Name of Unit	Drug acting on Autonomic nervous system.
Course/Subject Code	BP402T
Class	B. Pharm
Semester	IV
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Learning Outcome Module 02

LO	Learning Outcome	Course Outcome Code
LO1	Student will learn about the adrenergic receptors, Adrenergic neurotransmitter.	BP402.1
LO2	Biosynthesis and distribution.	BP402.2
LO3	Adrenergic agonist and Antagonist.	BP402.1
LO4	Structure activity relationship.	BP402.3
LO5	Synthesis of drugs.	BP402.4

Content Table

Topic
• Introduction of Autonomic nervous system. • Biosynthesis • Direct acting drugs with Synthesis • SAR • Indirect acting drugs. • Adrenergic antagonists • Beta blockers.

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)

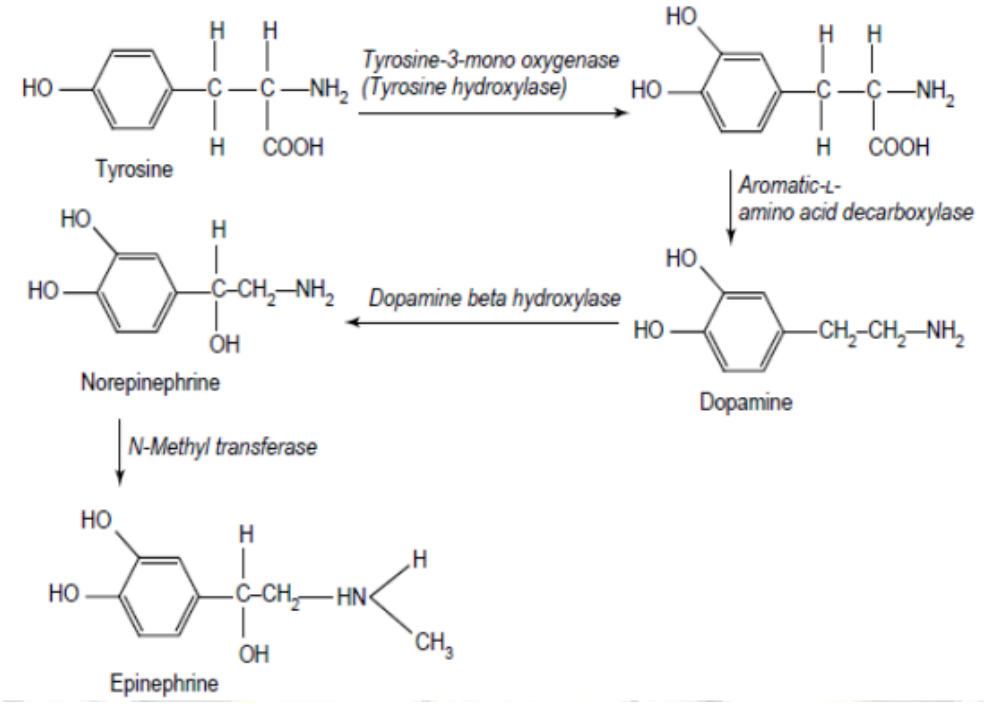
b) integrating centers in the CNS

c) autonomic motor neurons (efferent)

ADRENERGIC NEUROTRANSMITTERS

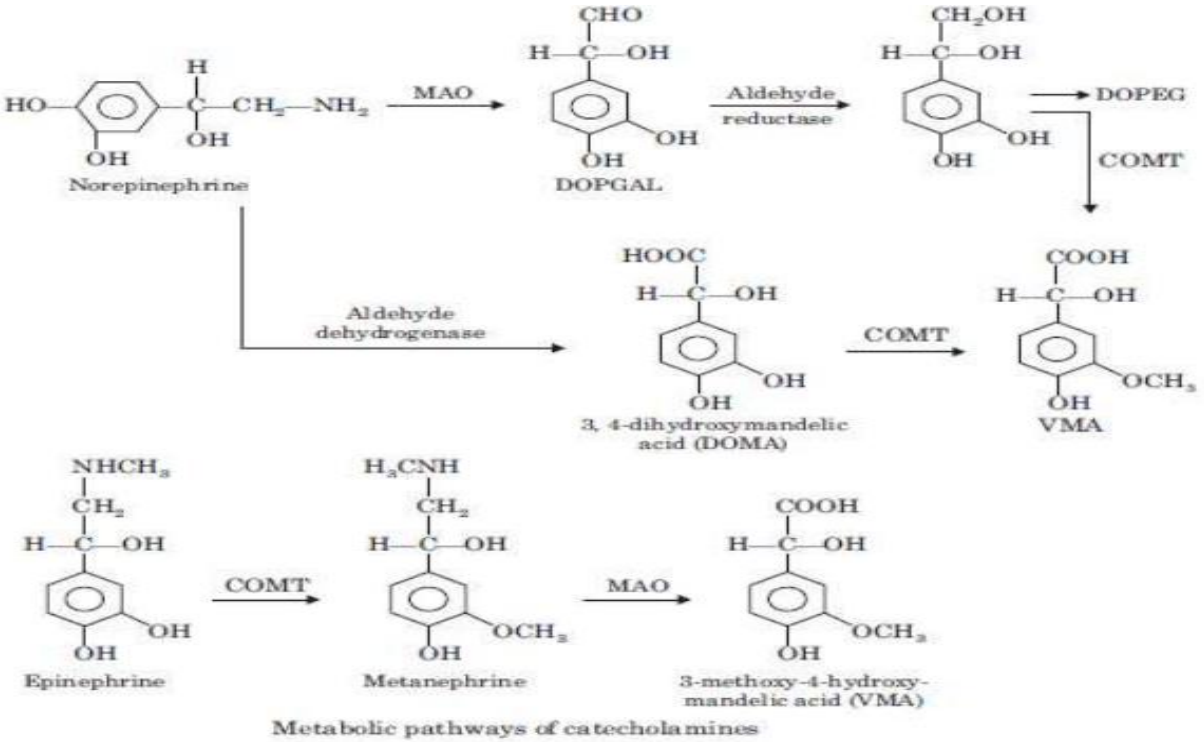
The sympathetic system activates and prepares the body for vigorous muscular activity, stress, and emergencies. Adrenergic drugs stimulate the adrenergic nerves directly by mimicking the action of nor epinephrine or indirectly by stimulating the release of nor epinephrine. Therapeutically, these drugs 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 nor epinephrine, which is also called nor adrenaline. 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 methyldopamine, and then, it is converted by dopamine β-hydroxylase to α-methyl norepinephrine. The steps involved in the synthesis of epinephrine and nor epinephrine 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 neuro peptide Y (NPY), these cotransmitters are simultaneously released. The release is modulated by pre synaptic receptors, of which α2 inhibitory control is dominant. Two enzymes namely mono amino oxidase (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.



Metabolic pathways of catecholamines

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 commonmetabolites formed by the action of COMT are DOMA (3-methoxy-4-hydroxy mandelic acid) isVMA (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 non-active 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) α1-Adrenergic receptors. They are found in the smooth muscles of iris, arteries, arterioles and veins.

(ii) α2-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) β1-Adrenergic receptors. They are found in the myocardium where their stimulation increases the force and rate of myocardial contraction.

(ii) β2-Adrenergic receptors. These are found in bronchial and vascularsmooth muscles where their stimulation causes smooth muscle dilation or relaxation.

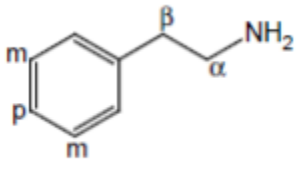
(iii) β3-Adrenergic receptors. These receptors are expressed on fat cells andtheir stimulation causes lipolysis.

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-1 adrenergic structure



β–Phenyl ethylamine

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 stereo chemical 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 β2-receptor agonist.
- In another approach, replacement of the meta hydroxyl of the catechol structure with a hydroxymethyl group afforded Salbutamol, which showsselectivity to the β2 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 β2 receptors.

II. Substitution at nitrogen

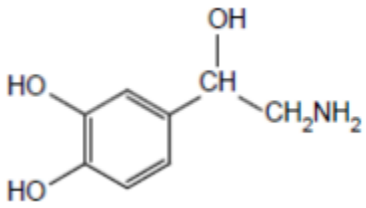
- Amino group in phenyl ethyl amines is important for direct agonistic activity.
- The amino group should be separated from the aromatic ring by two carbon atoms found among the potent direct-acting agonists.
- As the bulk of the nitrogen substituent increases, α-receptor agonistic activity decreases and β-receptor activity increases. Thus, NE that is an effective β1-receptor agonist is also a potent α-agonist, while epinephrine is a potent agonist at α, β1, and β2 receptors. N-tertiary butyl group enhances β2 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 phenyl ethylamine 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:

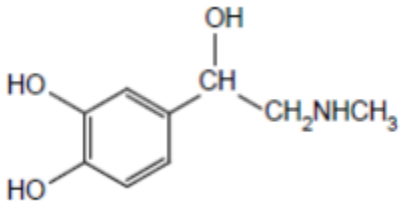
a. Nor-epinephrine



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. Nor adrenaline is a potent agonist for α1 receptors and has relative actions on β2 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

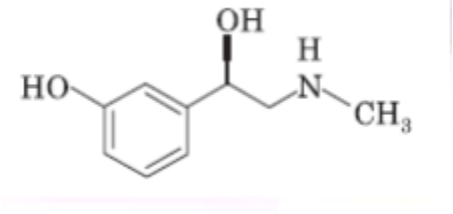


Properties and uses: Adrenaline is a catecholamine and belongs to the family of biogenic amines. It is a white or creamy white, sphaero-crystalline powder. It dissolves in solutions of mineral acids, potassium hydroxide, and of sodium hydroxide, but sparingly soluble in water, insoluble in ethanol and 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.

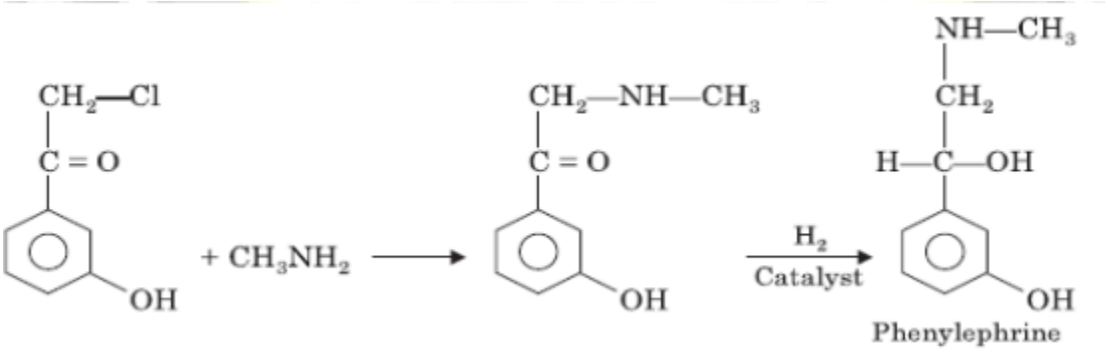
Storage: Epinephrine is light sensitive and easily oxidized on exposure to airbecause of the catechol ring system. The development of a pink to brown colour indicates oxidative breakdown. To system minimize oxidation, solutions of the drug are stabilized by the addition of a reducing agent, such as sodium bisulphate. 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*

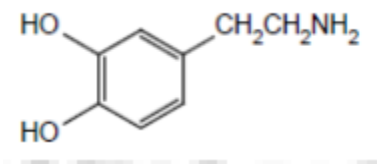


Synthesis



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 α1-receptoragonist. Oral absorption is not reliable and so it is given parenterally or topicallyas eye or nasal drops. phenylephrine predominantly acts on peripheral arteriolesresults in a rise in systolic and diastolic pressures accompanied by a marked reflex bradycardia. Phenylephrine is used as a nasal decongestant, mydriatric and as a vasopressor agent.

d. Dopamine



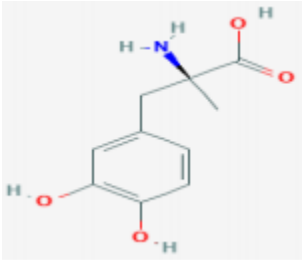
Properties and uses: It is a white or almost white crystalline powder, soluble in alcohol, sparingly soluble in acetone and methylene chloride, but freely soluble in water. It is used in the treatment of shock. It is ineffective orally in large parts because it is a substrate for both MAO and COMT. Dopamine exerts the CVS effects by interacting with D1-dopaminergic receptors especially in the renal, mesenteric, and coronary beds. At high concentrations, dopamine acts on β1adrenergic receptors and causes positive ionotropic effects and also dopamine causes the release of nor epinephrine.

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

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

Dosage forms: Dopamine intravenous infusion B.P.

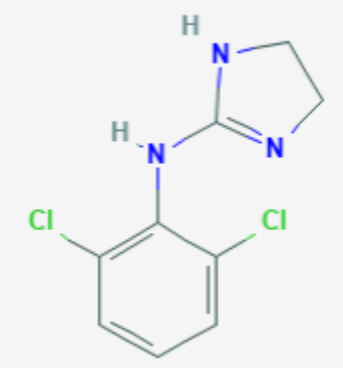
e. Methyldopa



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

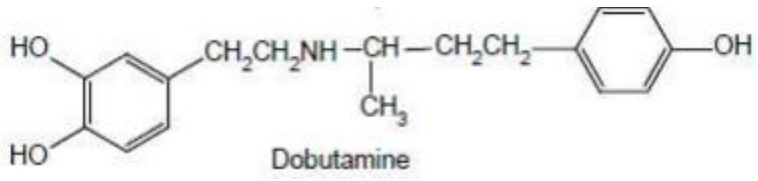
Storage: It should be stored in well-closed airtight containers, protected from light.

f. Clonidine



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

g. Dobutamine

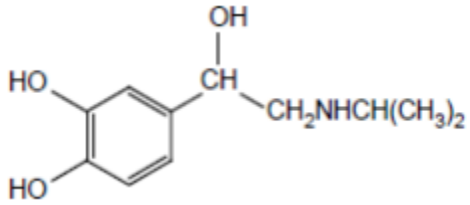


Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water and alcohol, and soluble in methanol. It resembles dopamine chemically, but possesses a bulky aromatic residue on the amino group despitethe absence of a β-OH group. This substitution gives a compound that 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 β1 and β2 receptors. The (–) enantiomer is 10 times less potent at β1 and

β2 receptors. The (–) enantiomer is a potent agonist at α1 receptors. It acts by directly interacting with α and β adrenergic receptors. Racemic dobutamine increases the inotropic action due to α1 receptor when compared to chronotropicactions, and the effects are mediated by β receptors. It enhances the automaticityof SA node.

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

h. Isoproterenol



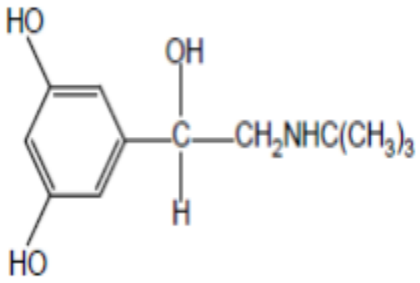
Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, sparingly soluble in alcohol, practically insoluble in methylene chloride. It is a synthetic Isopropyl analogue of adrenaline, acting almost exclusively at β-receptor. It stimulates the action of adrenaline and has the advantage of being effective when given orally. It is a nonselective β agonist and has strong β1 and β2 agonist activity. Its primary use is in the treatment of bronchial asthma. It is used as an anti-arrhythmic 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.

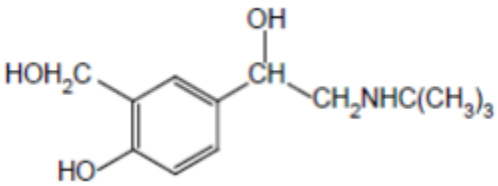
Dosage forms: Isoprenaline HCl injection I.P., Isoprenaline sulphate tablets I.P.Isoprenaline injection B.P.

i. Terbutaline

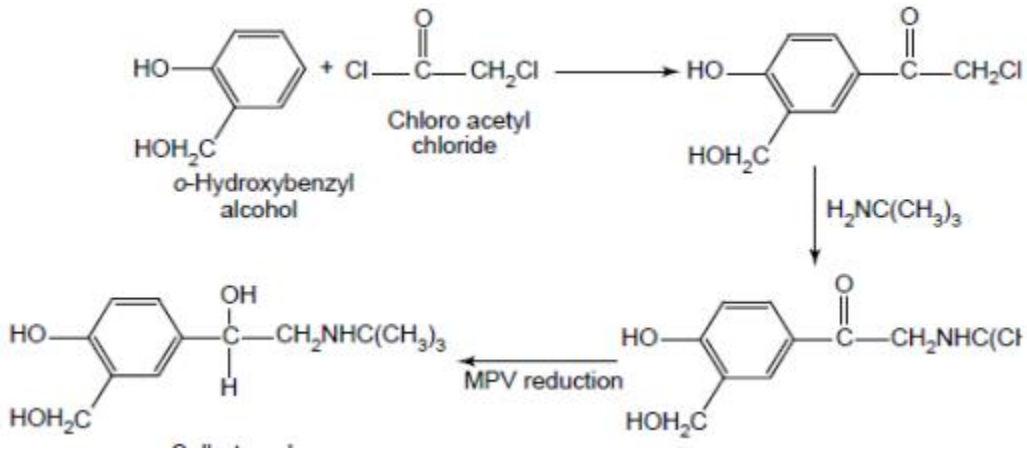


Properties and uses: It exists as a gray-white crystalline powder, odourless and with a bitter taste, soluble in water and alcohol. The drug exhibits the properties of a direct-acting sympathomimetic agent, having predominantly β2 adrenergic activity, and has a selective action on the β2 receptors (i.e. β2 agonist). It is used only as a bronchodilator and in the treatment of asthma. It is used β-agonistic activity.

j. Salbutamol*



Synthesis



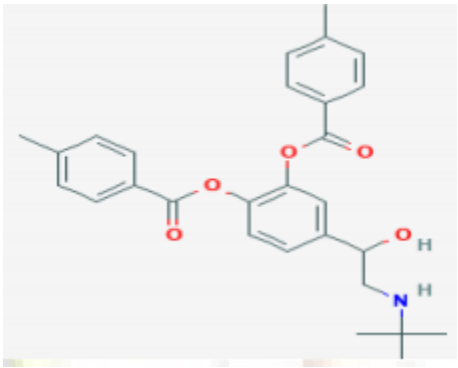
Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in water, but freely soluble in ethanol. It has strong β2 adrenergic activity. It is useful in the treatment of acute myocardial infarction, severe left ventricular failure. It has been used to arrest premature labour and is effective inocular 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.

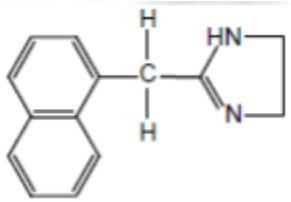
Dosage forms: Salbutamol tablets and inhaler I.P., Salbutamol pressurized inhalation B.

k. Bitolterol



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

l.Naphazoline

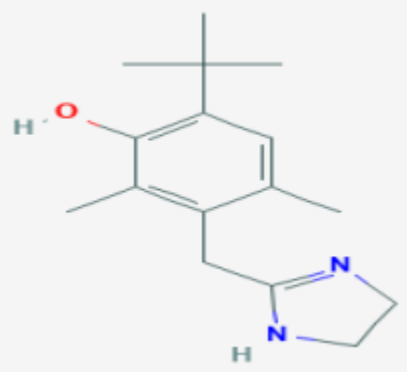


Properties and uses: It is a white crystalline, odourless, and bitter compound the salt is soluble in water and in alcohol. They essentially exist in an ionized form at physiological pH because of the very basic nature of the imidazoline ring (pKa 9 to 10). It is a directly acting sympathomimetic drug, 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.

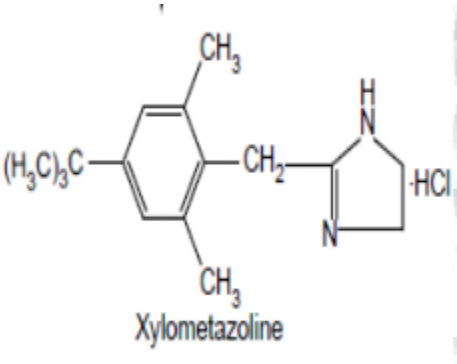
Storage: It should be stored in well-closed airtight containers, protected from light.

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

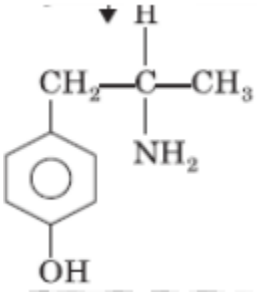


Properties and uses: It is a potent sympathomimetic agent, having marked and pronounced α-adrenergic pharmacologic profile. It is found to act as a vasoconstrictor, when applied topically to mucous membranes particularly. It is frequently employed as a local vaso-constrictor for nasal congestion caused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

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

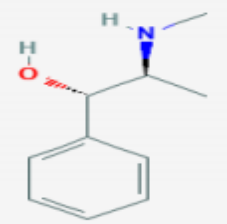
2.Indirect acting agents:

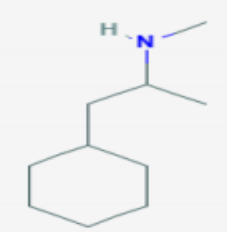
a. Hydroxyamphetamine



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

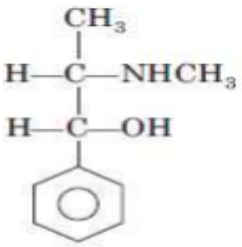
b. Pseudoephedrinec. **Propylhexedrine.**



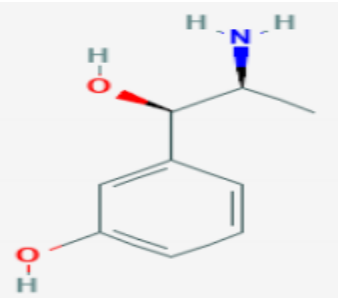


3. Agents with mixed mechanism:

a. Ephedrine **b. Metaraminol**



Ephedrine
(Non-catecholamine)

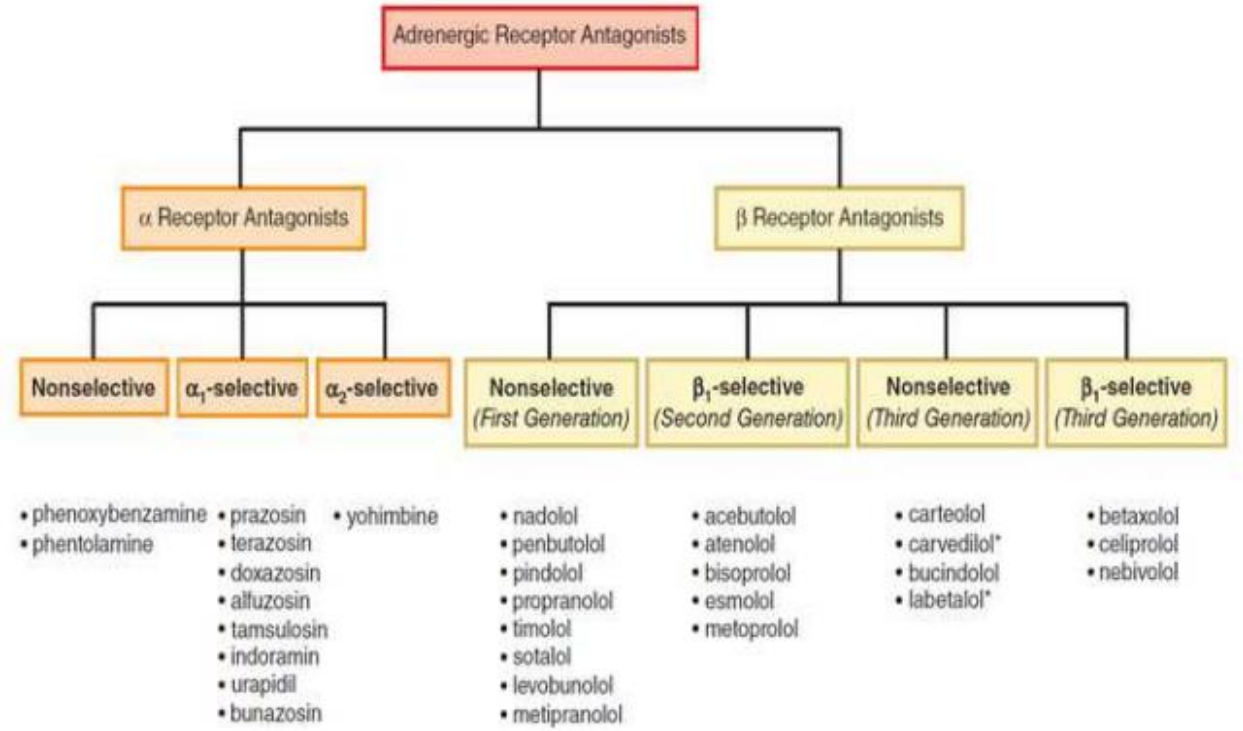


ADRENERGIC ANTAGONISTS

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 β1, β2, and β3 receptors. The second group contains the alpha (α) adreno receptors. There are only α1 and α2 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.

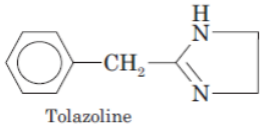
Classification :



Alpha adrenergic blockers

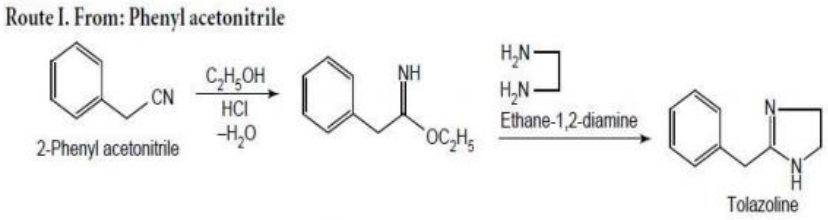
The α-receptor blockers in most cases do not show selectivity of action. Thus α-blockers have limited clinical use. α-blockers have been employed asantihypertensives for decades. These agents enjoy wide structural variations. Onthe chemical basis, various α-receptor blockers can be classified as:

1. Tolazoline



Tolazoline

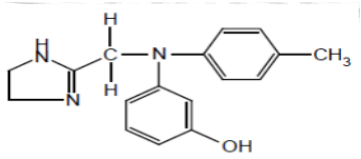
Synthesis:



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 either. It is an imidazolidine derivative. It is a competitive alpha adrenergic antagonist and possesses similar affinity for α1 and α2 receptors. It is a vasodilator and has a sympathomimetic effect to simulate the heart and causes mydriasis. 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 new born .

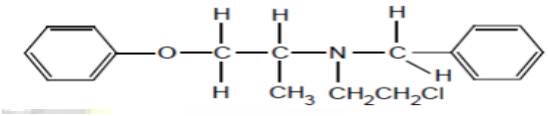
Dose: By I.M., I.V., S.C., for adults: 25 mg slowly, then increased up to 50 to 75 mg twice/day to 2 or 3 times/week**.**

2.Phentolamine



Properties and uses: It is a white, odourless, bitter powder, soluble in waterand alcohol. Phentolamine is a nonselective α-adreno receptor antagonist with an immediate onset and short duration of action. In addition to α-blocking activity,it has weak muscarnic 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 air tight containers and protected from light. Dosage forms: Phentolamine mesylate injection I.P., Phentolamine injection B.P.

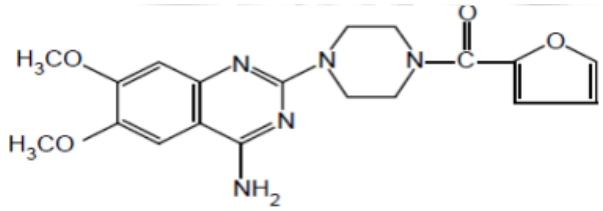
3.Phenoxybenzamine



Properties and uses: Colourless, crystalline compound soluble in alcohol,water, and chloroform. Irreversible antagonist with nonselective actions, amajor use of phenoxy bezamine 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 to improve blood flow to peripheral tissues. Used in the treatment of shock and in the treatment of pulmonary oedema.

Dose: The usual dose initially10 mg/day, increased gradually to 60 mg/day in divided doses. Dosage forms: Phenoxybenzamine capsules B.P.

4.Prazosin

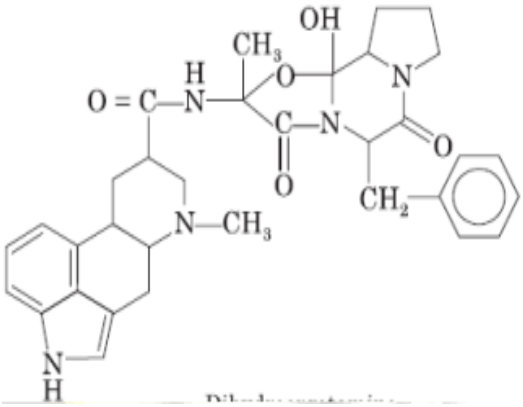


Properties and uses: It is a white crystalline powder, soluble in water and alcohol. A selective α-antagonist, prazosin, reduces peripheral vascular resistance and lowers arterial blood pressure in both supine and erect patients. Dizziness, headache, and palpitations can occur. Used to treat hypertension of any degree. It has been used in decreasing cardiac overload.

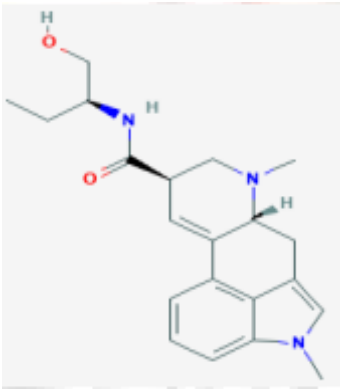
Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: For hypertension: the adult dose as hydrochloride: Initially, 500 µg 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



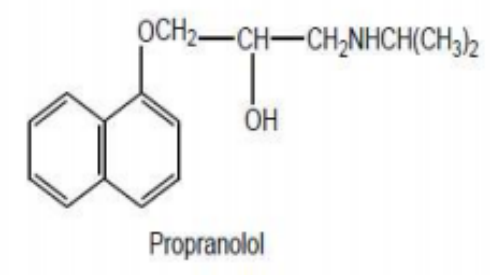
6.Methysergide.



BETA ADRENERGIC BLOCKERS

SAR of beta blockers

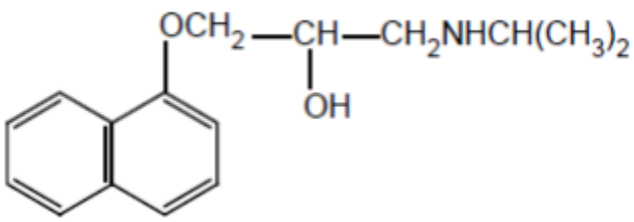
- Propranolol has become one of the most thoroughly studied and widely used drug . it is the standard against which all other β antagonists are compared.



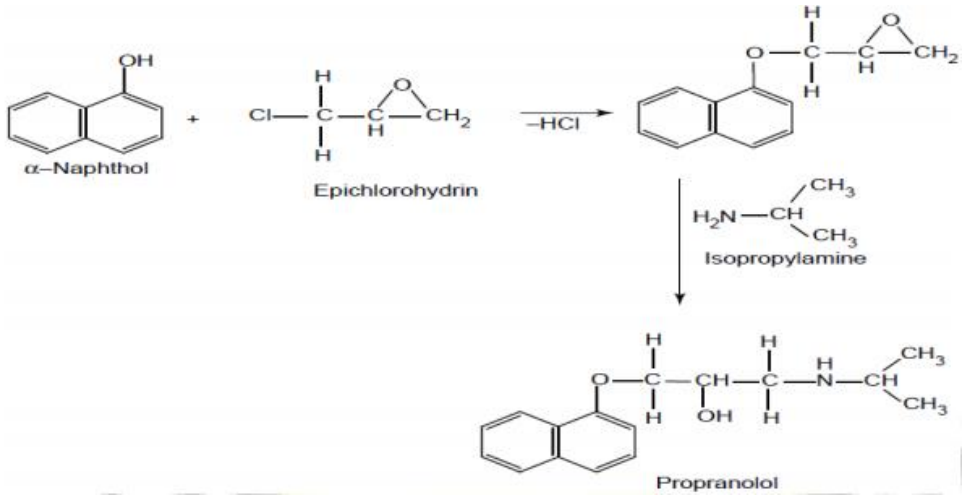
Propranolol

- The aromatic ring and its substituent is primary determinant of β1 antagonistic activity. The aryl group also affects the absoption, excretion, and metabolism of the β blockers.
- β blockers are strucrally 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 retain β blocking activity. Example: pronethalol, dichloroisoproterenol.
- N,N_ disubstitution decreases the β blocking activity, and the activity is maintained when the phenyl ethyle, 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 intp the molecule between the aromatic ring and the ethyl amine side chain provides β blocking agents, for example, pronethalol
- As in the sympathomimetics, bulky aliphatic groups, such as the tert-butyl and isopropyl groups are normally found on the amino function of the aryloxy propanolamine β receptor antagonists.

Propranolol*



Synthesis:

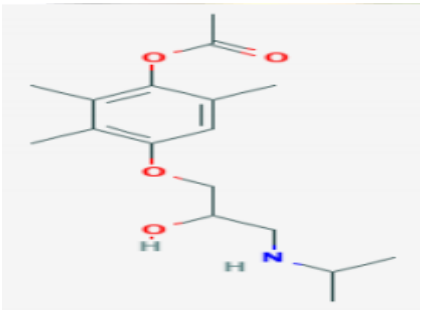


Properties and uses: It is a white or almost white powder, soluble in water and in ethanol. Currently, it is approved for hypertension associated cardiac arrhythmia, angina pectoris, due to coronary atherosclerosis and prophylaxis of migraine headache. It is a nonselective β-adrenergic antagonist and it has equal affinity for β1 and β2 receptors.

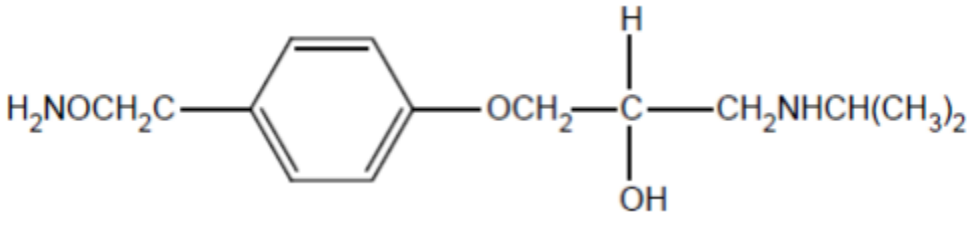
Dose: The oral adult dose for arrhythmias is 10 to 30 mg 3 to 4 times/day

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

2. Metibranolol



3.Atenolol

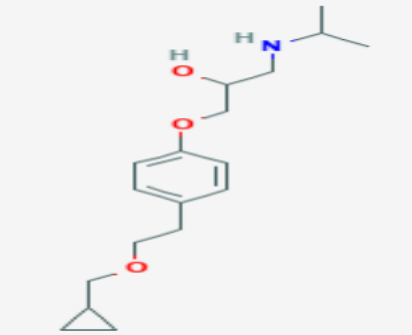


Properties and uses: It is a white or almost white powder, sparingly soluble in water, but soluble in ethanol. It is a β1 selective drug with low lipid solubility.Mainly used in the treatment of essential hypertension.

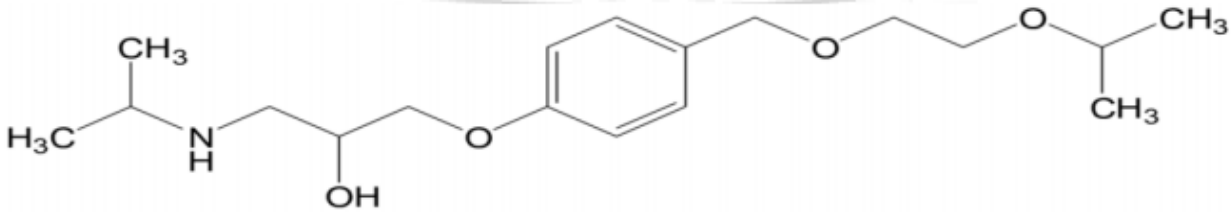
Dose: The usual dose is 50 mg/day once daily.

Dosage forms: Atenolol tablets I.P.,B.P., Atenolol injection B.P., Atenolol oralsolution B.P., Co-tenidonetablets B.P.

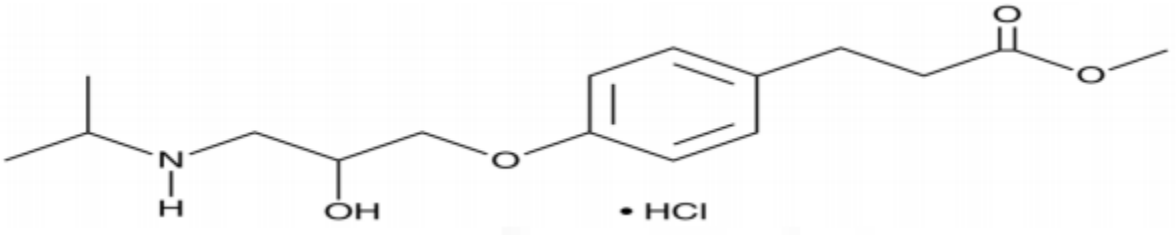
4. Betaxolol



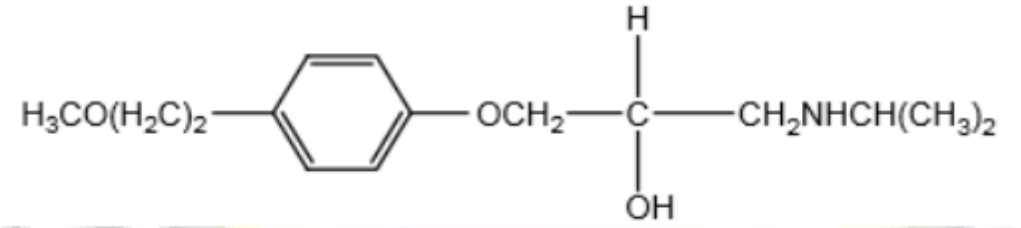
5. Bisoprolol



6. Esmolol



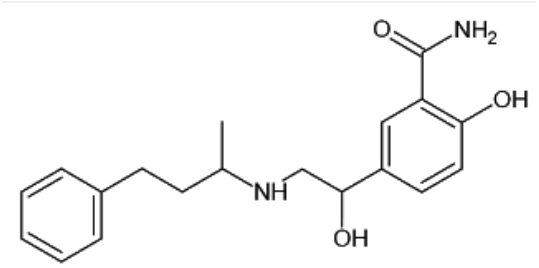
7. Metoprolol



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 β1selective antagonist used in the treatment of hypertension.

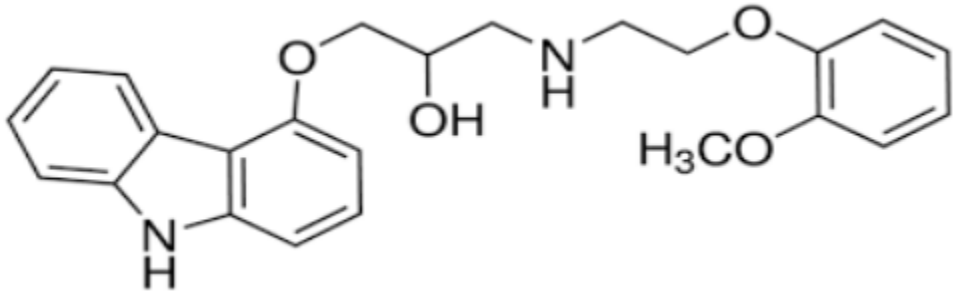
Dose: The usual initial oral dose is 100 mg given preferably once daily.

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.

MCQ'S (1 Marks)

1. The entire nervous system is divided into two main regions: The _____

A) Brain and the spinal chord

B) CNS and the PNS

C) Neurons and the glial cells

D) Motor neurons and the sensory neurons

2. All the nervous tissue outside the brain and spinal cord is the _____ nervous system.

A) Peripheral

B) Autonomic

C) Somatic

D) Central

3. Which of the following is not one of the basic functions of the nervous system?

A) Formulate responses to sensory stimulation

B) Send signals rapidly between body parts

C) Produce major body fluids such as plasma and interstitial tissue fluid

D) Detect sense stimuli

4. The cells of nervous tissue that are not neurons but that assist neurons are called

A) Amyloid plaques

B) Fibroblasts

C) Leukocytes

D) Neuroglia

5. The white fatty substance that coats axons to increase signal speed is

A) Myelin

B) Microfibrils

C) Dendrites

D) Adipocytes

6. One example of a function of neuroglial cells is to…

A) Add myelin to axons

B) Produce neurotransmitters

C) Bind neurotransmitters

D) Link one neuron cell to another at the synapse

7. ____ neuron transmits signals from the PNS to the central nervous system.

A) Interneuron

B) Sensory

C) Motor

D) Ganglion

8. An involuntary response by the nervous system to a stimulus is a

A) Synapse

B) Reflex

C) Motor response

D) Smooth muscle

9. The axon has voltage gated ion channels. The term "voltage gated" means that…

A) Ion channels open and close because of changes in the neuron's voltage

B) Neuron voltage is controlled by neuroglial cells

C) Iongates will not respond unless the neuron is in the CNS

D) Voltage can only be controlled by a reflex

10.Both the depolarization and repolarization changes that occur during the action potential are produced by

A) Ions moving across the cell membrane

B) Small neuroglial cells that act as batteries for the neuron itself

C) Negative stimuli

D) Enzymes creating new ions

Answers

1 = B 2 = A 3 = C 4 = D 5 = A 6 = A 7 = B 8 = B 9 = A 10 = A

Long question answer (10 Marks)

1. Write a note on sympathomimetic agents and their SAR.
2. Explain briefly the drugs used as sympathomimetic drugs.
3. Write down the synthesis and uses of salbutamol and phenyl epinephrine.
4. Outline the indirect acting adrenergic agent?
5. Enumerate the Biosynthesis of Noradrenaline and write the uses of sympathomimetic?
6. Define adrenergic blockers? Discuss the chemistry and SAR of beta adrenergic blocking agents with examples?
7. Give a detailed note on synthesis and uses of tolazoline and propanolol.
8. What are beta adrenergic blockers? Explain SAR of beta adrenergic blockers. Give synthesis of propranolol.
9. Highlight classification with structures and medicinal uses of alpha adrenergic blockers.
10. Write a note on Alpha adrenergic blockers.

Short Question Answer (5 Marks)

1. Write a note on sympathomimetic agents.
2. Write a note on beta blockers.
3. Write a note on Alpha adrenergic blockers.
4. Write a note on Synthesis of Phenylaphrine and salbutamol.

Very Short Question Answer (2 Marks)

1. What are sympathomimetic agents?
2. What are adrenergic neurotransmitters?
3. Explain beta adrenergic blockers.
4. Write classification of adrenergic antagonists.
5. Write down the structure of atenolol and prazosin.
6. Write down the properties, moa and uses of metoprolol.
7. Give the structure and uses of phenylepinephrine.
8. Write few examples of mixed action sympathetic drugs with structure?
9. Write in short pharmacological function of alpha and beta receptor.