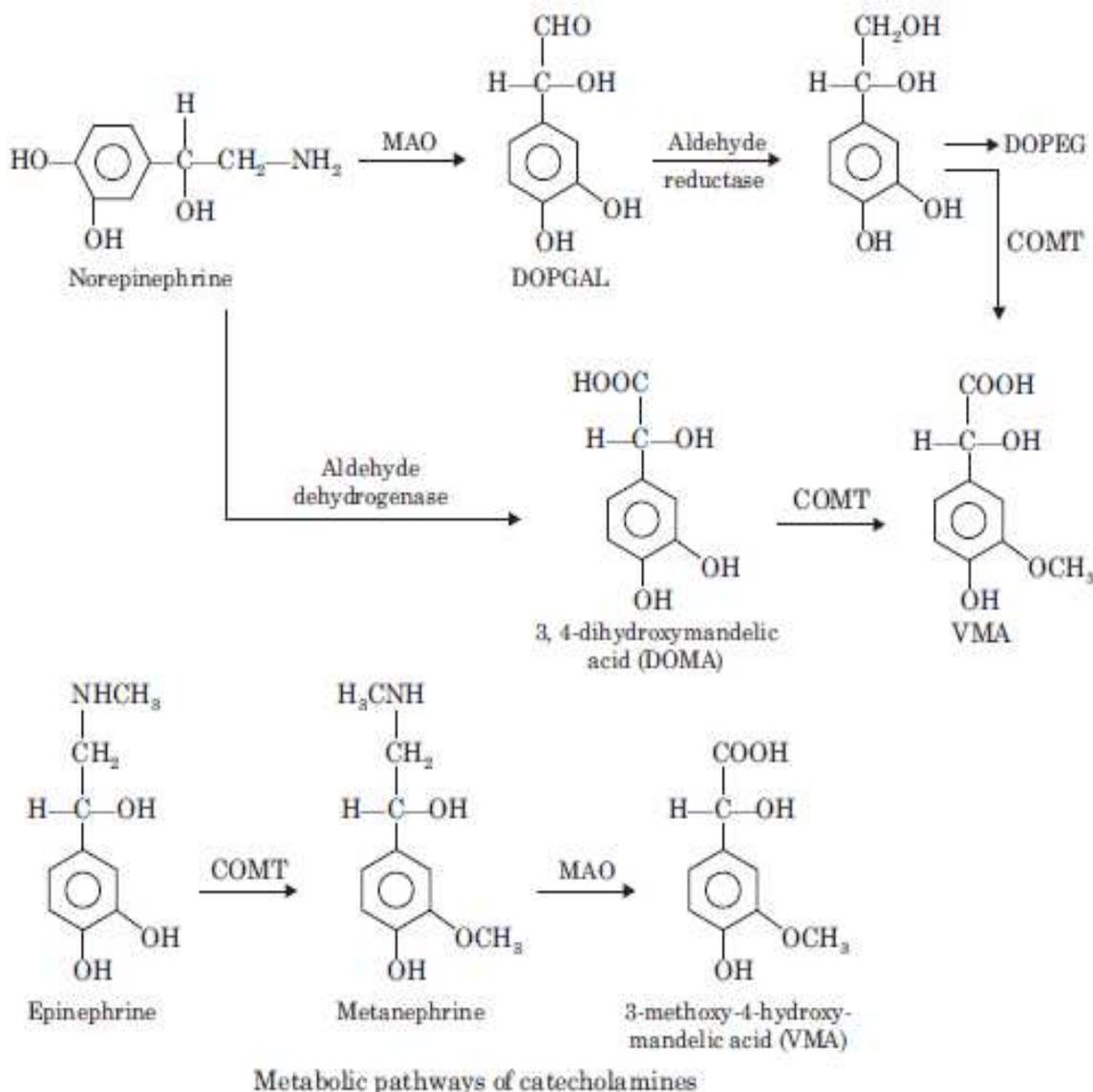
Storage of CAs NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal. The vesicular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β -hydroxylase. NA is then stored as a complex with ATP (in a ratio of 4 : 1) which is adsorbed on a protein chromogranin. In the adrenal medulla the NA thus formed within the chromaffin granules diffuses out into the cytoplasm, is methylated and Adr so formed is again taken up by a separate set of granules. The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.



Release of CAs The nerve impulse coupled release of CA takes place by exocytosis and all the vesicular contents (NA or Adr, ATP, dopamine β hydroxylase, chromogranin) are poured out. In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y (NPY), these cotransmitters are simultaneously released. The release is modulated by presynaptic receptors, of which α_2 inhibitory control is dominant.

Two enzymes namely monoaminoxidase (MAO) and catechol-o-methyl transferase (COMT) are important in the biotransformations of catecholamines. COMT and MAO are distributed widely throughout the body, including the brain the highest concentrations of each are found in the liver and kidney. They differ in their cytosolic locations.

NE released intraneurally is initially deaminated by MAO to 3,4-dihydroxyphenylglycoaldehyde (DOPGAL). The aldehyde group is reduced to glycol by aldehyde reductase, yielding 3,4-dihydroxy-phenylethylene glycol (DOPEG). Aldehyde dehydrogenase converts 3,4-dihydroxyphenylglycolaldehyde to 3,4-dihydroxy-mandelic acid (DOMA). The final common metabolites formed by the action of COMT are DOMA (3-methoxy-4-hydroxy mandelic acid) is VMA (3-methoxy-4-hydroxymandelic acid)



Adrenergic receptor site

Adrenergic drugs exert their effects by direct action on adrenergic receptors. There are at least two adrenergic receptor sites (alpha (α) and beta (β)). Norepinephrine activates primarily alpha- receptors and epinephrine activates primarily beta receptors, although it may also activate alpha receptors. Stimulation of alpha receptors is associated with constriction of small blood vessels in the bronchial mucosa and relaxation of smooth muscles of the intestinal tract. Beta receptor activation relaxes bronchial smooth muscles which cause the bronchi of the lungs to dilate. In addition beta receptor stimulatory



effects cause an increase in the rate and force of heart contractions. As a result increased amounts of blood leave the heart and is diverted from nonactive organs to areas that actively participate in the body's reaction to stress such as skeletal muscles, brain, and liver.

Alpha receptor site

Important features of alpha adrenergic receptor sites in order of preference are ;

1. An anionic site. The alpha-adrenergic receptor carries a negatively charged group (phosphate). The anionic site binds with the positive ammonium group.
2. One hydrogen bonding area
3. A flat area. A non-polar area for the aromatic ring binding.

The alpha receptors fall into two groups;

- (i) **α 1-Adrenergic receptors.** They are found in the smooth muscles of iris, arteries, arterioles and veins.
- (ii) **α 2-Adrenergic receptors.** They mediate the inhibition of adrenergic neurotransmitter release.

Beta receptor site

Important features of this receptor site are :

1. An anionic site. It is shown that an anionic negative acid group which binds with the positive ammonium group.
2. Two hydrogen bonding areas. It is shown as two serine with alcohol (OH) groups form hydrogen bonding with the phenolic—OH groups of the NE.
3. A flat area. A non-polar area for the aromatic ring.

β -Adrenergic receptors are of three types. They are

- (i) **β 1-Adrenergic receptors.** They are found in the myocardium where their stimulation increases the force and rate of myocardial contraction.



(ii) **β 2-Adrenergic receptors.** These are found in bronchial and vascular smooth muscles where their stimulation causes smooth muscle dilation or relaxation.

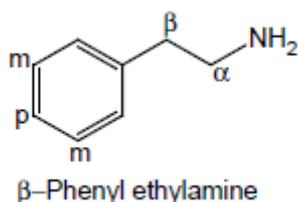
(iii) **β 3-Adrenergic receptors.** These receptors are expressed on fat cells and their stimulation causes lipolysis.

SYMPATHOMIMETIC AGENTS

Sympathomimetics are substances that mimic or modify the actions of endogenous catecholamines of the sympathetic nervous system. Direct agonists directly activate adrenergic receptors while indirect agonists enhance the actions of endogenous catecholamines. Sympathomimetics stimulate alpha-1 adrenergic receptors, beta-adrenergic receptors, and dopamine (D) receptors in various target tissues, such as the eyes, heart, and vascular smooth muscle. The clinical indications for sympathomimetics are broad and include asthma, heart failure, shock, and anaphylaxis.

SAR of Sympathomimetic agents

Many of the sympathomimetic drugs contain β -phenyl ethylamine as parent structure.



I. Phenyl ring substitution

- Substitution on the meta and para positions of the aromatic ring and on the amino, α , and β positions of the ethylamine side chain influences the mechanism of sympathomimetic action and the receptor selectivity of the drug.



- Maximal activity is seen in β -phenyl ethylamine derivatives, containing hydroxyl groups in the meta and para positions of the aromatic ring (catechol) and a β -hydroxyl group of the correct stereochemical configuration on the ethylamine portion of the molecule.
- Although the catechol moiety is an important structural feature to obtain maximal agonistic activity at adrenergic receptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonism.
- For example, replacement of the catechol function of isoproterenol with the resorcinol structure gives the drug metaproterenol, which is a selective β_2 -receptor agonist.
- In another approach, replacement of the meta hydroxyl of the catechol structure with a hydroxymethyl group afforded Salbutamol, which shows selectivity to the β_2 receptor.
- The naturally occurring noradrenaline has 3, 4-dihydroxy benzene ring (catechol) active at both α and β receptors. However, it has poor oral activity because it is rapidly metabolized by COMT, the change in substitution pattern 3, 5-dihydroxy as in metaproterenol gives good oral activity. This is due to its resistance to metabolism by COMT. It also provides selectivity for β_2 receptors.

II. Substitution at nitrogen

- Amino group in phenylethylamines is important for direct agonistic activity.
- The amino group should be separated from the aromatic ring by two carbon atoms found among the potent direct-acting agonists.
- As the bulk of the nitrogen substituent increases, α -receptor agonistic activity decreases and β -receptor activity increases. Thus, NE that is an effective β_1 -receptor agonist is also a potent α -agonist, while epinephrine is a potent agonist at α , β_1 , and β_2 receptors. N-tertiary butyl group enhances β_2 selectivity. As the



size increases from hydrogen in noradrenaline to methyl in adrenaline, isopropyl in isoproterenol, the activity of α receptor decreases and β receptor increases.

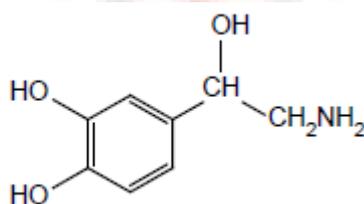
- Primary and secondary amines are more potent direct-acting agonists than 3° or 4° amines.

III. Substitution on the carbon side chain

- Methyl or ethyl substitution on the α -carbon of the ethylamine side chain reduces direct receptor agonist activity at both α and β receptors.
- Importantly, an α -alkyl group increases the duration of action of the phenylethylamine agonist by making the compound resistant to metabolic deamination by MAO.
- α -substitution also significantly affects receptor selectivity.
- Another effect of α -substitution is the introduction of a chiral centre, which has pronounced effects on the stereo-chemical requirements for activity.

1.Direct acting:

a.Nor-epinephrine



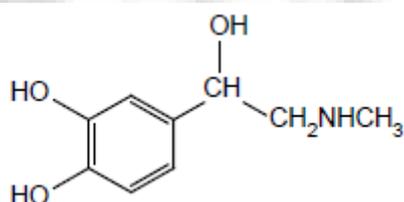
Properties and uses: It is a white or brownish-white, crystalline powder, slightly soluble in ethanol and soluble in water. It differs from adrenaline only by lacking the methyl substitution on the amino ethanol. L-isomer is pharmacologically active. Noradrenaline is a potent agonist for α_1 receptors and has relative actions on β_2 receptors. By acting on these receptors, the systolic



and diastolic pressures, and usually, pulse pressure are increased. It increases the peripheral vascular resistance. Its principle use is to support blood pressure in various acute hypotensive states, especially in myocardial shock. It is used as a vasoconstrictor in some local anaesthetic solutions for dental use.

Storage: It becomes coloured on exposure to air and light. It should be stored in well-closed airtight containers, preferably in a sealed tube under vacuum or under an inert gas and protected from light.

b. Epinephrine



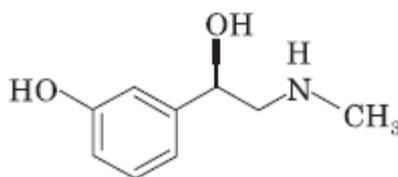
Properties and uses: Adrenaline is a catecholamine and belongs to the family of biogenic amines. It is a white or creamy white, sphaero-crystalline powder. It dissolves in solutions of mineral acids, potassium hydroxide, and of sodium hydroxide, but sparingly soluble in water, insoluble in ethanol and ether. It is used as a sympathomimetic, broncholytic, and antiasthmatic. It is used to prevent bleeding during surgery or in case of inner organ bleeding. Because adrenaline leads to constriction of blood vessel, it is administered in combination with local anaesthetics. In this combination, anaesthetics have long-lasting effect and can be administered in smaller doses. It is used in the treatment of heart block or circulatory collapse and open-angle glaucoma. It is usually the drug of choice in acute allergic disorders and histamine reactions.

Storage: Epinephrine is light sensitive and easily oxidized on exposure to air because of the catechol ring system. The development of a pink to brown colour indicates oxidative breakdown. To minimize oxidation, solutions of the drug are

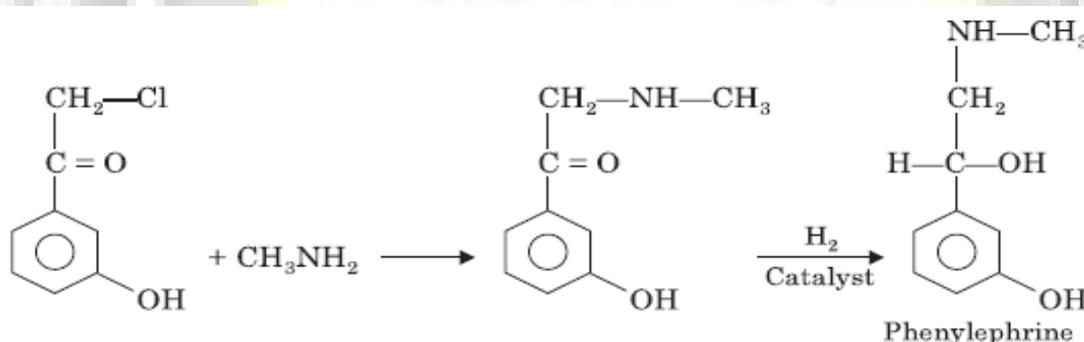
stabilized by the addition of a reducing agent, such as sodium bisulphite. Adrenaline should be stored in well-closed airtight containers, which is preferably filled with nitrogen, and protected from light.

Dose: By subcutaneous, 0.2 to 0.5 mg in 0.1% solution; intramuscularly 1 to 3 mg in a 0.2% oil suspension, repeated as required. Dosage forms: Adrenaline injection I.P., Adrenaline eye drops/epinephrine eye drops B.P., Dilute adrenaline injection (1 in 10,000)/dilute epinephrine injection (1 in 10,000) B.P.

c. Phenylephrine*



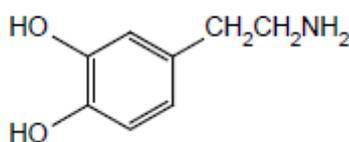
Synthesis



Properties and uses: Phenylephrine is available as hydrochloride salt. It is white, odorless, bitter taste, crystalline powder. It is soluble in water, alcohol, and glycerol. It should be stored in airtight container to protect from light because it is decomposed by light. Phenylephrine is a selective α_1 -receptor agonist. Oral absorption is not reliable and so it is given parenterally or topically as eye or nasal drops. Phenylephrine predominantly acts on peripheral arterioles results in a rise in systolic and diastolic pressures accompanied by a marked

reflex bradycardia. Phenylephrine is used as a nasal decongestant, mydriatic and as a vasopressor agent.

d. Dopamine



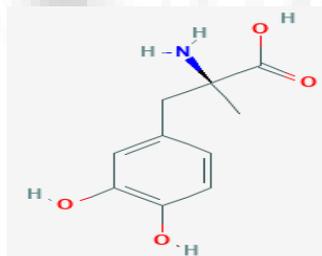
Properties and uses: It is a white or almost white crystalline powder, soluble in alcohol, sparingly soluble in acetone and methylene chloride, but freely soluble in water. It is used in the treatment of shock. It is ineffective orally in large parts because it is a substrate for both MAO and COMT. Dopamine exerts the CVS effects by interacting with D1-dopaminergic receptors especially in the renal, mesenteric, and coronary beds. At high concentrations, dopamine acts on β_1 adrenergic receptors and causes positive inotropic effects and also dopamine causes the release of norepinephrine.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: Acute heart failure: Adult: Initially, 1–5 $\mu\text{g}/\text{kg}/\text{min}$ increased gradually by up to 5–10 $\mu\text{g}/\text{kg}/\text{min}$ according to the patient's BP, cardiac output and urine output. Up to 20–50 $\mu\text{g}/\text{kg}/\text{min}$ may be required in seriously ill patients.

Dosage forms: Dopamine intravenous infusion B.P.

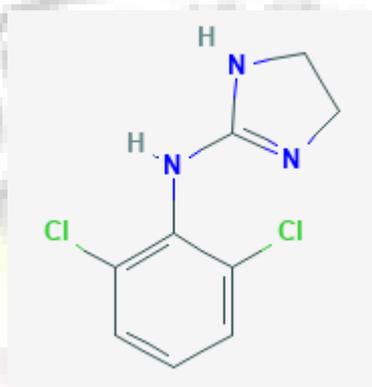
e. Methyldopa



Properties and uses: Methyldopa is a white to yellowish white, odorless fine powder, and is soluble in water.

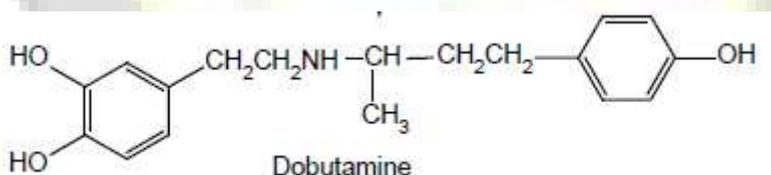
Storage: It should be stored in well-closed airtight containers, protected from light.

f. Clonidine



Properties and uses: Clonidine is an imidazole derivative that acts as an agonist of alpha-2 adrenoceptors. This activity is useful for the treatment of hypertension, severe pain.

g. Dobutamine



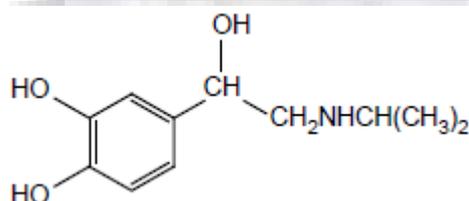
Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water and alcohol, and soluble in methanol. It resembles dopamine chemically, but possesses a bulky aromatic residue on the amino group despite the absence of a β -OH group. This substitution gives a compound that possesses an asymmetric carbon atom. Thus, dobutamine exists as a pair of enantiomers possessing a distinct pharmacology. The (+) enantiomer is a potent agonist at both β_1 and β_2 receptors. The (-) enantiomer is 10 times less potent at β_1 and



β_2 receptors. The (–) enantiomer is a potent agonist at α_1 receptors. It acts by directly interacting with α and β adrenergic receptors. Racemic dobutamine increases the inotropic action due to α_1 receptor when compared to chronotropic actions, and the effects are mediated by β receptors. It enhances the automaticity of SA node.

Storage: It should be stored in well-closed airtight containers, protected from light

h. Isoproterenol



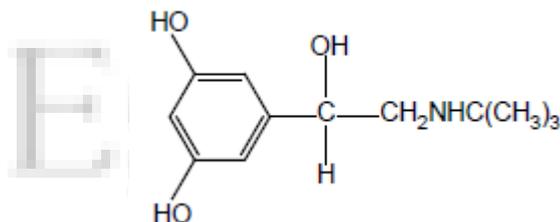
Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, sparingly soluble in alcohol, practically insoluble in methylene chloride. It is a synthetic Isopropyl analogue of adrenaline, acting almost exclusively at β -receptor. It stimulates the action of adrenaline and has the advantage of being effective when given orally. It is a nonselective β agonist and has strong β_1 and β_2 agonist activity. Its primary use is in the treatment of bronchial asthma. It is used as an antiarrhythmic agent and in the treatment of shock to increase heart rate.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: Sublingual, 10 to 15 mg 3 to 4 times/day; I.M. or S.C. 0.01 to 0.2 mg; repeated as necessary; infusion, 1 to 2 mg per 500 ml of 5% dextrose infusion at such a rate so as to maintain blood pressure.

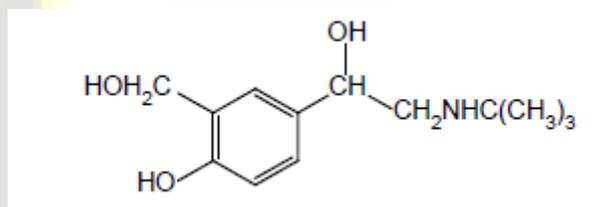
Dosage forms: IsoprenalineHCl injection I.P., Isoprenaline sulphate tablets I.P., Isoprenaline injection B.P.

i. Terbutaline

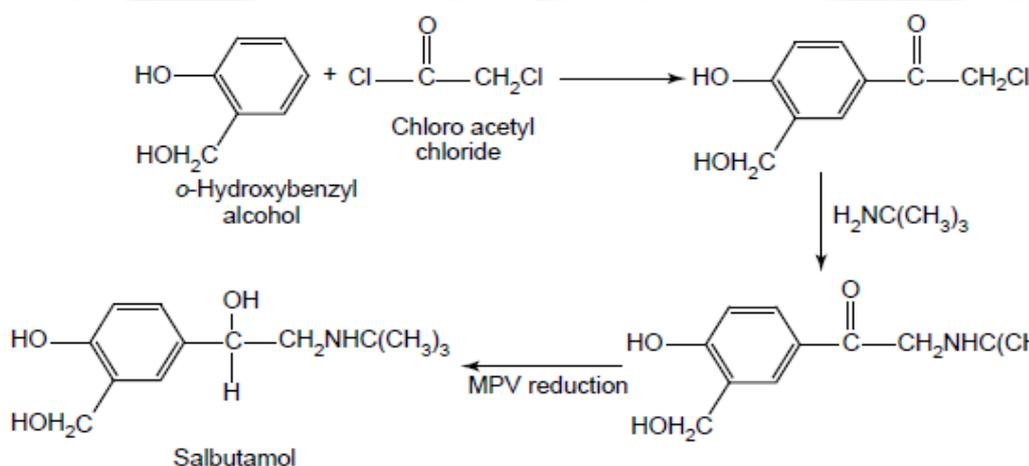


Properties and uses: It exists as a gray-white crystalline powder, odourless and with a bitter taste, soluble in water and alcohol. The drug exhibits the properties of a direct-acting sympathomimetic agent, having predominantly β_2 adrenergic activity, and has a selective action on the β_2 receptors (i.e. β_2 agonist). It is used only as a bronchodilator and in the treatment of asthma. It possesses strong β -agonistic activity.

j. Salbutamol*



Synthesis



Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water, but freely soluble in ethanol. It has strong β_2 adrenergic



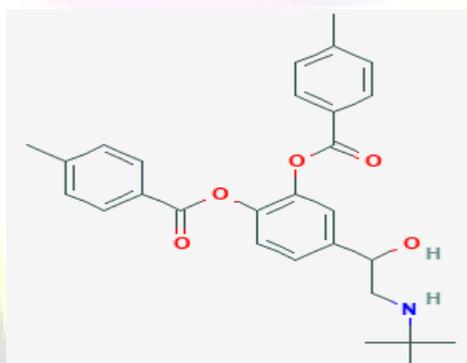
activity. It is useful in the treatment of acute myocardial infarction, severe left ventricular failure. It has been used to arrest premature labour and is effective in ocular hypotension by topical application. It is used only as a bronchodilator and is the drug of choice in the treatment of bronchial asthma.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dose: By oral inhalation the adult dose is 100 microgram, followed by a second dose after 5 min, if required.

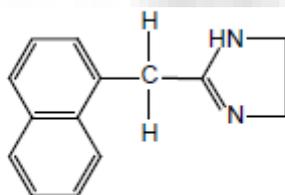
Dosage forms: Salbutamol tablets and inhaler I.P., Salbutamol pressurized inhalation B.

k. Bitolterol



Properties and uses: Bitolterol is a prodrug for colterol, a beta2-adrenergic receptor agonist, bitolterol is used as its methane sulfonate salt for relief of bronchospasm in conditions such as asthma, chronic bronchitis and emphysema.

l. Naphazoline



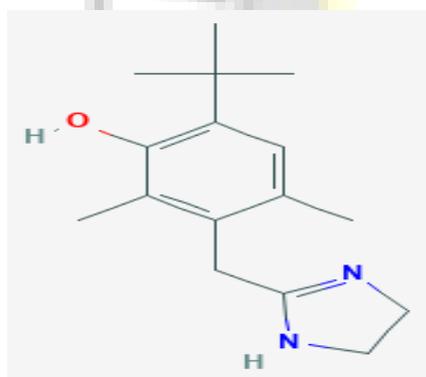
Properties and uses: It is a white crystalline, odourless, and bitter compound. The salt is soluble in water and in alcohol. They essentially exist in an ionized form at physiological pH because of the very basic nature of the imidazoline ring (pKa 9 to 10). It is a directly acting sympathomimetic drug, which is mostly used as a local vaso-constrictor for the relief of nasal congestion due to allergic or infarction manifestations. It is also employed as an ophthalmic solution for the relief of ocular congestion and blepharospasm.

Storage: It should be stored in well-closed airtight containers, protected from light.

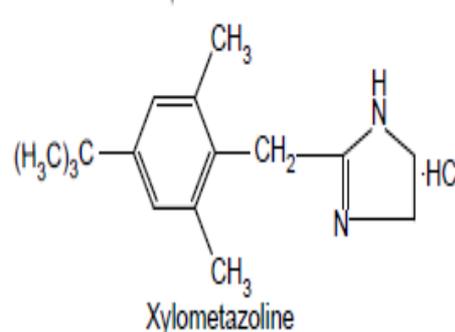
Dose: For nasal mucosa, 2 drops of 0.05% solution;

for conjunctivity, 1 to 2 drops of a 0.1% solution after every 3 to 4 hours.

m. Oxymetazoline



n. Xylometazoline.

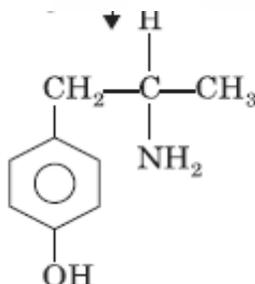


Properties and uses: It is a potent sympathomimetic agent, having marked and pronounced α -adrenergic pharmacologic profile. It is found to act as a vasoconstrictor, when applied topically to mucous membranes particularly. It is frequently employed as a local vaso-constrictor for nasal congestion caused by sinusitis or rhinitis.

Dose: By intranasal, 1 drop of a 0.1% solution in adult; or a spray of 0.05% solution

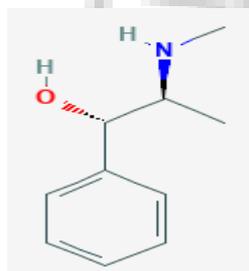
2. Indirect acting agents:

a. Hydroxyamphetamine

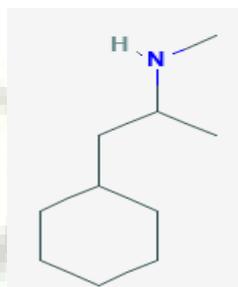


Hydroxyamphetamine possesses α -receptor stimulant activity but lacks CNS activity. It is a powerful vasoconstrictor. Hydroxyamphetamine is used in the following conditions; Narcolepsy (sudden attack of sleep in completely inappropriate situations), Hyperkinetic syndrome in children, As an anorexiant in the treatment of obesity.

b. Pseudoephedrine.

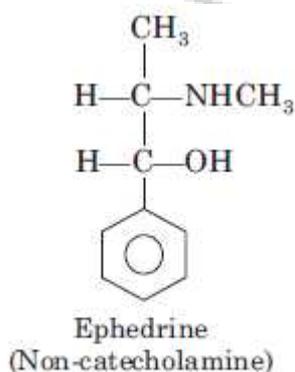


Propylhexedrine.

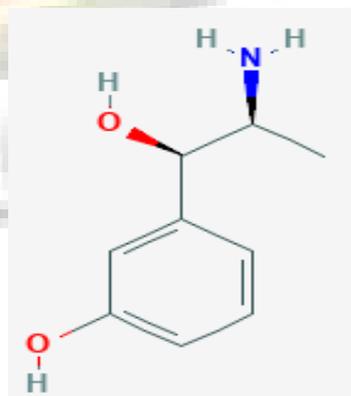


3. Agents with mixed mechanism:

a. Ephedrine



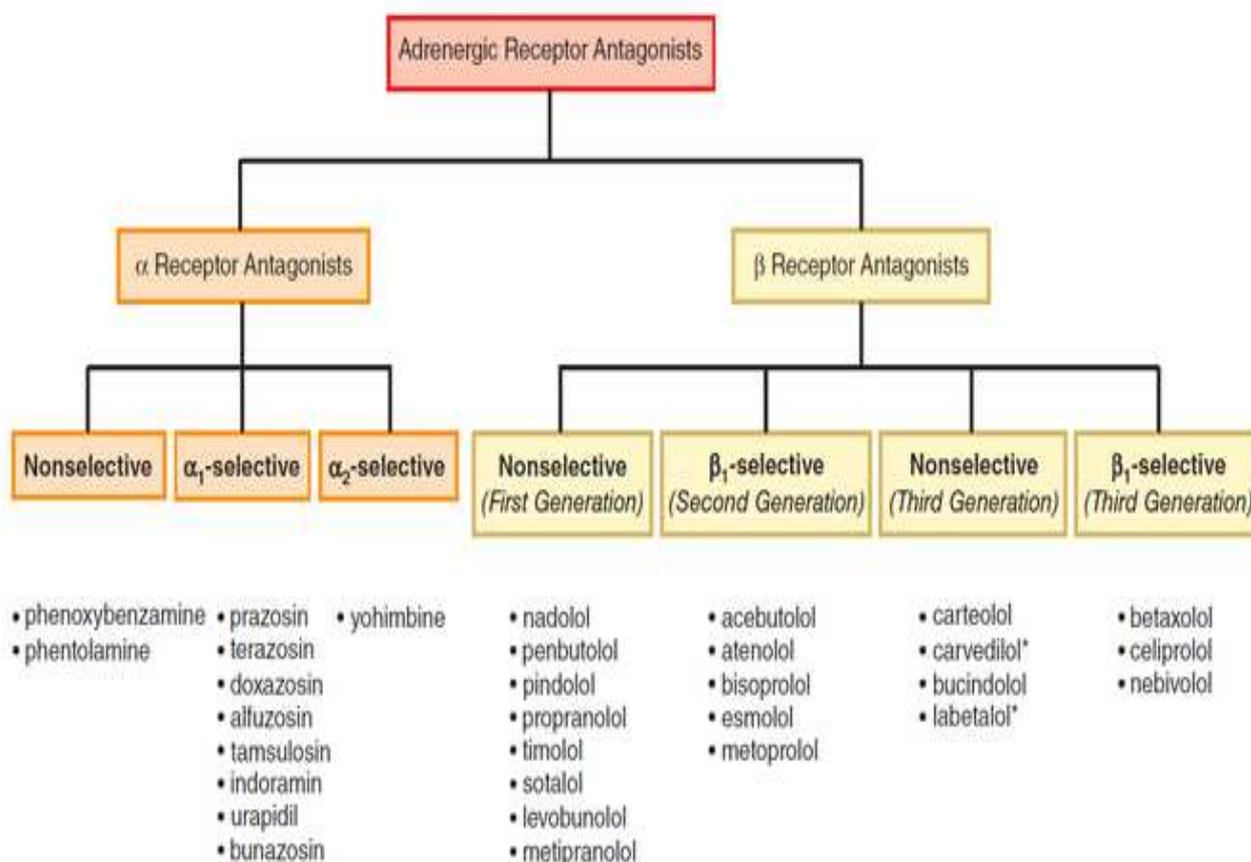
b. Metaraminol



ADRENERGIC ANTAGONISTS

An adrenergic antagonist is a drug that inhibits the function of adrenergic receptors. There are five adrenergic receptors, which are divided into two groups. The first group of receptors are the beta (β) adrenergic receptors. There are β_1 , β_2 , and β_3 receptors. The second group contains the alpha (α) adrenoceptors. There are only α_1 and α_2 receptors. Adrenergic receptors are located near the heart, kidneys, lungs, and gastrointestinal tract. There are also α -adreno receptors that are located on vascular smooth muscle. These agents competitively antagonise the effects of the catecholamines at α and/or β -adrenergic receptors. Many of the side effects of these agents are postural hypotension, sedation or depression, increased GIT motility, diarrhoea, impaired ability to ejaculate, increased blood volume and sodium retention.

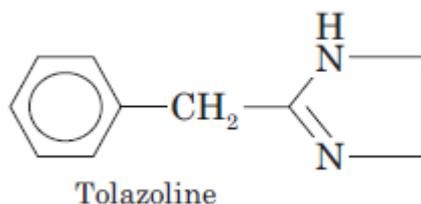
Classification :



Alpha adrenergic blockers

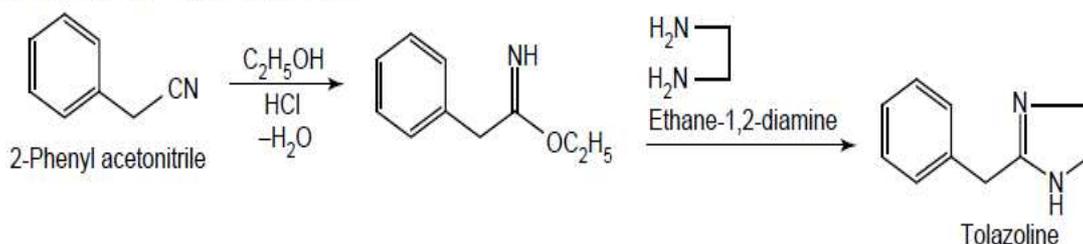
The α -receptor blockers in most cases do not show selectivity of action. Thus α -blockers have limited clinical use. α -blockers have been employed as antihypertensives for decades. These agents enjoy wide structural variations. On the chemical basis, various α -receptor blockers can be classified as:

1. Tolazoline



Synthesis

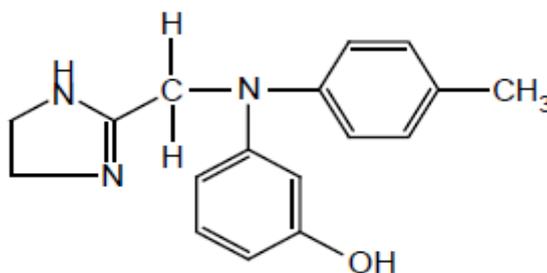
Route I. From: Phenyl acetonitrile



Properties and uses: It is a white, bitter taste, crystalline compound with a slight aromatic odour, soluble in water, alcohol, and chloroform, but sparingly soluble in ether. It is an imidazolidine derivative. It is a competitive alpha adrenergic antagonist and possesses similar affinity for α_1 and α_2 receptors. It is a vasodilator and has a sympathomimetic effect to stimulate the heart and causes mydriasis. It is of some use in the treatment of Raynaud's disease, cerebral vascular accidents. It has been used in the treatment of persistent pulmonary hypertension of the newborn.

Dose: By I.M., I.V., S.C., for adults: 25 mg slowly, then increased upto 50 to 75 mg twice/day to 2 or 3 times/week.

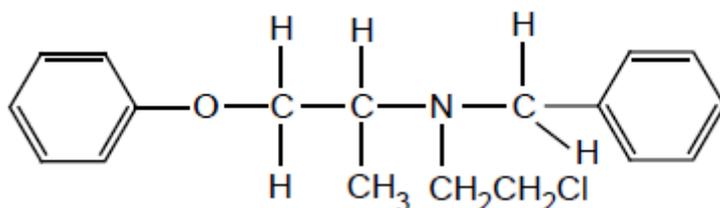
2. Phentolamine,





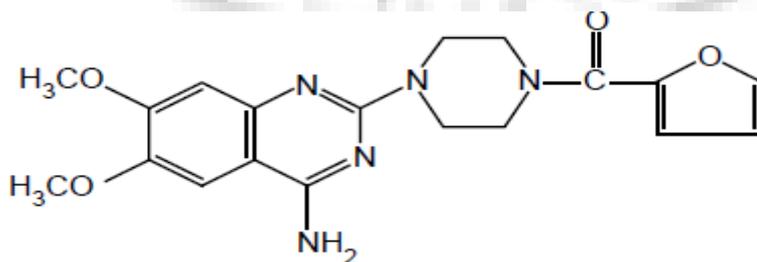
Properties and uses: It is a white, odourless, bitter powder, soluble in water and alcohol. Phentolamine is a nonselective α -adrenoreceptor antagonist with an immediate onset and short duration of action. In addition to α -blocking activity, it has weak muscarinic activity in the gastrointestinal tract and weak to mild histaminergic activity in the stomach. It is an α -adrenergic blocker used in urgent heart failure. Storage: It should be stored in well-closed airtight containers and protected from light. Dosage forms: Phentolaminemesylate injection I.P., Phentolamine injection B.P.

3. Phenoxybenzamine,



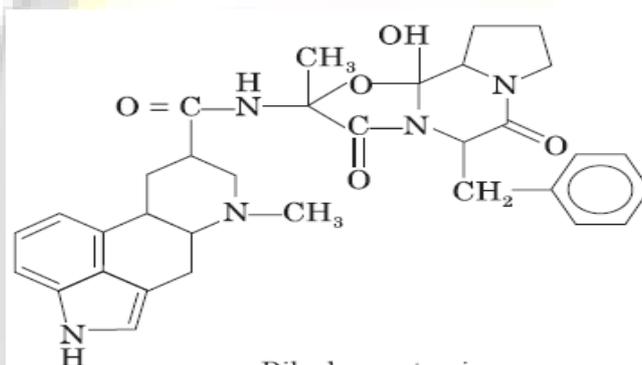
Properties and uses: Colourless, crystalline compound soluble in alcohol, water, and chloroform. Irreversible antagonist with nonselective actions, a major use of phenoxybenzamine is in the treatment of pheochromocytoma (tumours of the adrenal medulla). It is used to treat peripheral vascular diseases, such as Raynaud's syndrome. It has also been used in the case of shock and frostbite to improve blood flow to peripheral tissues. Used in the treatment of shock and in the treatment of pulmonary oedema. Dose: The usual dose initially 10 mg/day, increased gradually to 60 mg/day in divided doses. Dosage forms: Phenoxybenzamine capsules B.P.

4. Prazosin

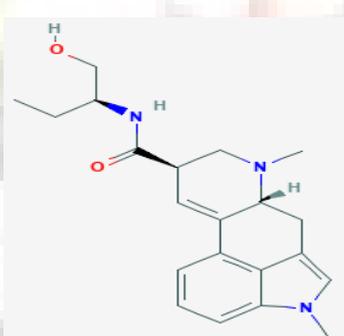


Properties and uses: It is a white crystalline powder, soluble in water and alcohol. A selective α -antagonist, prazosin, reduces peripheral vascular resistance and lowers arterial blood pressure in both supine and erect patients. Dizziness, headache, and palpitations can occur. Used to treat hypertension of any degree. It has been used in decreasing cardiac overload. **Storage:** It should be stored in well-closed airtight containers and protected from light. **Dose:** For hypertension: the adult dose as hydrochloride: Initially, 500 μ g twice to thrice/day for 3–7 days, increased to 1 mg two times to three times for the next 3–7 days if tolerated and gradually increased thereafter according to the patient's response. Maximum dose is 20 mg/day.

5. Dihydroergotamine



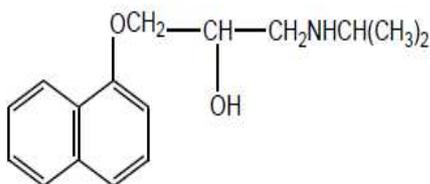
6. Methysergide.



BETA ADRENERGIC BLOCKERS:

SAR of beta blockers,

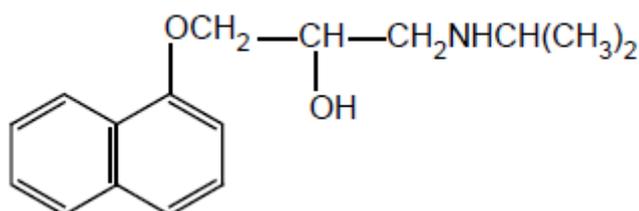
Propranolol has become one of the most thoroughly studied and widely used drug in the therapeutic armamentarium; it is the standard against which all other β antagonists are compared.



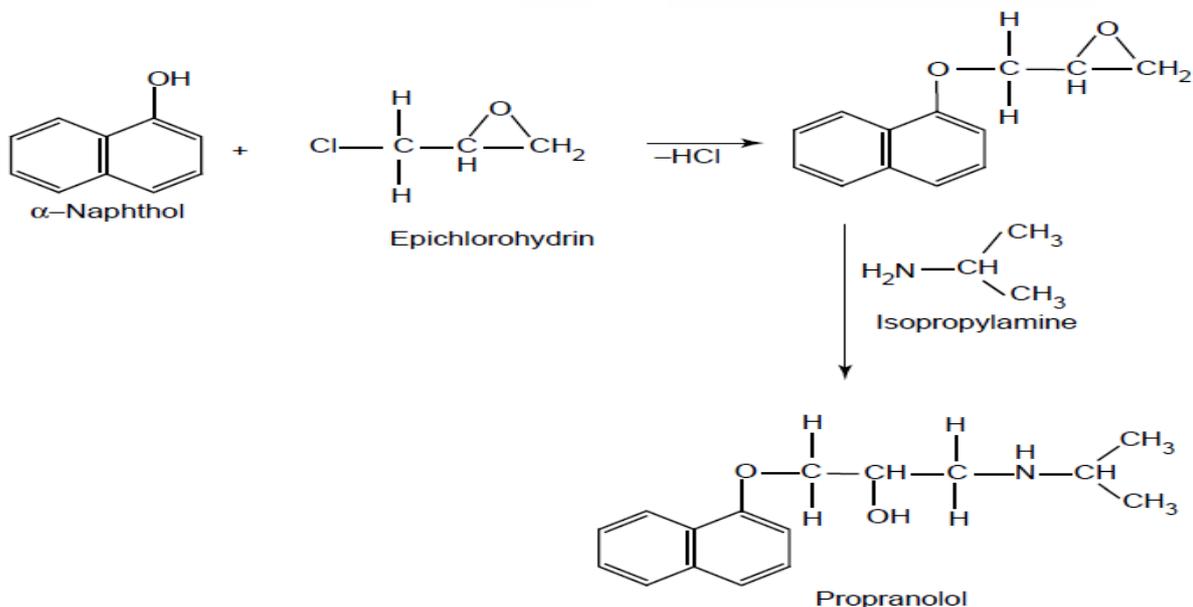
Propranolol

- The aromatic ring and its substituent is the primary determinant of β_1 antagonistic activity. The aryl group also affects the absorption, excretion, and metabolism of the β blockers.
- β blockers are structurally similar to β agonist. The catechol ring can be replaced by a variety of ring system without loss of antagonistic activity.
- Replacement of catechol hydroxyl group with chlorine of phenyl ring system retains β blocking activity. Example: pronethalol, dichloroisoproterenol.
- *N,N*-disubstitution decreases the β blocking activity, and the activity is maintained when the phenyl ethyl, hydroxy phenyl ethyl, or methoxy phenyl ethyl groups are added to amine as a part of the molecule.
- The two carbon chains are essential for activity.
- The introduction of -OCH₂ group into the molecule between the aromatic ring and the ethyl amine side chain provides β blocking agents, for example, propranolol.
- As in the sympathomimetics, bulky aliphatic groups, such as the tert-butyl and isopropyl groups are normally found on the amino function of the aryloxypropanolamine β receptor antagonists. It must

1. Propranolol*



Synthesis:

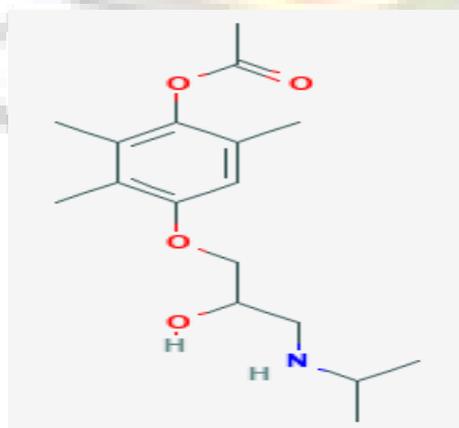


Properties and uses: It is a white or almost white powder, soluble in water and in ethanol. Currently, it is approved for hypertension associated cardiac arrhythmia, angina pectoris, due to coronary atherosclerosis and prophylaxis of migraine headache. It is a nonselective β -adrenergic antagonist and it has equal affinity for β_1 and β_2 receptors.

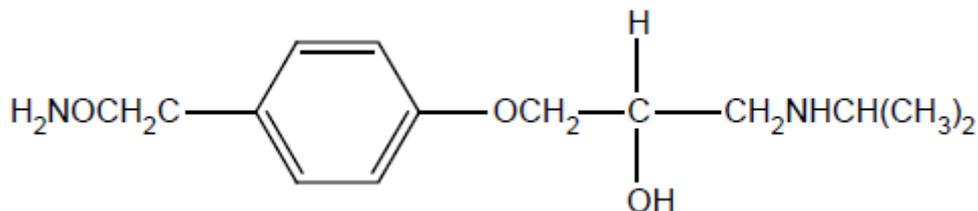
Dose: The oral adult dose for arrhythmias is 10 to 30 mg 3 to 4 times/day.

Dosage forms: Prolonged-release propranolol capsules B.P., Propranolol injection B.P., Propranolol tablets B.P.

2. Metibranolol



3. Atenolol

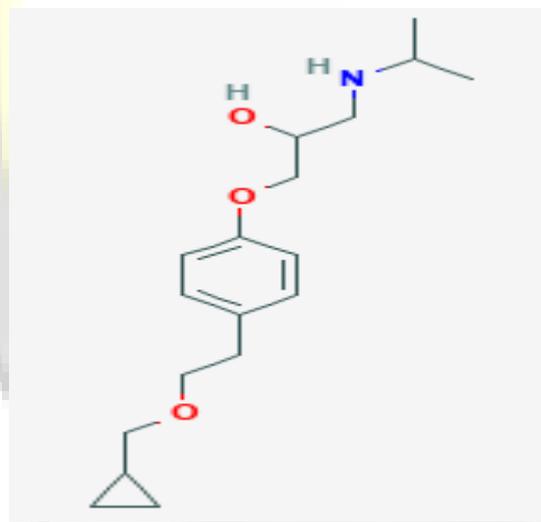


Properties and uses: It is a white or almost white powder, sparingly soluble in water, but soluble in ethanol. It is a β₁ selective drug with low lipid solubility. Mainly used in the treatment of essential hypertension.

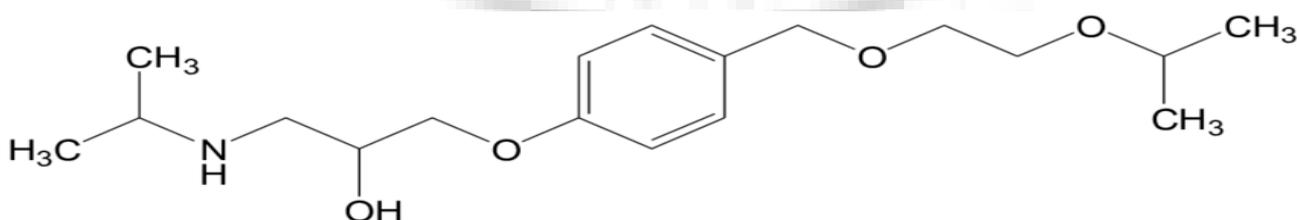
Dose: The usual dose is 50 mg/day once daily.

Dosage forms: Atenolol tablets I.P., B.P., Atenolol injection B.P., Atenolol oral solution B.P., Co-tenidonetables B.P.

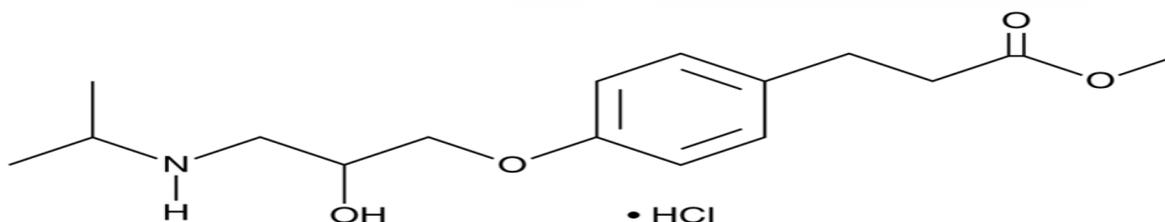
4. Betaxolol



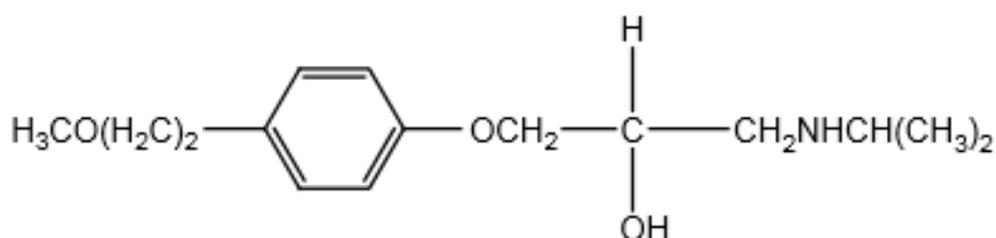
5. Bisoprolol



6. Esmolol



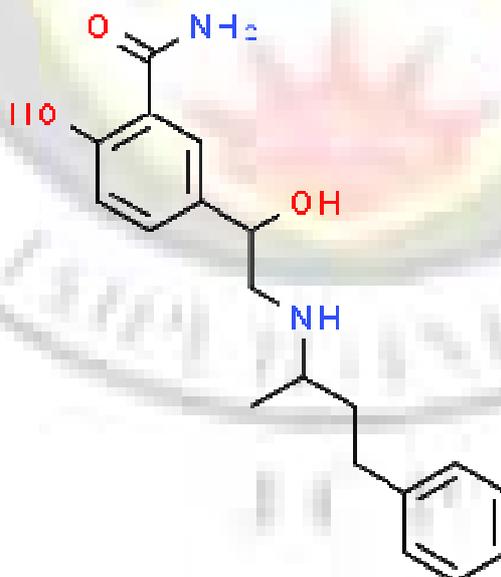
7. Metoprolol



Properties and uses: It is white, odourless powder, bitter in taste, soluble in water, alcohol, and chloroform, but insoluble in acetone and ether. It is a β_1 selective antagonist used in the treatment of hypertension.

Dose: The usual initial oral dose is 100 mg given preferably once daily.

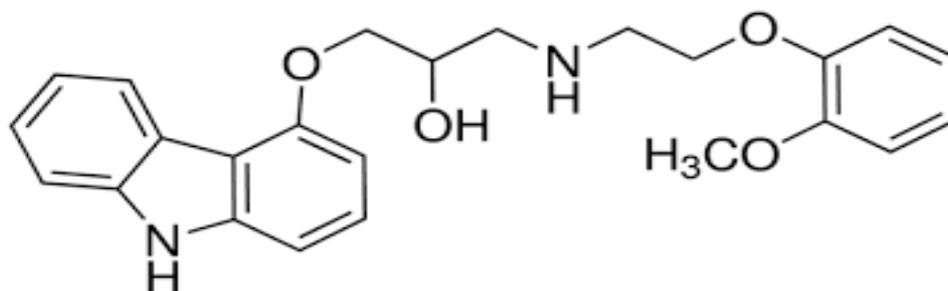
8. Labetolol





Properties and uses: It is a white or almost white powder, soluble in water and in ethanol. Labetalol is a medication used to treat high blood pressure and in long term management of angina.

9.Carvedilol



Properties and uses: Carvedilol is a racemic mixture where the S(-) enantiomer is a beta adrenoceptor blocker and the R(+) enantiomer is both a beta and alpha-1 adrenoceptor blocker. It is currently used to treat heart failure, left ventricular dysfunction, and hypertension.