Antiadrenergics/ sympatholytics

An **adrenergic antagonist** is a drug that inhibits the function of adrenergic receptors.

- Prevent the response of effector organs to endogenous as well as exogenous adrenaline and noradrenaline.
- Competitive antagonist except phenoxybenzamine, an irreversible antagonist that binds covalently to α-adrenergic receptors.

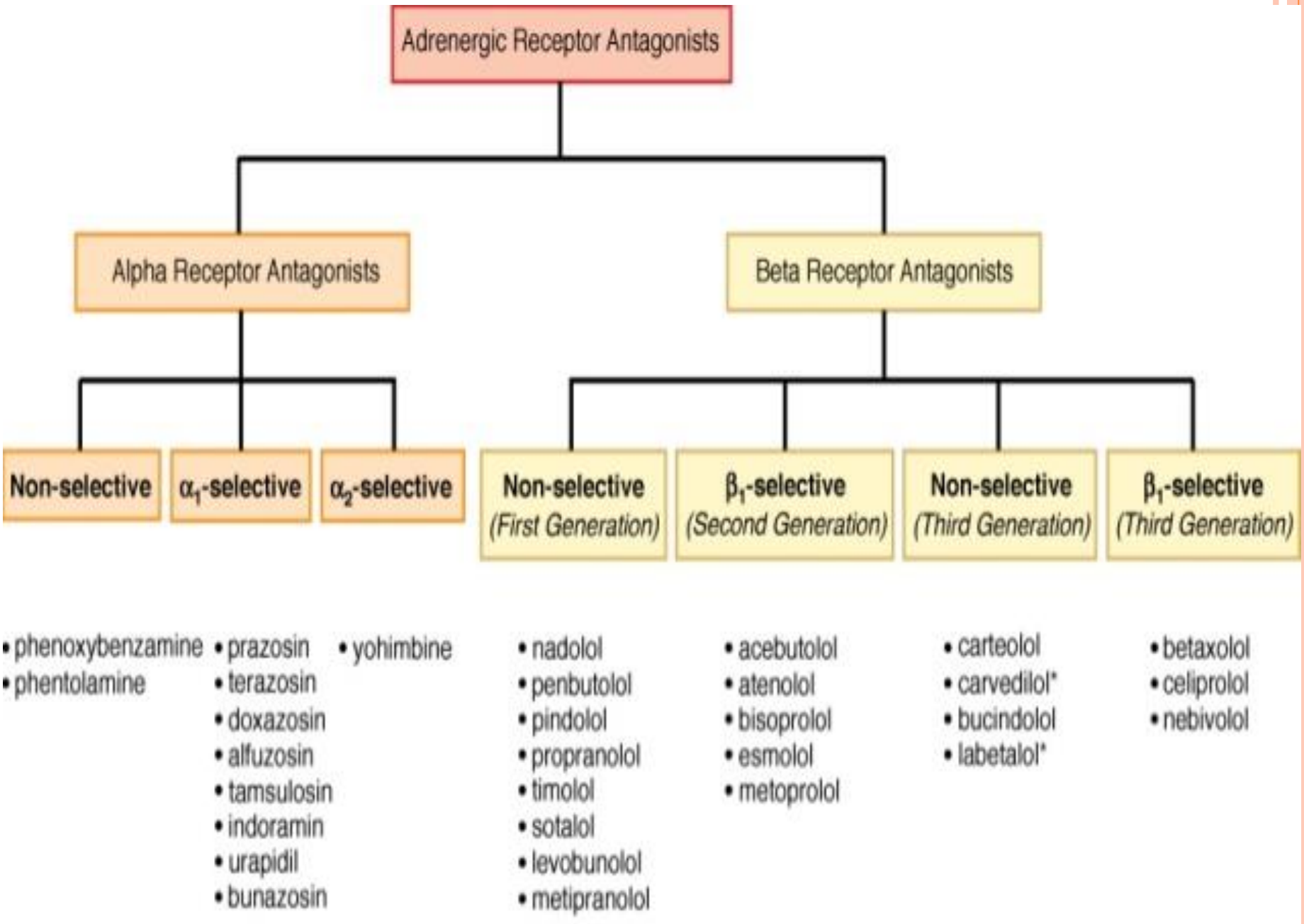
Competitive antagonists

These are reversible antagonists. A competitive antagonist will attach itself to the same binding site of the receptor that the agonist will bind to.

This type of binding is reversible as increasing the concentration of agonist will outcompete the concentration of antagonist, resulting in receptor activation.

Non-competitive antagonists can either bind to the ligand site or other site called the allosteric site. The binding of a non-competitive antagonist is **irreversible.**

Eg: phenoxybenzamine


Adrenergic Receptor Antagonists
Alpha Receptor Antagonists
Beta Receptor Antagonists
Non-selective
α1-selective
α2-selective
Non-selective (First Generation)
β1-selective (Second Generation)
Non-selective (Third Generation)
β1-selective (Third Generation)
• phenoxybenzamine
• phentolamine
• prazosin
• terazosin
• doxazosin
• alfuzosin
• tamsulosin
• indoramin
• urapidil
• bunazosin
• yohimbine
• nadolol
• penbutolol
• pindolol
• propranolol
• timolol
• sotalol
• levobunolol
• metipranolol
• acebutolol
• atenolol
• bisoprolol
• esmolol
• metoprolol
• carteolol
• carvedilol*
• bucindolol
• labetalol*
• betaxolol
• celiprolol
• nebivolol

- **Alpha adrenergic blockers: Tolazoline*, Phentolamine,** Phenoxybenzamine, Prazosin, Dihydroergotamine, Methysergide.

Alpha adrenergic blockers

Cardiovascular effects:

Alpha 1 adrenergic blockers inhibit vasoconstriction induced by endogenous catecholamines. It will result in vasodialation.

Non cardiac effects:

Miosis

Nasal stuffness

Use of alpha 1 blockers:

High blood pressure

Raynaud's disease (reduced blood flow in response causing discolouration of the fingers, toes, and occasionally other areas.....hyperactivation of sympathetic system)

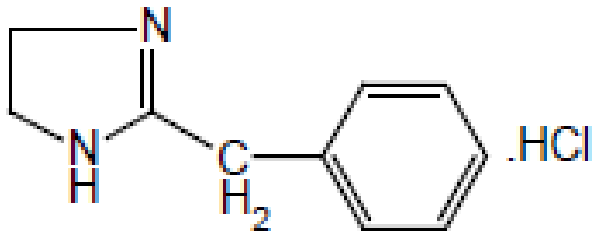
Pheochromocytoma (tumor of adrenal gland)

Alpha 2 blockers:

increase adrenergic, dopaminergic and serotonergic neurotransmitters, and induce insulin secretion and decreases blood sugar levels.

Used to treat depression.

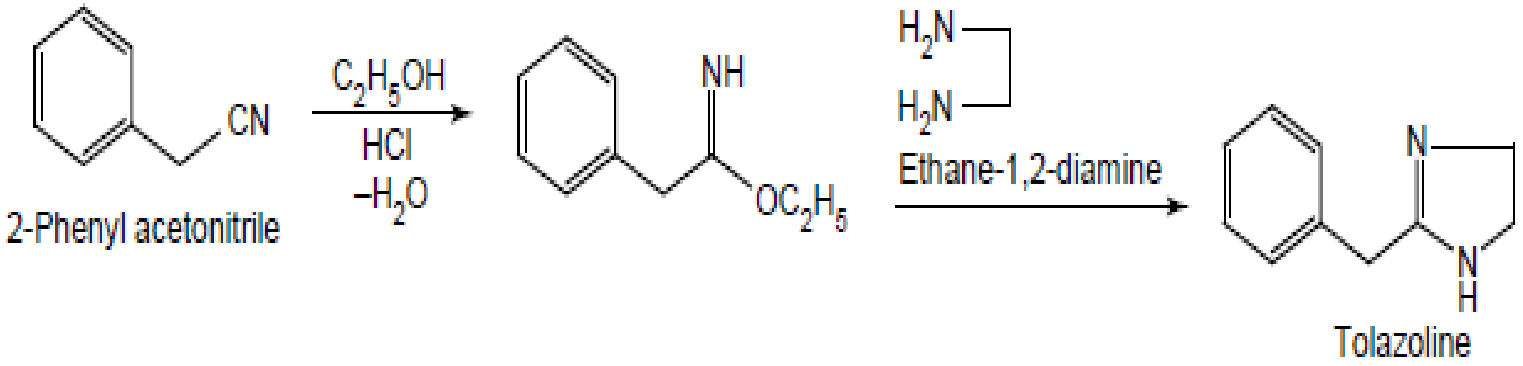
TOLAZOLINE



2-Benzyl-2-imidazoline mono hydrochloride

IUPAC- 2-Benzyl-4,5-dihydro-1*H*-imidazole

Non selective alpha blocker.

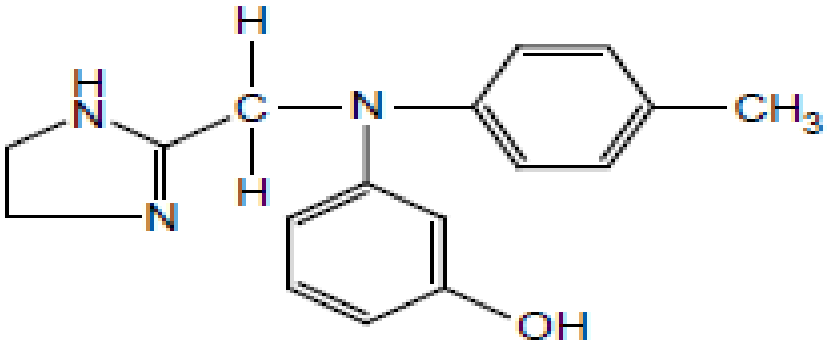


- It is a vasodilator
- Sympathomimetic effect to stimulate the heart,stimulate gasrointestinal smooth muscles, histaminergic action.

Uses:

- Used in peripheral vascular diseases (blood vessels outside heart and brain to narrow, block, or spasm)
- Treat pulmonary hypertension of new born.

PHENTOLAMINE



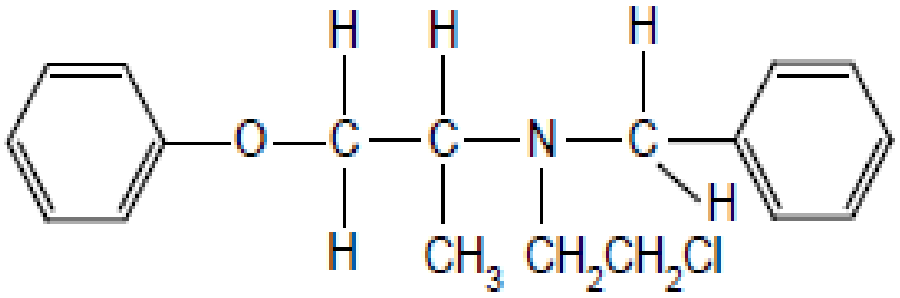
3-[(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)(4-methylphenyl)amino]phenol

Nonselective α-adrenoreceptor antagonist with an immediate onset and short duration of action.

It has weak **muscarnic** activity in the gastrointestinal tract and weak to mild **histaminergic** activity in the stomach.

Used in immediate heart attack.

Phenoxybenzamine (Dibenzyline)



(*RS*)-*N*-Benzyl-*N*-(2-chloroethyl)-1-phenoxypropan-2-amine

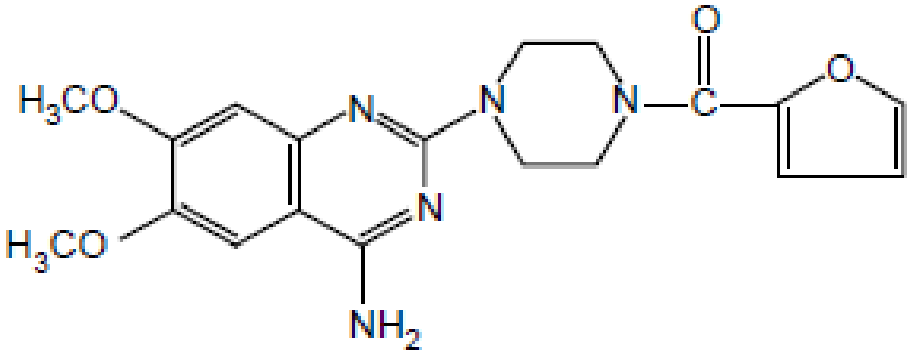
Ireversible alpha antagonist.

Uses-

Pheochromocytoma (tumours of the adrenal medulla) peripheral vascular diseases, such as Raynaud's syndrome.

Frostbite to improve blood flow to peripheral tissues, Pulmonary oedema.

PRAZOSIN

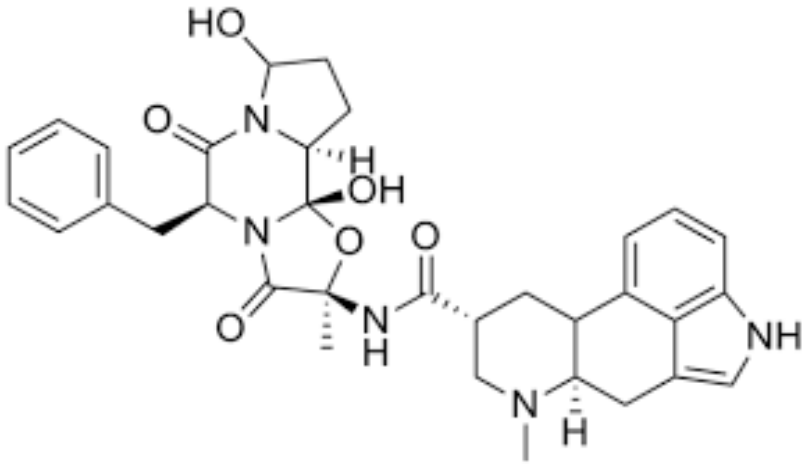


[4-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-1-piperazinyl](2-furyl)methanone

Selecive alpha 1 blocker (first of this class)

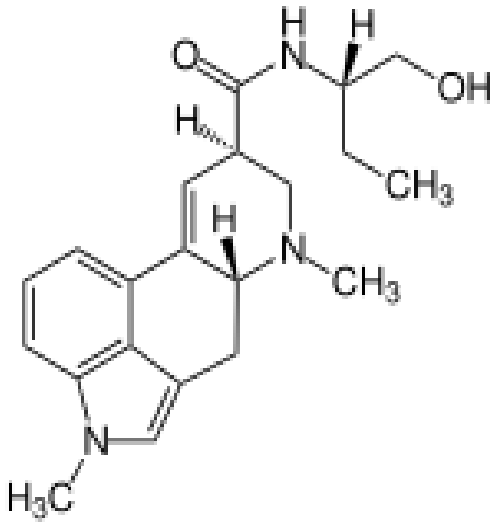
Used to treat hypertension and reduce cardiac overload

DIHYDROERGOTAMINE



Used to treat migraine headaches

METHYSERGIDE

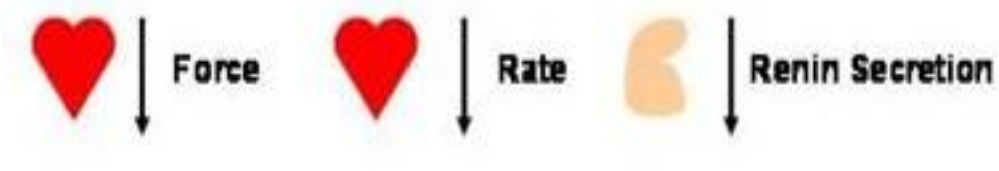


(1-methyl-D-lysergic acid butanolamide

Prevention of migraine

Receptor Type	Tissue Distribution	Physiological Effects	Agonist
α1	Vascular Smooth Muscles, Visceral smooth Muscles	Smooth muscle contractions, Gluconeogenesis, Vasoconstriction	Norepinephrine, Phenylephrine, Methoxamine
α2	Pre-synaptic terminals, pancreas, platelets, Ciliary epithelium, Salivary Glands	Inhibits release of Neurotransmitter	Clonidine, Monoxidine
β1	Heart, Kidney, some pre-synaptic terminals	Increase heart rate and Renin secretion	Isoproterenol, Norepinephrine, Dobutamine
β2	Visceral smooth muscles, Bronchioles, Liver, Skeletal Muscles	Vasodilation, Bronchodilation, Inhibits insulin secretion	Isoproterenol, Salbutamol, Salmeterol, Albuterol, Formoterol, Terbutaline, Levalbuterol
β3	Adipose Tissue	Increase lipolysis	Isoproterenol, Amibegron, Solabegron

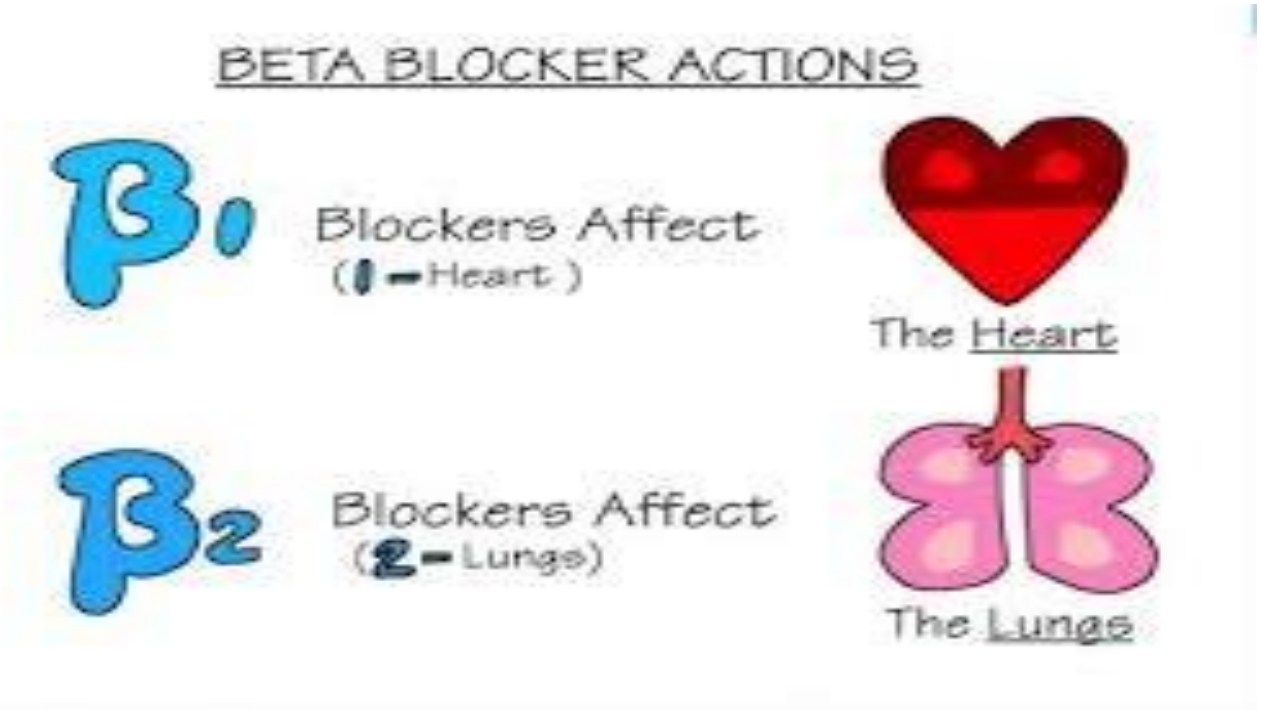
Blockade of the Beta$_1$ Receptor Blockers



Reduction in cardiac output, reduction in blood pressure.

Blockade of the Beta$_2$ Receptor Blockers

- Selective β1 antagonist : heart
- Selective β2 antagonist: respiratory system.



ISA- intrinsic sympathomimetic activity- some beta antagonist show some action of beta agonists. Eg- pindolol, labetalol.

Less dangerous to give patients of bronchial asthma.

Membrane stabilizing action [MSA]- some beta blockers stabilize membrane by blocking sodium channels. Therefore produce local anaesthetic action.

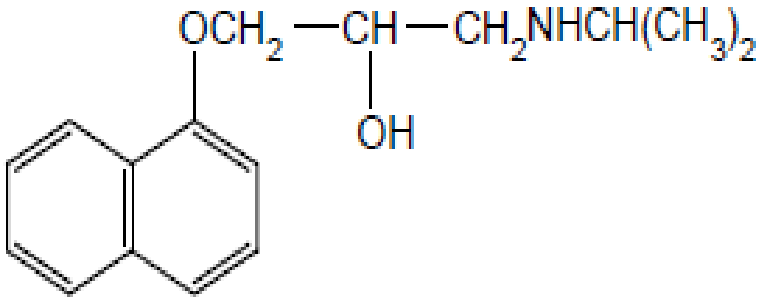
Eg- propranolol, pindolol.

Sde effects

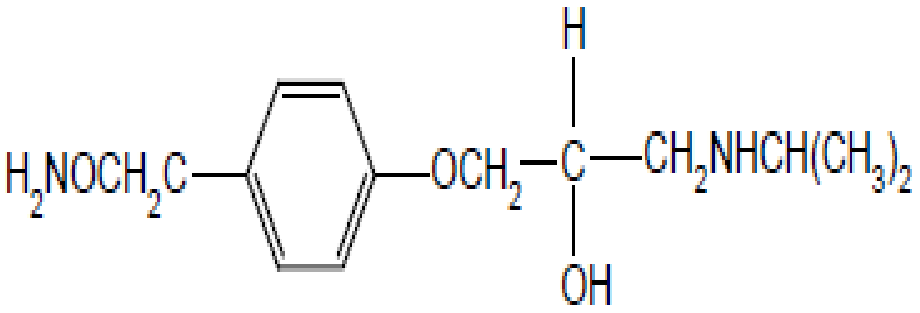
- Rash and fever
- Worsening of asthma
- Sedation, depression
- Heart failure

- **Propranolol*,**
- Metipranolol, **Atenolol**, Betazolol, Bisoprolol, Esmolol, **Metoprolol,**
- **Labetolol, Carvedilol.**

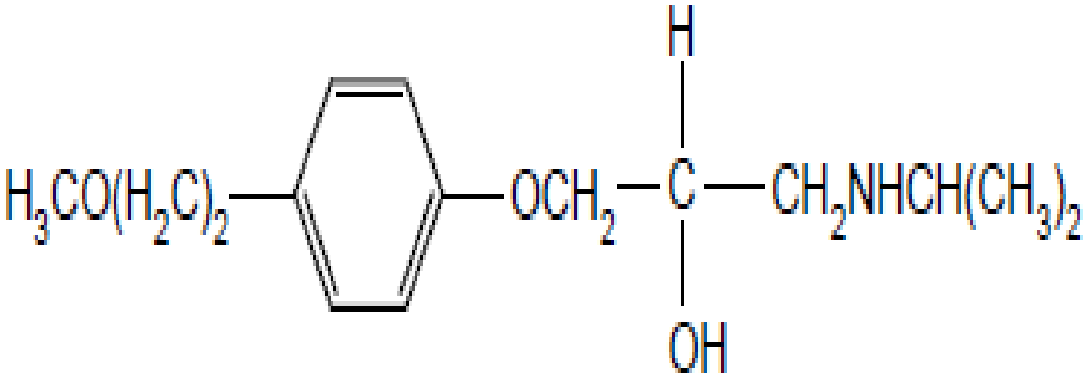
PROPRANOLOL



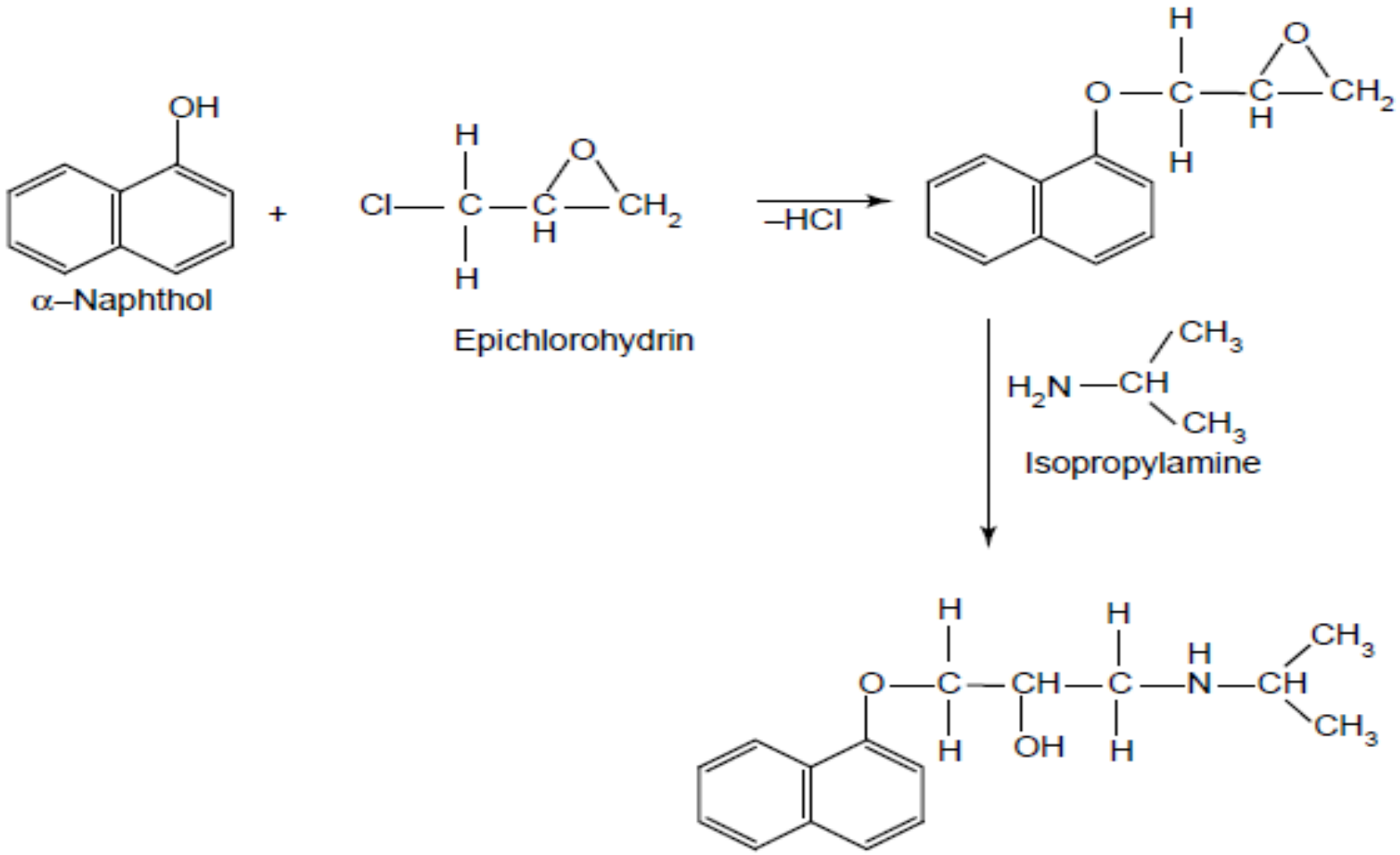
ATENOLOL



METAPROLOL



PROPRANOLOL



Non selective beta blocker.

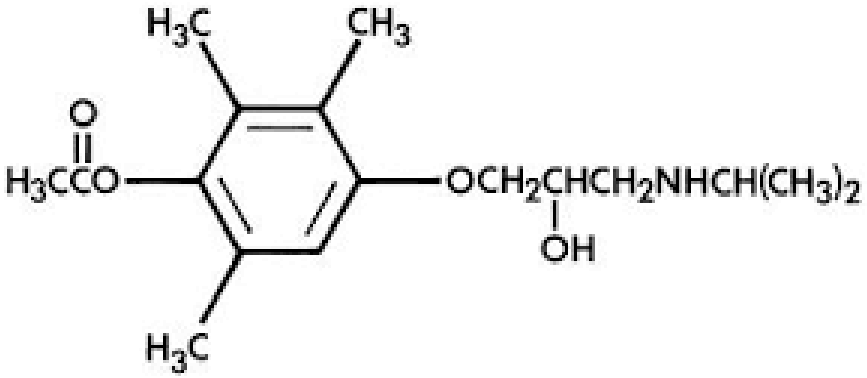
- ✓ **MSA**
- x **ISA**

Uses

- cardiac arrhythmia,
- angina pectoris, due to coronary atherosclerosis
- prophylaxis of migraine headache.

Crosses blood brain barrier

METIPRANOLOL



(*RS*)-4-{[-2-hydroxy-3-(isopropylamino)propyl]oxy}-2,3,6-trimethylphenyl acetate

Non selective beta blocker

Antiarrhythmic

Antihypertensive

Antiglaucoma agent

ATENOLOL

ß1 selective drug .

Developed as a replacement for propranolol.

Reduces force of contraction and blood pressure.

Mainly used in the treatment of essential hypertension.

Used to treat angina

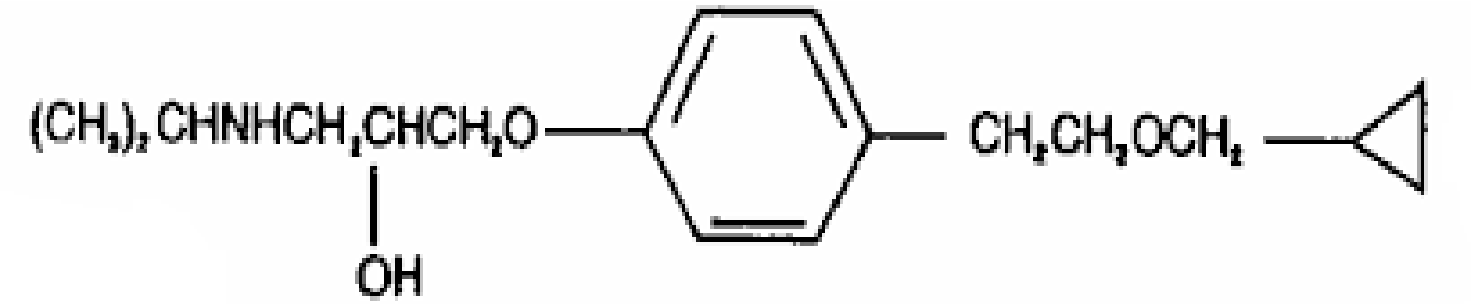
Does not crosses BBB.

METOPROLOL

ß1 selective drug

Hypertension
Angina pectoris
Tachycardia

BETAXOLOL

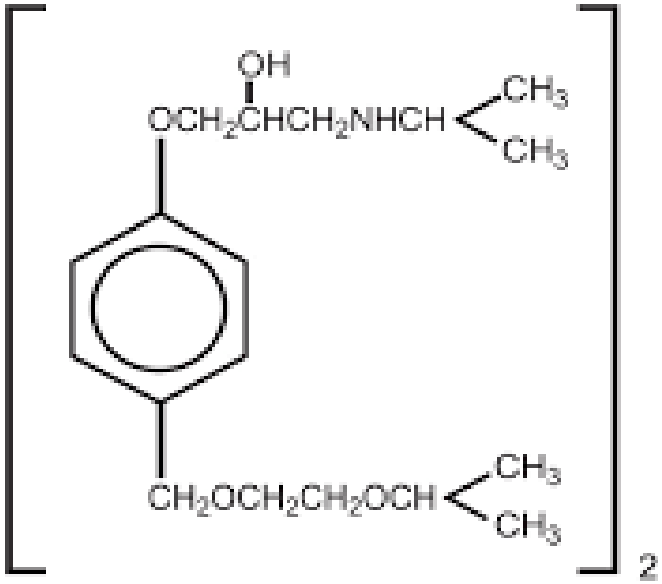


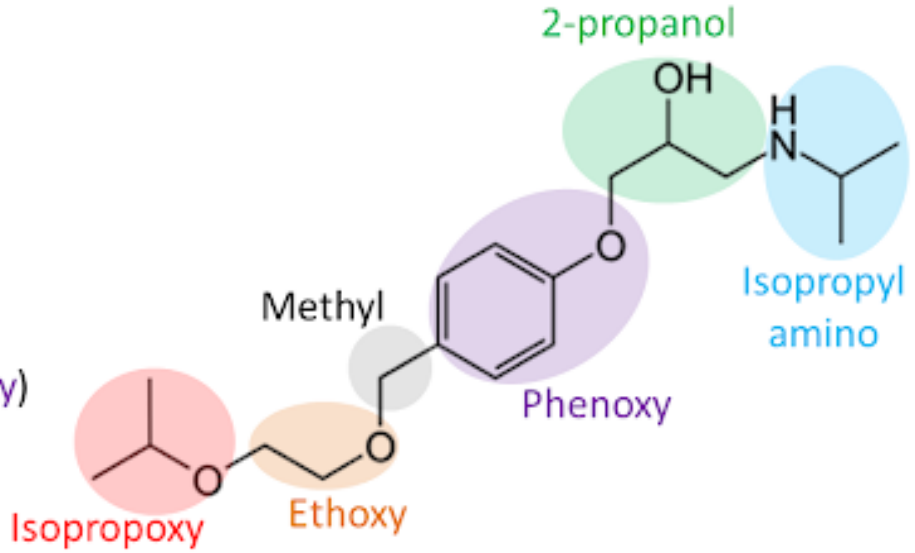
Greater affinity for beta$_1$ receptors than metoprolol.

Used to treat hypertension and glaucoma.

BISOPROLOL

(RS)-1-(4-(2-isopropoxyethoxymethyl)phenoxy)-3-(isopropylamino)-2-propanol





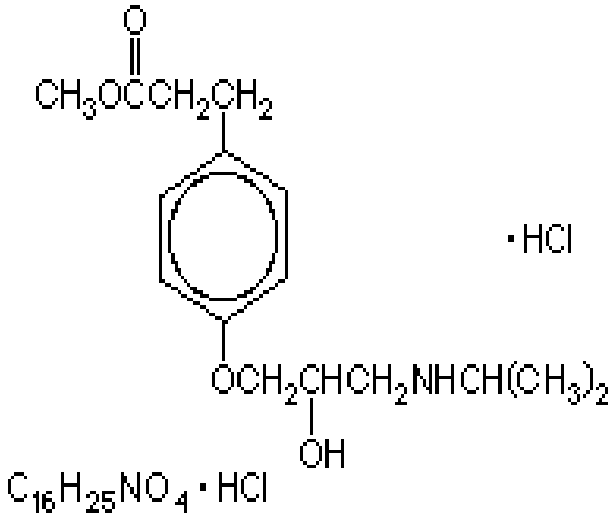
Mechanism of action: beta 1 selective.

Bisoprolol has a higher degree of β_1-selectivity compared to other β_1-selective beta blockers such as atenolol, metoprolol, and betaxolol

Highly potent.

Uses; management of hypertension, stroke and myocardial infarction.

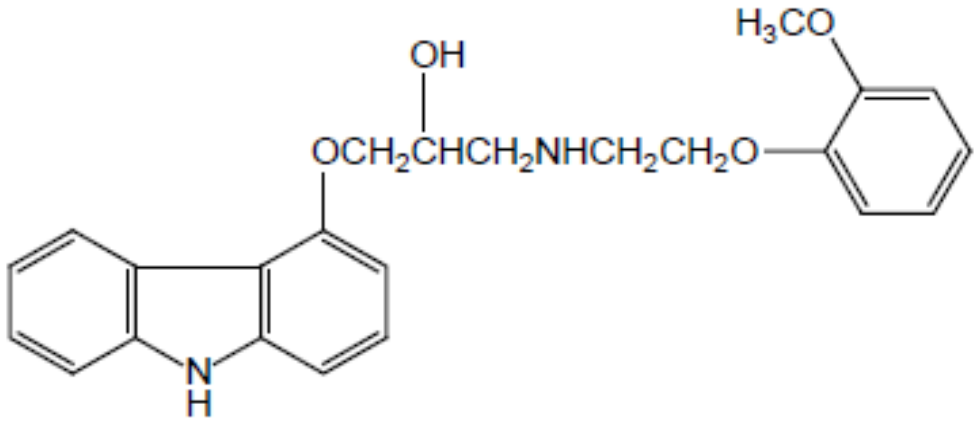
ESMOLOL



Cardioselective beta$_1$ receptor blocker with rapid onset, a **very short duration of action**, and no significant intrinsic sympathomimetic or membrane stabilising activity at therapeutic dosages.

Used during surgery to help regulate blood pressure and heart rate

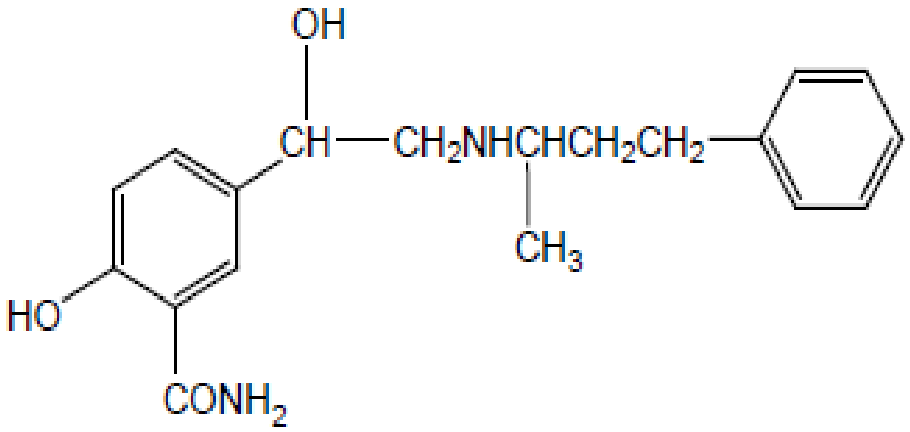
CARVEDILOL



Acts on both alpha and beta receptors.

Used to treat hypertension and congestive heart failure

LABETALOL

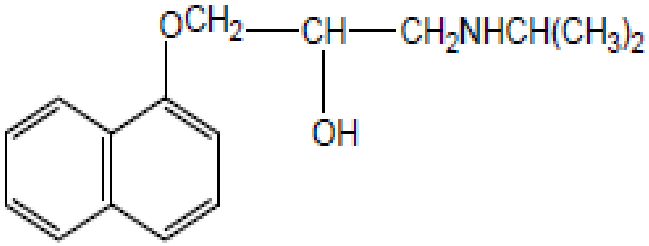


Blocks ß1 and ß2 and α1-adrenergic receptor.

More potent ß antagonist than α antagonist

Used to treat hypertension and angina.

SAR of Beta blockers



Propranolol

- The aromatic ring and its substituent is the primary determinant of β1 antagonistic activity. The aryl group also affects the absorption, excretion, and metabolism of the β blockers.
- 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 ß blocking agents, for example, propranolol.
- Secondary amine group is necessary for optimal activity.

- The configuration of the hydroxyl bearing carbon of the aryloxypropanolamine side chain play a critical role in the interaction of ß antagonist drugs with ß receptor. The carbon must possess the (S) configuration for optimal affinity to the ß receptor.

The enantiomer with the (R) configuration is typically 100 times less potent.

Some imp terms

Essential hypertension[primary hypertension]is due to-

Genetic and environmental factors.

Secondary hypertension is due to- kidney problems, narrowing of aorta, adrenal gland tumors.