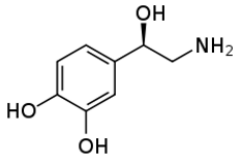
Adrenergic Agonists

Study

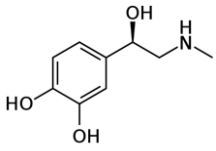
- α receptors agonists
- α receptor antagonists
- β receptor agonists
- β receptor antagonists

Study

- α receptors agonists
- α receptor antagonists
- β receptor agonists
- β receptor antagonists



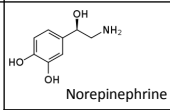
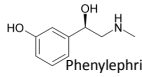
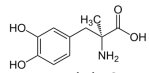
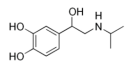
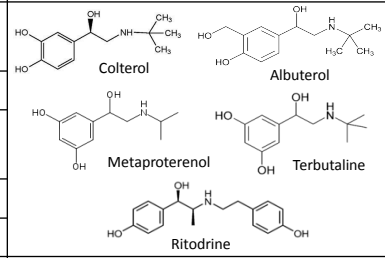
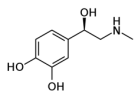
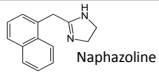
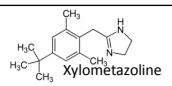
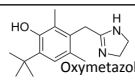
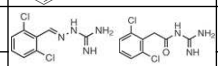
Norepinephrine



Epinephrine

Adrenergic agonists - Classification

- Phenylethanol amines -SAR
- Aryl imidazolines
- Amino imidazolines
- Open ring imidazolines

	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	 Norepinephrine	 Phenylephrine	 Methyl DOPA	 Isoproterenol		 Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	 Epinephrine					
Aryl imidazolines		 Naphazoline				
		 Xylometazoline				
		 Oxymetazoline				
Amino imidazolines			 Clonidine			
Open ring imidazolines			 Guanabenz Guanafacine			

Draw structures

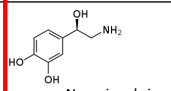
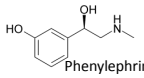
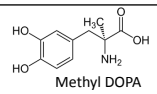
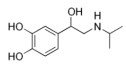
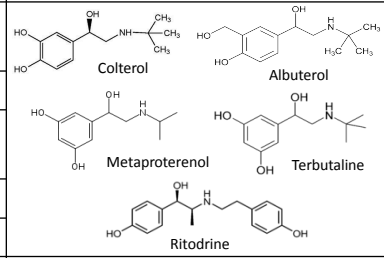
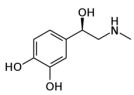
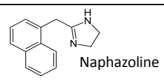
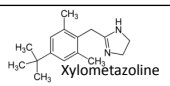
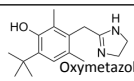
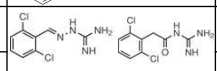
- Norepinephrine
  - 4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol
- Epinephrine
  - *(R)*-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol
- Phenylephrine
  - *R*)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol
- Naphazoline
  - 2-(naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole
- Xylometazoline
  - 2-[(4-*tert*-butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1*H*-imidazole
- Oxymetazoline
  - 3-(4,5-dihydro-1*H*-imidazol-2-ylmethyl)- 2,4-dimethyl-6-tert-butyl-phenol

Draw structures

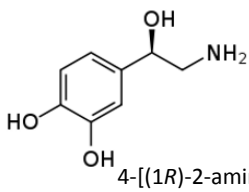
- Methyl DOPA
  - (*S*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid
- Clonidine
  - *N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine
- Guanabenz
  - 2-(2,6-dichlorobenzylidene)hydrazinecarboximidamide
- Guanafacine
  - *N*-(diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide

Draw structures

- Isoproterenol
  - 4-[1-hydroxy-2-(isopropylamino)ethyl]benzene-1,2-diol
- Colterol
  - 4-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,2-diol
- Albuterol
  - 4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol
- Metaproterenol
  - 5-[1-hydroxy-2-(isopropylamino)ethyl]benzene-1,3-diol
- Terbutaline
  - 5-[2-(*tert*-butylamino)-1-hydroxyethyl]benzene-1,3-diol
- Ritodrine
  - 4-(2-((1*R*,2*S*)-1-hydroxy-1-(4-hydroxyphenyl)propan-2-ylamino)ethyl)phenol

	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	 Norepinephrine	 Phenylephrine	 Methyl DOPA (phenyl ethyl amine)	 Isoproterenol		 Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	 Epinephrine					
Aryl imidazolines		 Naphazoline				
		 Xylometazoline				
		 Oxymetazoline				
Amino imidazolines			 Clonidine			
Open ring imidazolines			 Guanabenz Guanafacine			

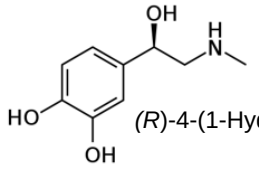
Norepinephrine



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

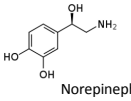
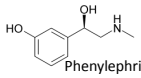
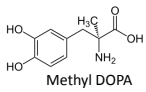
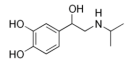
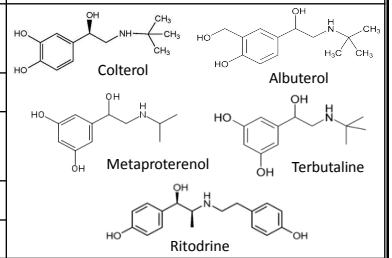
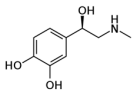
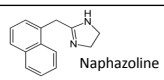
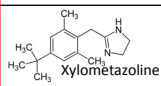
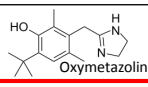
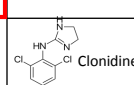
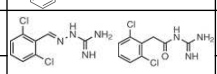
- Direct acting sympathomimetic
- Nonselective α + β
- Potent α and β1 receptor agonist
  - Limited clinical application because of nonselective action, which causes both vasoconstriction and cardiac stimulation.
- Substrate for MAO and COMT
  - Rapid metabolism by MAO and COMT limits its duration of act ion to only 1 or 2 minutes, even when given by infusion.
- Parenteral administration
  - Cannot be given orally as a result of rapid metabolism by intestinal and liver COMT and MAO, 3′-O-glucuronidation/ sulfation in the intestine, and low lipophilicity.
- Used as a vasopressor and cardiac stimulant in emergency crisis situations
  - The drug is used to counteract various hypotensive crises, because its α-activity raises blood pressure and as an adjunct treatment in cardiac arrest , where its β-activity stimulates the heart.

Epinephrine

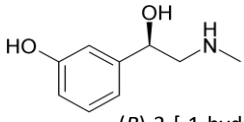


(*R*)-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol

- Direct acting sympathomimetic
- Nonselective α + β
- Potent α, β1, and β2 receptor agonist
- Substrate for MAO and COMT
- Parenteral administration
  - Cannot be given orally as a result of rapid metabolism by intestinal and liver COMT and MAO, 3′-O-glucuronidation/ sulfation in the intestine, and low lipophilicity.
- Uses
  - Epinephrine, similar to norepinephrine, is used to treat hypotensive crises and, because of its greater β-activity, to stimulate the heart in cardiac arrest .
  - The β2-activity of epinephrine leads to its administration intravenously and in inhalers to relieve bronchoconstriction in asthma and to application in inhibiting uterine contractions.
  - Because it has significant α-activity, epinephrine has been used in nasal decongestants. Constriction of dilated blood vessels in mucous membranes shrinks the membranes and reduces nasal congestion, although significant after-congestion may limit its utility.

	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	 Norepinephrine	 Phenylephrine	 Methyl DOPA	 Isoproterenol		 Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	 Epinephrine					
Aryl imidazolines		 Naphazoline				
		 Xylometazoline				
		 Oxymetazoline				
Amino imidazolines			 Clonidine			
Open ring imidazolines			 Guanabenz, Guanafacine			

Phenylephrine

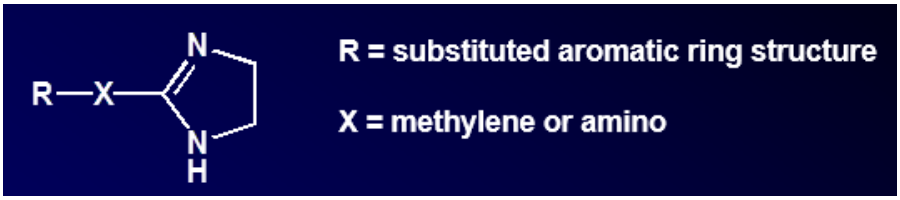


(*R*)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol

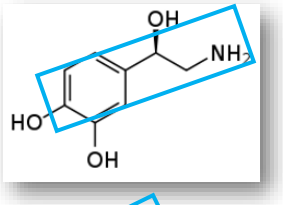
- Direct acting sympathomimetic
- α1 agonist – minimal cardiac stimulatory properties
- Metabolism
  - Substrate for MAO
  - Duration of action is significantly longer than norepinephrine as it is not a substrate for COMT
- Administration: Parenteral, oral, local
- Uses:
  - Their α1-agonist activity makes them strong vasoconstrictors, however , and their primary **systemic** use is limited to **treating hypotension** during surgery or severe hypotension accompanying shock.
  - It also has widespread use as a nonprescription **nasal decongestant** in both **oral and topical** preparations.
  - Phenylephrine preparations applied **topically** to the **eye** constrict the dilated blood vessels of bloodshot eyes
- Its oral bioavailability is less than 10% because of its hydrophilic properties and intestinal 3′-O-glucuronidation/sulfation.

2-Arylimidazoline α1-Agonists

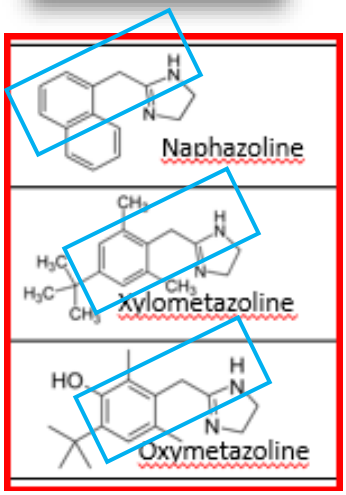
- In addition to phenylethanolamine derivatives, α-adrenoceptors accommodate a diverse assortment of structures.
- The imidazoline derivatives also are selective α1-agonists and, therefore, are called vasoconstrictors/vasopressors.



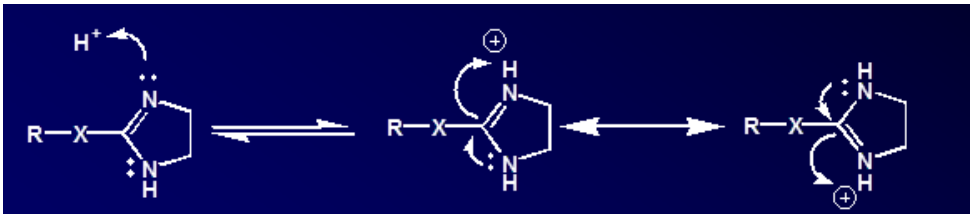
2-Arylimidazoline α1-Agonists



- They all contain a one-carbon bridge between C2 of the imidazoline ring (pKa range, 10–11) and a phenyl substituent ; therefore, the general skeleton of a phenylethylamine is contained within the structures.
- Lipophilic substitution on the phenyl ring *ortho* to the methylene bridge appears to be required for agonist activity at α-receptors
- Bulky lipophilic groups attached to the phenyl ring at the meta or para positions provide selectivity for the α1- receptor by diminishing affinity for α2-receptors.



2-Arylimidazoline α1-Agonists



The imidazoline cation is resonance stabilized allowing the + charge to be spread over the entire three atom system. Thus, imidazolines are more basic than simple aliphatic amines.

2-Arylimidazoline α1-Agonists

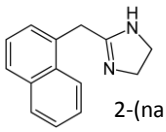
- These highly ionic compounds are widely used only in topical preparations as nasal decongestants and eye drops

Table 13.5 Imidazoline α_1-Agonists in Over-the-Counter Vasoconstrictors

Drug	Nasal Decongestant	Eye drops
Xylometazoline	Otrivin, Inspire	—
Oxymetazoline	Afrin, Duration, Neo-Synephrine, Vicks Sinex	Visine L.R. Ocu Clear
Naphazoline	4-Way Fast Acting, Privine	Naphcon, Clear Eyes

- Systemically, they are potent vasoconstrictors.

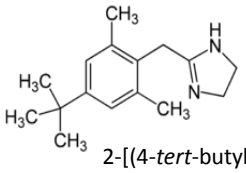
Naphazoline



2-(naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole

- Direct acting sympathomimetic
- α1 agonist
- Administered locally/topically to promote vasoconstriction
- Basic nature of imidazoline ring causes compounds to exist in ionized form at physiologic pH
- Uses: Nasal and ophthalmic decongestants

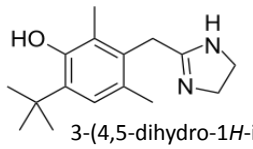
Xylometazoline



2-[(4-*tert*-butyl-2,6-dimethylphenyl)methyl]-4,5-dihydro-1*H*-imidazole

- Direct acting sympathomimetic
- α1 agonist
- Administered locally/topically to promote vasoconstriction
- Basic nature of imidazoline ring causes compounds to exist in ionized form at physiologic pH
- Uses: Nasal and ophthalmic decongestants

Oxymetazoline

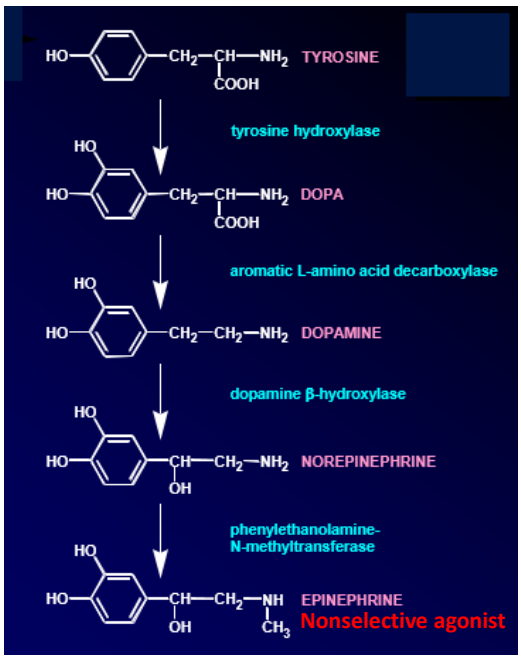


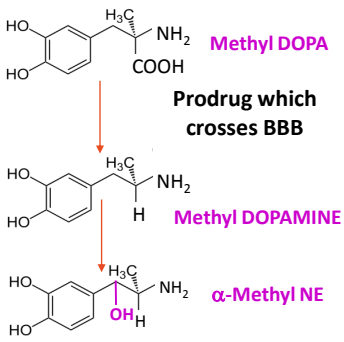
3-(4,5-dihydro-1*H*-imidazol-2-ylmethyl)- 2,4-dimethyl-6-tert-butyl-phenol

- Direct acting sympathomimetic
- α1 agonist
- Administered locally/topically to promote vasoconstriction
- Basic nature of imidazoline ring causes compounds to exist in ionized form at physiologic pH
- Uses: Nasal and ophthalmic decongestants

	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	Norepinephrine	Phenylephrine	Methyl DOPA	Isoproterenol		Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	Epinephrine					
Aryl imidazolines		Naphazoline				
		Xylometazoline				
		Oxymetazoline				
Amino imidazolines			Clonidine			
Open ring imidazolines			Guanabenz, Guanafacine			

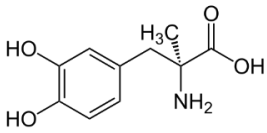
Biosynthesis of Catecholamines





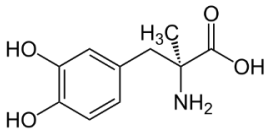
Selective α2-agonist
(inhibits adrenergic stimulation via negative feedback mechanism
Antihypertensive)

Methyl DOPA



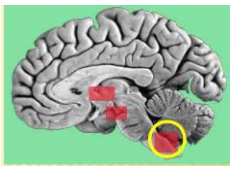
- The pro-drug L-α-methyldopa (methyldopa) is an α2-agonist acting in the CNS via its active metabolite, α-methylnorepinephrine
- Methyldopa is transported across the blood-brain barrier, where it is decarboxylated by aromatic L-amino acid decarboxylase in the brain to α-methyldopamine, which is then stereospecifically hydroxylated to 1R,2S-α-methylnorepinephrine.
- This stereoisomer is a selective α2-agonist and acts as an antihypertensive agent to inhibit sympathetic neural output from the CNS, thus lowering blood pressure.

Methyl DOPA

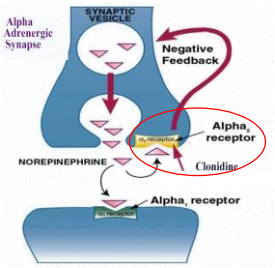


- Previously thought to act by mechanism of 'false neurotransmitter'
  - Originally synthesized as a norepinephrine biosynthesis inhibitor
  - Methyldopa was thought to act by inhibiting norepinephrine biosynthesis and itself getting metabolised to generate α-methylnorepinephrine.
  - The latter was thought to replace norepinephrine in the nerve terminal and, when released, to have less intrinsic activity than the natural neurotransmitter .
  - This latter mechanism is an example of the concept of a false neurotransmitter.
- But now the mechanism of inhibiting norepinephrine release by negative feedback mechanism is accepted. But it is still known as a false neurotransmitter because it takes the place of norepinephrine but is not a true neurotransmitter.

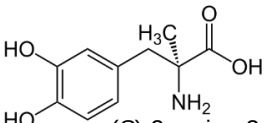
Centrally acting α-2 agonists



- Site of Action
  - CNS medullary
  - Cardiovascular centre
- Mechanism of action
  - Stimulate α2 receptors
  - Stimulation of this presynamptic α2 receptor inhibits further release of adrenaline and noradrenaline. (feedback mechanism for modulating the release of norepinephrine)
  - Decrease sympathetic activity
  - Decrease epinephrine/norepinephrine release
  - Decrease peripheral vascular resistance
- Drugs
  - Methyl DOPA (Aldomet) – False neurotransmitter
  - Clonidine (Catapres) – Direct α2 agonist

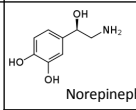
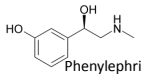
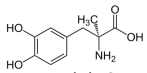
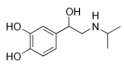
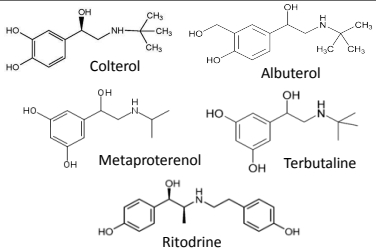
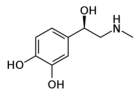
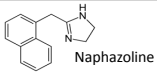
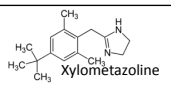
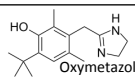
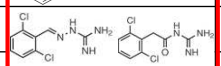


Methyl DOPA



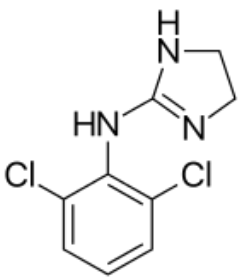
(*S*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid

- Direct acting sympathomimetic
- α2 agonist
- Methyldopa (Aldomet)
- A prodrug metabolized to active α2 receptor agonist, (1*R*, 2*S*)-α-methylnorepinephrine
- Act at CNS α2 receptors to decrease sympathetic outflow
- Water soluble, ester hydrochloride salt Methyldopate is used for parenteral solutions
- Administration: Methyldopa, oral; Methyldopate; parenteral
- Uses: Hypertension
- Methyldopa is used in the treatment of moderate to severe hypertension in conjunction with a diuretic.
- Drug of choice for treating hypertension during pregnancy
- The side effects and toxicity limit its usefulness.

	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	 Norepinephrine	 Phenylephrine	 Methyl DOPA	 Isoproterenol		 Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	 Epinephrine					
Aryl imidazolines		 Naphazoline				
		 Xylometazoline				
		 Oxymetazoline				
Amino imidazolines			 Clonidine			
Open ring imidazolines			 **Guanabenz** **Guanafacine**			

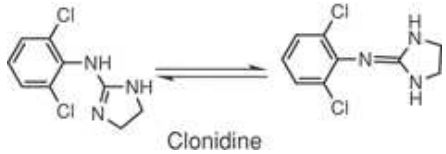
Clonidine

- Clonidine, was introduced as an antihypertensive, an effect attributed to central α2A-adrenoceptors in cardiovascular control areas of the brain



Clonidine

- Similar to the imidazoline α1-agonists, clonidine has lipophilic *ortho*-dichloro substituents on the phenyl ring, but the most readily apparent difference between clonidine and the α1-agonists is the replacement of the CH2 bridge on C1 of the imidazoline by an amine NH.
- This makes the imidazoline ring part of a guanidine group, and the uncharged form of clonidine exists as a pair of tautomers as shown.

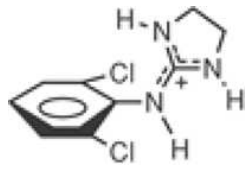


Clonidine

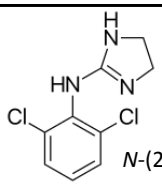
Clonidine

- **Basicity** : Clonidine has a pKa of 8.3 and is approximately 80% ionized at physiologic pH.
  - The positive charge is shared through resonance by all three nitrogens of the guanidino group.
- **Bioactive conformation**: Steric crowding by the bulky *ortho*-chlorine groups does not permit a coplanar conformation of the two rings – bioactive conformation
- **Duration of action**: The o, o'-dichloro-substituents in clonidine can be replaced by a methyl group without losing any potency or selectivity.
  - A methyl group is approximately similar in size (volume) as a chlorine atom; thus, it will exhibit similar steric interactions to force the phenyl ring to assume proper conformation for binding to the α2-receptors
  - Thus, replacement of the o-dichlorines by bulky groups in clonidine will retain its agonist potency.
  - The aromatic methyl group, however , will be readily metabolized by the cytochrome P450 enzyme to the corresponding hydroxymethyl and then to the carboxylic acid group, both of which are inactive at the α2-receptors.
  - Thus, the methyl analogue will have a shorter duration of action.

Protonated clonidine



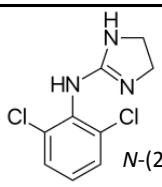
Clonidine



N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine

- Direct acting sympathomimetic
- α2 agonist
- (Phenylimino)imidazolidine
- α receptor agonist
- Dual activity:
  - Being an α receptor agonist, Clonidine was originally synthesized as a vasoconstricting nasal decongestant but, in early clinical trials, was found to have dramatic hypotensive effects—in contrast to all expectations for a vasoconstrictor.
  - Subsequent pharmacological investigations showed that clonidine not only has some α1-agonist (vasoconstrictive) properties in the periphery but also that it is a powerful α2-adrenergic agonist in the CNS and exhibits specific binding to nonadrenergic imidazoline binding sites in the CNS (mainly in the medulla oblongata) causing inhibition of sympathetic output (sympathoinhibition).
  - Thus,
    - initial doses of clonidine first may produce a transient vasoconstriction (peripheral α1-agonist) and an increase in blood pressure that is soon overcome by
    - vasodilation as clonidine penetrates the blood-brain barrier and interacts with CNS α2- receptors.

Clonidine



N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine

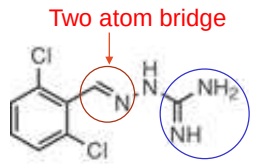
- The basicity of the guanidine group (pKa = 13.6) is decreased (to pKa = 8.0) because of the attachment to the dichlorophenyl ring
- Administration: Oral, parenteral, transdermal
- Uses: Hypertension, opiate withdrawal

Open ring imidazolines

- Following the discovery of clonidine, extensive research into the SAR of central α2-agonists showed that the imidazoline ring was not necessary for activity in this class
- but that the phenyl ring required at least one ortho chlorine or methyl group. Two clinically useful antihypertensive agents resulting from this effort are guanfacine and guanabenz.
- These are ring-opened analogues of clonidine, and their mechanism of action is the same as that of clonidine.

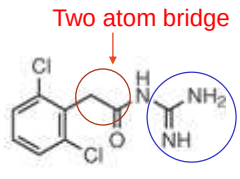
Guanabenz, Guanfacine

- Direct acting sympathomimetic
- α2 agonist
- Open-ring" imidazolidines
- Two atom bridge to the guanidine group decreases the pKa so that the drug is mostly non-ionized at physiological pH
- Guanabenz has the shortest t-1/2 at ~ 6 hours.
  Half-life of clonidine and guanfacine is 12-16 hours
- Administration: oral
- Uses: Hypertension



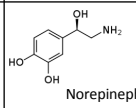
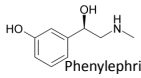
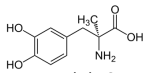
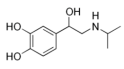
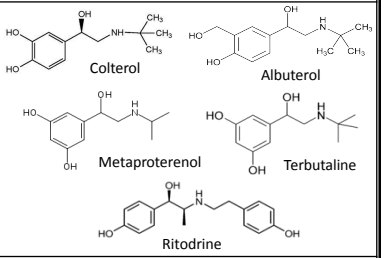
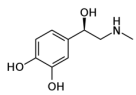
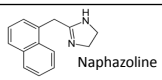
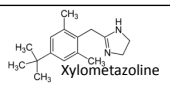
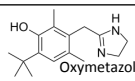
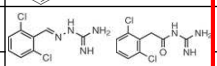
Guanabenz

2-(2,6-dichlorobenzylidene)hydrazinecarboximidamide

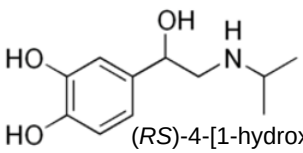


Guanfacine

N-(diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide

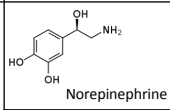
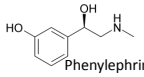
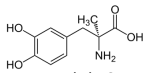
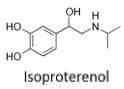
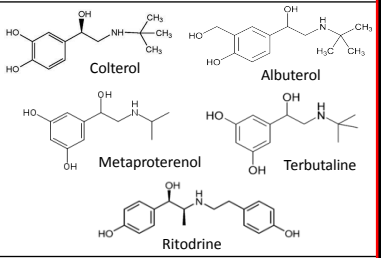
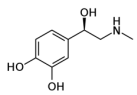
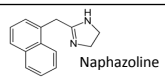
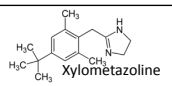
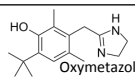
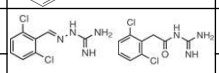
	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	 Norepinephrine	 Phenylephrine	 Methyl DOPA	 Isoproterenol		 Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	 Epinephrine					
Aryl imidazolines		 Naphazoline				
		 Xylometazoline				
		 Oxymetazoline				
Amino imidazolines			 Clonidine			
Open ring imidazolines			 Guanabenz, Guanafacine			

Isoproterenol

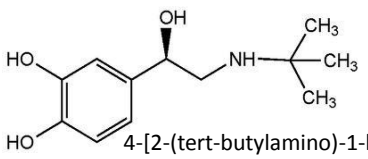


(*RS*)-4-[1-hydroxy-2-(isopropylamino)ethyl]benzene-1,2-diol

- Direct acting sympathomimetic
- Non-selective β receptor agonist
- Increased cardiac output (β1)
- Bronchodilation (β2)
- Not sensitive to MAO
- Metabolized by conjugation reactions (Phase II) and by COMT
- Administration: Oral, parenteral, local (inhaled)
- Uses: Asthma, Chronic Obstructive Pulmonary Disease (COPD), Cardiostimulant

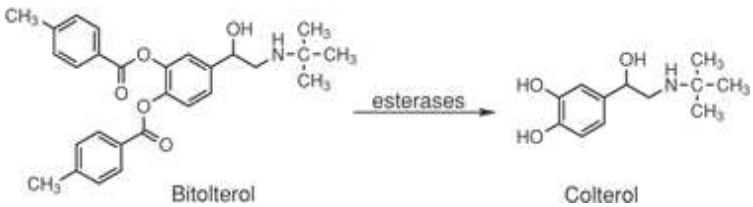
	nonselective α + β	α1	α2	nonselective β	β1	β2
Phenylethanol amines	 Norepinephrine	 Phenylephrine	 Methyl DOPA	 Isoproterenol		 Colterol, Albuterol, Metaproterenol, Terbutaline, Ritodrine
	 Epinephrine					
Aryl imidazolines		 Naphazoline				
		 Xylometazoline				
		 Oxymetazoline				
Amino imidazolines			 Clonidine			
Open ring imidazolines			 Guanabenz, Guanafacine			

Colterol



4-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,2-diol

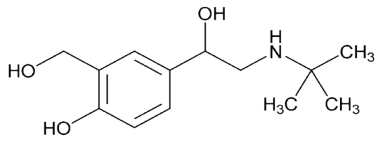
- Direct acting sympathomimetic
- β2 receptor agonist
- Subject to metabolism by COMT which decreases its duration of action. Hence it is given as a prodrug - bitolterol
- Bitolterol is a pro-drug form of colterol in which the catechol hydroxyl groups have been converted to 4-methylbenzoic (p-toloyl) acid esters, providing increased lipid solubility and prolonged duration of action.



Bitolterol → Colterol

- Bitolterol is administered by inhalation, and the ester groups are hydrolyzed by esterases to liberate the active drug, colterol.
- Colterol is then subject to metabolism by COMT, but the duration of action of a single dose of the pro-drug bitolterol, up to 8 hours, is twice that of a single dose of colterol, permitting less frequent administration and greater convenience to the patient .

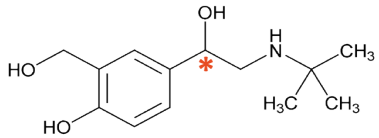
Albuterol



(*RS*)-4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol

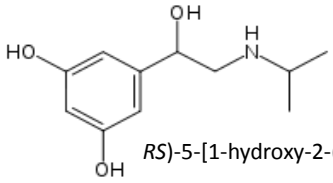
- Direct acting sympathomimetic
- β2 receptor agonist
- Salbutamol
- *Meta* hydroxymethyl derivatives
- Selective β2 receptor agonists
- Bronchodilation
- Cardiac effects observed only at high doses
- Not metabolized by MAO or COMT
- Longer duration of action than isoproterenol
- Administration: Oral, local (inhaled)
- Uses: Asthma, COPD

Albuterol



- Two stereoisomers – R and S
- Effect on Activity
  - (R)-enantiomer – bronchodilator (levoalbuterol), rapid metabolism (sulfation)
  - (S)-enantiomer – proinflammatory, slower metabolism (longer duration of adverse effects)
    - exacerbates airway reactivity to a variety of spasmogens and, thereby, enhancing bronchial muscle contraction, thus opposing the bronchodilation effects of the (R) -enantiomer levoalbuterol.
- Effect on Metabolism
  - Levalbuterol undergoes more rapid metabolism (sulfation) than the (S)-(+)-isomer , resulting in a lower oral bioavailability and rapid elimination.
  - Because of its slower metabolism, (S)-albuterol thus has a higher and prolonged tissue concentrations than levalbuterol, increasing airway reactivity.
- These prolonged adverse effects of (S)-albuterol are completely avoided by using the (R)-enantiomer, levalbuterol.
- Removal of (S) -albuterol from racemic albuterol increases the clinical potency of levalbuterol, such that bronchodilator efficacy is achieved at one- fourth the dose of racemic albuterol along with a marked reduction in side effects.

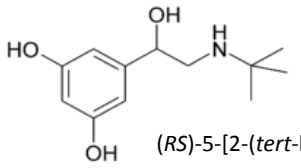
Metaproterenol



RS)-5-[1-hydroxy-2-(isopropylamino)ethyl]benzene-1,3-diol

- Direct acting sympathomimetic
- β2 receptor agonist
- Resorcinol derivatives
- Selective β2 receptor agonists
- Bronchodilation
- Not metabolized by MAO or COMT
- Longer duration of action than isoproterenol
- Administration: Oral, parenteral, local (inhaled)
- Uses: Asthma, COPD

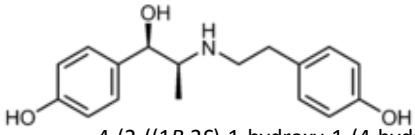
Terbutaline



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

- Direct acting sympathomimetic
- β2 receptor agonist
- Resorcinol derivatives
- Selective β2 receptor agonists
- Bronchodilation
- Not metabolized by MAO or COMT
- Longer duration of action than isoproterenol
- Administration: Oral, parenteral, local (inhaled)
- Uses: Asthma, COPD; Terbutaline used as tocolytic (prevent premature labor)

Ritodrine



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

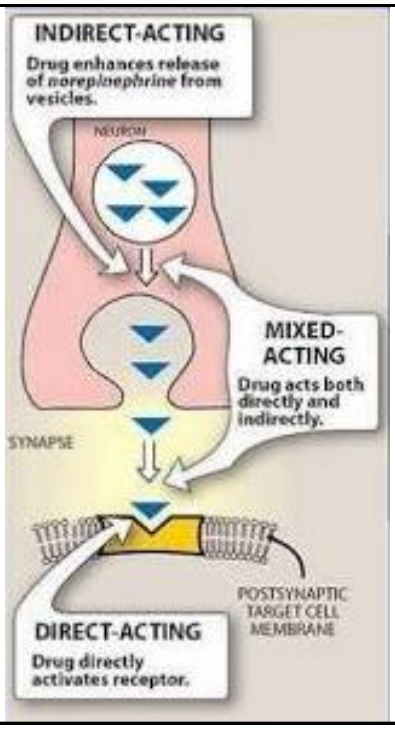
- Direct acting sympathomimetic
- β2 receptor agonist
- Selective β2 receptor agonists
- Administration: Oral, parenteral
- Uses: Tocolytic
- Ritodrine is a selective β2-agonist that is used exclusively for relaxing uterine muscle and inhibiting the contractions of premature labor .

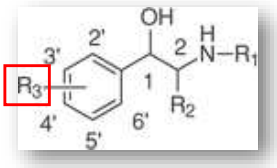
Uterine relaxants

- The previously mentioned ritodrine is a selective β2-agonist that is used exclusively for relaxing uterine muscle and inhibiting the contractions of premature labor .
- Terbutaline, in addition to its use as a bronchodilator , also has been used for halting the contractions of premature labor.

Direct / Indirect activity

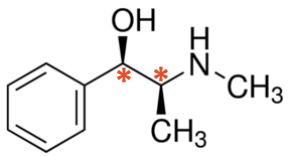
- Direct activity (i.e., agonist) is the stimulation of an adrenoceptor by the drug itself;
- Indirect activity is the result of displacement of norepinephrine from its storage granules or reuptake inhibition, resulting in nonselective stimulation of the adrenoceptors by the displaced norepinephrine.
  - Because norepinephrine stimulates both α- and β-adrenoceptors, indirect activity cannot be selective.
  - Stereochemistry of the various substituents also may play a role in determining the extent of direct / indirect activity.



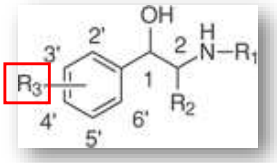


R3, Substitution on the aromatic ring

- When the phenyl ring has no phenolic substituents (i.e. , R3 = H), these phenylethanolamines may have both direct and indirect activity.

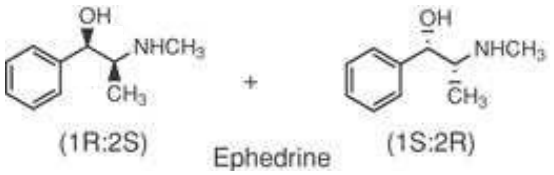


Ephedrine
α + β



R3, Substitution on the aromatic ring

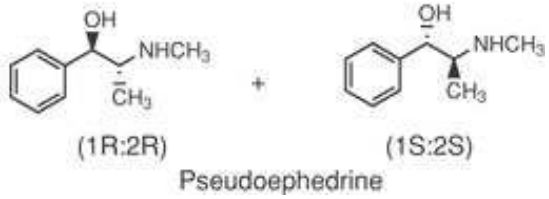
- Stereochemistry of the various substituents also may play a role in determining the extent of direct / indirect activity.
  - For example, ephedrine and pseudoephedrine have the same substitution pattern, but substitution of both carbons 1 and 2 means four stereoisomers are possible.



Naturally occurring stereoisomer
mixed direct activity (α- and β)
some indirect activity

primarily indirect activity

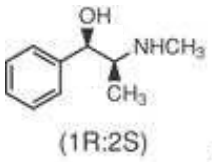
Racemic (—)-ephedrine



Racemic (—)-pseudoephedrine

primarily indirect activity

Mixed-Acting Sympathomimetics

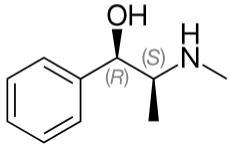


- Phenylpropanolamines
  - ***(–)-Ephedrine***
    - Natural product isolated from several species of ephedra plants
    - **Good Oral activity** – not a substrate for COMT
      - Ephedrine does not have any phenolic substituents on the phenyl ring, giving it a mixed-acting response
    - **More lipophilic** – Crosses into CNS
      - Lacking hydrogen bonding phenolic substituents, ephedrine is less polar and crosses the blood-brain barrier far better than the catechols do.
      - Because of its ability to penetrate the CNS, ephedrine has been used as a stimulant and exhibits side effects related to its action in the brain.
    - Ephedrine is widely used for many of the same indications as epinephrine, including use as a bronchodilator, vasopressor , cardiac stimulant, and nasal decongestant.

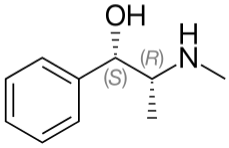
Ephedrine

- Ephedrine is obtained from the plant *Ephedra sinica*
- Ephedrine, is the erythro diastereomer, with one of the stereoisomers (1R, 2S) having direct activity
- Ephedrine exhibits CNS side effects.
- Ephedrine is a medication used to prevent low blood pressure during spinal anesthesia

(1*R*,2*S*)-(–)-Ephedrine
(–)-*erythro*-Ephedrine

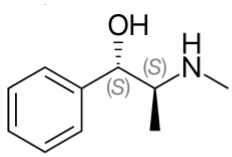


(1*S*,2*R*)-(+)-Ephedrine
(+)-*erythro*-Ephedrine

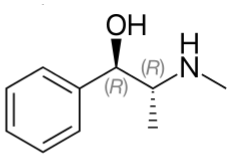


Mixed-Acting Sympathomimetics

- Phenylpropanolamines
  - ***Pseudoephedrine***
    - Pseudoephedrine, is the threo diastereomer of ephedrine, with virtually no direct activity and fewer CNS side effects than ephedrine.
    - (+)-Pseudoephedrine is widely used as a nasal decongestant.

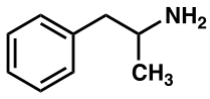


(1*S*,2*S*)-(+)-Pseudoephedrine
(+)-*threo*-Ephedrine

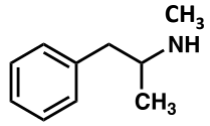


(1*R*,2*R*)-(–)-Pseudoephedrine
(–)-*threo*-Ephedrine

Phenylisopropylamines



Amphetamine



methamphetamine

- **Amphetamine and methamphetamine**
- Methyl-substituted phenylethylamines (phenylisopropylamines)
- Lack both ring substituents and a side-chain hydroxyl. Hence are sufficiently lipophilic to cross the blood-brain barrier readily and cause dramatic CNS stimulation, which gives them serious abuse potential.
- The clinical utility of (S) -(+) -amphetamine and its derivatives is entirely based on CNS stimulant and central appetite suppressant effects.