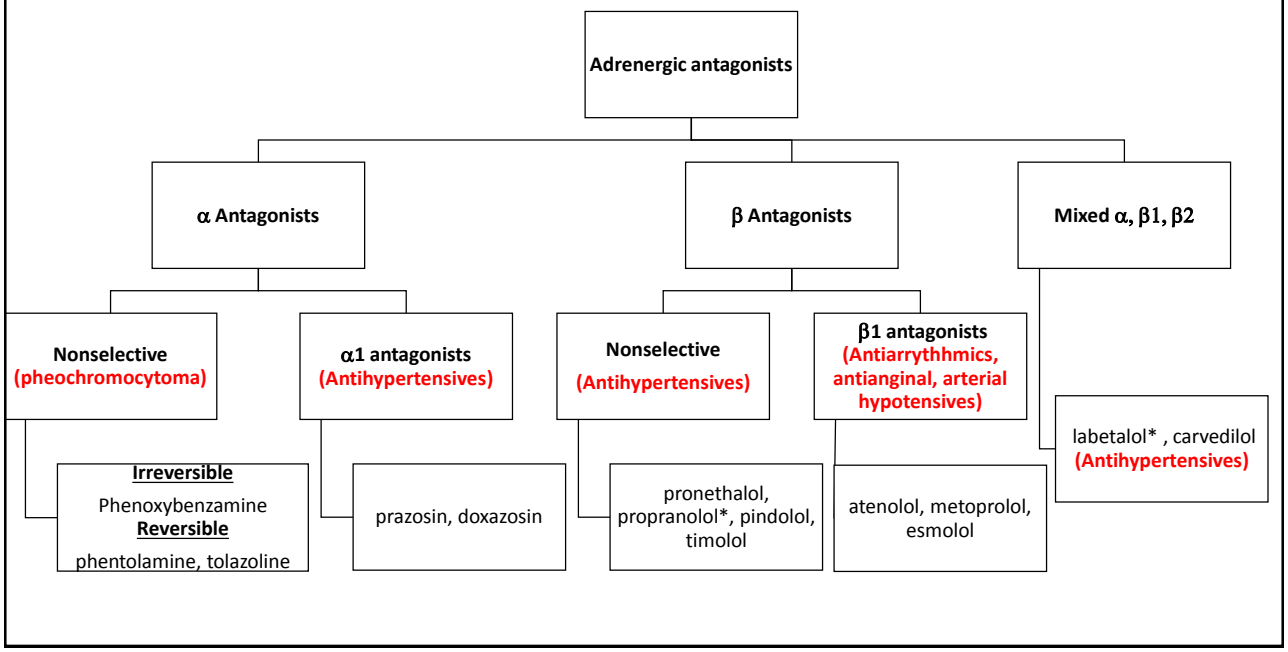
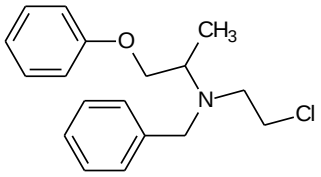
Adrenergic Antagonists



Non-selective alpha antagonists

Phenoxybenzamine

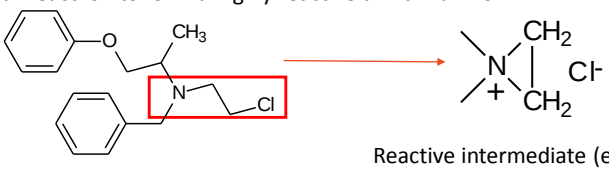
- **β-haloalkylamine** that alkylates α-receptors.
- Irreversible - alkylates the receptor
- Long acting (14-48 hours)



N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzylamine

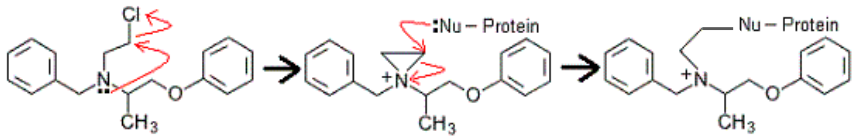
Non-selective alpha antagonists

- β-haloalkylamines are present in nitrogen mustard anticancer agents and are highly reactive alkylating agents.
- The unshared electrons of the amino group are nucleophilic and displace the β-chlorine atom in an intramolecular react ion to form a highly reactive aziridinium ion



Reactive intermediate (ethyleneimonium)

Phenoxybenzamine

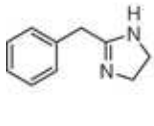


- The other 2 substituents attached to the haloalkylamine provide selectivity for binding to α-adrenoceptors
- As the drug binds to the α- receptor, a nucleophile group X on the receptor (amino acid side chain, such as a cysteine thiol, serine hydroxyl, or lysine amino group) opens the aziridinium ion in a nucleophilic reaction to form a covalent bond between the receptor and the drug.
- Because the reaction in which phenoxybenzamine forms covalent bonds with the receptors is irreversible, new receptors must be synthesized before the effects can be overcome.
- Therefore, the α-blockade is long-lasting.

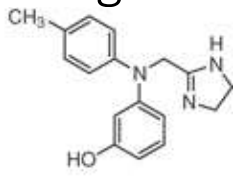
Phenoxybenzamine

- Unfortunately, other biomolecules besides the target α-receptor also are alkylated resulting in toxicity.
- Because of its receptor nonselectivity and toxicity, the use of phenoxybenzamine largely is limited to alleviating the sympathetic effects of pheochromocytoma.
- This tumor of chromaffin cells of the adrenal medulla produces large amounts of epinephrine and norepinephrine, which are released into the bloodstream, producing hypertension and generalized sympathetic stimulation.

Non-selective alpha antagonists



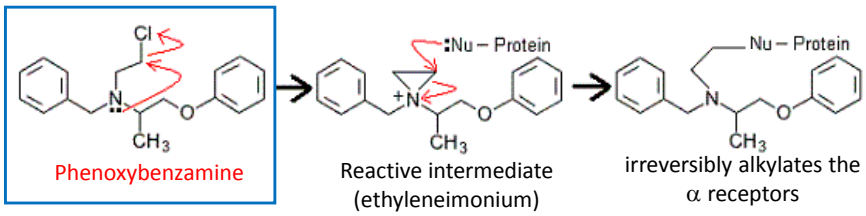
Tolazoline
2-benzylimidazoline



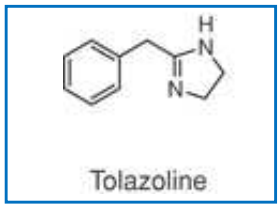
Phentolamine
2-[N-(3–hydroxyphenyl), N-(4-methylphenyl)methyl]imidazoline

- Tolazoline and phentolamine are two imidazoline α-antagonists that also have antihypertensive activity
- Reversible antagonists of alpha adrenergic receptors
- Tolazoline is structurally similar to the imidazoline α1-agonists, such as naphazoline and xylometazoline but does not have the lipophilic aromatic substituents required for agonist activity
- Both phentolamine and tolazoline are potent but rather nonspecific α-antagonists.
  - Both drugs have cholinergic and histaminic activity and stimulate gastrointestinal smooth muscle (cholinergic) and they both stimulate gastric secretion (release of histamine).
- Because of these and other side effects, the clinical applications of tolazoline and phentolamine also are limited to treating the symptoms of pheochromocytoma.

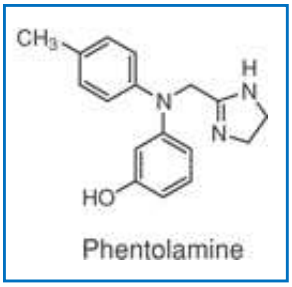
Non-selective alpha antagonists



- Long acting (14-48 hrs)
- nonselectivity and toxicity limits its use to alleviating the sympathetic effects of pheochromocytoma.



Tolazoline



Phentolamine

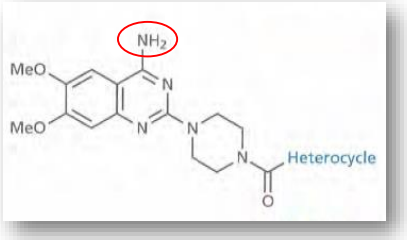
- imidazoline α-antagonists
- Reversible antagonists
- nonselectivity limits its use to alleviating the sympathetic effects of pheochromocytoma.

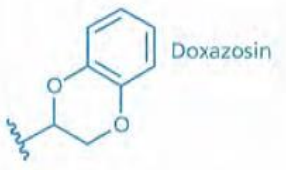
Selective α1- Adrenergic Antagonists

Antihypertensives - These agents relieve hypertension by

- blocking the action of noradrenalin/adrenaline at the α1 receptors of smooth muscle in blood vessels
- resulting in smooth muscle relaxation and dilatation of the blood vessels lowering of BP

Selective α1- Adrenergic Antagonists

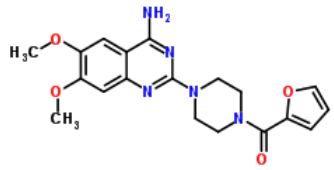


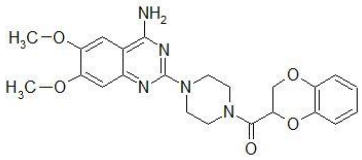


- Contain a 4-amino-6,7-dimethoxyquinazoline ring system attached to a piperazine ring and a heteroacyl moeity
- The presence of amino group at 4th position and hetero moiety at 2nd position is essential for α1-receptor antagonistic activity
- The heterocyclic acyl groups attached to the second nitrogen of the piperazine varies between different dugs which afford dramatic differences in some of the pharmacokinetic properties of these agents
- The benzodioxine moiety of doxazosin alters the pharmacokinetics of the drug giving it a longer-lasting action – 22 hrs half-life than prazosin (half life – 2 to 3 hrs)
- The long half- lives and durations of action doxazosin permit once-a-day dosing and generally lead to increased patient compliance.

α1- Adrenergic Antagonists

- Prazosin is a piperazinylquinazoline and selective α_1 antagonist.
  - 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine
  - The affinity of prazosin for α^1 receptors is about 1000 fold greater than for α_2 receptors.
  - Short-acting – 2- 3 hrs half-life
- Doxazosin –
  - 2-[4-(2,3-Dihydro-1,4-benzodioxine-2-carbonyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine
  - The benzodioxine moiety alters the pharmacokinetics of the drug giving it a longer-lasting action – 22 hrs half-life
  - Can be given as once-daily doses
- These are used in the treatment of all grades of hypertension usually as a second step agent in conjunction with a diuretic or other antihypertensive agent.

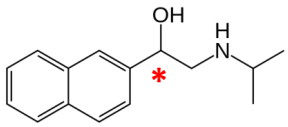




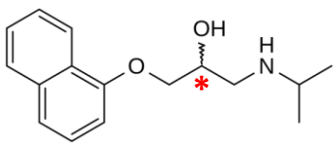
β - Adrenoceptor antagonists

Classification

- Aryl ethanol amines –



- Aryloxy propanol amines –



In general, aryloxypropanolamines are more potent β-blockers than the corresponding arylethanolamines and are the β-blockers currently used most often clinically

β - Adrenoceptor antagonists

Stereochemistry

- The relative positions in space of the four functional groups are the same in the arylethanolamines and aryloxypropanolamines
- However, one is designated (R) and the other (S).
- This is because the introduction of an oxygen atom into the side chain of the aryloxypropanolamine changes the priority of two of the groups used in the nomenclature assignment.

Development of β-blockers

(i) First-generation β-blockers,

(ii) Second-generation β-blockers

First Generation β-Blockers

Aim – The first main objective towards the exploratory development of these agents was to accomplish selectivity for β-receptors with respect to α-receptors.

Salient Features

(1) Isoprenaline [I] -'lead compound',

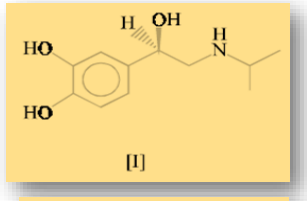
- It is beta-adrenergic agonist and structurally similar to adrenaline
- **active at β-receptors and not α-receptors.**
- is an 'agonist'* and not an 'antagonist' – needed to be changed

(2) Dichloroisoprenaline [II]

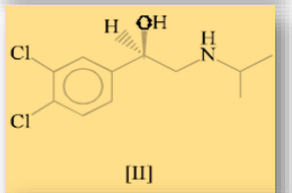
- 'Phenolic functional moieties' when present bestow 'agonist activity'
- Changing the two phenolic functions in isoprenaline and replacing by chloro- (DCI) [II] proved to be a 'partial agonist'.
- can be regarded as an antagonist because it lowered the adrenergic activity appreciably.

(3) Pronethalol [III]

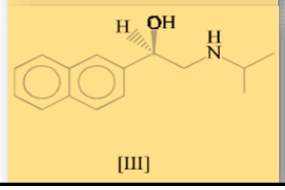
- Removing the 2 Cl and replacing with a fused aromatic ring improved the antagonist potential
- First β-blocker to be employed profusely for the control, management and treatment of angina, high BP, and arrhythmias.



[I]

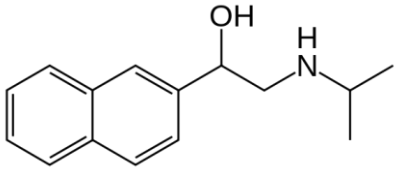


[II]



[III]

Pronethalol

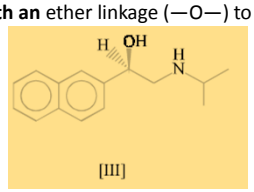


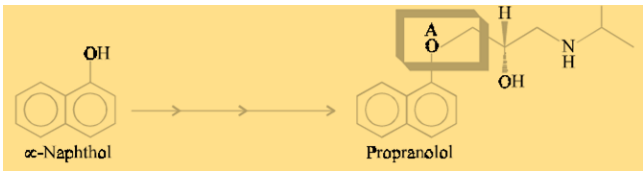
- 1-(naphthalen-2-yl)-2-(propan-2-ylamino)ethanol
- Pronethalol was an early non-selective beta blocker clinical candidate.
- It was never used clinically due to carcinogenicity in mice, which was thought to result from formation of a carcinogenic naphthalene epoxide metabolite

First Generation β-Blockers

(3) Propranolol - Serendipitous, epoch-making discovery

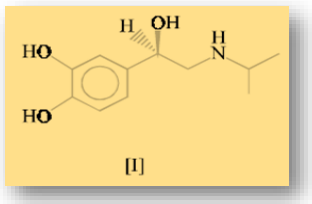
- Synthesising pronethalol from β-naphthol was challenging
- **1 Synthesis trial**
  - **extending the linking moiety with an** ether linkage (—O—) to an ethanolamine residue from the α-naphthol



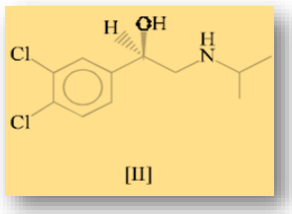


Propranolol was observed to be a pure antagonist which was approximately 20 times more potent in comparison to pronethalol

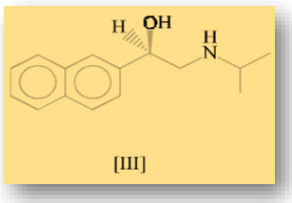
Development of beta blockers



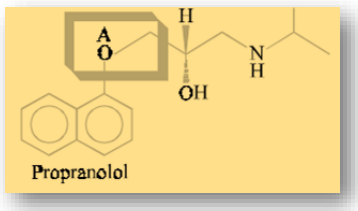
Isoprenaline [I]
'lead compound',
Beta-adrenergic agonist
No alpha activity



Dichloroisoprenaline [II]
Partial agonist
Partial antagonist

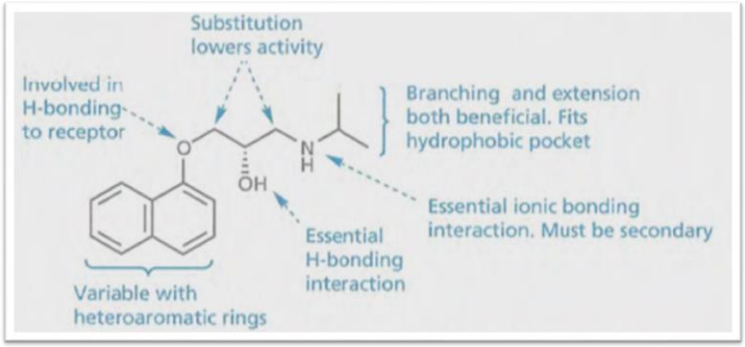


Pronethalol [III]
Full antagonist



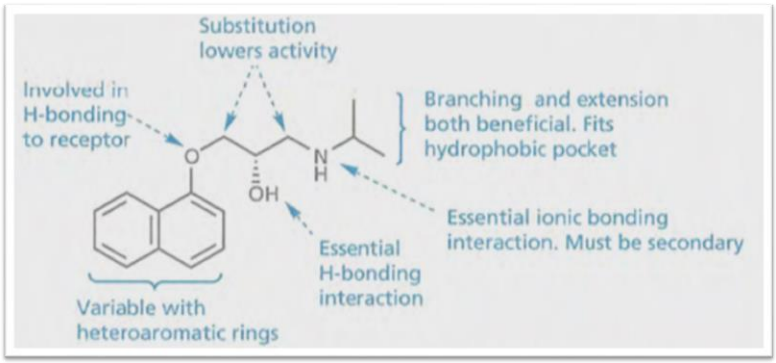
Propranolol
Highly potent
Full antagonist

SAR



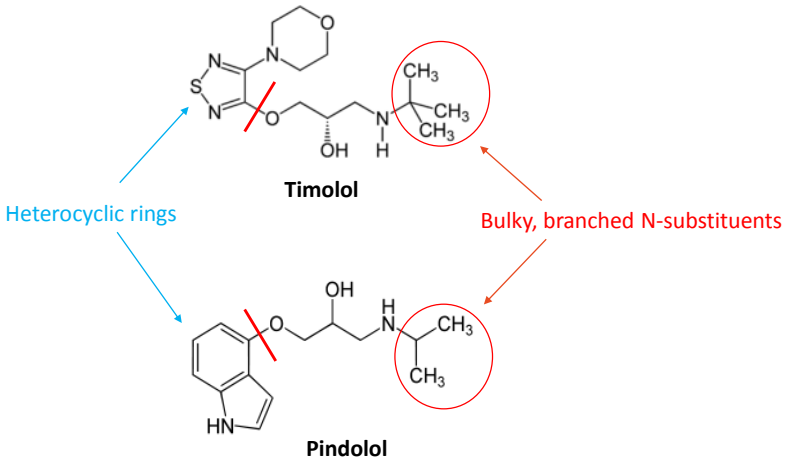
1. The 'amine nitrogen' should always be a secondary in character with regard to the optimum activity.
2. The 'branched and bulky N-alkyl functional moieties', such as : tert-butyl, iso-propyl etc., proved to be extremely vital for attributing the β-antagonist activity, thereby suggesting a possible interaction taking place with a hydrophobic pocket strategically located in the binding site.
3. The introduction of relatively longer alkyl substituents in comparison to 'isopropyl' or 'tertbutyl' are found to be much less therapeutically potent and efficient.
4. The addition of an arylethyl functional moiety, for instance : CH(CH3)—CH2—C6H5 or CH(CH3)2—CH2—C6H5 has proved to be useful in having better efficacious drug substances.

SAR



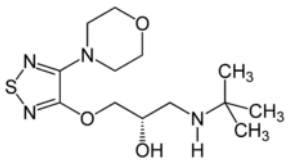
5. The 'alcoholic function' on the side-chain is an absolute necessary requirement for its activity.
6. Isosteric replacement of the ethereal linkage (—O—) with such moieties as : CH2, S or NCH3 is found to be more or less detrimental; but can be replaced with NH
7. The probable substitution of the two methylene moieties present in the 'side-chain' enhances the metabolic stability at the expense of therapeutic potency (lowering of activity).
8. Variation of the aromatic ring system are well tolerated. heteroaromatic rings are found in timolol, pindolol

Non-selective beta-adrenergic antagonist

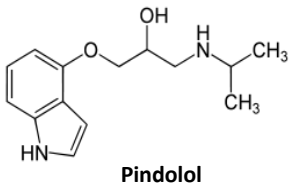


Non-selective beta-adrenergic antagonist

- Timolol
  - (*S*)-1-(*tert*-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol
  - Timolol is a non-selective beta-adrenergic receptor antagonist indicated for treating heart attacks, hypertension.
  - It is used in the form of eyedrops to decrease intraocular pressure in glaucoma
- Pindolol
  - 1-(1*H*-indol-4-yloxy)-3-(isopropylamino)propan-2-ol
  - Pindolol is a
    - nonselective beta blocker
  - Pindolol is used for treating hypertension, angina pectoris and arrhythmias



Timolol



Pindolol

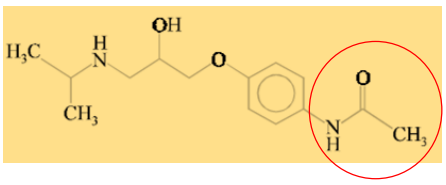
Side effects

Nonselective β blocker

- Bronchoconstriction (minimized by using beta-1 selective drug; bad for asthmatics)
- Increase in LDL/HDL ratio (bad for atherosclerosis)
- Depression, loss of energy (CNS effect)
- Decreased cardiac contractility (good for angina, good or bad for CHF)

Second Generation β-Blockers (Selective β1-Blockers)

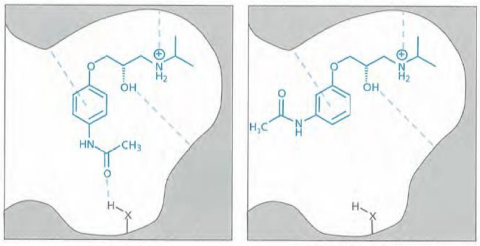
- It was suspected that propranolol's centrally induced side effects could be due to its high lipophilicity
- Hydrophilic analogues substituted with groups such as acylamino groups as the hydrophilic moiety were synthesized
  - Para acyl amino substitution – eg. Practolol
    - No central side effects.
    - β1 selectivity exhibited
  - Meta / ortho acyl amino substitution
    - No central side effects.
    - No β selectivity exhibited
- Practolol exhibited cardioselectivity (β1 selectivity) but was less potent than propranolol. Practolol for nominated for clinical trials.



Practolol was eventually withdrawn due to relatively rare, but nevertheless extremely serious dermatologic as well as ophthalmic toxicological actions that ultimately led to total blindness and fatalities.

Second Generation β-Blockers (Selective β1-Blockers)

- Studies from practolol analogs showed that moving the acylamino group to meta or ortho positions, on the benzene ring, caused a loss of selectivity but not loss of the β-blockade itself.
- With para-substitution (practolol) there exists an extra H-bonding interaction in the β1-receptors but not the β2-receptors ; whereas, in the meta-substitution there is no feature of an extra H-bonding interaction

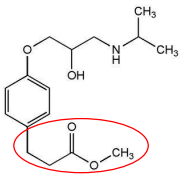


Binding interactions of antagonists with β_1-receptors.

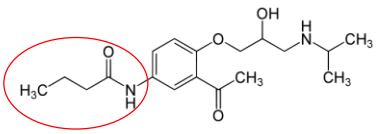
- Para substitution – gives β1-selectivity
- Meta / ortho substitution - Nonselective β blockade

β1 - Adrenoceptor antagonists

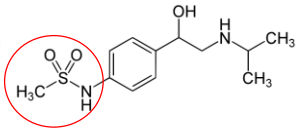
- Replacement of the acetamido group with other H-bond forming groups lead series of cardioselective β1-blockers which reached the market.



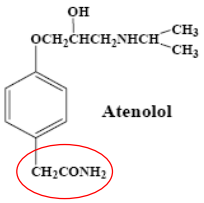
Esmolol



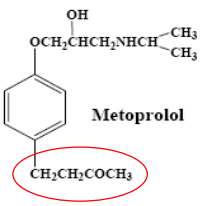
Acebutolol



Sotalol



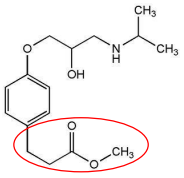
Atenolol



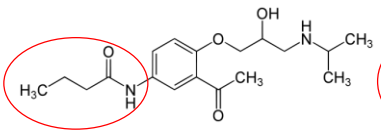
Metoprolol

- Selective β1 antagonists
  - Antihypertensives – used to treat arterial hypertension
  - Slows down heart and reduces its workload – used to treat chest pain due to poor blood flow to the heart – used to treat angina
  - Slows down heart and reduces its workload – used to treat arrythmias

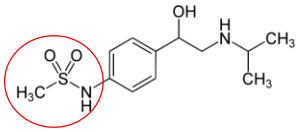
β1 - Adrenoceptor antagonists



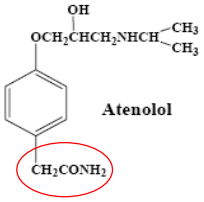
Esmolol



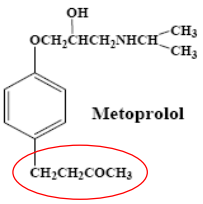
Acebutolol



Sotalol



Atenolol



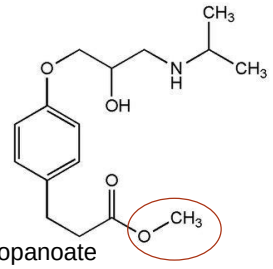
Metoprolol

Acebutolol: (*RS*)-*N*-{3-acetyl-4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}butanamide
Sotalol: (*RS*)-*N*-{4-[1-hydroxy-2-(propan-2-ylamino)ethyl]phenyl}methanesulfonamide
Atenolol: (*RS*)-2-{4-[2-Hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide
Metoprolol: (*RS*)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol
Esmolol: methyl (*RS*)-3-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}propanoate

β1 - Adrenoceptor antagonists

- Unlike propranolol, which blocks both β1- and β2-adrenoreceptors, the selective β1 - adrenoceptor antagonists exhibit cardioselective action, i.e in therapeutic doses, it blocks β1-adrenoreceptors with insignificant reaction on β2-adrenoreceptors.
- These possess antianginal, antihypotensive, and antiarrhythmic action. It is used for arterial hypertension, preventing attacks of angina, and cardiac rhythm disturbances

β1 - Adrenoceptor antagonists



Esmolol

short -acting β1-adrenergic antagonist

methyl (*RS*)-3-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}propanoate

- Esmolol is a cardioselective beta1 receptor blocker with rapid onset, a very short duration of action
- It is a class II antiarrhythmic.
- Esmolol decreases the force and rate of heart contractions by blocking beta-adrenergic receptors of the sympathetic nervous system, which are found in the heart and other organs of the body.
- Esmolol is the methyl ester of the carboxylic metabolite of metoprolol, which makes it is susceptible to hydrolysis by serum esterases.
- The acid metabolite generated by hydrolysis is essentially inactive and readily excreted as its zwitterion.
- For this reason, esmolol has a half-life of only approximately 8 minutes and is used to control supraventricular tachycardia during surgery when a short -acting β1-adrenergic antagonist is desirable.

Antiarrhythmia

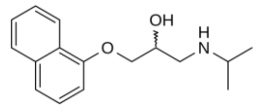
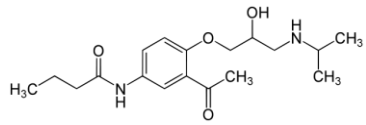
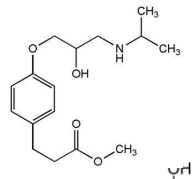
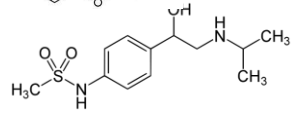
- Sympathetic nerves supply the SA, AV nodes and the atrial and ventriclar muscle of the heart.
- Sympathetic nerves help maintain rhythm of the heart
- Sympathetic stimulation increases the rate and force of the heart beat
- The atrial contraction and ventricular contraction are not synchronised
  - Atrial fibrillation
    - Multiple erratic electric impulses generated from various places in the atria
  - Ventricular fibrillation
    - Disorganised and very rapid contraction of ventricles
- **Treatment – Reduction in heart rate would give it time to coordinate between atria and ventricles (complete filling before contraction)**

Class II-Antiarrhythmic Drugs β-Receptor antagonists

- These drugs are primarily effective in treatment of tachyarrhythmias caused by increased sympathetic activity.
- Blocking sympathetic activity with β-blockers
  - Their dominant electrophysiological effect is on SA node and AV node
  - Decrease the frequency of SA node firing
  - Heart rate decreases
  - They depress adrenergically enhanced calcium influx via β-receptor blockade.
  - They raise the threshold of excitation
  - Used for atrial and ventricular arrhythmias
- They are used for arrhythmias associated with nervous stress, myocardial infarction, and thyrotoxicosis accompanied by elevated adrenergic activity.

β-blockers as antiarrhythmics

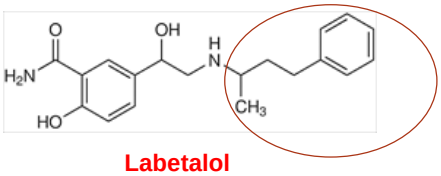
- Propranolol
  - is primarily **given orally for long-term treatment** of cardiac arrhythmias.
  - Propranolol slows heart rate, increases the effective refractory period of atrioventricular ganglia, suppresses automatism of heart cells, and reduces excitability and contractibility of the myocardium.
  - It is useful in ventricular arrhythmias that are due to enhanced adrenergic stimulation (from emotional stress, exercise).
- Acebutolol
  - is a **β^1-selective** adrenergic receptor blocker and is used chiefly for controlling ventricular pressure beats.
  - The principal metabolite is N-acetylacebutolol (diacetolol) which is more potent and selective for β^1-receptors than the parent drug.
- Esmolol
  - is particularly useful because of its very **brief action** (half-life 9 minutes) for the treatment of atrial tachycardias
  - It is used to control supraventricular tachycardia during surgery when a short - acting β1-adrenergic antagonist is desirable
- Sotalol
  - is effective against both atrial and ventricular arrhythmias. It is a much safer drug than amiodarone. It has a **long half-life** (about 15 hours).

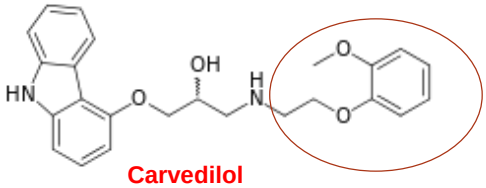
Mixed α, β - adrenoceptor antagonists

- Selective β1-blockers slow down the heart along with reduction of cardiac output as peripheral vascular resistance is not affected.
- Administration of a mixed α, β1-blockers slows down heart and reduces peripheral vascular resistance. Thus cardiac output is not decreased.
- Chemical classification
  - Arylethanolamine - Labetalol
  - Aryloxypropanolamine - Carvedilol

Mixed α, β - adrenoceptor antagonists



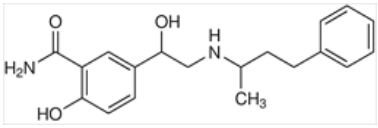
Labetalol
(Arylethanolamine)



Carvedilol
(Aryloxypropanolamine)
(±)-[3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl][2-(2-methoxyphenoxy)ethyl]amine

- Labetalol and carvedilol are antihypertensives with α1-, β1-, and β2-blocking activity
- In terms of SAR, large substituents on the amine N (N-isopropyl and N-t –butyl) eliminated α-receptor agonist activity; however, larger arylalkyl groups (sometimes with an α-methyl substituent eg. Labetalol) returned α1-affinity but not intrinsic activity making these drugs mixed antagonists
- Thus, these two drugs have structural features that permit binding to the α1- receptor and nonselectively to both β-receptors.
- Carvedilol has an estimated β-blocking activity 10- to 100-fold its α-blocking activity.

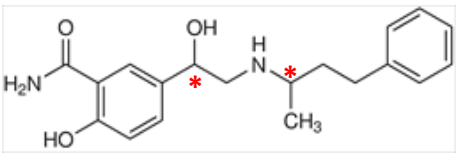
Mixed α, β - adrenoceptor antagonists



(*RS*)-2-hydroxy-5-{1-hydroxy-2-[(4-phenylbutan-2-yl) amino]ethyl}benzamide

- Labetalol has a large substituent on the amine nitrogen (greater in size than a t-butyl group) which gives it receptor affinity without intrinsic activity, and is therefore an antagonist.
- Labetalol combines both selective, competitive, α -1-adrenergic blocking and nonselective, competitive, β -adrenergic blocking activity in a single substance.
    - Competitively blocks α1-receptors within vascular smooth muscle – decreases peripheral vascular resistance
    - Competitively blocks β1-receptors within the myocardium – slows down the heart, decreases arterial vascular resistance
    - Competitively blocks β2-receptors within bronchial and vascular smooth muscle
- Thus, inspite of being a mixed antagonist, labetolol causes a decrease in systemic arterial blood pressure and systemic vascular resistance **without a substantial reduction in cardiac output or stroke volume** (as peripheral vascular resistance is less)

Stereospecific action of Labetalol



- Labetalol has two chiral carbons and consequently exists as four stereoisomers
    - the (*R*,*R*)-isomer which is also known as dilevalol, is a mixed α_1 β1 β2 blocker
    - the (*S*,*R*)-isomer, is a powerful α_1 blocker.
    - the (*S*,*S*)- and (*R*,*S*)- forms are inactive.