الأدوية الأدرينية

Adrenergic Agents

By Pr.Dr. M.A. Al–Khayat

Adrenergic agents

Sympathomimetic and Sympatholytic agents

-Adrenergic drugs are divided into:

• **Sympathomimetics** or **adrenergic stimulants** **المنبهات الأدرينية** **which** enhance the activity of the various components of the sympathetic division of the autonomic nervous system.

• **Sympatholytics** or **antiadrenergics**, or **adrenergic blocking agents** **الحاصرات الأدرينية** which reduce the activity of the sympathetic system

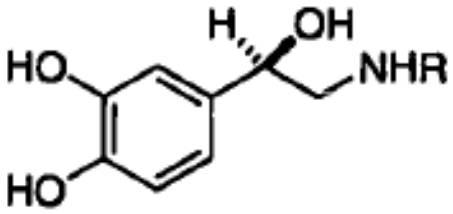
Adrenergic agents:

Adrenergic neurotransmitters: النواقل العصبية الأدرينية

-The adrenergic neurotransmitters comprise **norepipephrine (NE) and epinephrine**

• In the peripheral sympathetic neurons الأعصاب الودية المحيطية , norepinephrine is synthesized and serves as a neurotransmitter.
• In the CNS الجملة العصبية المركزية , both Norepinephrine and Epinephrine (in certain neurons) serve as neurotransmitters.
• Epinephrine is also synthesized and stored in the adrenal medulla , then released into circulation.

Adrenergic agents:
Adrenergic neurotransmitters



Norepinephrine: R = H

Epinephrine: R = CH_3

NE and epinephrine

-They belong to chemical class of catecholamines.

-They are biosynthesized from **tyrosine تيروزين** (figure below)

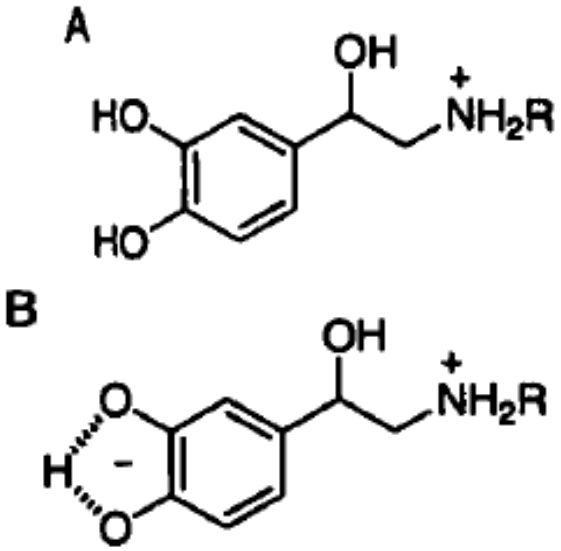
-Both possess a chirality center: C atom,

-R enantiomer المصاوغ المرآتيof each is biosynthesized by the body and is biologically active.

-They have **acidic phenolic** groups **and basic amino** group.

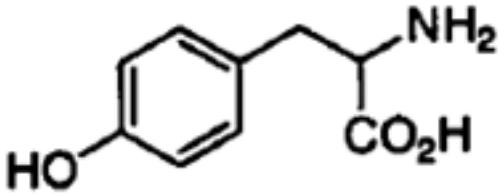
For example, the pKa values the epinephrine cation are 8.7 and 9.9 and are attributed to the phenolic group and the protonated amino group, respectively.

-At physiological pH 7.4, for either epinephrin or NE, there are more than 95% as cation form, about 3% zwitterionic كهرل مذبذب form, and less than 2% of nonionized form.



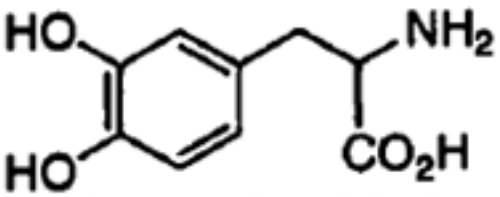
Adrenergic agents:
Adrenergic neurotransmitters

Biosynthesis of the catecholamines



Tyrosine

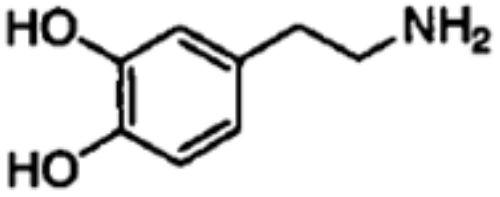
Tyrosine Hydroxylase



L-Dihydroxyphenylalanine

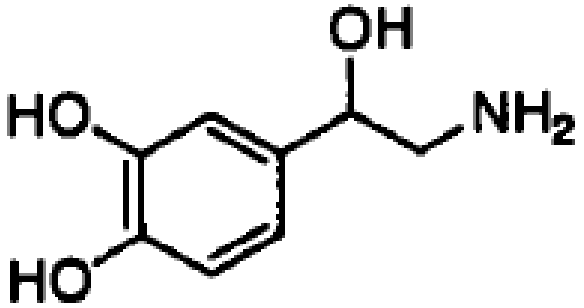
L-Dopa, S-(-)-Dopa

L-Aromatic Amino Acid Decarboxylase



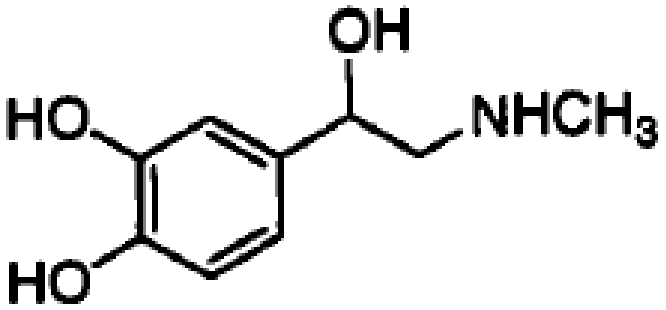
Dopamine

Dopamine β-Hydroxylase



Norepinephrine

Phenylethanolamine-*N*-methyltransferase

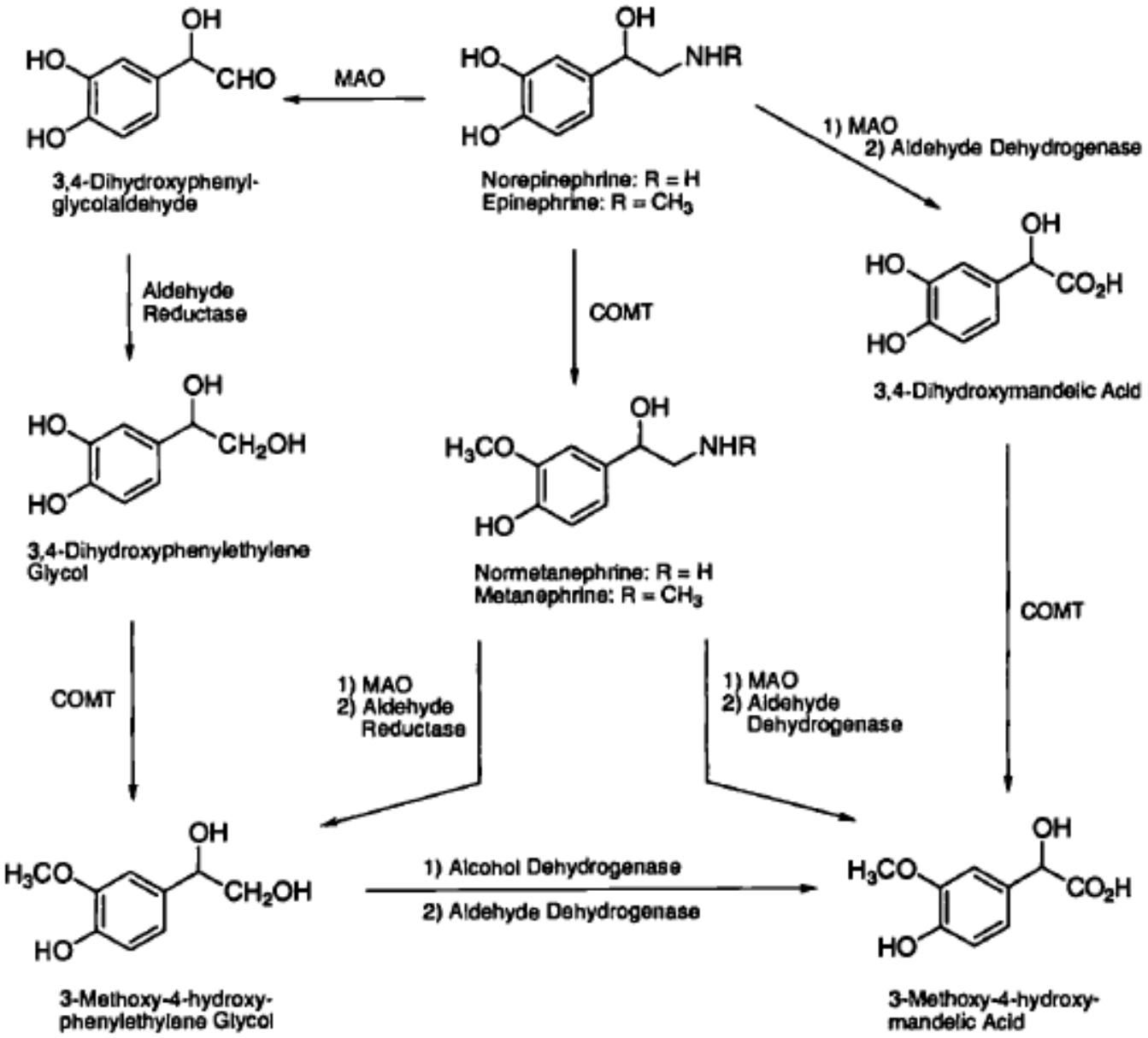


Epinephrine

Adrenergic agents:
Adrenergic neurotransmitters

Metabolism of Norepinephrine and Epinephrine

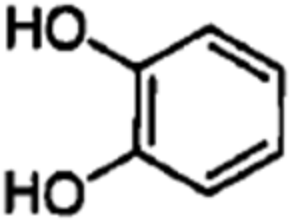
(COMT):
Catechol-*O*-methyltransferase



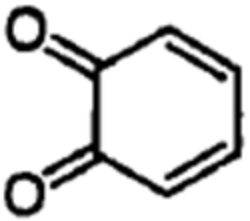
Adrenergic agents:
Adrenergic neurotransmitters

- Catechols are highly susceptible to oxidation (air or other oxidizing agents) : they give first orthobenzoquinone derivative then colored products.

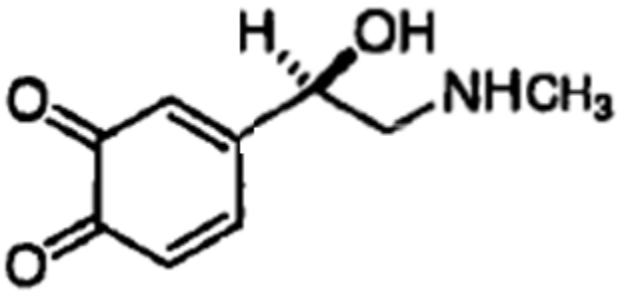
Catechols solutions are often stabilized by antioxidant مضاد أكسدة like ascorbic acid or sodium bisulfite $NaHSO_3$ صوديوم بيسلفيت



Catechol



ortho-Quinone



Adrenergic agents:
Adrenergic neurotransmitters

α- Adrenergic receptors

-α- adrenergic receptors of the CNS and peripheral tissues are involved in control of the cardiovascular system.

-In the heart

• Activation of α_1 receptors results in a selective inotropic مؤثر في التقلص العضليresponse .

• Activation of β_1-receptor results in both inotropic and chronotropic مؤثر على الميقاتية effects.

- **In the blood vessels**: activation of α_1 receptors results in vasoconstriction تقبض الأوعية .

- **In brain:** activation of α_2 receptors reduces sympathetic outflow تدفق from CNS which in turn causes a lowering of blood pressure.

- Both α_1 and α_2 play an important role in the regulation of number of **metabolic processes** such as insulin secretion and glycogenolysis تحلل الغليكوجين.

Adrenergic agents:
Adrenergic neurotransmitters

β- Adrenergic receptors

They are divided into β_1, β_2 and β_3

- **β_1 receptors** activation

- Activation in **heart** results in inotropic and chronotropic effects.
- Activation in **kidney** results in renin secretion increase
- Activation in **liver** results in glycogenolysis.

- **β_2 receptors** activation in **smooth muscles of bronchi** results in bronchodilation.

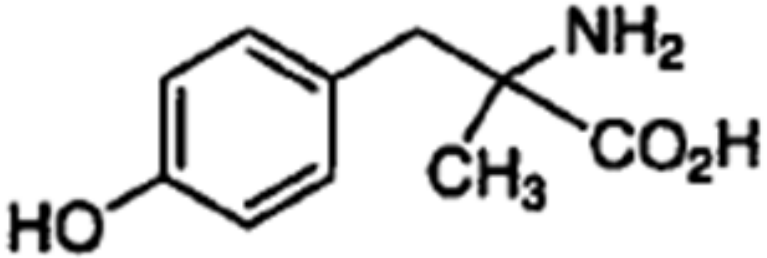
- **β_3 receptors in adipose tissue** is involved in the stimulation of lipolysis تحلل الشحم

Adrenergic Agents

Drug affecting adrenergic neurotransmission

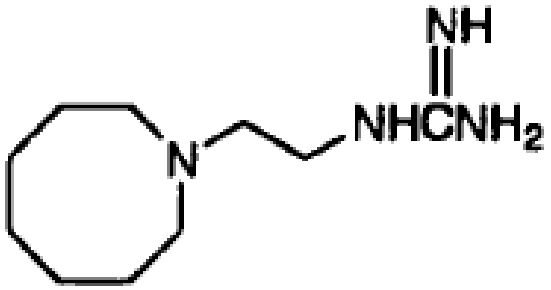
الأدوية المؤثرة على النقل العصبي الأدريني

-Drugs affecting catecholamine biosynthesis: **metyrosine**

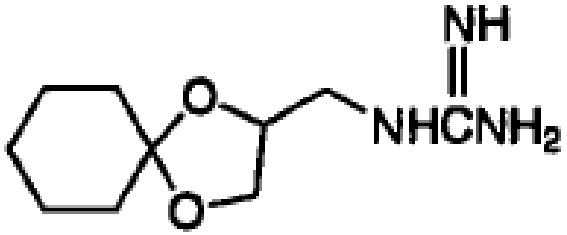


Metyrosine

-Drugs affecting catcholamine storage and release: **Reserpine**, **Guanethidine and Guanadrel**



Guanethidine

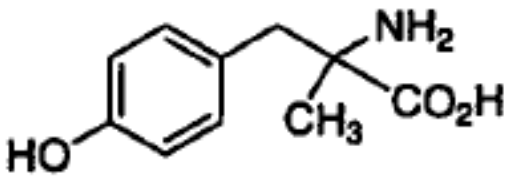


Guanadrel

Adrenergic receptors

Drug affecting adrenergic neurotransmission

Drugs affecting catecholamine biosynthesis:



Metyrosine

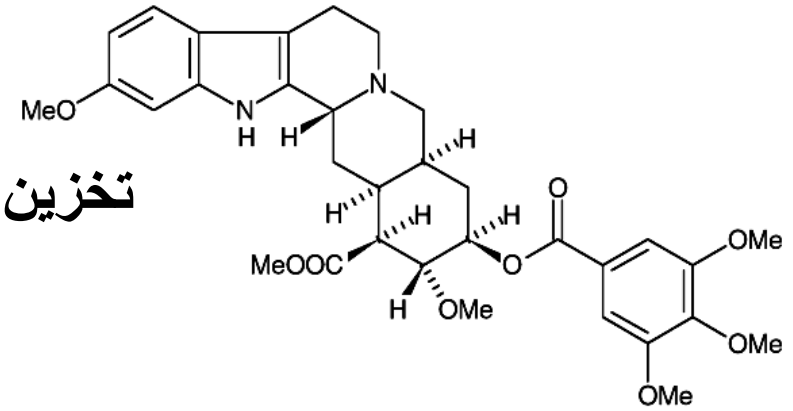
الأدوية المؤثرة على الاصطناع الحيوي للكاتيكول أمين

Metyrosine, (2*S*)-2-amino- 3-(4-hydroxyphenyl)- 2-methylpropanoic acid, α-methyltyrosine

-It is a competitive inhibitor of tyrosine hydroxylase**)** : NE and Epinephrine biosynthesis inhibitor

- The (-) isomer is the active isomer; however it is used as racemic mixture.
- It is used principally for the preoperative management of pheochromocytoma وَرَمُ القَواتِم , benign cell tumer , which produces high amounts of NE and Epinephrine causing hypertension.

- It is given orally in dosage form ranging from 1-4 g/ day



Drugs affecting catcholamine storage تخزين and release إطلاق

Reserpine

-It is an indol alkaloid obtained from the root of a Rauwolfia serpentina (Indian snakeroot) plant.

-This drug blocks the transporter of NE, serotonin and dopamine from cytoplasm of the presynaptic nerve العصب سابق مشبك terminal into storage vesicles تخزين حويصلات for subsequent release into the synaptic cleft فلح مشبكي

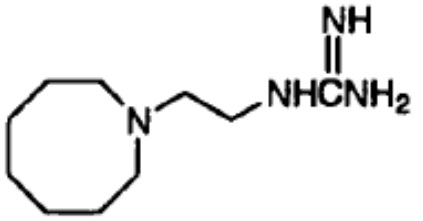
Thus unprotected neurotransmitters are metabolized by MAO and COMT) in the cytoplasm and consequently never reach the synapse **(** depletion نفاد).

-It is administered orally for the treatment of hypertension

-The maximum effect is seen after few weeks.

-The antihypertensive daily dose is as low as 0.1 to 0.25 mg

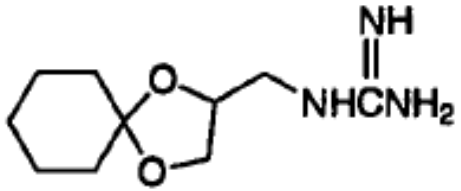
Drugs affecting catcholamine storage and release



Guanethidine

Guanethidine monosulfate: 2-[2-(azocan-1-yl) ethyl]guanidine sulfate.

- It is a white to off-white crystalline powder, very soluble in water, sparingly soluble in alcohol.



Guanadrel

Guanadrel sulfate: 2-(1,4-Dioxaspiro[4.5] decan-2-ylmethyl)guanidine

-Both Guanethidine and guanadrel prevent the release of NE from storage vesicles into the synaptic cleft by stabilization the neuronal storage vesicle membrane.

-The presence of the **very basic guanidino group (pKa> 12)** in these drugs means that at physiological pH they are essentially completely protonated. Thus, these agents **do not get into the CNS**.

-Guanethidine and Guanadrel differ in their pharmacokinetic properties

Adrenergic receptors
Drug affecting adrenergic neurotransmission

Drugs affecting catcholamine storage and release:

Guanethidine is absorbed incompletely after oral administration (3 to 50%), with half life about 5 days.

Guanadrel is well absorbed, with a bioavailability of 85% and a half-life of 12 hours.

-Both are used as antihypertensive agents.

-Dosage forms:

Guanethidine monosulfate: 10, 25mg/tablet .

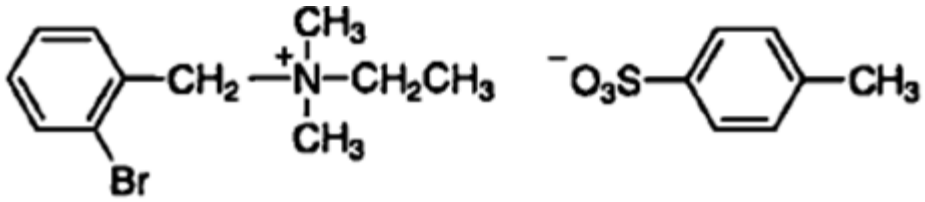
Guanadrel sulfate: 5,10mg/tablet.

Adrenergic receptors

Drug affecting adrenergic neurotransmission

Drugs affecting catcholamine storage and release:

Bretylium Tosylate,



N-(2-bromobenzyl)-*N,N*-dimethylethanaminium tosylate.

-It is an aromatic quaternary ammonium compound.

-It is accumulates selectively in the neurons and block the release of NE.

- It was used initially as antihypertensive agent, but this use is discontinued because of rapid development of tolerance تحمل, erratic oral absorption and other side effects.

-It is used as antiarrhythmic (ventricular arrhythmias)

Sympathomimetic agents

محاكيات الودي

-Sympathomimetic agents produce effects resembling those produced by stimulation of the sympathetic nervous system.

- Classified as agents that produce effect by a direct, indirect and mixed mechanism of action.

-The **direct** action: interacting directly with adrenergic receptors.

-Indirect action: produces effects by releasing the NE from adrenergic nerve terminals and this NE activates the receptors.

-Compounds with **mixed** mechanism interact directly with adrenergic receptors and cause the release of NE.

Direct -Acting Sympathomimetics

ذات الفعل المباشر

The study includes:

-The structure activity relationship studies (SAR)

- Endogenous catecholamines: dopamine, norepinephrine, dipivefrine (prodrug).

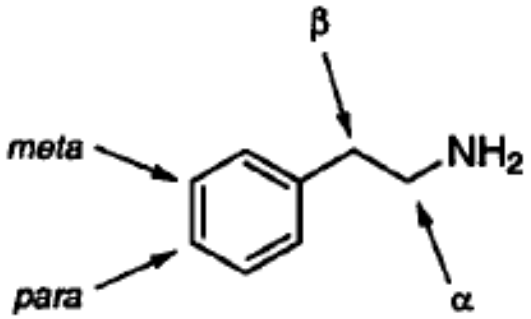
-α-adrenergic receptor agonists. ناهض

-Dual α-and β-adrenergic receptor agonists

- β-adrenergic receptor agonist

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Structure Activity Relationship: SAR)



β-Phenylethylamine

-The structural features needed for the optimal activity الفعالية المثلى of the **direct-acting agents are** :

- The presence of two phenolic catechol groups m and p positions
- The presence of β -hydroxyl group on the ethylamine portion.
- R (-) enantiomer is the more potent, R (-) epinephrine is typically several 10 times more potent than S (+) configuration.
- Two carbon between amino group and aromatic ring

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Structure Activity Relationship SAR)

-Primary and secondary amines are potent direct agonists, but tertiary and quaternary amines are poor direct agonists.

- α-Methyl or ethyl substitution:

• **This <u>reduces</u> direct** receptor agonist activity at both α and β receptors, but this <u>increases duration of action</u> (MAO metabolic resistance), <u>enhances oral effectiveness الفعالية</u> and greater CNS activity.

• **This significantly affects receptor selectivity**.

For example, in the case of β- receptors, this substitution results in compounds with selectivity انتقائية toward the β_2-receptors,while in the case of α-receptors, this substitution gives compounds with selectivity toward the α_2-receptors.

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Structure Activity Relationship: SAR)

-The nature of the amino substituent dramatically affects the **receptor selectivity** of the compound.

As the bulk of the nitrogen substituent increases, α-receptor agonist activity decreases and β-receptor activity increases.

•Thus **NE** is a potent α- agonist, and an effective β_1-receptor agonist, while **epinephrine** is a potent α, β_1,β_2 receptors.

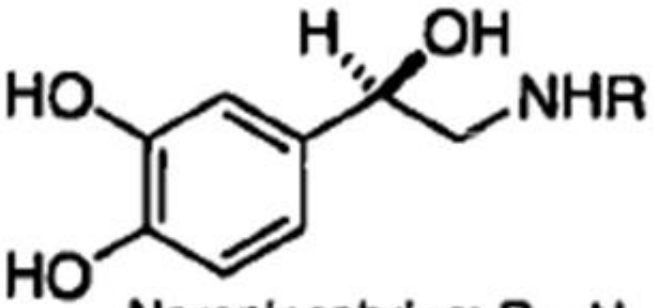
• **Isoproterenol**, is a potent $\beta_1$and β_2 receptors agonist but has little affinity for α receptors.

• N-tert-butyl norepinephrine **(Colterol)** is 9 to 10 times as potent an agonist at tracheal رغامی β_2 receptors than at cardiac β_1 receptors.

- Large substituents on the amino group also protect the amino group from undergoing oxidative deamination by MAO.

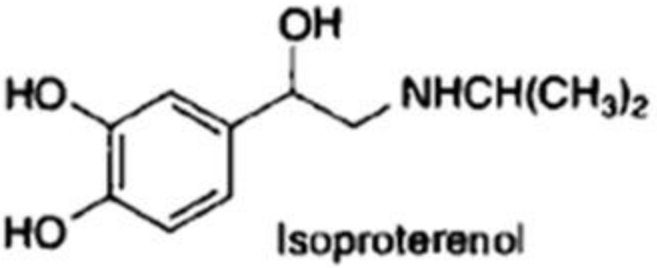
Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Structure Activity Relationship: SAR)

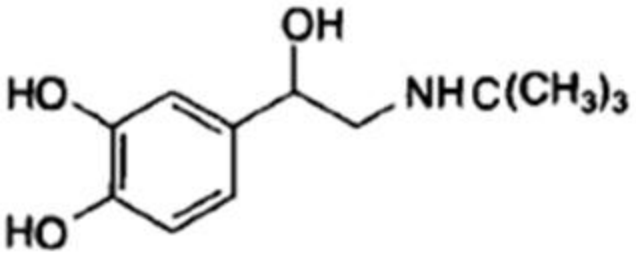


Norepinephrine: R = H

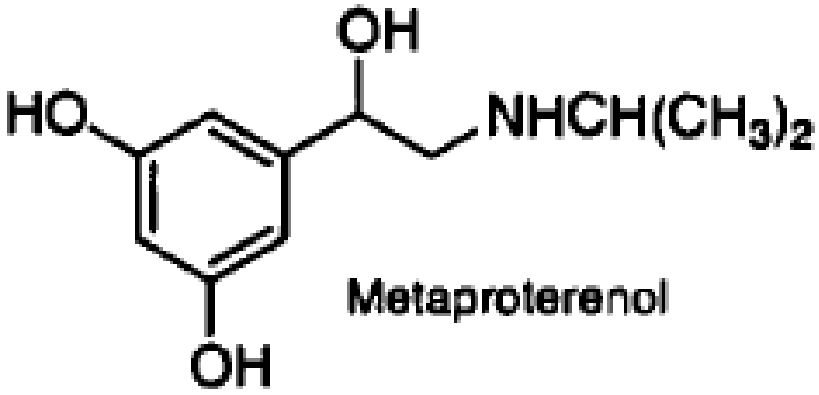
Epinephrine: R = CH_3



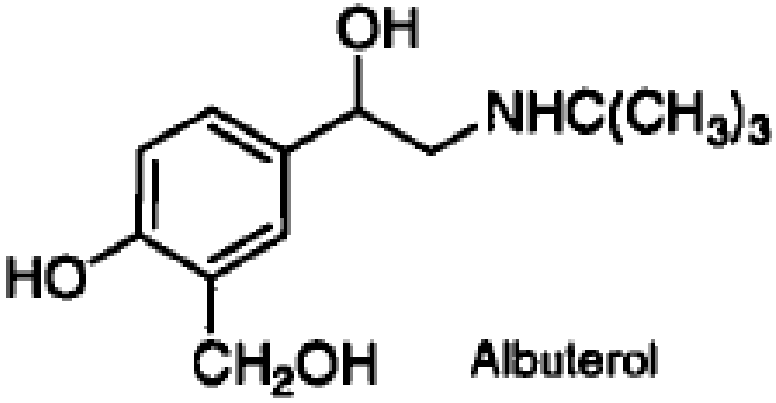
Isoproterenol



N-tert-Butylnorepinephrine (Colterol)



Metaproterenol



Albuterol

Adrenergic receptors

Sympathomimetic agents

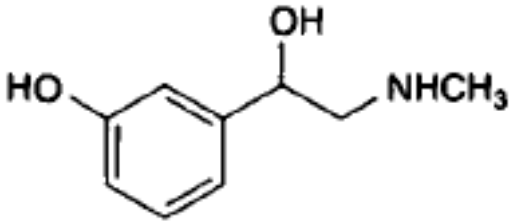
Direct -Acting Sympathomimetics

Structure Activity Relationship: SAR)

-Replacement of the catechol function of isoproterenol with **resorcinol structure** gives the drug metaproterenol, which is a selective β_2- receptor agonist (resorcinol structure is not a substrate for COMT, better absorption and longer duration of action).

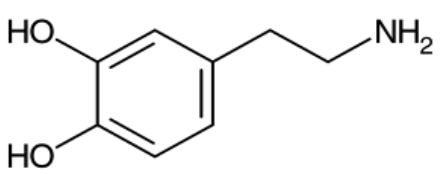
-Replacement of the meta-hydroxyl of the catechol structure with a **hydroxymethyl group** gives agents (such albuterol),that have selectivity to the β_2 receptor, and also are not metabolized by COMT, have better absorption and longer duration of action).

-Removal of the p-hydroxyl group from epinephrine gives phenylephrine, which is selective for the α_1-adrenergic receptor.



Phenylephrine

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics



,HCl

Endogenous Catecholamines كاتيكول أمينات داخلية المنشأ

Dopamine HCl, 4-(2-Aminoethyl)benzene-1,2-diol hydrochloride

- It is a fine colorless powder, highly water-soluble
- It undergoes oxidation when exposed to oxygen or other oxidants.
- It is ineffective orally (metabolized by MAO and COMT).
- It is used in the treatment of shock.
- It is used intravenously.

• **Low doses** of dopamine increases blood flow to the **kidney** (not affect blood pressure): the dilation of renal blood vessels is due to of its agonist action on D_1-dopamine receptor.

- **Slightly higher doses** stimulates the β_1 receptors of **the heart**: increases cardiac output نتاج القلب .

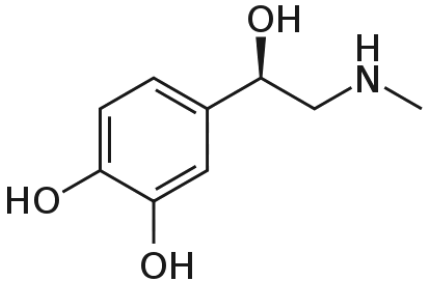
-**Infusion in much higher doses** (greater than 10 microgram/Kg/ minute stimulates $\boldsymbol{\alpha_1}$ receptors: **vasoconstriction** increase blood pressure (treatment of shock).

Adrenergic receptors

Sympathomimetic agents

Direct -Acting Sympathomimetics

Endogenous Catecholamines



Epinephrine HCl, (*R*)-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol,.

- It occurs as nearly white crystalline powder, insoluble in water .
- Like other catechols, it is light sensitive and easily oxidized on exposure to air (development of a pink to brown color).

Thus, solutions are stabilized by the addition of reducing agents such as sodium bisulfite.

-It is readily destroyed in alkaline solutions.

It is not effective orally (poor absorption and rapid metabolism by MAO and COMT).

- It forms salts with acids, it is used as hydrochloride and the bitartrate for injection.

Sympathomimetic agents

Direct -Acting Sympathomimetics

Endogenous Catecholamines

Epinephrine HCl,

-It is primarily used:

As **constrictor (**potent α-receptors) in hemorrhage النزف or nasal congestion الاحتقان (nasal spray).

Emergency اسعاف medical treatment to treat life-threatening allergic reactions caused by insect bites or stings.

In asthma (by inhalation or injection) to relax bronchial smooth muscle (β_2 receptor stimulant),

In open angle glaucoma زرق مفتوح الزاوية : it apparently reduces intraocular pressure by increasing the rate of outflow of aqueous humor الخلط المائي from its anterior chamber of the eye.

To enhance the activity of local anesthetics

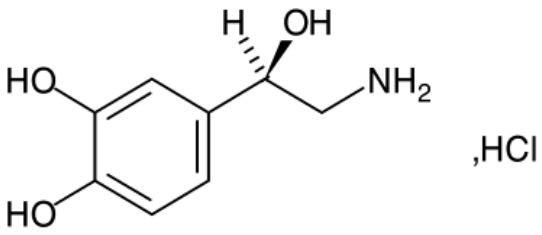
-Dosage forms: subcutaneous, IM, and IV, Inhalation aerosol ضبوب ….

Dosage (anaphylaxis تأق): subcutaneously, IM 0.3-0.5mg (0.3-0.5ml) repeated every 5-10 minutes as needed.

Sympathomimetic agents

Direct -Acting Sympathomimetics

Endogenous Catecholamines



Norepinephrine tartrate , 4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol

-NE is not effective orally.

-It is given by IV injection.

- It is used to maintain blood pressure in acute hypotensive states حالات انخفاض الضغط (surgical or nonsurgical trauma, hemorrhage…).

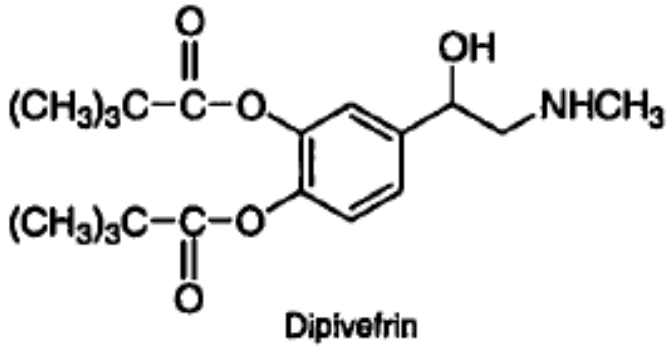
-Dosage forms: IV (as tartrate): 2mg/ml (equival. to 1mg norepinephrine base)

-Dosage: Initial dose: IV infusion تسريب وريدي 2 to 4 mcg/min

Sympathomimetic agents

Direct -Acting Sympathomimetics

Endogenous Catecholamines



Dipivefrin

Dipivefrine HCl is a catechol-pivalic acid ester of epinephrine **(prodrug)** - It is used for the treatment of open-angle glaucoma. .

-It is much more lipophilic than epinephrine, better eye penetration, less irritating, and can be used in lower concentration

- It is activated by eye esterase in cornea and anterior chamber.

Dosage form : as HCl salt 0.1% ophthalmic soution

Adrenergic receptors

Sympathomimetic agents

Direct -Acting Sympathomimetics

α_1-adrenergic receptor agonists

Phenylephrine

Midodrine: prodrug

Methoxamine

α_1,α_2-adrenergic receptor agonists

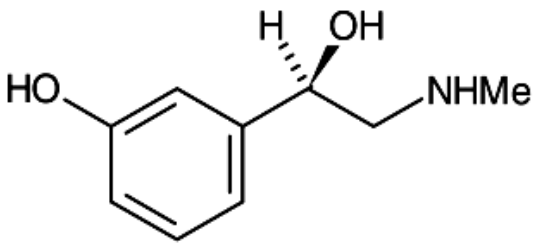
Naphazoline, Tetrahydrozoline,
Oxymetazoline and Xylometazoline

Adrenergic receptors

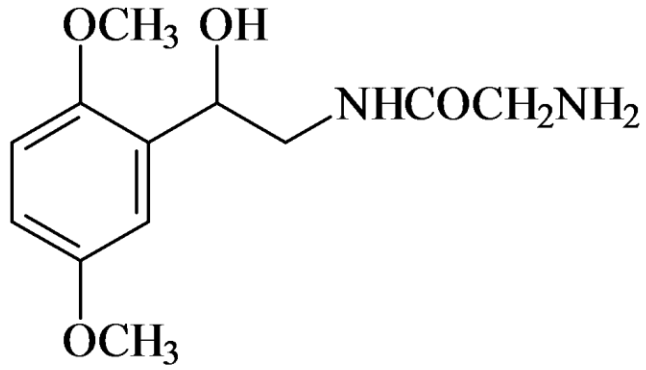
Sympathomimetic agents

Direct -Acting Sympathomimetics

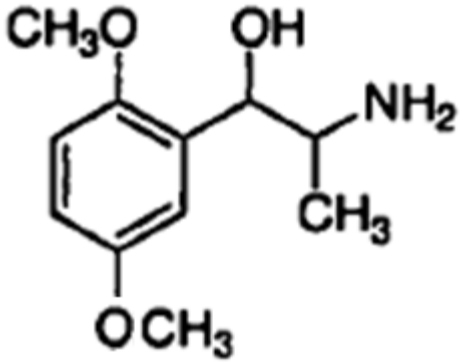
α_1-adrenergic receptor agonists



Phenylephrine



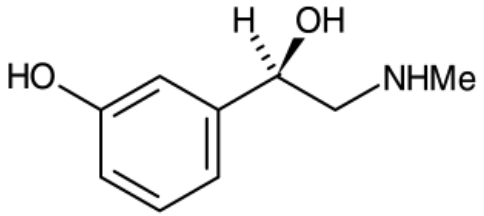
Midodrine: prodrug



Methoxamine

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

α_1-adrenergic receptor agonists



Phenylephrine HCl, (*R*)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol

- It is the prototypical أنموذجي selective direct-acting α_1 receptor agonist .
- It is a potent vasoconstructor but less potent than epinephrine.

-Orally active with more duration of action (about twice that of epinephrine) , little CNS stimulation**.**

-It is primarily used as:

Nasal decongestant : 0.5% . Spray (رذ) بخ or gel هلامة

Tablets (phenylephrine HCl 8mg+ chlorpheneramine maleate 4mg + paracetamol 650mg)

Mydriatic موسع للحدقة in open-angle glaucoma: 10% / eye drops (as HCl).

Hypertensive agent : 2-5mg subcutaneously , IM

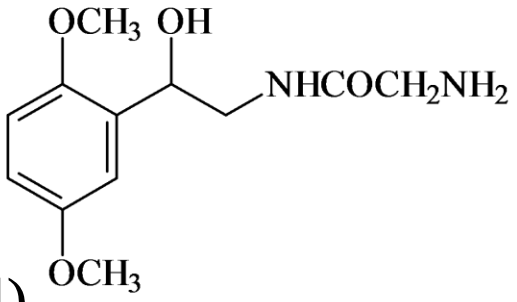
To prolong the spinal anesthesia تخدير activity**.**

Adverse reactions: headache, dizziness, nausea, respiratory difficulty

Adrenergic receptors
Sympathomimetic agents

Direct -Acting Sympathomimetics

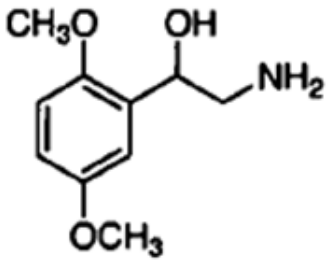
α_1-adrenergic receptor agonists



Midodrine HCl, (*RS*)- *N*-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]glycinamide .

-It is a prodrug.

-It is metabolized, primarily in liver by amidase to give **desglymidodrine,** the active drug that is a selective α_1 –receptor.



desglymidodrine

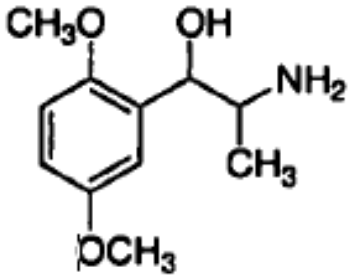
-It is **orally active**.

-It is used for the treatment of symptomatic **orthostatic hypotension** نَقْصُ ضَغْطِ الدَّمِ الاِنْتِصابِيّ

-Dosage forms: tablets 2.5, 5 ,10 mg

- Adverse reactions**:** Headache, Abdominal pain, urinary retention احتباس البول

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics
α_1-adrenergic receptor agonists



Methoxamine

Methoxamine HCl : 2-amino-1-(2,5-dimethoxyphenyl)propan-1-ol
- It is a selective direct-acting α_1-receptor agonist .
-This drug is a vasoconstrictor that has no stimulant effect on the heart.
- It is less vasoconstrictive than phenylephrine.
-It is used primarily during surgery to **maintain adequate arterial blood pressure** ضغط دم شرياني كافي, especially in conjunction with spinal anesthesia.
Dosage form:
20mg/ 1ml /injection (as HCl).

Adrenergic receptors
Sympathomimetic agents

Direct -Acting Sympathomimetics

α_1 and α_2 adrenergic receptors agonist.

Naphazoline, Tetrahydrozoline, Oxymetazoline and Xylometazoline

-Arylalkylimidazoline derivatives

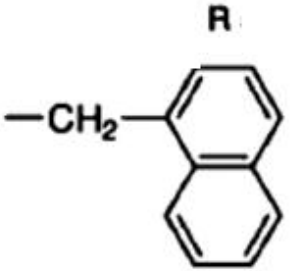
- Nasal and ophthalmic decongestants.

- They have limited access to CNS: This is due to the presence of basic imidazoline ring with Pka = 9-10. Thus they exist in ionized form at physiological pH

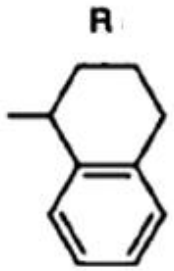
Dosage forms:

• Nasal drops of oxymetazoline HCl: 0.025% 0.05%

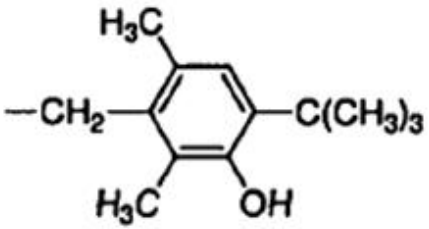
• Nasal drops of x ylometazoline HCl: 0.05%,, 0.1%



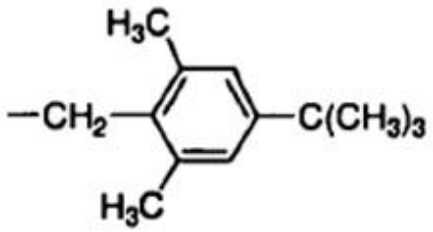
Naphazoline:



Tetrahydrozoline



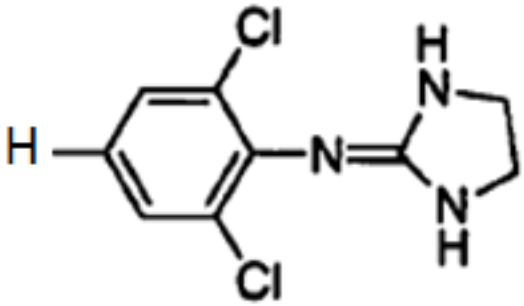
Oxymetazoline



Xylometazoline:

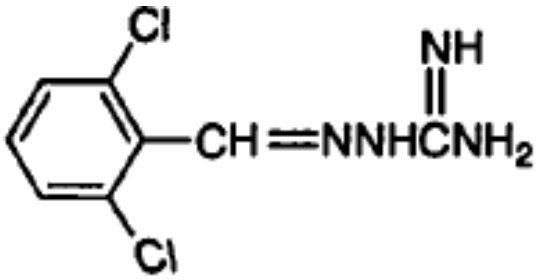
Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Central selective α_2-adrenergic receptor agonists



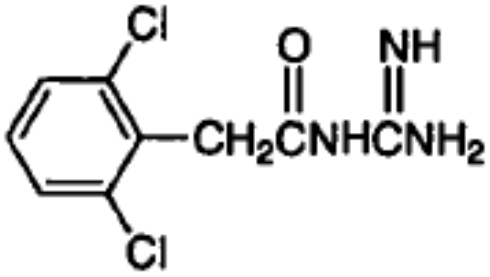
Clonidine

(Antihypertensive)



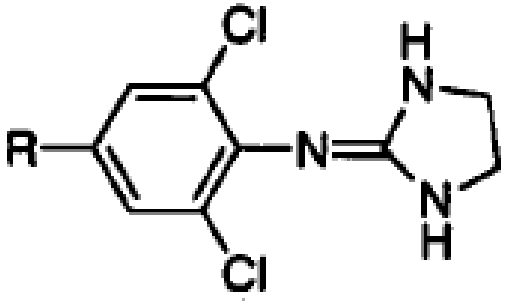
Guanabenz

(Antihypertensive)



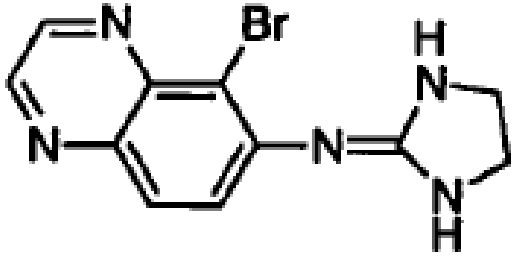
Guanfacine

(Antihypertensive)



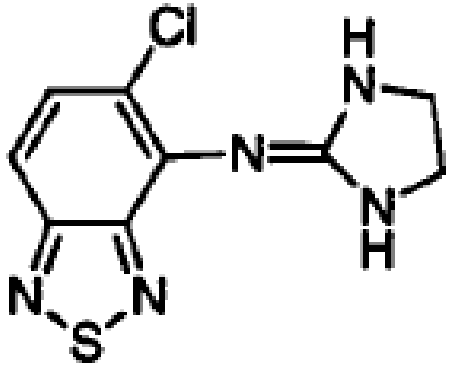
Apraclonidine: R = NH_2

(to control elevation of intraocular pressure during Lazer surgery)



Brimonidine

(glaucoma)



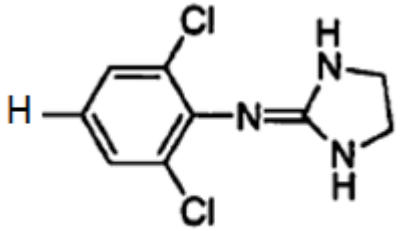
Tizanidine

(spasticity)

فرط توتر تشنجي (شناج)

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Central selective α_2-adrenergic receptor agonists



Clonidine

Clonidine

- It is an example of a (phenylimino) imidazolidine derivative that possesses selectivity for the α_2-adrenergic receptor : α_2 :α_1 ratio is 300: 1.

-Under certain conditions, such as intravenous infusion, clonidine can briefly exhibit vasoconstrictive activity as a result of stimulation of peripheral α-adrenergic receptors.

-However, this hypertensive effect, if it occurs, is followed by a much longer lasting hypotensive effect as a result of the ability of clonidine to enter into the CNS and stimulate α_2 receptors located in the brain.

-Stimulation of these α_2 receptors brings about a decrease in sympathetic outflow انخفاض التدفق الودي from the CNS, which in turn leads to decreases in peripheral vascular resistance and blood pressure.

Central selective α_2-adrenergic receptor agonists

Clonidine

-The ability of clonidine to exert an antihypertensive effect depends on its ability not only to interact with the α_2 receptor but also to gain entry into the CNS.

-Typically the pka of guanidine group is 13,6.

- In clonidine, the basicity is decreased, and its pka is 8.0. This is due to the direct attachment of guanidine group with **dichlorophenyl ring**. Thus, at physiological pH, clonidine will exist to a **significant extent in the nonionized** form required for passage into the CNS.

-Substitutions on the aromatic ring also affect the ability of clonidine to gain entry into the CNS to produce an antihypertensive effect. Halogen substituents at two ortho positions, such as chlorine provides the optimal characteristics in this regard.

Adrenergic receptors
Sympathomimetic agents
Direct -Acting Sympathomimetics

Central selective α_2-adrenergic receptor agonists

Clonidine

-Clonidine, as well as some other imidazolines, shows high affinity for the "imidazoline“ receptor which are also implicated in the antihypertensive effects of clonidine.

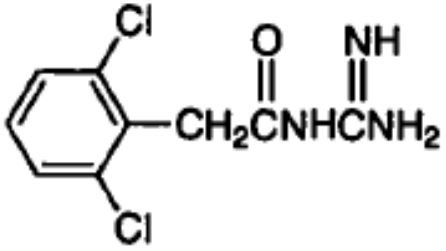
Dosage forms :

Oral tablets 0.1, 0.2, 0.3mg :

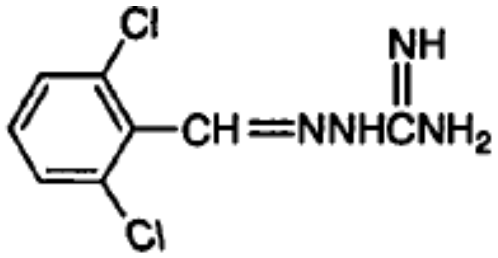
0.1mg/24H weekly patch رقعة

α_2–adrenergic receptor agonists

Guanabenz and Guanfacine



Guanfacine



Guanabenz

Guanfacine and Guanabenz are analogues of clonidine, and are also used as antihypertensive drugs. Their mechanism of action is the same as that of clonidine.

- Structurally, they are considered as open imidazolidine ring: dichlorophenyl group is attached to guanidino group by two atom bridge $-CH_2CO-$ in guanfacine and $-CH=N-$ in guanabenz.

-For both compounds, conjugation of the guanidino moiety with the bridging moiety helps to decrease the pKa of this normally very basic group so that at physiological pH a **significant portion of each drug exists in its nonionized form**.

Sympathomimetic agents, Direct acting agents, α–adrenergic receptor agonists:

α_2–adrenergic receptor agonists

Guanabenz and Guanfacine

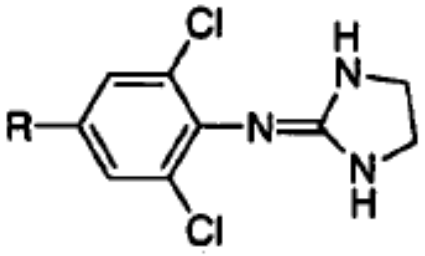
-Differences between clonidine and its two analogues are seen in their elimination half-life values and in their metabolism and urinary excretion patterns.

The elimination half-life of clonidine 20-25 h, guanfacine:17h guanabenz: 6 h.

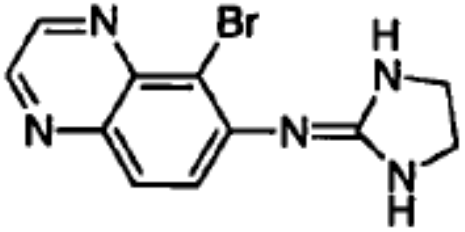
Sympathomimetic agents, Direct acting agents, α–adrenergic receptor agonists:

α_2–adrenergic receptor agonists

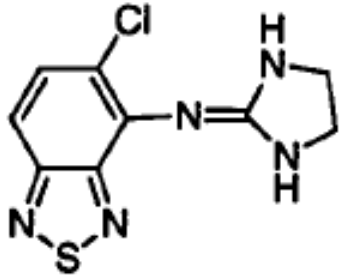
Apraclonidine Brimonidine, and Tizanidine



Apraclonidine: R = NH_2



Brimonidine



Tizanidine

Clonidine has been found to provide beneficial effects in a number of other situations (migraine prophylaxis اتقاء الشقيقة , glaucoma الزرق , opiate withdrawal syndrome متلازمة سحب الأفيون , and anesthesia.

- This has prompted the development of analogues of clonidine for specific use in some of the above areas.

-Two such examples are **apraclonidine** and **brimonidine**

Both are selective α_2 -receptor agonists .

They both lower intraocualr pressure by decreasing aqueous humor production and increasing aqueous humor outflow.

Sympathomimetic agents, Direct acting agents, α–adrenergic receptor agonists:

α_2–adrenergic receptor agonists

Apraclonidine Brimonidine, and Tizanidine

–**Apraclonidine** is specifically used during laser surgery on the eye.

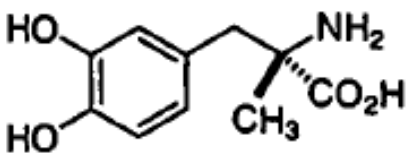
– **Brimonidine** also is used in such a manner: in addition, it is approved treating glaucoma.

Tizanidine finds use in treating spasticity associated with spinal cord injury أذية في الحبل الشوكي . Stimulating adrenergic receptors decrease the release of excitatory amino acid neurotransmitters from spinal cord interneurons.

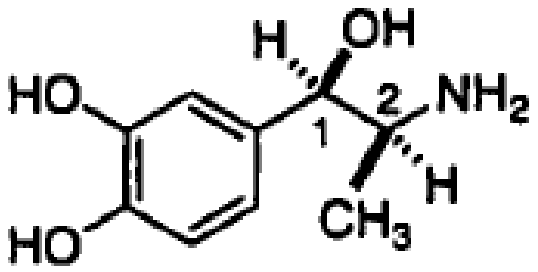
spasticity فرط توتر تشنجي (شناج)

Sympathomimetic agents, Direct acting agents, α–adrenergic receptor agonists:

α_2–adrenergic receptor agonists



Methyldopa



(1*R*,2*S*)-α-Methylnorepinephrine

Methyldopa is an α - methyl L–Dopa.

– It acts on α_2 receptors in the CNS as clonidine, but this action is through its metabolite (1R,2S)– α-methylnorepinephrine which shows selectivity toward the α_2 receptor.

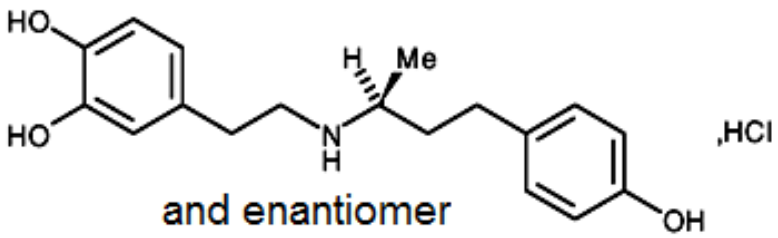
- The oral absorption of methyldopa involves amino acid transporter

–It is used orally 250 mg 2–3 times/ day.

Methyldopate : an ethyl ester HCl salt of methyldopa, which is used to make parenteral preparations.

Sympathomimetic agents, Direct acting agents

Dual α and β- Adrenergic receptor agonists



Dobutamine, (*RS*)-4-(2-{[4-(4-hydroxyphenyl)butan-2-yl]amino}ethyl)benzene-1,2-diol

- It is a synthetic direct–acting on both α– and β– adrenergic receptors. It can be viewed as **an analogue of dopamine**.

–Dobutamine exists as a **pair of enantiorners**:

The (+) enantiomer is a potent full agonist at both $\beta_1$and β_2 receptors.

In contrast, the (–) **enantiomer** is some 10 times less potent at $\beta_1$and β_2 receptors, but it is a **potent agonist at α_1 receptors**.

- In vivo, racemic dobutamine increases the **inotropic activity** of the heart to a **much greater** extent than it increases chronotropic activity (a result of combination of the inotropic effect of (+)-dobutamine on β_1 receptors and that of (–) dobutamine).

Sympathomimetic agents, Direct acting agents:

Dual α and β- Adrenergic receptor agonists

Dobutamine

- Racemic mixture is used in treating **congestive heart failure** فشل القلب الاحتقاني .
-Dobutamine is given by intravenous infusion
-It has a plasma **half–life of about 2 minutes**.
-It is metabolized by COMT and conjugation.
-It is not metabolized by MAO.
- It is not effective orally

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists

Isoproterenol

Isoetharine

Bitolterol, prodrug: colterol

Metaproterenol and **Terbutaline**

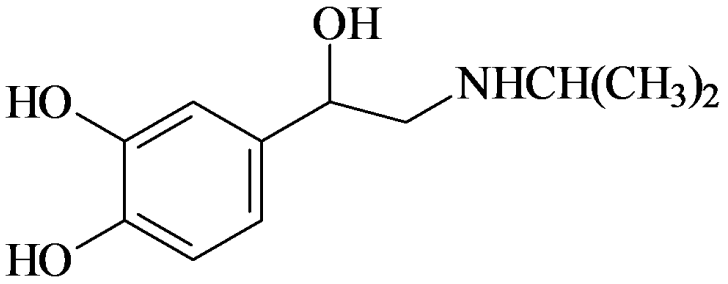
Albuterol, Levalbuterol , Pirbuterol

Salmeterol and Formoterol and

Ritordine

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists



Isoproterenol, *(RS)*-4-[1-hydroxy-2-(isopropylamino)ethyl]benzene-1,2-diol

-Isoproterenol HCl is white to off-white crystalline powder, soluble in water

-Isoproterenol acts on both β1 (increase of cardiac output) and β_2 (Bronchodilator) receptors.

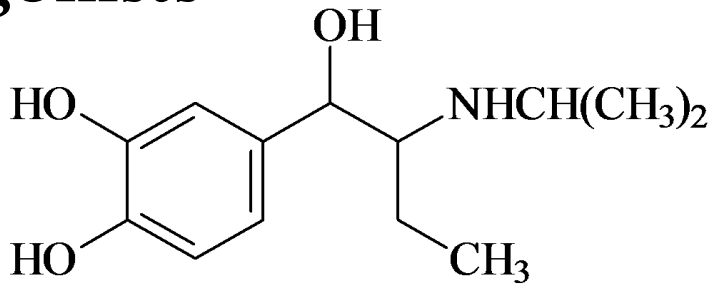
- **It is not used orally**, Its oral absorption is erratic and undependable, with short duration of action (due to COMT and conjugate metabolism). No MAO metabolism.

-It is used by **inhalation** as Bronchodilator in **asthma,** The duration of action after inhalation is 1-3 h.

and **by injection** in treatment of **heart shock** to produce a cardiac stimulation.

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists



Isoetharine

-It is an **α–ethyl–isoproterenol** .

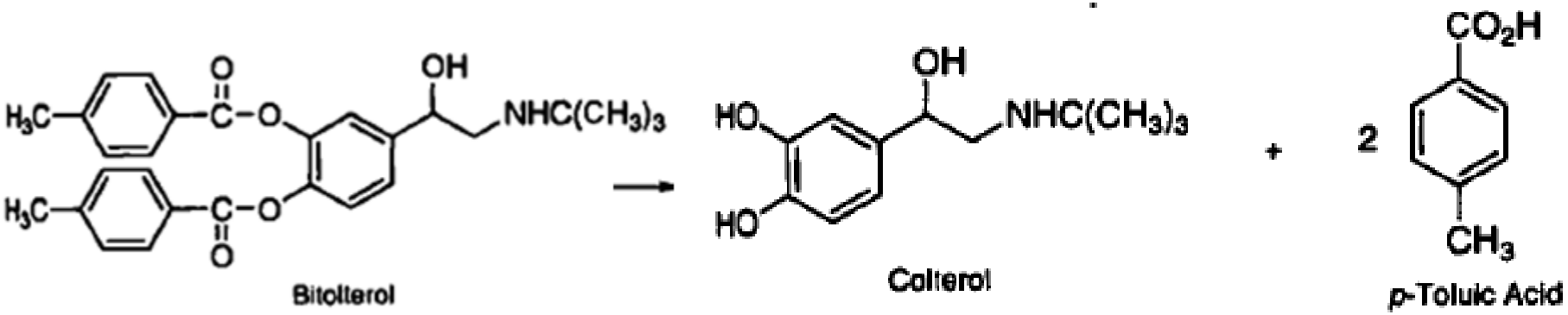
– It is **more selective than isoproterenol for β_2 receptors** (α-ethyl group), but less selective than albuterol and terbutaline.

–It is not metabolized by MAO but metabolized by COMT.

–It is used for treatment of **asthma by inhalation**

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists

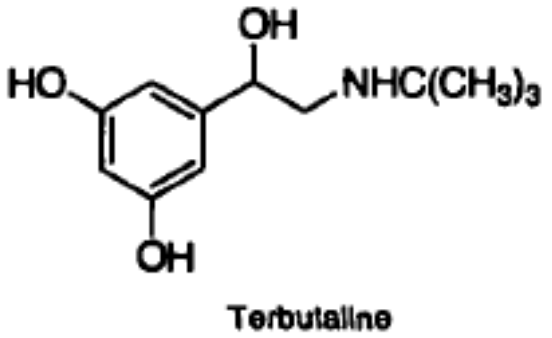


Bitolterol

- It is a prodrug of the β_2 selective adrenergic agonist.
-It is activated by lung esterase to give colterol, the N-tert-butyl analogue of NE
-It is more lipophilic than colterol due to the presence of two *p*-toluic acid esters.
-It has longer duration of action (5-8 h) than isoproterenol (1-3h)
-It is administered by inhalation for bronchial asthma.

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists



Terbutaline

Terbutaline: (*RS*)-5-[2-(*tert*-butylamino)-1-hydroxyethyl]benzene-1,3-diol

-Terbutaline is resorcinol derivatives are β_2 selective.

- Terbutaline is **effective orally**, it is not metabolized by COMT or MAO).

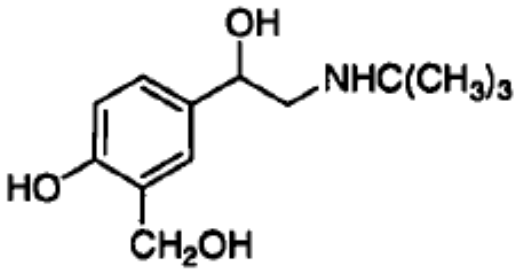
- It is used as **bronchodilator** in the treatment of **asthma** in children over 6 years and for the inhibition of **premature delivery** الولادة المبكرة

- Dosage forms: as sulfate: tablets 5mg, IV injection 1.5mg/5ml

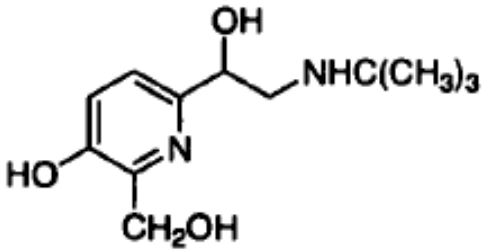
- Side effects: tachycardia, nervousness, tremors, headache, hyperglycemia, hypokalemia

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists



Albuterol



Pirbuterol

Albuterol (salbutamol) and Pirbuterol, are selective β_2 receptor agonists.

-The β_2 selectivity is due to the replacement of the meta OH of the catechol ring with the hydroxyl methyl moiety.

-These drugs are not metabolized by either COMT or MAO.

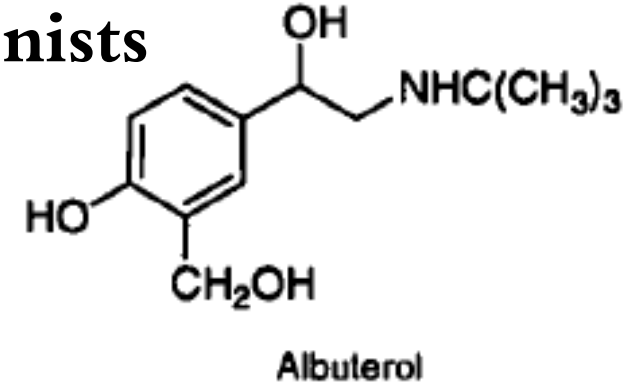
-Instead, they are conjugated with sulfate.

- They thus are **active orally**, and they, and terbutaline, exhibit, a longer duration of action than isoproterenol: 3-6h

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists

Albuterol (salbutamol)



Albuterol

Albuterol , (*RS*)-4-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl) phenol

-Albuterol is used as **a <u>bronchodilator in asthma</u>** (by inhalation, oral route or intravenous injection).

- It is also used to **<u>inhibit the premature</u> delivery**.

-Dosage forms: as sulfate, tablets 2mg,

IV injection2mg/5ml,

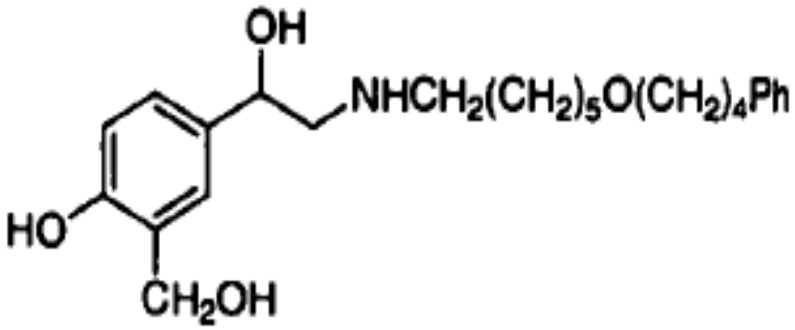
metered aerosol 100mcg/puff

Levalbuterol is the R(-) isomer of racemic albuterol.

- It is used in attempt to reduce the side effects.

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists



Salmeterol

Salmeterol , (*RS*)-2-(hydroxymethyl)-4-{1-hydroxy-2-[6-(4-phenylbutoxy) hexylamino]ethyl}phenol .

-It is a **long-acting β_2 -**adrenergic receptor agonist drug .

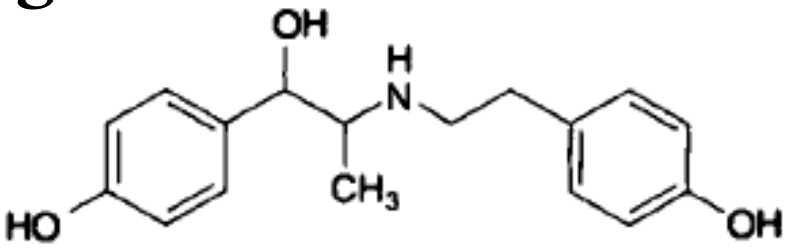
-This drug associates to the receptor slowly and dissociates at slower rate. Its duration of action is 12 h**.**

Formoterol

-It , as l, long –acting **β_2 -**adrenergic receptor agonist drug It is also used by inhalation for the treatment of asthma, usually in conjunction with an inhaled corticosteroid.

Sympathomimetic agents, Direct acting agents:

β –adrenergic receptor agonists



Ritodrine

Ritodrine HCl, 4-(2-((1*R*,2*S*)-1-hydroxy-1-(4 -hydroxyphenyl)propan-2-ylamino)ethyl)phenol

- It is a selective β_2 receptor agonist**.**

-It is used to control **premature labor** المخاض الباكر (inhibition premature delivery)

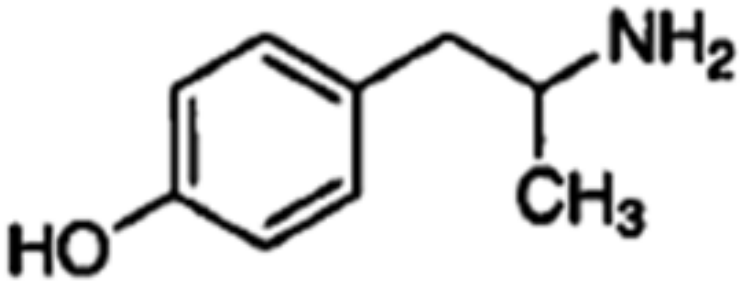
-It has mild cardiovascular effect (tachycardia تسرع القلب), slight diastolic pressure decrease. انخفاض الضغط الانبساطي

- Usually, it is administered initially by intravenous infusion to stop premature labor.

Subsequently, it may be given orally.

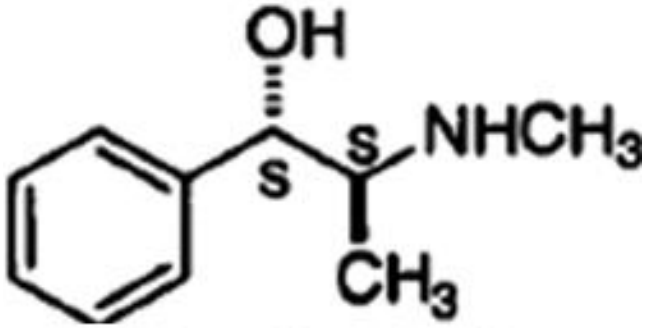
-Dosage forms: as hydrochloride, tablets 10mg, ampule 10mg

Indirect–Acting Sympathomimetics



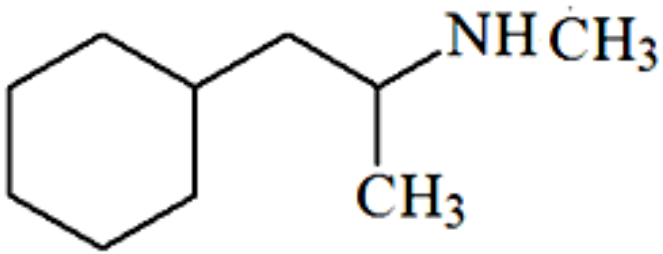
Hydroxyamphetamine

Mydriatic



L-(+)-Pseudoephedrine

Nasal decongestant



Propylhexedrine

Nasal decongestant (locally)

Indirect–Acting Sympathomimetics

-Indirect-acting sympathomimetics act by releasing endogenous NE. They enter the nerve ending by way of the active uptake process and displace NE from its storage granules.

-**Certain structural characteristics** tend to impart indirect sympathomimetic activity to phenylethylamines:

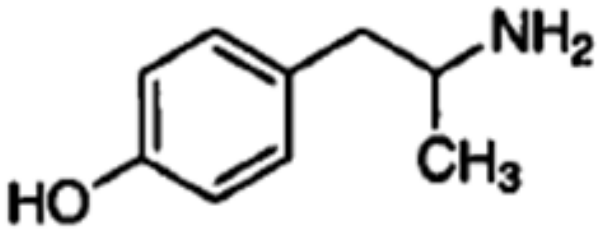
- The presence of the catechol hydroxyls enhances the potency of indirect-acting phenylethylamines.
- The presence of a β-hydroxyl group decreases the indirect activity
- An **α–methyl group increases indirect activity**
- The presence of nitrogen substituents decreases indirect activity.

-**Amphetamine** is, primarily, **prototypical CNS** indirect-acting sympathothomimetics. (amphetamine -like drugs are discussed in more detail in CNS stimulants).

-**α- methyltyramine (p-hydroxyamphetamine)** is primarily, **prototypical peripheral** indirect-acting sympathomimetic (the agents of this chapter).

Sympathomimetic agents

Indirect-Acting Sympathomimetics



Hydroxyamphetamine

α- methyltyramine

Hydroxyamphetamine ,α-methyltyramine.

- Tyramine is not a clinically useful agent.

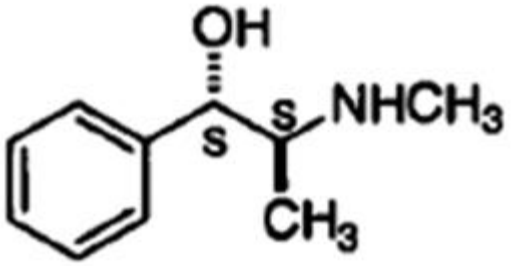
- Hydroxyamphetamine is an effective, indirect-acting sympathomimetic drug.

- It has little or no ephedrine-like, CNS-stimulating action.

-It is used as **mydriatic** for **diagnostic eye** examinations and for surgical procedures on the eye.

It is used sometimes with anticholinergic drugs like atropine to produce more pronounced effect.

Pseudoephedrine



(1S,2S) **(+)-Pseudoephedrine**

L(+)–Pseudoephedrine, (*S*,*S*)–2–methylamino–1–phenylpropan–1–ol ,

– It is the (**S**,**S**) **diastereoisomer of ephedrine**.

– It is a naturally occurring alkaloid from the Ephedra species.

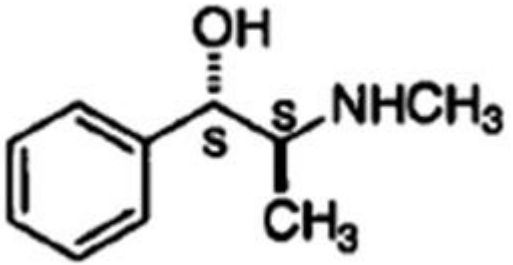
– Ephedrine has a mixed mechanism of action.

–Pseudoephedrine acts principally by an indirect mechanism.

–The structural basis for **this difference in mechanism** is the stereochemistry of the carbon atom possessing the β–hydroxyl group:

In pseudoephedrine, this carbon atom possesses the (S) configuration, which is the wrong stereochemistry at this center for a direct–acting effect at adrenergic receptors.

Pseudoephedrine



(1S,2S) **(+)-Pseudoephedrine**

-This agent is found in many over-the-counter nasal decongestant and cold medications.

-It is less prone to increase blood pressure than ephedrine.

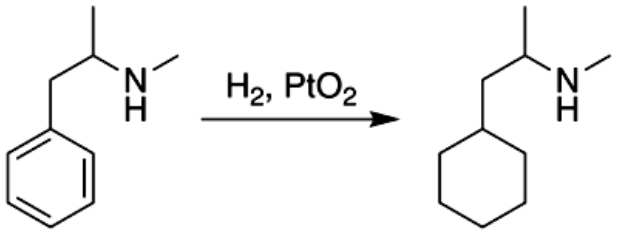
- it should be used with caution in hypertensive individuals,

-It should not be used in combination with MAO inhibitors.

-Pseudoephedrine salts, hydrochloride and sulfate, are found in many **OTC preparations**, either as a single ingredient or (more commonly) in combination with antihistamines, guaifenesin, dextromethorphan, and/or paracetamol or an NSAID (such as aspirin or ibuprofen).

- Dosage forms as hydrochloride or sulfate: tablets 30,60,100mg; syrups; **nasal spray**.

Propylhexedrine



Propylhexedrine has the methamphetamine structure with cyclohexane instead of benzene.

–Propylhexedrine is more commonly prepared by reduction of methamphetamine with Adams' catalyst to give a racemic mixture (R,S).

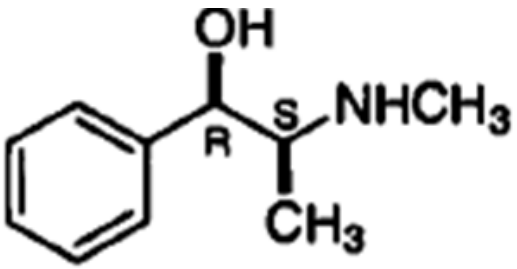
–It is a volatile, oily liquid at room temperature.

–Acid salts (such as propylhexedrine HCl) often present as a stable, clear to off–white crystalline powder that readily dissolves in water.

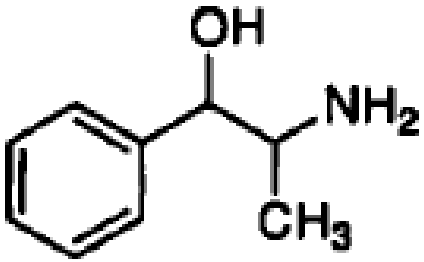
–It is used as topical **nasal decongestant**

Sympathomimetics With Mixed Mechanism of Action

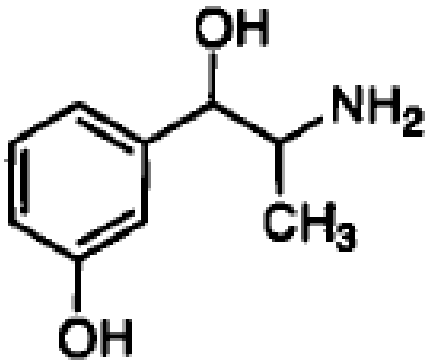
–D(–)Ephedrine–Phenylpropanolamine- Metaraminol



D-(-)-Ephedrine



Phenylpropanolamine

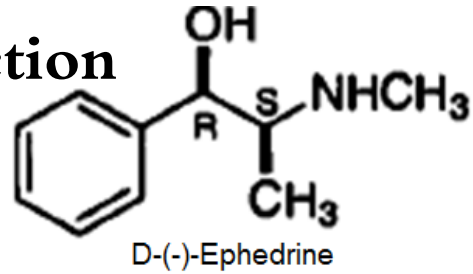


Metaraminol

TABLE 16–1 Relative Pressor Activity of the Isomers of Ephedrine

Isomer	Relative Activity
D-(-)-Ephedrine	36
L-(+)-Ephedrine	11
L-(+)-Pseudoephedrine	7
D-(-)-pseudoephedrine	1
DL-Ephedrine	26
DL-pseudoephedrine	4

Sympathomimetics With Mixed Mechanism of Action



D-(-)-Ephedrine

Ephedrine, D-(-)-Ephedrine, (1R,2S)-(-) ephedrine

- It is the classic example of a sympathomimetic with a mixed mechanism of action.

-This drug is an alkaloid that can be obtained from the stems of various species of Ephedra.

-Ephedrine has **two asymmetric carbon atoms**.

-There are **four optically active forms**.

-The erythro racemate is called "ephedrine." and the threo racemate is known "pseudoephedrine" .

-Natural ephedrine is D(-) isomer, and it is the most active of the four isomers as a pressor رافع للضغط amine (Table 16-1).

This is largely due to the fact that this isomer has the correct (R) configuration at the carbon atom bearing the hydroxyl group and the desired (S) configuration at the carbon bearing the methyl group for optimal direct action at adrenergic receptors.

Sympathomimetics With Mixed Mechanism of Action

Ephedrine

-Ephedrine decomposes gradually and darkens when exposed to light
-The free alkaloid is a weak base: the salt form has a pKa of 9.6.
-The pharmacological activity of ephedrine resembles that of epinephrine.
The drug acts **on both α- and β-adrenergic receptors**.
-Although it is **less potent than epinephrine**. Its pressor and local vasoconstrictive actions are of **greater duration**, and causes more pronounced **stimulation of the CNS** than epinephrine.
-It is effective when given orally.
-The drug is not metabolized by either MAO or COMT, it is p-hydroxylated and N-demethylaled by cytochrome P-450 mixed-function oxidases.

Sympathomimetics With Mixed Mechanism of Action

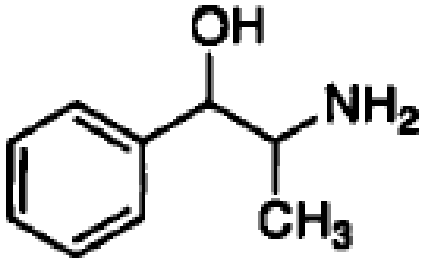
Ephedrine

-Ephedrine and its salts are used **orally**, **intravenously**, **intramuscularly**. **and topically f**or a variety of conditions, as allergic disorders, colds. hypotensive conditions, and narcolepsy تغفيق.

-It is used **locally** as a nasal decongestant and to dilate the pupil or the bronchi.

-Systemically, it is effective for asthma, hay fever حمى الكلأ(rhinitis) , and urticaria الشرى .

Sympathomimetics With Mixed Mechanism of Action



Phenylpropanolamine

Phenylpropanolamine

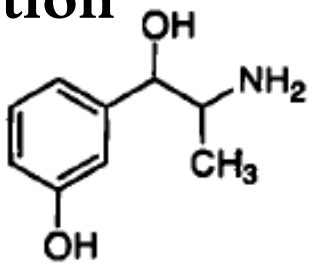
-It has two chiral centers (four stereoisomers).

-It was used frequently in oral cough, nasal decongestant and cold medications until 2001.

- FDA recommended its removal due to hemorrhagic stroke in young women.

صدمة نزفية

Sympathomimetics With Mixed Mechanism of Action



Metaraminol

Metaraminol, (1*R*,2*S*)-3-[-2-amino-1-hydroxy-propyl]phenol

-It is structurally **similar to phenylephrine** except that it is a primary instead of a secondary amine

-It possesses a mixed mechanism of with its direct-acting effects mainly on α-adrenergic receptors.

-It is used **parenterally as a vasopressor**.

- It is used in the treatment and prevention of the acute hypotensive state occurring with spinal anesthesia التخدير النخاعي الشوكي.

It also has been used to treat severe hypotension brought on by other traumas that induce shock.

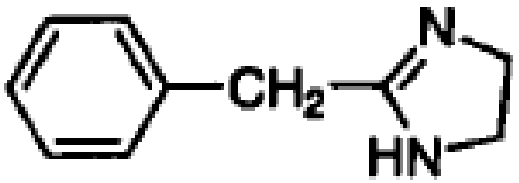
Adrenergic receptor antagonists

α- Adrenergic receptor antagonists

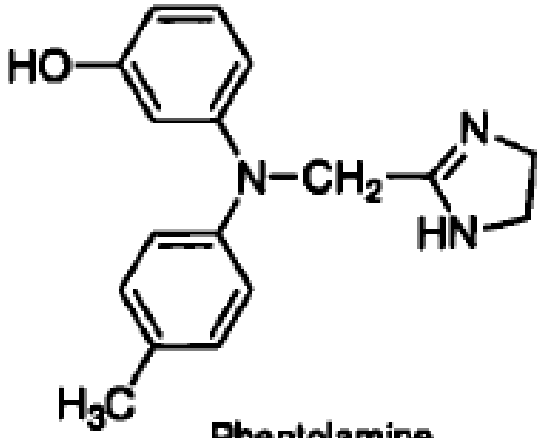
unlike the β- adrenergic receptor antagonists, which bear clear structural similarities to the adrenergic agonists NE, Epinephrine, and isoproterenol, the α -adrenergic receptor antagonists consist of a number of compounds of diverse chemical structure that bear little obvious resemblance to α-adrenergic receptor agonists.

Nonselective α- Adrenergic receptor antagonists

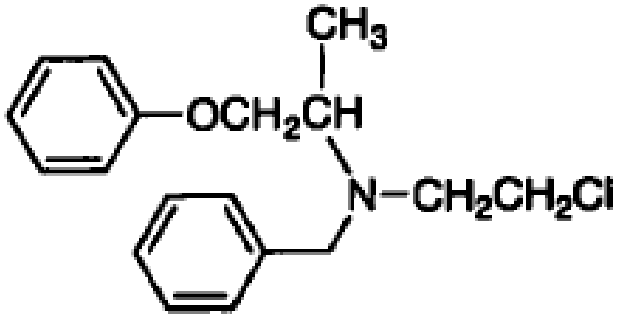
Tolazoline, phentolamine and Phenoxybenzamine



Tolazoline



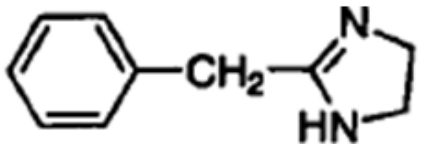
Phentolamine



Phenoxybenzamine

α- Adrenergic receptor antagonists

Tolazoline



Tolazoline and phentolamine are structurally similar to the imidazoline α-agonists, such as naphazoline.

-Tolazoline possesses a weak α_1 and α_2 antagonist activity (competitive).

- Phentolamine is more active than tolazoline, but both are **not useful** in treating essential hypertension.

- Both produce tachycardia, due to presynaptic α_2- antagonism.

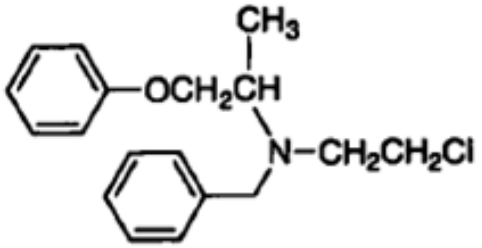
- Both tolazoline and phentolamine have a **direct vasodilatory action** on vascular smooth muscle that may be more prominent than their α - receptor antagonistic effects.

- **Tolazoline** is indicated for use in persistent pulmonary hypertension of the newborn, (IM,IV preparations).

-**Phentolamine** is indicated as antihypertensive in patients with pheochromocytoma.

- Phentolamine has been used in combination with papaverine to treat impotence عنانة .

α- Adrenergic receptor antagonists



Phenoxybenzamine,(*RS***)-*N*-benzyl-*N*-(2-chloroethyl)-1-phenoxypropan-2-amine.**

-It is a β-haloethylamines derivative

- It an **irreversible α- adrenergic** receptor blocker (Figure 16-7).

-The onset of action of is slow, but the effects of a single dose of drug may last 3 to 4 days.

-The common side effects are miosis تقبض الحدقة , tachycardia, nasal stuffiness انسداد الانف(زكام), and postural وضعي hypotension (orthostatic hypotension).

- Oral form indicated as antihypertensive in patients with pheochromocytoma.

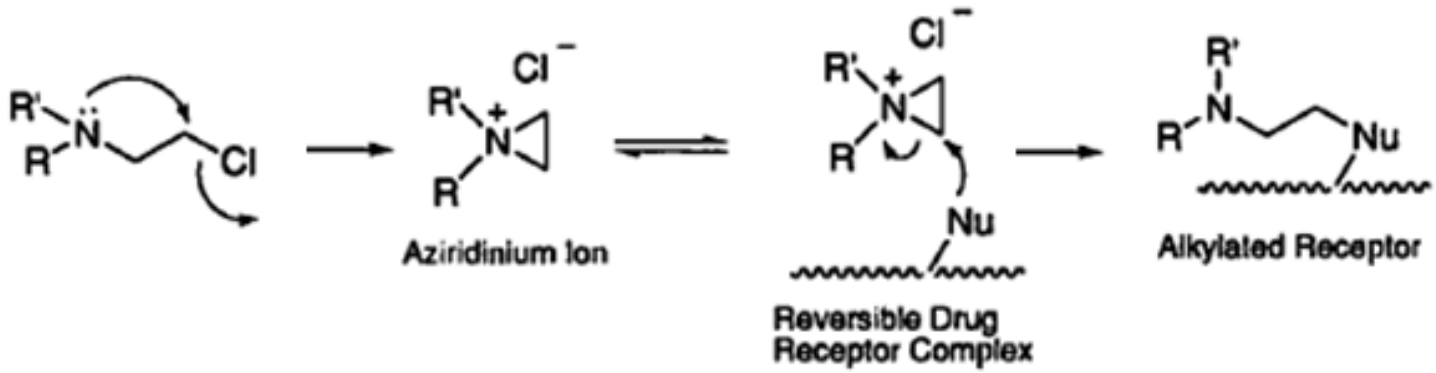
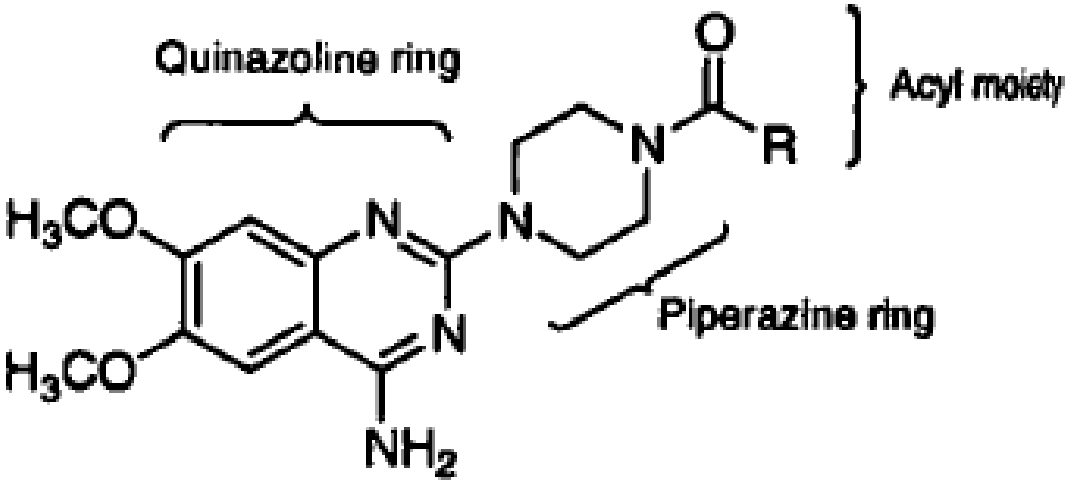


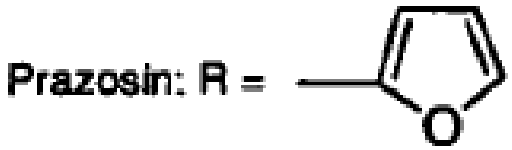
Figure 16–7

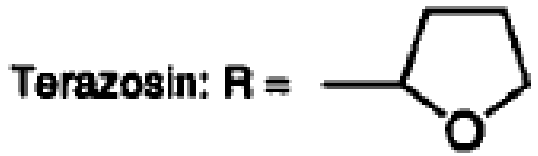
α- Adrenergic receptor antagonists

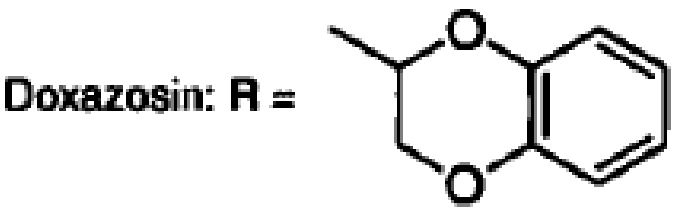
Selective α_1- receptor antagonists

Prazosin, Terazosin, Doxazosin









α- Adrenergic receptor antagonists

Selective α_1- receptor antagonists

Prazosin, **Terazosin**, **Doxazosin**:

- One group of highly selective α_1- receptor antagonists are the quinazolines.

-Structurally, they compose of three components: the quinazoline ring, the piperazine ring, and the acyl moiety.

-The 4-amino group on the quinaloline ring is very important for **α_1-** receptor affinity.

- Piperazine moiety can be replaced with other heterocyclic moieties (e.g. Piperidire moiety) without loss of affinity.

-The nature of the acyl group has a significant effect on the pharmacokinetic properties

Agent	Bioavailability (%)	Half-life (hours)	Duration of Action (hours)
Prazosin	50–70	2–3	4–6
Terazosin	90	9–12	18
Doxazosin	65	22	36

α- Adrenergic receptor antagonists

Selective α_1- receptor antagonists

Prazosin, Terazosin, Doxazosin

-These drugs are used in the treatment of hypertension.

- No increase in heart rate or cardiac output is produced with these selective agents (no presynaptic α_2 receptor antagonist activity).

-These agents also find use in the treatment of benign prostatic hyperplasia فرط تنسج الموثة السليم(BPH), where they help improve urine flow rates.

- The most frequent adverse effect of these drugs is postural hypotension (dose-dependent phenomenon).

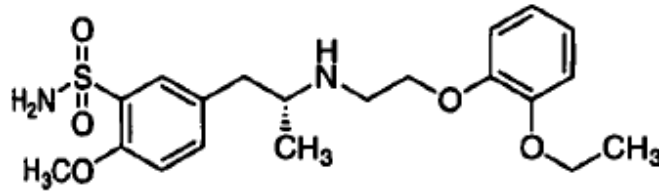
-These drugs are metabolized extensively, with the metabolites excreted in the bile.

Dosage forms:

Doxazosin (as mesylate, HCl): 1,2,4,5mg/tablet

α- Adrenergic receptor antagonists

Selective α_{1A}- receptor antagonists



Tamsulosin

Tamsulosin, an aryl sulfonamide

-It is selective α_{1A}- receptor antagonist.

-This receptor seems to predominate in the prostate.

- It is used for the treatment of benign prostatic hyperplasia (BPH).

- Unlike non-selective quinazoline derivatives ,it has no or less orthostatic hypotension.

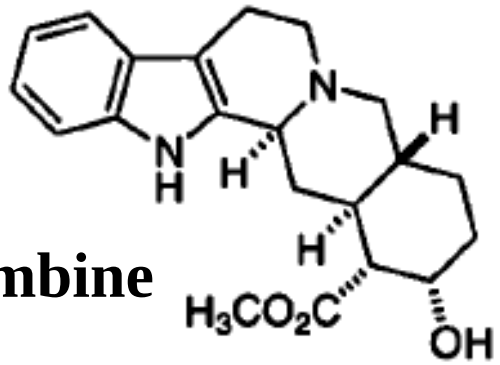
- Dosage form: 0.4mg/tablet

- Dosage: once daily

α- Adrenergic receptor antagonists

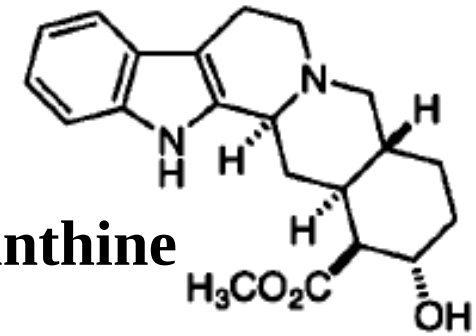
Selective α_2- receptor antagonists

Yohimbine



Yohimbine

corynanthine



Corynanthine

Yohimbine is an indole alkaloids, a diastereomer متصاوغ فراقي of corynanthine. - It differs only by stereochemistry of carbon attached to carbonylmethoxy substituent ($COOCH_3$ in yohimbine in the plane of indole, while out of plane, axial, in corynanthine).

-Yohimbine is **an α_2 selective antagonist and thus it is stimulant**.

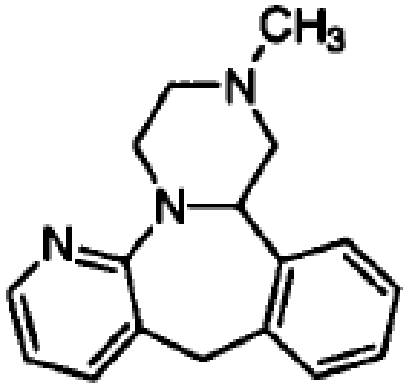
- Corynanthine is more selective α_1 receptor antagonist (depressant)

-Yohimbine increases heart rate and blood pressure as a result of blocking CNS-α_2 receptors.

- It is used in the treatment of male erectile impotence.

α- Adrenergic receptor antagonists

Selective α_2- receptor antagonists



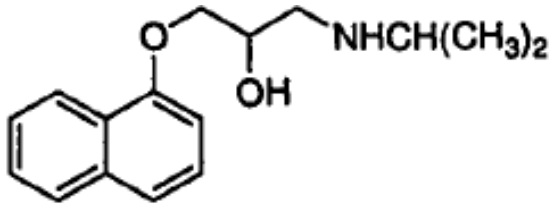
Mirtazapine

M**irtazapine**

- It is another example of **selective α_2– antagonist** .
- It produces in an increased release of NE and serotonin.
- This has prompted its use as **antidepressant** (**see CNS stimulants**)

β- Adrenergic receptor antagonists

STRUCTURE–ACTIVITY RELATIONSHIPS (SAR)



Propranolol

Propranolol (aryloxypropanolamine derivative) is the first standard nonselective β- adrenergic antagonists

-The nature of the aromatic ring and its substituents is the primary determinant of β- antagonistic activity.

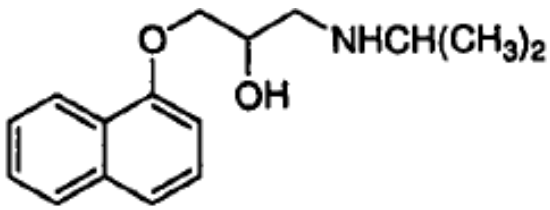
-The aryl group also affects absorption ,distribution, metabolism and elimination of the β- blockers.

- One common structural feature of many cardioselective antagonists (**selective β_1– antagonist**) is the presence of a **para substituent** of sufficient size on the aromatic ring along with the absence of meta substituents.

-Tertiary butyl or isopropyl group (**bulky group**) are normally found on the amino function of β- adrenergic antagonists. The amino group must be a **secondary amine** for optimal activity.

β- Adrenergic receptor antagonists

STRUCTURE–ACTIVITY RELATIONSHIPS (SAR)



Propranolol

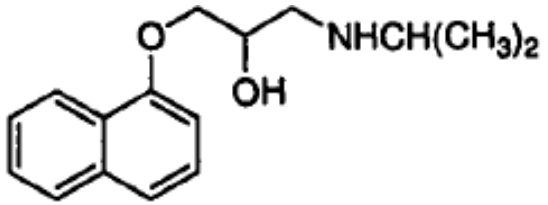
-For optimal activity of β- antagonist activity, the hydroxyl-bearing carbon should possess (**S**) **configuration**.

The enantiomer with R̄-configuration is 100 times less potent, and in spite of that, racemic mixtures are mostly used.

- The only exceptions are levobunolol, timolol, and penbutolol, with which the (S) enantiomer is used.

Nonselective β- blockers

Propranolol



Propranolol

Propranolol, (*RS*)-1-(1-methylethylamino)-3-(1-naphthyloxy)propan-2-ol.

-Propranolol (Inderal) is the prototypical non selective β -adrenergic receptor antagonist. It blocks competitively, β_1, β_2 equally well.

-It is approved for use for **hypertension**, **cardiac arrhythmias**, **angina pectoris**, **post–myocardial infarction**, **migraine prophylaxis**, **pheochromocytoma** .

-Propranolol is under investigation for treatment of a variety of other conditions, (schizophrenia, alcohol withdrawal syndrome..).

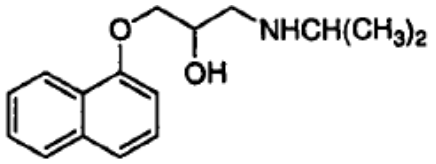
- The antihypertensive action, at least in part, may be attributed to its ability to reduce cardiac output (due to β_1 blockade), as well as to its suppression of renin release from the kidney.

-it is **contraindicated** in the presence of conditions such as a**sthma** and bronchitis. This due to its β_2-receptors antagonist activity.

β- Adrenergic receptor antagonists

Nonselective β- blockers

Propranolol



Propranolol

Propranolol has a local anesthetic effect or a quinidine-like effect but the concentrations required far exceed those obtained with normal therapeutic doses of propranolol.

-Propranolol is well absorbed after oral administration, but it undergoes extensive first-pass metabolism.

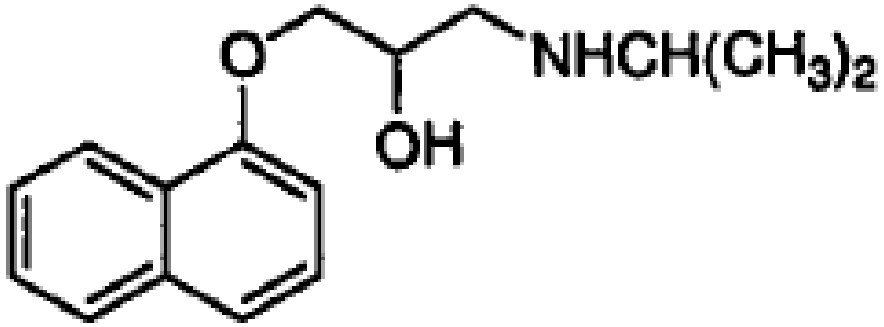
-The active **S– enantiomer** is cleared more slowly than the inactive enantiomer

-The major metabolite is naphthoxylactic acid, which is formed by a series of metabolic reactions involving N-dealkylation, deamination, and Oxidation.

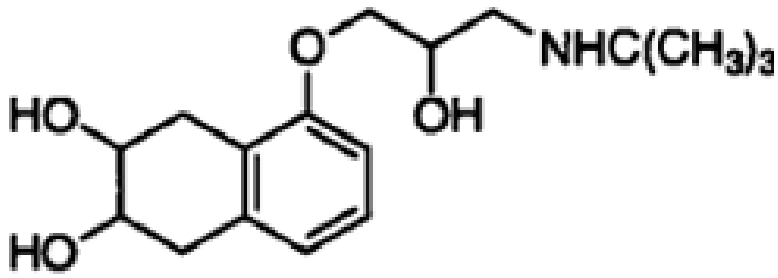
-The half-life of propranolol after a single oral dose is 3 to 4 hours, which increases to 4 to 6 hours after long-term therapy.

Dosage forms: tablets 10-80 mg

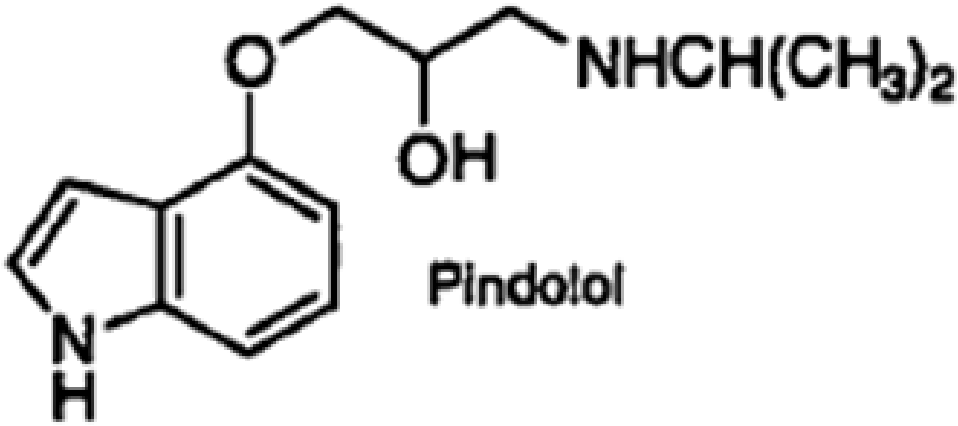
β– Adrenergic receptor antagonists
Nonselective β- Blockers



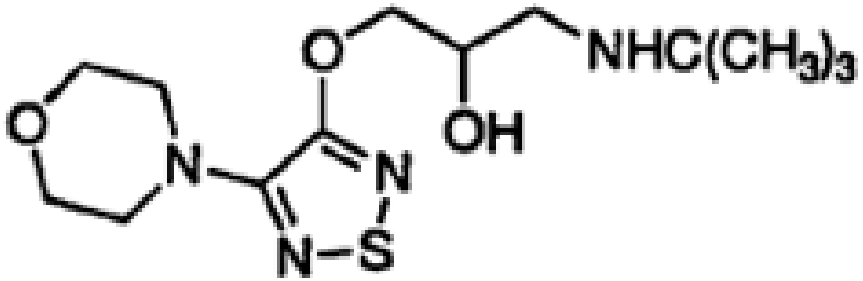
Propranolol



Nadolol



Pindolol



Timolol

Other Nonselective β- blockers

-**Several other nonseletive β- blockers** are used clinically. These include **nadolol**, **pindolol**, **penbutolol**, **carteolol**, **timolol**, **levobunolol**, **sotalol and metipranolol**

-The first five of these agents are used to treat hypertension.

-**Nadolol** is also used in the long-term management of angina pectoris, in the treatment of cardiac arrhythmiasis, and in the preventive treatment of headache (nadolol: 40,80mg/tab.).

Nadolol half-life is about 20 hours, making it one of the **longest-acting** β-blockers

- **Timolol** finds use in the prophylaxis of migraine headaches.

- **Sotalol** is used as an antiarrhythmic in treating ventricular **arrhythmias**

-**Levobunolol**, **timolol**, and **metipranolol** are used topically to treat open-angle **glaucoma**. They lower intraocular pressure by perhaps,reducing the production of aqueous humor.

β- Adrenergic receptor antagonists

β_1- selective blockers

-β_1- selective blockers, cardioselective β antagonists

-They are drugs that have a greater affinity for the β_1- receptors of the heart than for β_2 receptors in other tissues.

-Cardioselective agents should provide two important therapeutic advantages.

• This would make β_1 blockers **saf**e for use in patients who have bronchitis or bronchial **asthma**.

• **No increase** in peripheral resistance.

BUT unfortunately,cardioselectivity is usually observed with relatively low doses and at normal therapeutic doses, much of the selectivity is lost.

β- Adrenergic receptor antagonists

β_1- selective blockers

- The following **β_1– –selective agents** are used therapeutically: **acebutolol** , **atenolol**, **betaxolol**, **bisoprolol**, **esmolol and metoprolol** .

–All of these agents except esmolol are indicated for the treatment of hypertension.

Atenolol and metoprolol are also approved for use in treating angina pectoris.

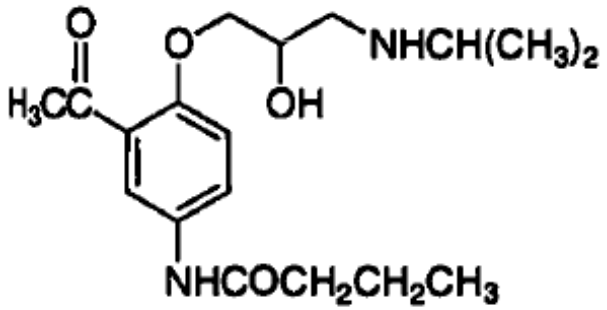
Esmolol and acebutolol are indicated for treating certain cardiac arrhythmias

Betaxolol

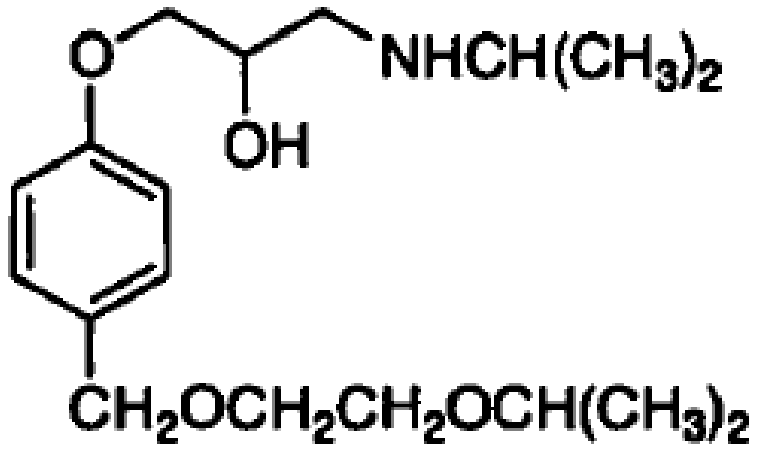
–It has longest duration of action of the β_1–selective blockers, a half–life ranging between 14 and 22 hours. It is the only $\beta_1$blocker indicated for the treatment of **glaucoma**.

β– Adrenergic receptor antagonists

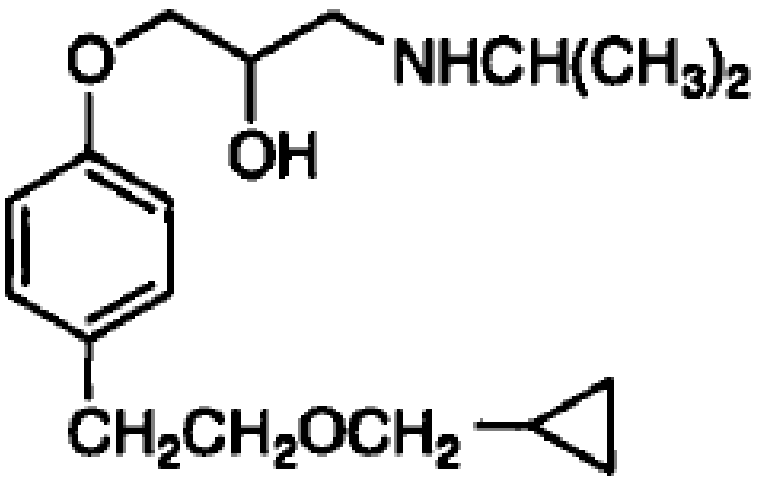
β_1– Selective Blockers



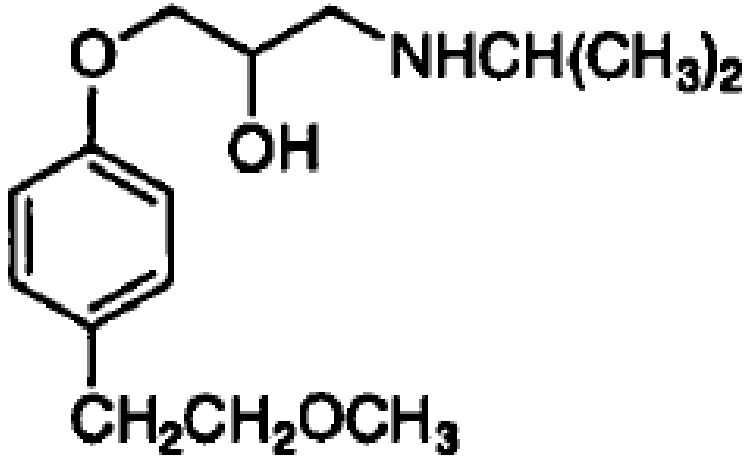
Acebutolol



Bisoprolol



Betaxolol



Metoprolol

β- Adrenergic receptor antagonists

β_1- selective blockers

Esmolol

-It has a **rapid onset**

-It has a **short duration of action** (half-life of 9 minutes), its effects disappear within 20 to 30 minutes after the infusion is discontinued.

-Esmolol is used for control of ventricular rate in patients with atrial flutter رفرفة أذينية , atrial fibrillation رجفان , or sinus tachycardia (cardiac **arrhythmias**).

Dosage forms:

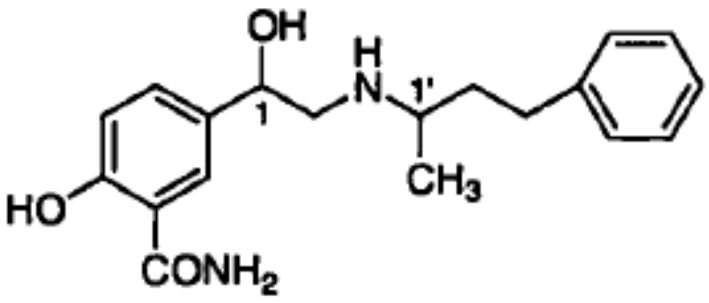
- Atenolol coated tablets 50,100mg

-Metoprolol tartrate ctd tablets 50,100,200mg

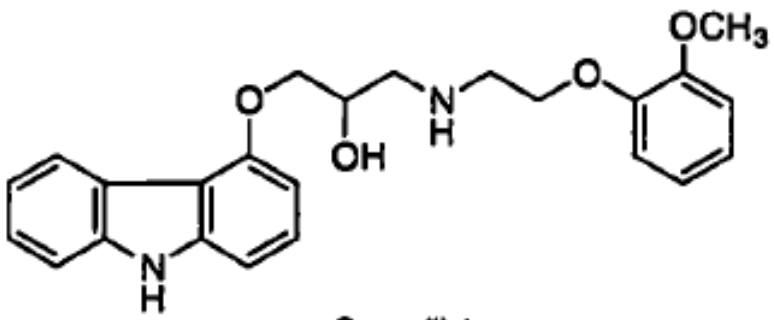
Bisoprolol fumarate tablets 5,10mg

β- Adrenergic receptor antagonists

β- blockers with α_1-receptor antagonist activity



Labetalol



Carvedilol

-Several drugs have been developed that possess both β-and α -receptor-blocking activity within the same molecule.

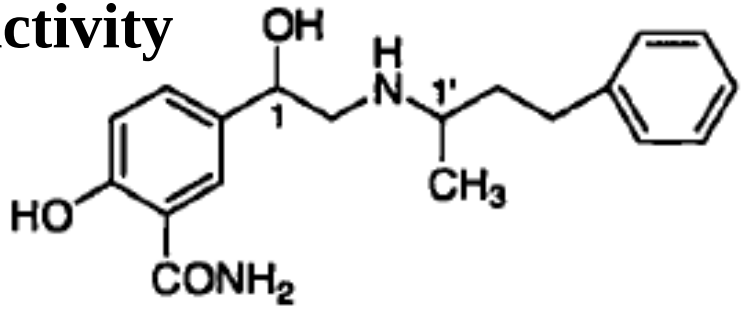
- The rationale for use of these drugs in the management of hypertension is that its α –receptor-blocking effects produces vasodilation and its β –receptor-blocking effects prevent the reflex tachycardia usually associated with vasodilation.

Two examples of such molecules are **labelalol** and **carvedilol**

β- Adrenergic receptor antagonists

β- blockers with α_1-receptor antagonist activity

Labetalol



Labetalol

Labetalol

-It is a phenylethanolamine derivative.

- It is a competitive inhibitor at β_1- β_2 and α_1 antagonist. It is more potent β- antagonist than α- antagonist

- It has two asymmetric carbon atoms (1,1') : It is a mixture of **four stereoisomers**.

-The S,R and the S,S isomers are α_1 blocker, and the R,R isomer is β blocker.

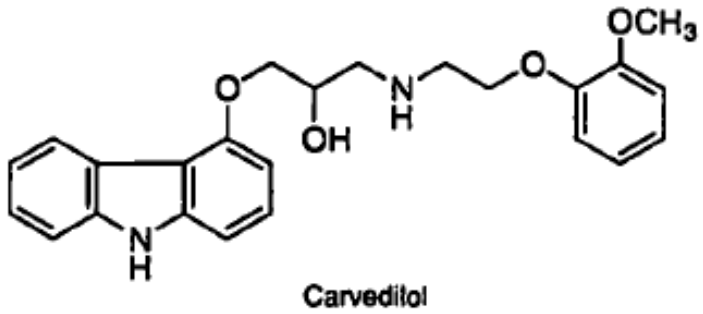
-Labetalol is a clinically useful **antihypertensive a**gent.

Dosage forms: **tablets** (100,200,300mg), **IV** (5mg/ml)

β- Adrenergic receptor antagonists

β– blockers with α_1–receptor antagonist activity

Carvedilol



Carvedilol

-**Carvedilol**

–It is an aryloxypropanolamine derivative.

– It is β_1- β_2 and α_1 antagonist.

-It is a racemic mixture:

The S- enantiomer possesses the β-blocking activity, while both S and R enantiomers are α_1 blocker .

-Carvidilol possesses antioxidant activity and an antiproliferative ضد التكاثر على خلايا العضلات الملساء للأوعيةeffect on vascular smooth muscle cells.

- It thus has a neuroprotective محصن عصبي effect and provide major cardiovascular organ protection.

-It is used in the **treatment of hypertension** and congestive heart failure.

- Dosage forms: coated **tablets** 3.25,6.25,12.5,25mg.

THE END