ENDOGENOUS CATECHOLAMINES

The three naturally occurring catecholamines DA, NE, and E are used as therapeutic agents.

Dopamine.

(DA, 3,4-dihydroxyphenylethylamine) differs from NE in lacking of 1-OH group. It is the immediate precursor of NE and is a central NT particularly important in the regulation of movement. As a catechol and primary amine, DA is rapidly metabolized by COMT and MAO and has a short DOA with no oral activity. It is used intravenously in treatment of shock. In contrast with the NE and E, DA increases blood flow to the kidney in doses that have no chronotropic effect on the heart or that cause no increase in blood pressure. The increased blood flow to the kidneys enhances glomerular filtration rate, Na+1 excretion, and, in turn, urinary output. The dilation of renal blood vessels produced by DA is the result of its agonist action on the D1-DA receptor.

In doses slightly higher than those required to increase renal blood flow, DA stimulates the β1-receptors of the heart to increase cardiac output. Some of the effects of DA on the heart are also caused by NE release. Infusion at a rate greater than 10 µg/kg per minute results in stimulation of α1receptors, leading to vasoconstriction and an increase in arterial blood pressure. DA should be avoided or used at a much reduced dosage (one tenth or less) if the patient has received an MAO inhibitor. Careful adjustment of dosage also is necessary in patients who are taking tricyclic antidepressants.

Note: Outside the central nervous system, dopamine functions primarily as a local paracrine messenger. In blood vessels, it inhibits norepinephrine release and acts as a vasodilator (at normal concentrations);

Norepinephrine (NE, Levophed)

differs from DA only by addition of a 1-OH substituent (β-OH-DA) and from E only by lacking the N-methyl group. Like DA, it is polar and rapidly metabolized by both COMT and MAO, resulting in poor oral bioavailability and short DOA (1 or 2 minutes even when given intravenously). It is a stimulant of α1-, α2-, and β1-adrenoceptors (notice that lacking the N-methyl group results in lacking β2- and β3-activity). It is used to counteract various hypotensive crises, because its α-activity raises blood pressure and as an adjunct treatment in cardiac arrest because its β-activity stimulates the heart. It has limited clinical application caused by the nonselective nature of its activities.

Epinephrine (E, Adrenalin)

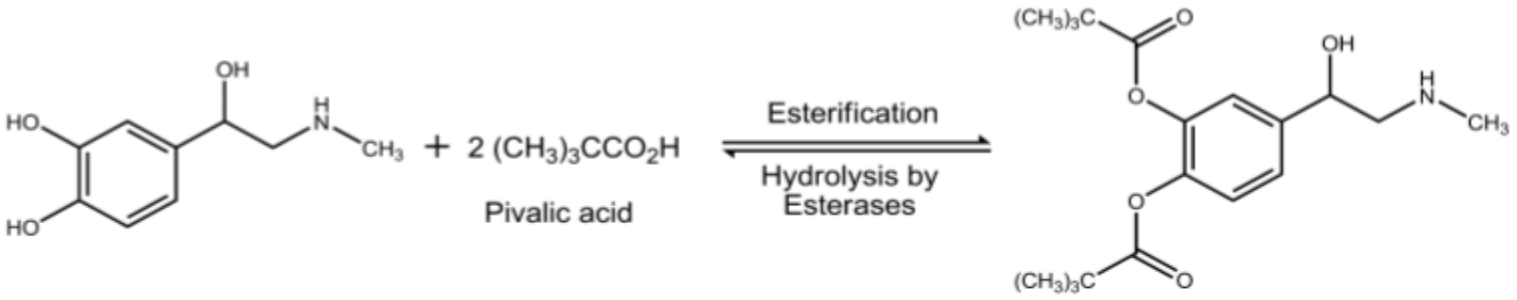
differs from NE only by the addition of an N-methyl group. Like the other CAs, E is light sensitive and easily oxidized on exposure to air because of the catechol ring system. The development of a pink-to-brown color indicates oxidative breakdown. To minimize oxidation, solutions of the drug are stabilized by the addition of reducing agents such as sodium bisulfite. E is also destroyed readily in alkaline solutions and by metals (e.g., Cu, Fe, Zn) and weak oxidizing agents. It is used in aqueous solution for inhalation as the free amine. Like other amines, it forms salts with acids, hydrochloride, and the bitartrate being the most common. Like NE, it lacks oral activity and has short DOA. However, it is much more widely used clinically than NE. E is a potent stimulant of all α1-, α2-, β1-, β2-, and 3adrenoceptors, and thus it switches on all possible adrenergic receptors, leading to a whole range of desired and side effects. Particularly prominent are the actions on the heart and on vascular and other smooth muscle. It is a very potent vasoconstrictor and cardiac stimulant. NE has, in general, greater β-activity caused by an additional N-methyl group. Therefore, E is used to stimulate the heart in cardiac arrest.

Although intravenous infusion of E has pronounced effects on the cardiovascular system, its use in the treatment of

heart block or circulatory collapse is limited because of its tendency to induce cardiac arrhythmias. The ability of epinephrine to stimulate β2-receptors has led to its use by injection and by inhalation to relax bronchial smooth muscle in asthma and in anaphylactic reactions. Several OTC preparations (e.g., Primatene, Bronkaid) used for treating bronchial asthma use E. It is also used in inhibiting uterine contraction. Because of its α-activity, E is used to treat hypotensive crises and nasal congestion, to enhance the activity of local anesthetics, and as a constrictor in hemorrhage. In addition, E is used in the treatment of open-angle glaucoma, where it apparently reduces intraocular pressure by increasing the rate of outflow of aqueous humor from the anterior chamber of the eye. The irritation often experienced on instillation of E into the eye has led to the development of other preparations of the drug that potentially are not as irritating. One such example is dipivefrin.

Dipivefrin (Propine, Dipivalyl Epinephrine).

To overcome several of the pharmacokinetic and pharmaceutical shortcomings of E as an ophthalmic agent, the prodrug approach has been successfully applied. Dipivefrin is a prodrug of E that is formed by the esterification of the catechol OH groups of E with pivalic acid. Most of the advantages of this prodrug over E stem from improved bioavailability. The greatly increased lipophilicity allows much greater penetrability into the eye through the corneal epithelial and endothelial layer. The stroma in between requires hydrophilicity for penetration. Dipivefrin has that, too, due to the 1-OH group and cationic nitrogen (the eyedrops contain the hydrochloride [HCl] salt). This dual solubility permits much greater penetrability into the eye than the very hydrophilic E hydrochloride. Increased DOA is also achieved because the drug is resistant to the metabolism by COMT. In addition to its increased in vivo stability, it is also less easily oxidized by air due to the protection of the catechol OH groups. This high bioavailability and in vivo and in vitro stability translate into increased potency such that the 0.1% ophthalmic solution is approximately equivalent to a 2% E solution. After its absorption, it is converted to E by esterases slowly in the cornea and anterior chamber. Dipivefrin also offers the advantage of being less irritating to the eye than E.



Epinephrine (E)
catechol: easily oxidized
less lipophilic than dipivefrin
poor absorption and poor penetration of the eye
irritating to eyes when used in treatment of glaucoma

Dipivefrin: Ester and prodrug of E
Noncatechol: less easily oxidazied
more lipophilic than E
better absorption and penetration of the eye
less irritating to the eye than E

α-ADRENERGIC RECEPTOR AGONISTS

All selective α 1-agonists have therapeutic activity as vasoconstrictors. Structurally, they include (a) phenylethanolamines such as phenylephrine, metaraminol, and methoxamine and (b) 2-arylimidazolines such as xylometazoline, oxymetazoline, tetrahydrozoline, and naphazoline.

Phenylephrine. (Neo-Synephrine, a prototypical selective direct-acting α 1-agonist)

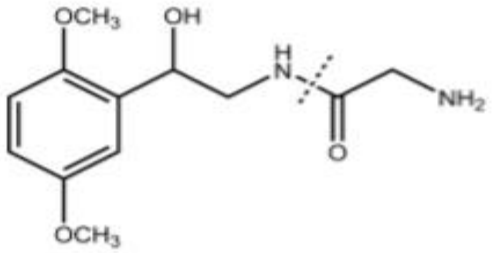
differs from E only in lacking a p-OH group. It is orally active, and its DOA is about twice that of E because it lacks the catechol moiety and thus is not metabolized by COMT. However, its oral bioavailability is less than 10% because of its hydrophilic properties (log P= -0.3), intestinal 3-O-glucuronidation/sulfation and metabolism by MAO. Lacking the p-OH group, it is less potent than E and NE but it is a selective α1-agonist and thus a potent vasoconstrictor. It is used similarly to metaraminol and methoxamine for hypotension. Another use is in the treatment of severe hypotension resulting from either shock or drug administration. It also has widespread use as a nonprescription nasal decongestant in both oral and topical preparations. When applied to mucous membranes, it reduces congestion and swelling by constricting the blood vessels of the membranes. In the eye, it is used to dilate the pupil and to treat open-angle glaucoma. In addition, it is used in spinal anesthesia to prolong the anesthesia and to prevent a drop in blood pressure during the procedure. It is relatively nontoxic and produces little CNS stimulation. Metaraminol is just another example.

Methoxamine (Vasoxyl)

is another α1-agonist and parenteral vasopressor used therapeutically and so have few cardiac stimulatory properties. It is bioactivated by O-demethylation to an active m-phenolic metabolite. In fact, it tends to slow the ventricular rate because of activation of the carotid sinus reflex. It is less potent than phenylephrine as a vasoconstrictor. Methoxamine is used primarily during surgery to maintain adequate arterial blood pressure, especially in conjunction with spinal anesthesia. It does not stimulate the CNS. Because it is not a substrate for COMT, its DOA is significantly longer than NE.

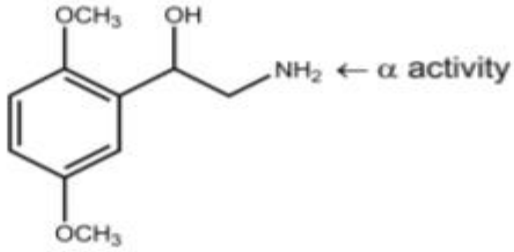
Midodrine (ProAmatine)

is the N-glycyl prodrug of the selective α1-agonist desglymidodrine. Removal of the N-glycyl moiety from midodrine occurs readily in the liver as well as throughout the body, presumably by amidases. Midodrine is orally active and represents another example of a dimethoxy-β-phenylethylamine derivative that is used therapeutically for its vasoconstrictor properties. Specifically, it is used in the treatment of symptomatic orthostatic hypotension.

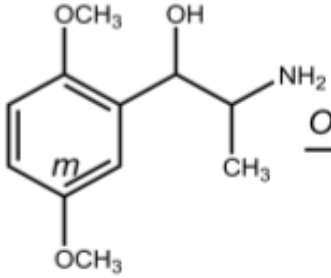


Midodrine: *N*-glycyl prodrug of desglymidodrir

amidases in the liver
and throughout the body

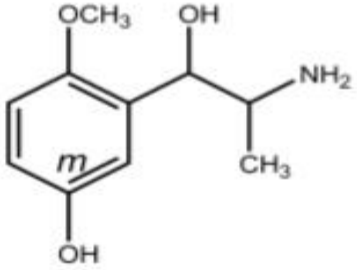


Desglymidodrine
α_1 agonist and vasoconstrictor
differs from methoxamine in lacking α-CH_3



Methoxamine
Prodrug

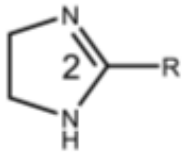
O-demethylatiion



An active *m*-phenolic metabolite
α_1 agonist and vasoconstrictor

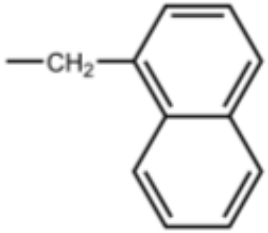
Naphazoline (Privine), tetrahydrozoline (Tyzine, Visine), xylometazoline (Otrivin), and oxymetazoline (Afrin)

are 2-aralkylimidazolines α1-agonists. These agents are used for their vasoconstrictive effects as nasal and ophthalmic decongestants. Although nearly all β-agonists are phenylethanolamine derivatives, α-receptors accommodate more diverse chemical structures. All 2-aralkylimidazoline α1-agonists contain a one-carbon bridge between C-2 of the imidazoline ring and a phenyl ring, and thus a phenylethylamine structure feature is there. Ortho-lipophilic groups on the phenyl ring are important for α-activity. However, meta or para-bulky lipophilic substituents on the phenyl ring may be important for the α1-selectivity. They have limited access to the CNS, because they essentially exist in an ionized form at physiological pH caused by the very basic nature of the imidazoline ring (pKa = 10–11). Xylometazoline and oxymetazoline have been used as topical nasal decongestants because of their ability to promote constriction of the nasal mucosa. When taken in large doses, oxymetazoline may cause hypotension, presumably because of a central clonidine-like effect. Oxymetazoline also has significant affinity for α2A-receptors.

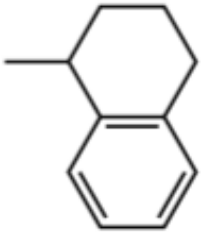


Imidazoline moity
pKa 9-10
Limited access to the CNS

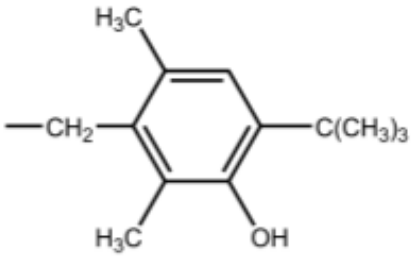
Naphazoline R =



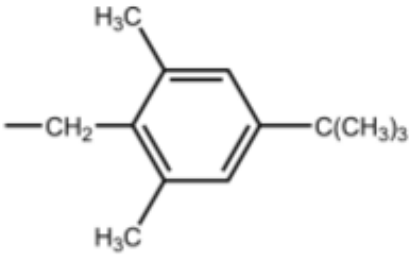
Tetrahydrozoline R =



Oxymetazoline R =



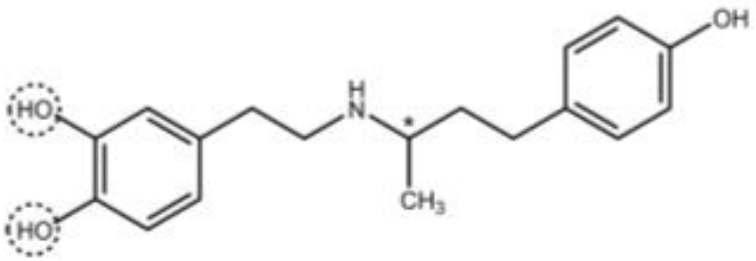
Xylometazoline R =



DUAL α- AND β-AGONISTS/ANTAGONISTS Dobutamine (Dobutrex)

is a positive inotropic agent administered intravenously for congestive heart failure. It resembles DA structurally but possesses a bulky 1-(methyl)3-(4-hydroxyphenyl)propyl group on the amino group. It possesses a center of asymmetry, and both enantiomeric forms are present in the racemic mixture used clinically. The (-) isomer of dobutamine is a potent α1-agonist, which is capable of causing marked pressor responses. In contrast, (+)-dobutamine is a potent α1-antagonist, which can block the effects of (-)-dobutamine. Importantly, the effects of these two isomers are mediated via β1-receptors. Both isomers appear to be full agonists, but the (+) isomer is a more potent β1-agonist than the (-) isomer (approximately tenfold).

Dobutamine contains a catechol group and is orally inactive and thus is given by intravenous infusion. Solutions of the drug can exhibit a slight pink color because of oxidation of the catechol function. It has a plasma half-life of about 2 minutes because it is metabolized by COMT and by conjugation, although not by MAO.



Dobutamine
oxidazed slightly by air
COMT metabolism and conjugation →
orally inactive and short DOA

Alpha <beta1<beta 2

β -ADRENERGIC RECEPTOR AGONISTS

-1Isoproterenol (Isuprel)

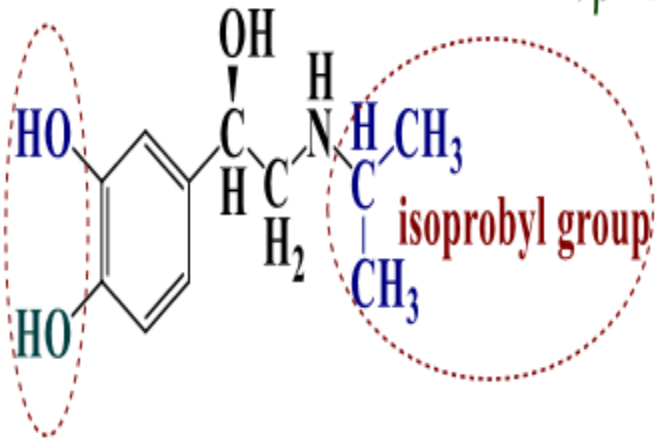
3,4-Di-OH group result in:

sensitive to air and light→

metabolized by COMT, sulfate and glucuronide conjugation→

poor absorption and short DOA

orally inactive



↑β-activity(non selective β-agonist(β1/β2)=1)

and no α-activity

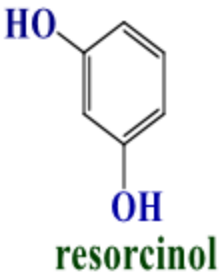
resistance to MAO

used inhalation and injection

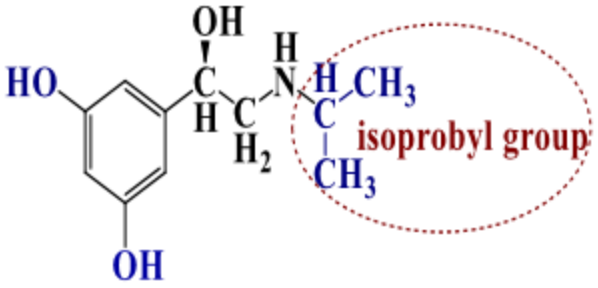
cardiac–β1 stimulation=↑ cardic out put→(treatment heart block)

bronchial–β2 stimulation= bronchodilation→(treatment of acute and chronic bronchial asthma)

-2Metaproterenol terbutaline



resorcinol



Metaproterenol

3,5-Di-OH group result in:

↑β2 activity

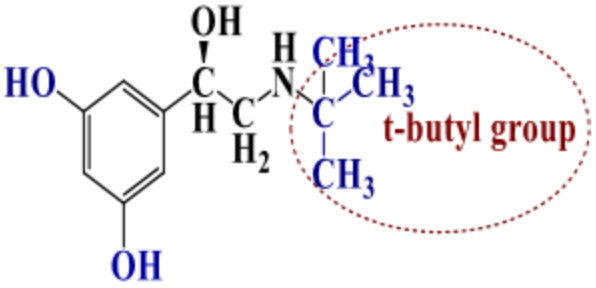
relax the bronchial musculature in patients with asthma but do less direct cardiac stimulation than do the non selective β agonist

because metaproterenol has a β-directing N-isopropyl and is less β2 selective than terbutaline or albuterol

both have β2-directing t-butyl group, henc is more cause cardiac stimulation

not metabolized by COMT and MAO

orally active and longer DOA



Terbutaline

Bulk N- t-butyl group results in:

3,5-Di-OH group result in:

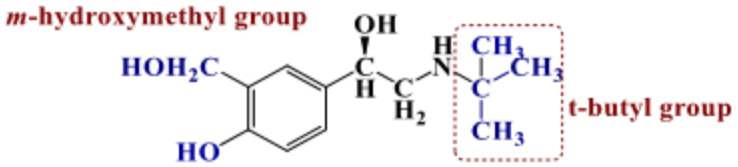
↑β2 activity and virtually no α activity

relax the bronchial musculature in patients with asthma but do less direct cardiac stimulation than do the non selective β agonist

not metabolized by COMT and MAO

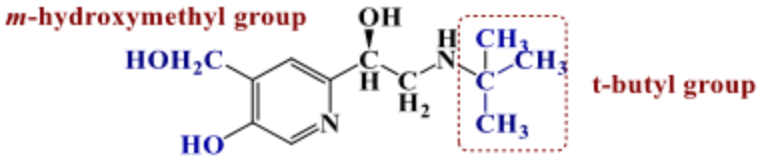
orally active and longer DOA

-3Albuterol, pirbuterol, and salmetrol.



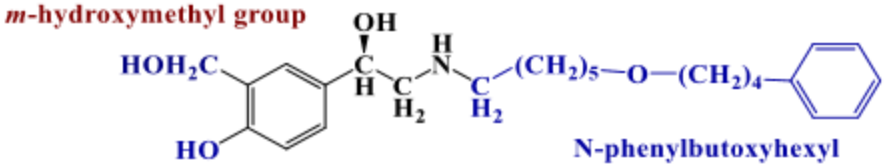
Albuterol

β2 selectivity results from:
replacement of the meta-OH group of
the aromatic ring with a hydroxymethyl moiety
not metabolized by COMT and MAO,
sulfate conjugation
orally active, longer DOA than ISO



PirbuterolN

β2 selectivity results from:
replacement of the meta-OH group of
the aromatic ring with a hydroxymethyl moiety
not metabolized by COMT and MAO,
sulfate conjugation
orally active, longer DOA than ISO

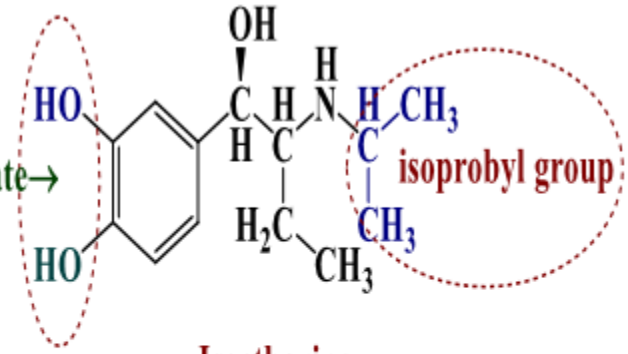


Salmeterol

β2 selectivity results from:
replacement of the meta-OH group of
the aromatic ring with a hydroxymethyl moiety
and N-phenylbutoxyhexyl
higly lipophilic (log p=3.88) due to N-phenylbutoxyhexyl
not metabolized by COMT and MAO,
sulfate conjugation
orally active, longer DOA than ISO, Albuterol and pirbuterol

-2Isoetharine

3,4-Di-OH group result in:
sensitive to air and light→
metabolized by COMT, sulfate→
shorer DOA similar to ISO

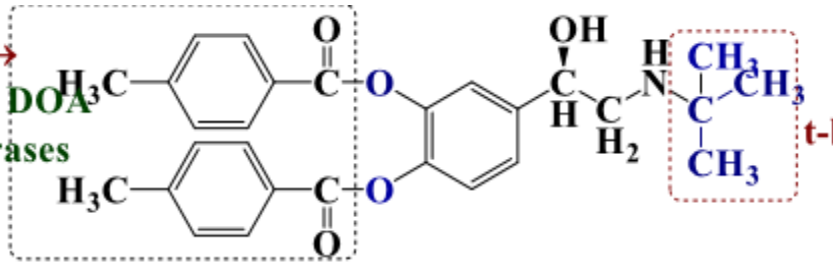


↑β2 selective((α-ethyl group and N-isopropyl group)
β2-activity < ISO
resistance to MAO

Isoetharine
(α-ethyl ISO)
used only by inhalation

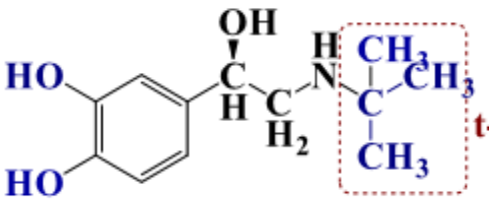
5- Bitolterol

Bulk di ester group and bulk N- t-butyl gruop→
not metabolized by COMT and MAO→ longer DOA
due to bulk di ester group→ hydrolyze by esterases
slowly in the lung
Longer DOA than colterol



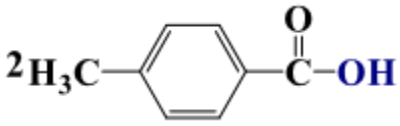
Bitolterol (prodrug of colterol)
β2-selective(N-t-butyl)
inhalation administration in asthma

Esterase in the lung
and other tissue



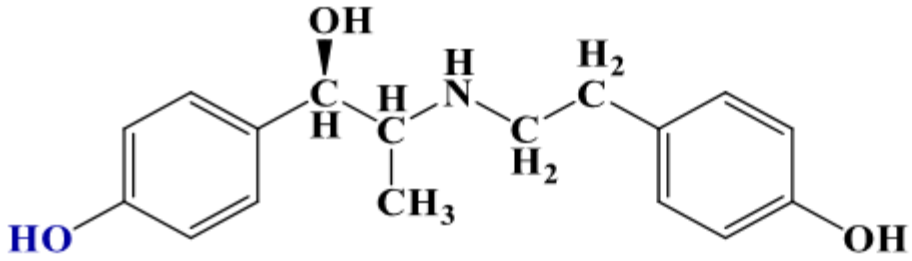
colterol

+



p-toluic acid

7-Ritodrine



Ritodrine

β2-selective(N-ethylphenol)

IV infusion

uterine relaxant(stop premature labor→it may given orally

β3-Adrenergic Receptor Agonists

The β_3-receptor has been shown to mediate various pharmacological effects such as-:

- **Lipolysis.**
- **Thermogenesis.**
- **relaxation of the urinary bladder.**

Activation of the β_3-receptor is thought to be a possible approach for the treatment of obesity.

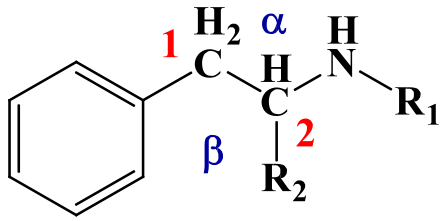
Indirect-Acting Sympathomimetics

Indirect-acting sympathomimetics

↓ **act by**

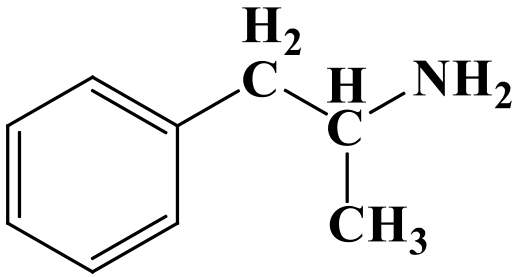
- **releasing endogenous NE**
- **displace NE from its storage granules by entering the nerve ending by way of the active-uptake process**

SAR (β-phenyl ethyl amine)



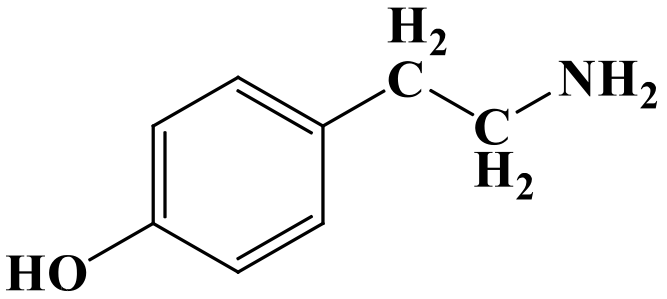
Example

Amphetamine and *p*-tyramine are often cited as prototypical indirect-acting sympathomimetics.



Amphetamine

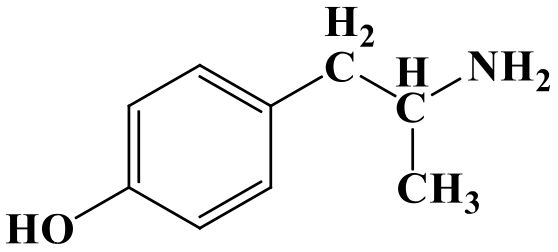
LogP =2.81(centrally effect)



***p*-tyramine**

Peripherally indirect acting sympathomimetic agents

1-Hydroxyamphetamine (Paredrine)



Hydroxyamphetamine

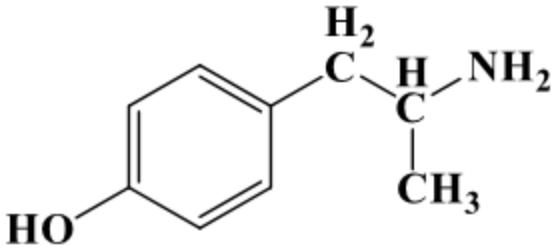
differs from amphetamine in the presence of p-OH group
it has little or no CNS-stimulating action than amphetamine

Uses-:

1- It is used to dilate the pupil for diagnostic eye examinations and for surgical procedures on the eye.

2- It is sometimes used with cholinergic blocking drugs like atropine to produce a mydriatic effect, which is more pronounced than that produced by either drug alone.

1- Propylhexedrine (Benzedrex)



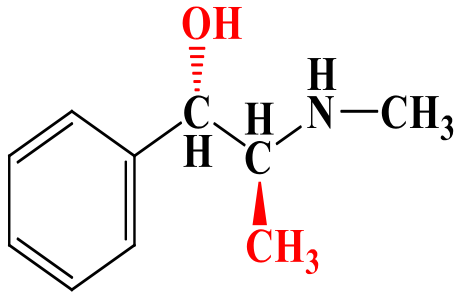
Propylhexedrine

analog of amphetamine in which the aromatic ring has been replaced with a cyclohexane ring.

This drug produces vasoconstriction and a nasal decongestant effect.

but it has only about one half the pressor effect of amphetamine and produces fewer effects on the CNS

2 -L-(+)-Pseudoephedrine. (Sudafed, Afrinol, Drixoral)



L-(+)-Pseudoephedrinethe

(1S,2S) diastereoisomer of ephedrine.

mostly indirect mechanism

virtually no direct activity

(wrong stereochemistry of the carbon atom possessing theβ-OH group)

(log P = 1.05, pKa = 9.38) it cross the BBB but it fewer CNS effects than does ephedrin

found in many OTC nasal decongestant and cold medications

should not be used in combination with MAO inhibitors

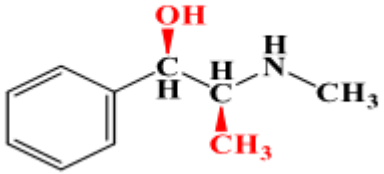
Sympathomimetics with a Mixed Mechanism of Action

Those phenylethylamines considered to have a mixed mechanism of action usually have no hydroxyls on the aromatic ring but do have a β-hydroxyl group.

1- D-(-)-Ephedrine

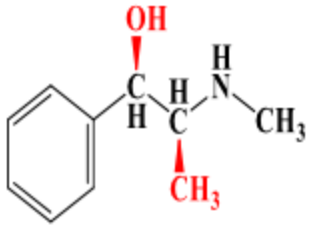
NO 3,4-Di-OH group result in:
non sensitive to air and light→
not metabolized by COMT
excreted unchanged, p- hydroxylation, and N-demethylated
more orall effectiveness longer DOA
Because it is a weak base, its excretion can be accelerated by acidification of the urine

not metabolized by MAO

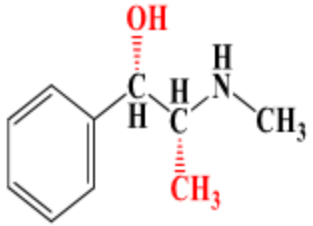


D-(-)-ephedrinethe
(1R,2S) correct configuration
Direct activity on α and β
Some indirect activity
(log P = 1.05, pKa = 9.6) it cross the BBB better than do other CAs
used as CNS stimulant(cause more stimulation of the CNS than E)

Ephedrine= erythro racemate *cis*
Mixed mechanism of action



(1R,2S)-D-(-)-Ephedrine
direct activity on α and β
some indirect activity
the most active of the four
isomers as a pressor amine
has correct (1R,2S) configuration
for optimal direct action on adrenergic
rec.

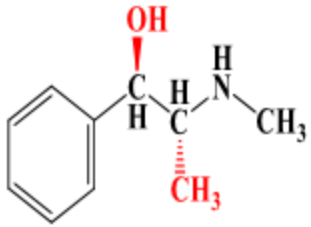


(1S,2R)-L-(+)-Ephedrine
Mixed mechanism of action
but primarily indirect activity

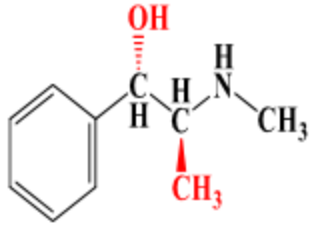
Diastereomers

Diastereomers

PseudoEphedrine(ψ-ephedrine)= threo racemate *trans*
principally, indirect acting

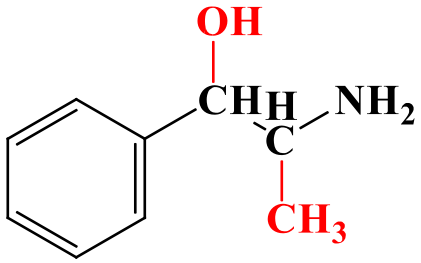


(1R,2R)-D-(-)-PseudoEphedrine=
threo racemate *trans*
principally, indirect acting



(1S,2S)-L-(+)-PseudoEphedrine
virtually no direct activity
Most indirect activity

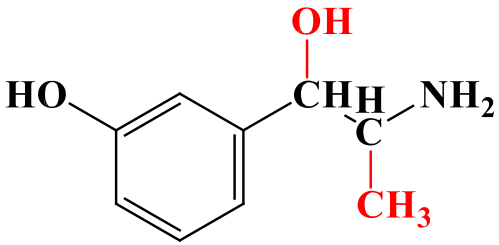
2-Phenylpropanolamine (Propadrine)



Phenylpropanolamine
N-desmethyl analog of ephedrine
Lacking the N-methyl group, phenylpropanolamine is slightly more polar, and therefore does not enter the CNS as well as ephedrine

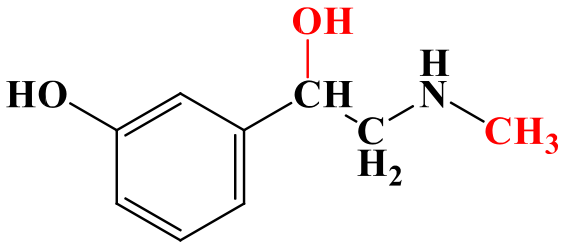
This modification gives an agent that has slightly higher vasopressive action and lower central stimulatory action than ephedrine. Its action as a nasal decongestant is more prolonged than that of ephedrine. It is orally active.

3-Metaraminol (Aramine)



Metaraminol

N-desmethyl-α-methyl analog of phenylephrine
possesses a mixed mechanism of action
with its direct-acting effects mainly on α1-receptors



Phenylephrine

It is used parenterally as a vasopressor in the treatment and prevention of the acute hypotensive state occurring with spinal anesthesia. It also has been used to treat severe hypotension brought on by other traumas that induce shock.

ADRENERGIC RECEPTOR ANTAGONISTS (BLOCKERS)

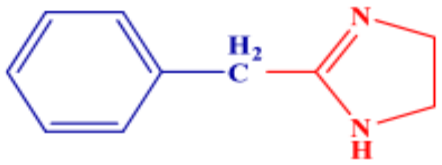
α-Blockers

1- **Reversible α-blockers (nonselective α-blockers).**

2- **Irreversible α-blockers.**

3- **Selective α-blockers.**

1- Nonselective α-blockers

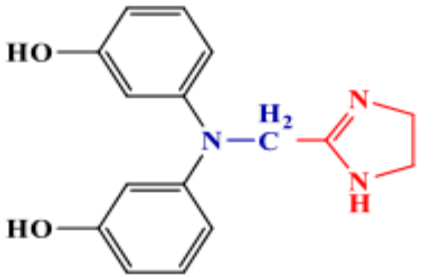


Tolazoline (priscoline)

imidazoline competitive α-blockers

have both α1- and α2-blocking activity and produce tachycardia

used to treat Raynaud syndrome and other conditions involving peripheral vasospasm (available in an injectable form)



phentolamine (Regitine)

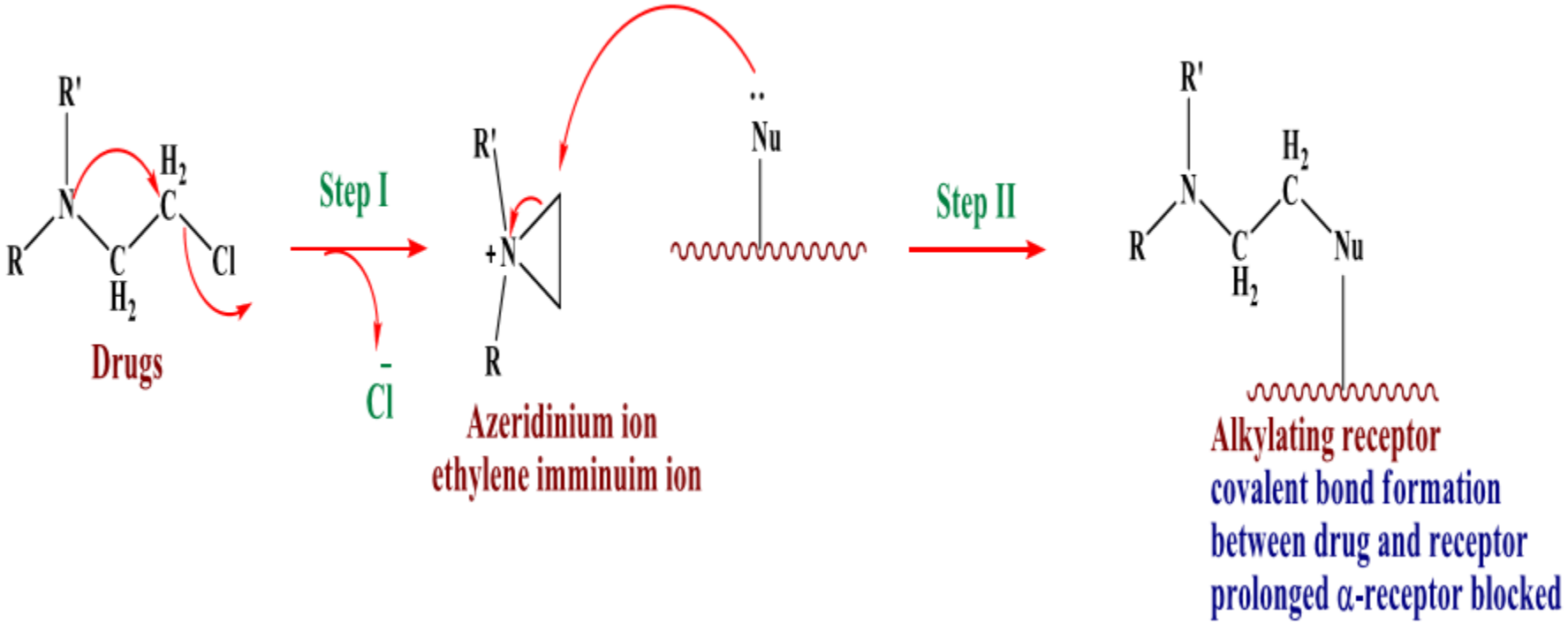
imidazoline competitive α-blockers

have both α1- andα2-blocking activity and produce tachycardia

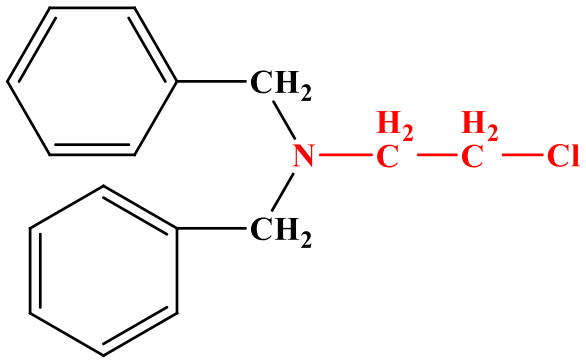
used to prevent or control hypertensive episodes that occur in patients with pheochromocytoma

used in combination with papaverine to treat impotence

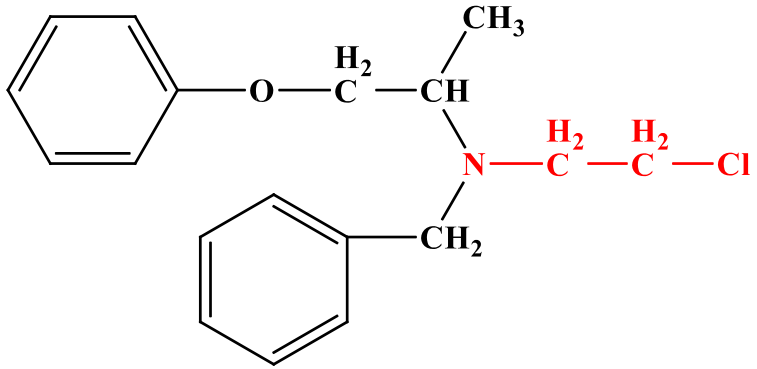
2-Irreversible α-blockers (β-haloalkylamines derivatives)



Examples



Dibenamine
N,N-dibenzyl-β-chloroethylamine
blocks α1- and α2-receptors irreversibly



Phenoxybenzamine (Dibenzyline)
blocks α1- and α2-receptors irreversibly, produce tachycardia
block ACh, histamine and serotonin.
produce vasodilation due to block α1 rec.
lockade of presynaptic rec. contribute to the increase heart rate