DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM PART-II: ADRENERGIC ANTAGONISTS

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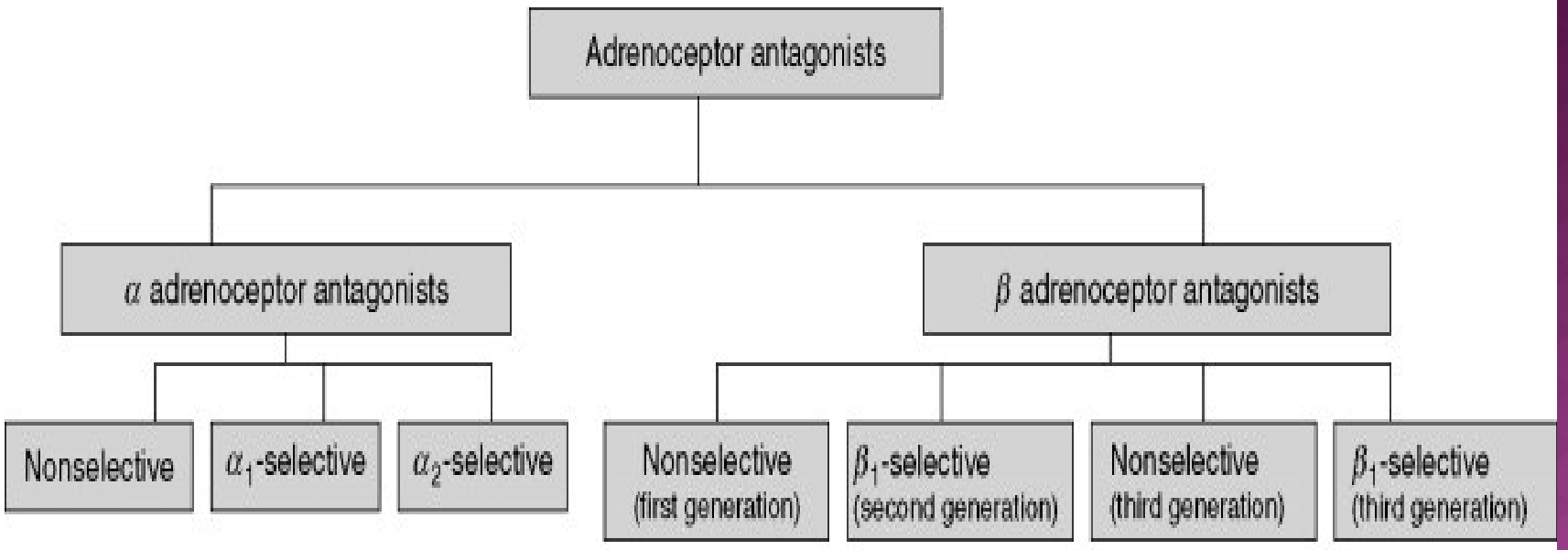
OUTLINE OF PRESENTATION

- **Adrenergic Antagonists:**
  - **Alpha adrenergic blockers:** Tolazoline*, Phentolamine, Phenoxybenzamine, Prazosin, Dihydroergotamine, Methysergide.
  - **Beta adrenergic blockers:** SAR of beta blockers, Propranolol*, Metibranolol, Atenolol, Betazolol, Bisoprolol, Esmolol, Metoprolol, Labetolol, Carvedilol.

DEFINITION

- Anti-adrenergic Drugs /Adrenergic Receptor Antagonists/ sympatholytics are drugs which **antagonize the receptor action** of adrenaline and related drugs.
- They are **competitive antagonists** at α or β or both α and β adrenergic receptors.
- Many types of adrenergic antagonists are used and several of these are clinically useful in medicine, particularly in the treatment of cardiovascular diseases.
- Selective β1 antagonist drugs act on the heart and selective β2 antagonists act on the respiratory system.

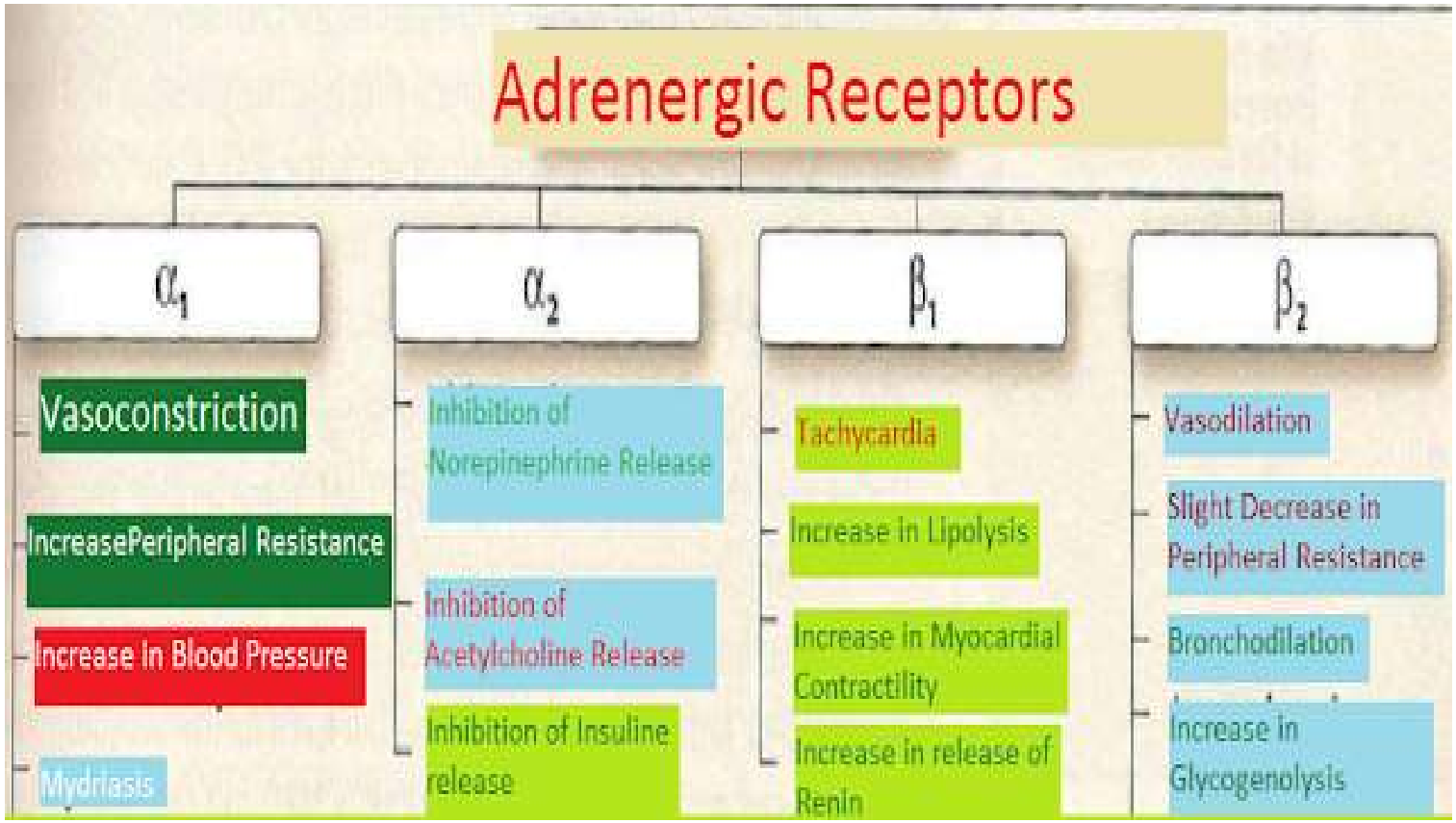
CLASSIFICATION*



- Phenoxybenzomine
- Phentolamine
- Prazosin
- Terazosin
- Doxazosin
- Alfuzosin
- Tamsulosin
- Indoramin
- Urapidil
- Bunazosin
- Yohimbine
- Nadolol
- Penbutolol
- Pindolol
- Propranolol
- Timolol
- Acebutolol
- Atenolol
- Bisoprolol
- Esmolol
- Metoprolol
- Carteolol
- Carvedilol*
- Bucindolol
- Labetalol*
- Betaxolol
- Celiprolol
- Nebivolol

***Include at least one chemical structure from each class**

FUNCTION: ALPHA AND BETA RECEPTORS



***Adrenergic blockers block these receptor actions and thus show opposite effects**

PHYSIOLOGICAL EFFECTS OF ADRENERGIC RECEPTOR ANTAGONISM

- Blockade of **vasoconstrictor α1 receptors** reduces peripheral resistance and causes reduced cardiac output leads to decreased blood pressure.
- The α blockers abolish the pressor action of adrenaline, which then produces fall in the blood pressure due to ß2 mediated vasodilatation called ***Dale's vasomotor reversal***.
- Reflex tachycardia occurs due to the **presynaptic α2 receptors.**
- Nasal stiffness and miosis result due to the **blockade of α1 receptors.**
- The therapeutic application of drugs coming under the adrenergic antagonists are receptor oriented, **especially ß blockers** are used as antihypertensive agents.
- **α adrenergic antagonists** are used to control the peripheral vascular resistance.

α-Adrenergic blockers

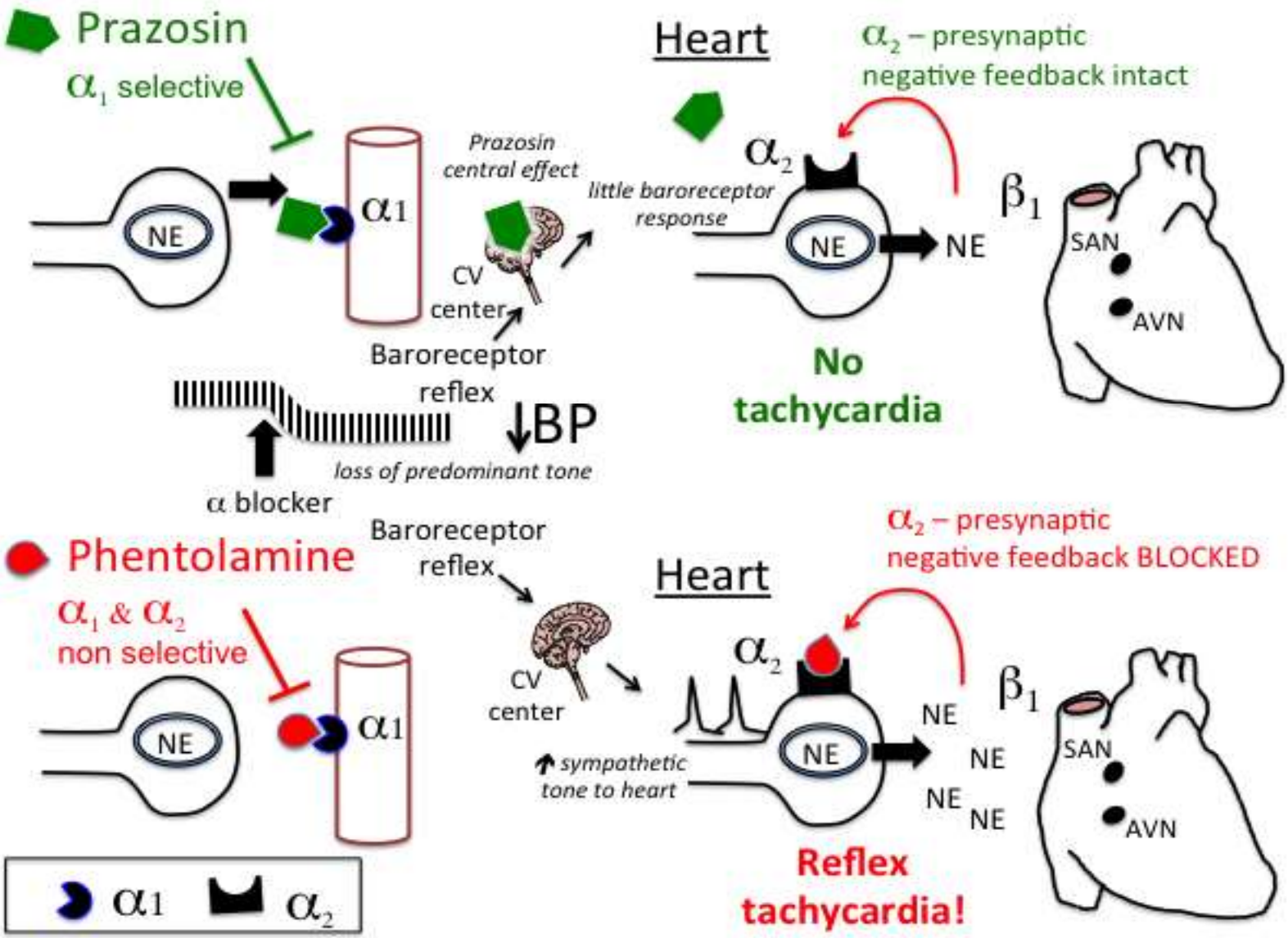
MECHANISM OF ACTION OF ALPHA-ADRENERGIC BLOCKERS

- α-Adrenergic receptor response in clinical relevance include α1 receptor mediated contraction of arterial and venous smooth muscle.
- α2 adrenergic receptors are involved in suppressing sympathetic output, increasing vagal tone, facilitating platelet aggregation and inhibiting the release of norepinephrine from nerve endings.
- Blockade of α1 receptors inhibits vasoconstriction induced by endogenous catecholamines- Vasodilatation may occur in both arteriolar resistance vessels and veins.
- α2 receptor regulates both central and peripheral sympathetic neurons. Acceleration of presynaptic α2 receptors inhibits the norepinephrine release.

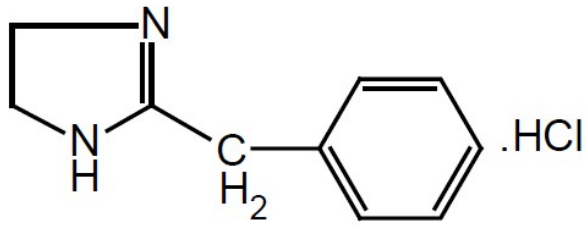
MECHANISM OF ACTION OF ALPHA-ADRENERGIC BLOCKERS

- In some vascular beds, these drugs promote vasodilatation through the release of nitric oxide (endothelial relaxing factor).
- Phenoxybenzamine inhibits the uptake of catecholamine from the nerve terminals.
- Phentolamine and tolazoline are competitive α adrenergic antagonists and block the receptor for 5-HT and it causes the release of histamine from the mast cells, which is a potent vasodilator.

MECHANISM OF ACTION: CARDIOVASCULAR EFFECTS OF ALPHA BLOCKERS

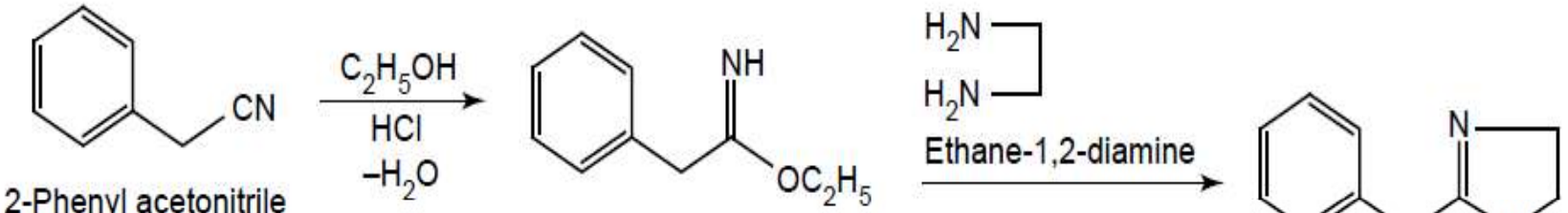


TOLAZOLINE



2-Benzyl-2-imidazoline mono hydrochloride

Synthesis:



2-Phenyl acetonitrile

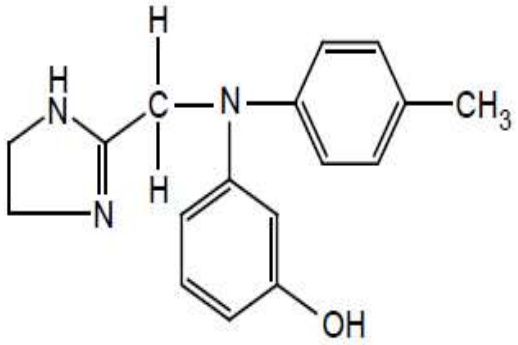
Tolazoline

- It is an imidazolidine derivative.
- It is a competitive alpha adrenergic antagonist and possesses similar affinity for α1 and α2 receptors.

TOLAZOLINE

- It is a vasodilator and has a sympathomimetic effect (α2) to stimulate the heart and causes mydriasis (dilatation of pupil).
- 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.

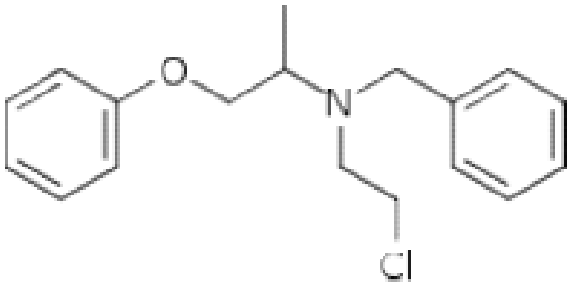
PHENTOLAMINE



3[(4,5-Dihydro-1-imidazole-2yl)methyl](4-methyl-phenyl)amino phenol

- 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 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.

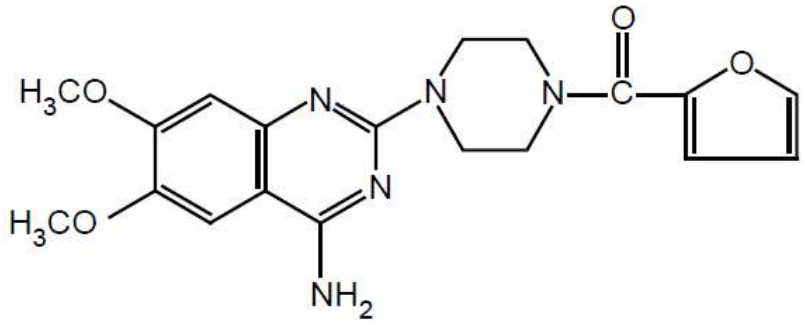
PHENOXYBENZAMINE



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

- Phenoxybenzamine is a nonselective, irreversible antagonist that binds covalently to α-adrenergic receptors (an exception to that of other antagonists that are competitive in nature).
- It cyclizes spontaneously in the body giving rise to a highly reactive ethyleniminium intermediate which reacts with α adrenoceptors and other biomolecules by forming strong covalent bonds.
- It is used in the treatment of hypertension, and specifically that caused by pheochromocytoma.
- It has a slower onset and a longer-lasting effect compared with other alpha blockers.

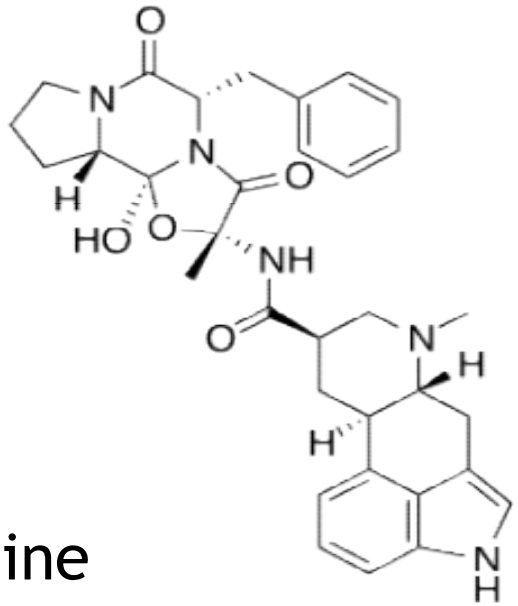
PRAZOSIN



1-(4-Amino-6-7-dimethoxy-2-quinazolinyl)-
4-(-2-furanyl carbonyl)-piperazine

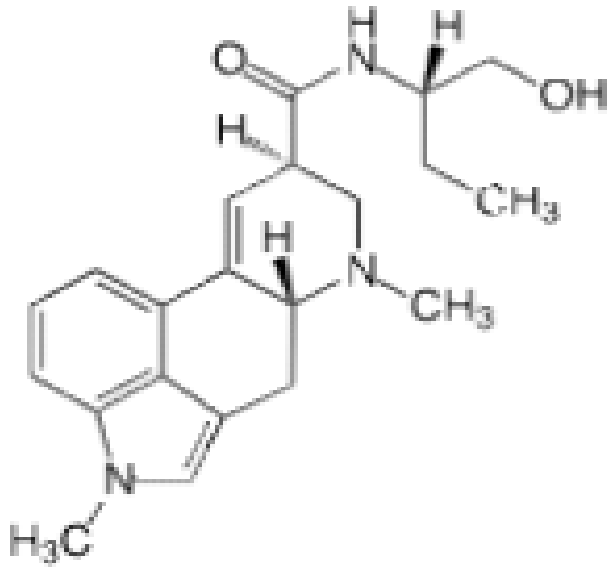
- It is a selective α-1antagonist.
- Prazosin reduces peripheral vascular resistance and lowers arterial blood pressure hence used to treat hypertension of any degree.
- It has been used in decreasing cardiac overload.
- Dizziness, headache, and palpitations can occur.

DIHYDROERGOTAMINE



- Dihydroergotamine (DHE) is a semi-synthetic form of ergotamine used to treat migraines. Ergotamine is an ergot alkaloid obtained from the fungus Claviceps purpurea.
- Administered as a nasal spray or injection.
- Along with dopamine and adrenergic receptors, it acts as an agonist to the serotonin receptors and cause vasoconstriction of the intracranial blood vessels (migraine is due to sudden vasodilatation of intracranial vessels).

METHYSERGIDE



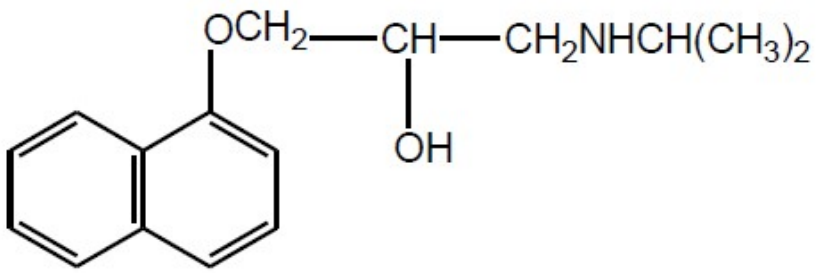
- Methysergide (1-methyl-D-lysergic acid butanolamide) also known as methysergide maleate, is an ergot derived drug used for the prophylaxis of difficult to treat migraine and cluster headaches.
- Not recommended now as first line drug due to many side effects and availability of safer triptans.

β-Adrenergic blockers

MECHANISM OF ACTION OF BETA-ADRENERGIC RECEPTOR BLOCKERS

- β adrenergic receptor antagonists slow the heart rate and decrease the myocardial contractility, these prolong the systolic conduction and disturbs the ventricular fibres.
- Dimensions of the ventricle is decreased, oxygen consumption is decreased, and thereby decreases the heart rate and aortic pressure.
- In blood vessels, these drugs reduce the noradrenaline release from the sympathetic terminals and decrease the renin from kidney due to the blockade of β receptors.

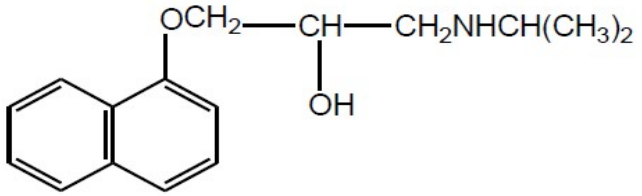
BETA ADRENERGIC BLOCKERS: SAR OF BETA BLOCKERS



Propranolol

- As Propranlol is the prototype drug ß-blockers, the SAR of propranolol is discussed as SAR of ß- blockers. Following are the important points to discuss:
  1. The **aromatic ring and its substituent** is the primary determinant of ß1 antagonistic activity. The aryl group also affects the absorption, excretion, and metabolism of the ß blockers.

SAR OF BETA BLOCKERS



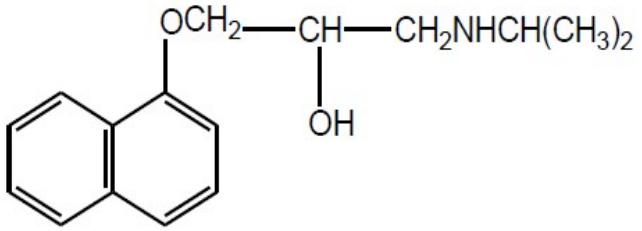
Propranolol

2. ß blockers are structurally similar to ß agonist. The catechol ring can be replaced by a variety of ring system without loss of antagonistic activity.
3. Replacement of catechol hydroxyl group with chlorine of phenyl ring system retains ß blocking activity.

Example: pronethalol, dichloroisoproterenol.

4. *N*, *N*-disubstitution decreases the ß 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.
5. The two carbon chains are essential for activity.

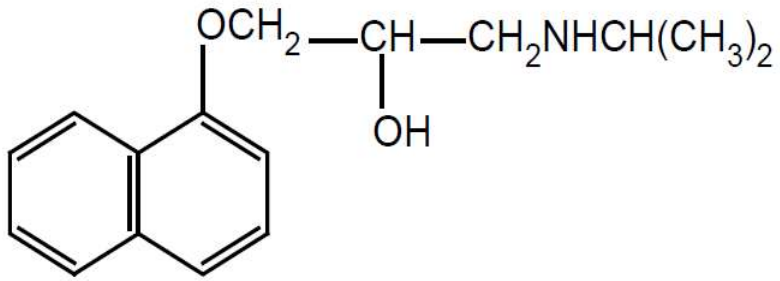
SAR OF BETA BLOCKERS



Propranolol

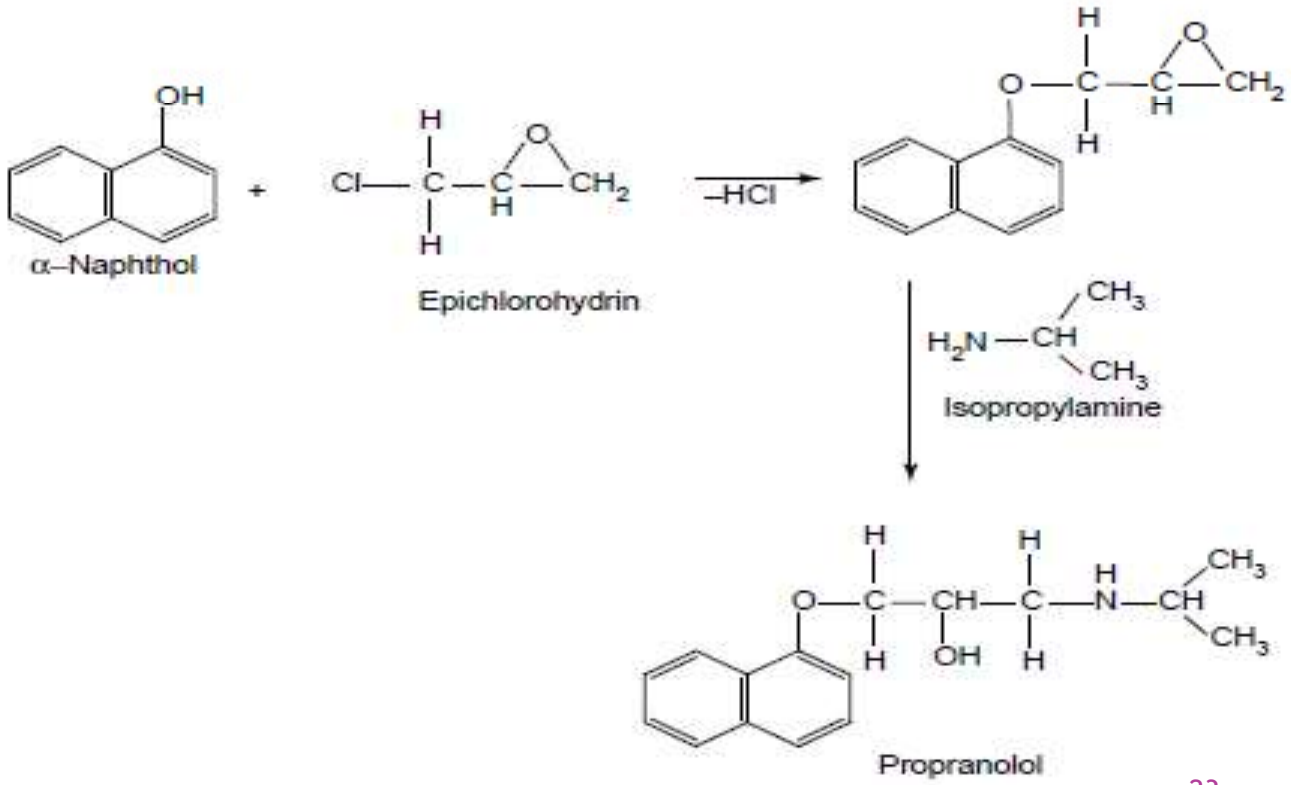
6. The introduction of -OCH_2 group into the molecule between the aromatic ring and the ethyl amine side chain provides ß blocking agents, for example, propranolol.
7. As in the sympathomimetics, bulky aliphatic groups, such as the tert-butyl and isopropyl groups are normally found on the amino function of the aryloxypropanolamine ß receptor antagonists. It must be a secondary amine for optimal activity.
8. As with the sympathomimetic agents, 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.

PROPRANOLOL*



1-(Isopropyl amino)-3-(1-napthyloxy)-2-propanol

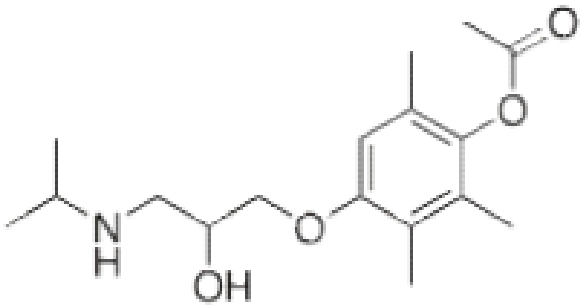
Synthesis:



PROPRANOLOL

- Propranolol is a nonselective ß-adrenergic antagonist and it has equal affinity for ß1 and ß2 receptors.
- By blocking ß1 receptors in heart, propranolol decreases heart rate, force of contraction (at relatively higher doses)and cardiac output.
- It causes fall in BP and increase in bronchial resistance (ß2 blockade).
- Currently, it is approved for hypertension associated cardiac arrhythmia, angina pectoris, due to coronary atherosclerosis and prophylaxis of migraine headache.

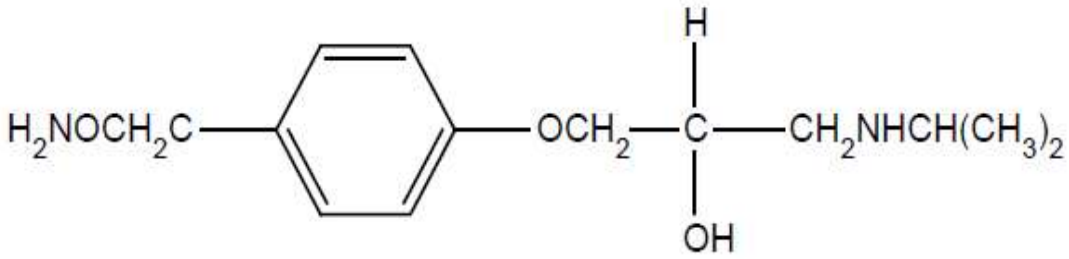
METIBRANOLOL



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

- Metipranolol is a beta-adrenergic antagonist effective for both beta-1 and beta-2 receptors.
- It is used as an antiarrhythmic, antihypertensive, and antiglaucoma agent.

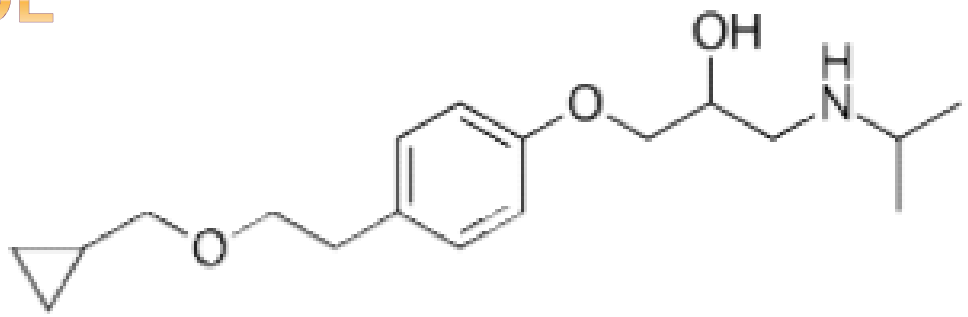
ATENOLOL



4-{2-Hydroxy-3-[(1-isopropyl) amino]propoxy}benzeneacetamide

- Atenolol is a cardioselective beta-blocker used in a variety of cardiovascular conditions.
- Various uses include hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, and the symptoms of alcohol withdrawal.

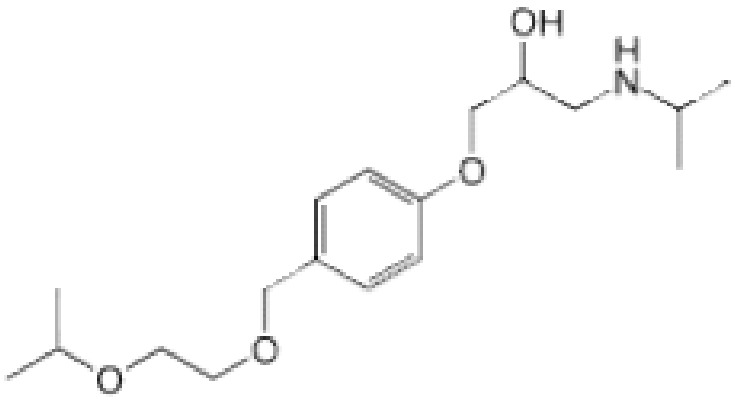
BETAXOLOL



(*RS*)-1-{4-[2-(cyclopropylmethoxy)ethyl]-phenoxy}-3(isopropylamino)propan-2-ol

- Betaxolol is a selective beta1 receptor blocker used in the treatment of hypertension and glaucoma.
- Being selective for beta1 receptors, it typically has fewer systemic side effects than non-selective beta-blockers, for example, not causing bronchospasm (mediated by beta2 receptors) as timolol may.

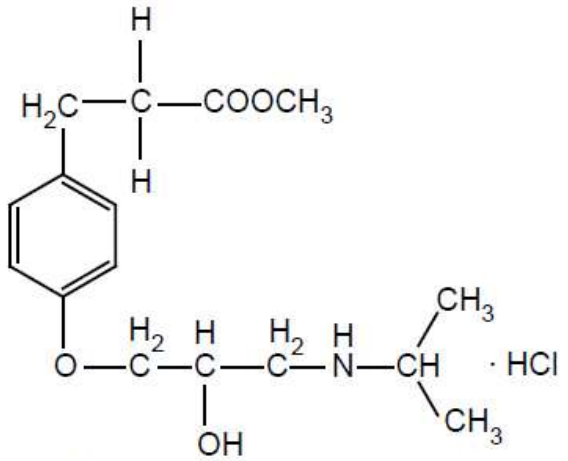
BISOPROLOL



(*RS*)-1-{4-[(2-Isopropoxyethoxy)methyl]phenoxy}-3-(isopropylamino)propan-2-ol

- Bisoprolol is a cardioselective β1-adrenergic blocking agent used to treat high blood pressure.
- It is considered a potent drug with a long-half life that can be used once daily to reduce the need for multiple doses of antihypertensive drugs

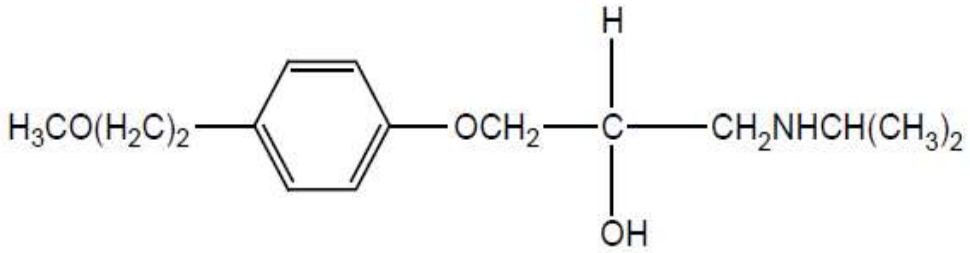
ESMOLOL



Methyl 3-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)propanoate hydrochloride

- **Esmolol** is a cardioselective beta$_1$ receptor blocker with rapid onset and a very short duration of action.
- it is used in the treatment of supraventricular tachycardia.

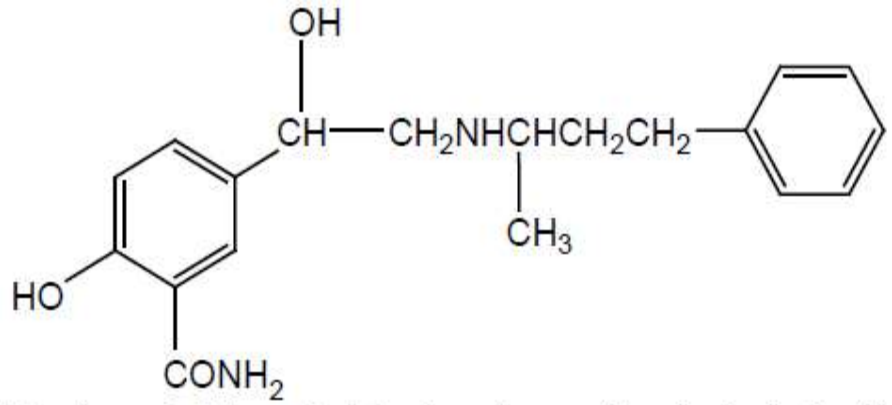
METOPROLOL



1-[4-(2-methoxy ethyl)phenoxy]-3-(isopropylamino]-2-propanol

- It is a ß1 selective antagonist used in the treatment of hypertension.
- Metoprolol is also used for a number of other conditions, such as hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches.

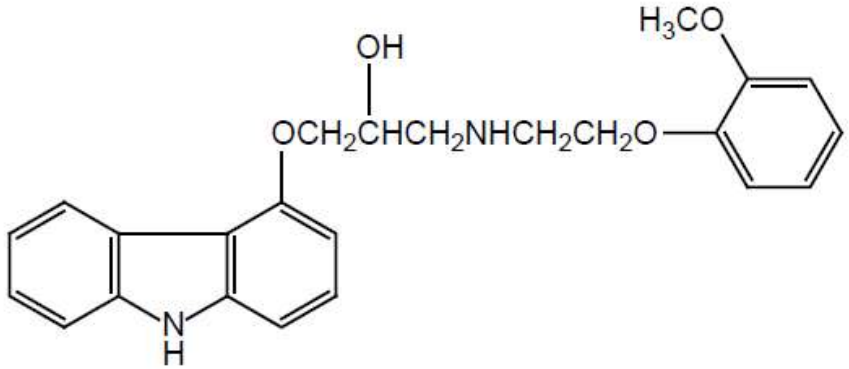
LABETALOL



5-{1-hydroxy-2-[(1-methyl-3-phenyl propyl)amino}ethyl]salicylamide

- Labetolol is a phenyl ethanol amine derivative that is a competitive inhibitor at both ß1 and ß2 adrenergic receptors and at the α1-adrenergic receptor.
- It is more potent ß antagonist than α antagonist, since it has two asymmetric carbon atoms (1 and 1'), it exists as a mixture of four isomers.
- It is the mixture that is used clinically in treating hypertension.
- The different isomers, however, posses different α- and ß-antagonistic activities.

CARVEDILOL



1-(Carbazol-4-yloxy)-3-[2-(2-methoxyl phenoxy)ethyl amino]-2-propanol

- 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.
- The dual action of carvedilol is advantageous in combination therapies as moderate doses of 2 drugs have a decreased incidence of adverse effects compared to high dose monotherapy in the treatment of moderate hypertension.

THANK YOU....