UNIT II (PART II)

DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

SYMPATHOMIMETIC AGENTS

PREPARED BY:

NEETU SABARWAL (ASST. PROF)

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

SOS PHARMACEUTICAL SCIENCES

JIWAJI UNIVERSITY GWALIOR

Sympathetic "Fight or Flight

Definition of Sympathomimetic drugs

- Drugs that partially or completely mimic the actions of epinephrine (Epi) or norepinephrine (NE)
- They produce effects similar to the effects of sympathetic nerve fibers.

Sympathomimetic drugs

- Sympathomimetic drugs are stimulant compounds which mimic the effects of agonists of the sympathetic nervous system such as the catecholamines. (epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine, etc.)
- Sympathomimetic drugs are used to treat cardiac arrest and low blood pressure, or even delay premature labor, among other things.
- These drugs can act through several mechanisms, such as directly activating postsynaptic receptors, blocking breakdown and reuptake of certain neurotransmitters, or stimulating production and release of catecholamines

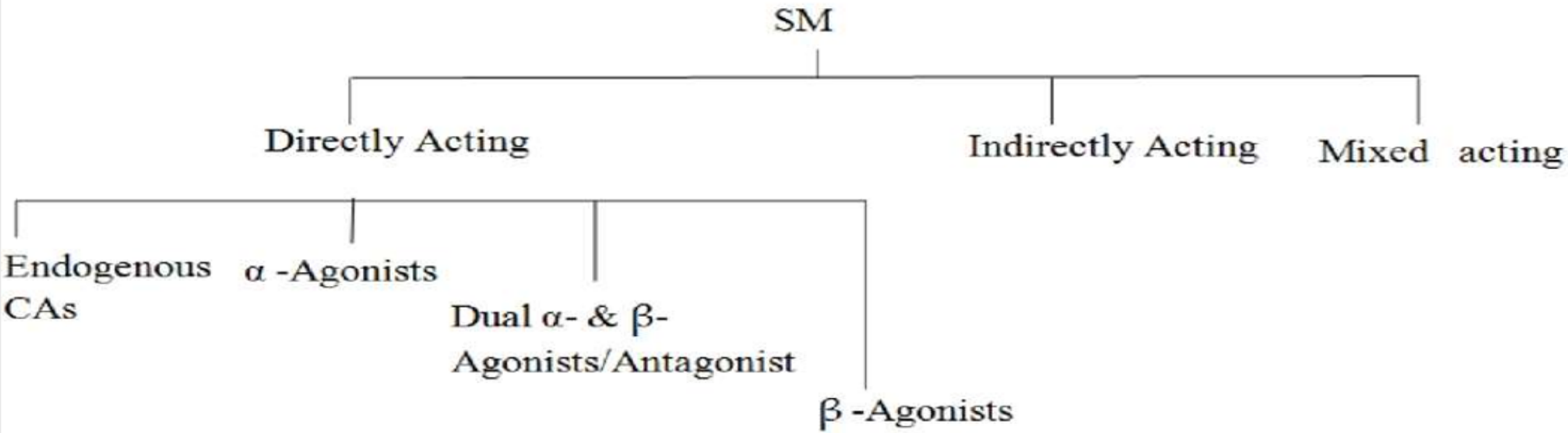
Mechanisms of action

- The mechanisms of sympathomimetic drugs can be direct-acting, such as α-adrenergic agonists, β-adrenergic agonists, and dopaminergic agonists; or indirect-acting, such as MAOIs, COMT inhibitors, release stimulants, and reuptake inhibitors that increase the levels of endogenous catecholamines.

Structure-activity relationship

- For maximum sympathomimetic activity, a drug must have:
- Amine group two carbons away from an aromatic group
- A hydroxyl group at the chiral beta position in the R-configuration
- Hydroxyl groups in the meta and para position of the aromatic ring to form a catechol which is essential for receptor binding
- The structure can be modified to alter binding. If the amine is primary or secondary, it will have direct action, but if the amine is tertiary, it will have poor direct action. Also, if the amine has bulky substituents, then it will have greater beta adrenergic receptor activity, but if the substituent is not bulky, then it will favor the alpha adrenergic receptors.

CLASSIFICATION



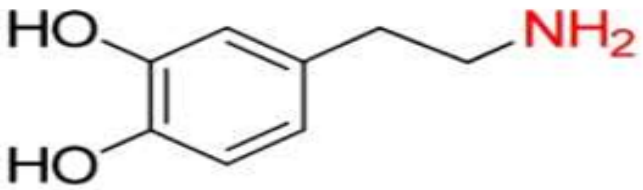
CLASSIFICATION

Endogenous CAs

(1) Dopamine

(2) Norepinephrine

(3) Epinephrine



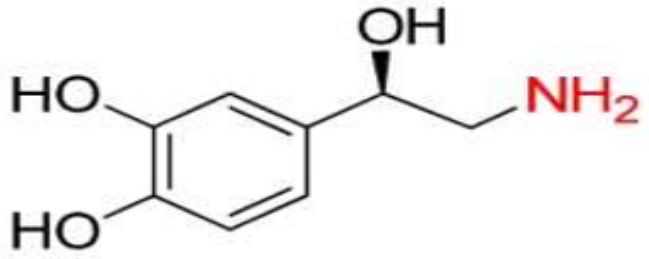
Dopamine

i.v. high dose

Vasoconstriction (α_1 action)

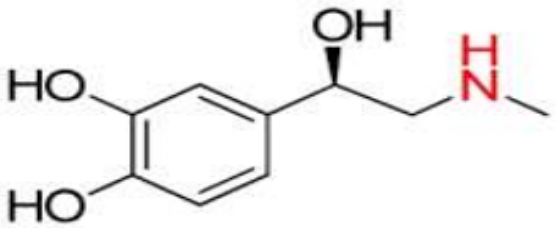
↑ HR (β_1-receptors)

Use: treatment of shock



Norepinephrine

Use: in hypotensive crises



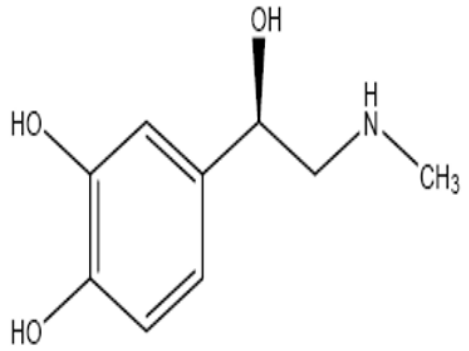
Epinephrine

Use: treat hypotensive crises and nasal congestion (α action)

in asthma (β_2 action)

Endogenous catecholamines are synthesized in neurons and in the chromaffin cells of the adrenal medulla, and stored in intracellular vesicles.

Epinephrine



- Potent stimulant of both α and β adrenoceptors;
- Drug of choice for reversal of acute hypersensitivity reactions
- Enhances the action of local anesthetics
- Poor oral absorption. Rapidly metabolized by MAO and COMT;
- Degrades on exposure to air and light;
- Serious side effects include cerebral hemorrhage and cardiac arrhythmias.

Epinephrine/ Adrenaline

- Epinephrine interacts with both α and ß receptors.
- At low doses – β2 effects (vasodilation) on the vascular system predominate,
- At high doses – α1 effects (vasoconstriction) are strongest.
- Actions :

1. Cardiovascular

– Strengthens the contractility of the myocardium and increases its rate of contraction.

– Activates β 1receptors on the kidney to cause renin release.

– Constricts arterioles in the skin, mucous membranes, and viscera (α1 effects), and it dilates vessels going to the liver and skeletal muscle (β 2 effects).

– **Cumulative effect is an increase in systolic blood pressure & slight decrease in diastolic pressure.**

Dales vasomotor reversal phenomenon

- Intravenous injection of adrenaline normally causes increase in blood pressure (α1 effect) followed by prolonged fall (β 2 effect).
- If it is administered after giving α blockers, only fall in blood pressure is seen.
- This phenomenon is called as Dales vasomotor reversal.

2. Respiratory – causes powerful bronchodilation by acting directly on bronchial smooth muscle (ß 2 action).

3. Hyperglycemia - significant hyperglycemic effect because of

- increased glycogenolysis in the liver (β 2 effect),
- increased release of glucagon (β 2 effect), and
- decreased release of insulin (α 2 effect).

4. Lipolysis – it has agonist activity on the β 3 receptors of adipose tissue

Therapeutic uses

1. Anaphylactic shock :

- Epinephrine is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.

2. Relieves Bronchospasm :

3. Cardiac arrest :

- Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest like drowning & electrocution.

4. with local Anesthetics :

- Local anesthetic solutions - contain 1:100,000 parts epinephrine - to increase the duration action of the local anesthesia.

5. To control epistaxis :

- Very weak solution (1:100,000) - used topically to vasoconstrict the mucous membranes to control oozing of capillary blood.

Nor Epinephrine/Nor Adrenaline

- They are agonist at α1, α 2 and β 1 receptors with similar potency as epinephrine, but has relatively little effect on β 2 receptors.

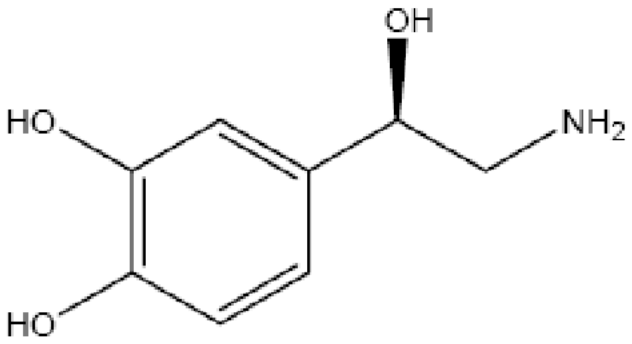
Therapeutic uses:

carefully used to treat cardiogenic shock but dopamine is preferred as nor epinephrine is associated with renal shutdown.

Adverse effects:

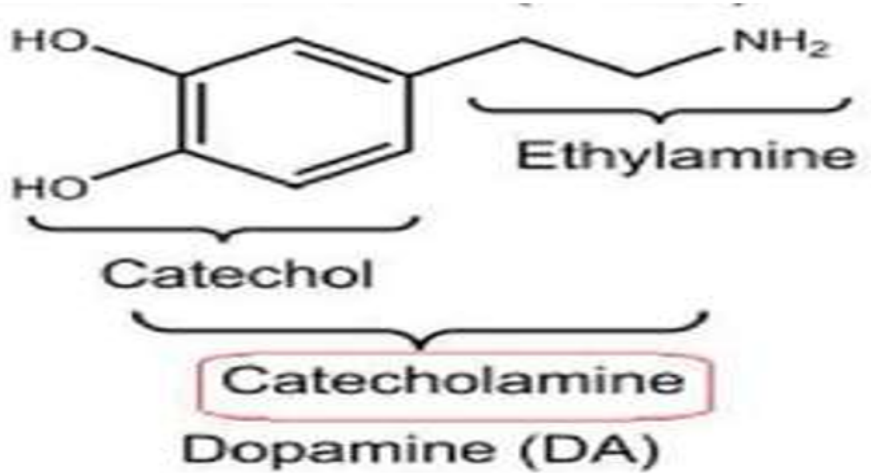
- Excessive doses can cause severe hypertension.
- Not suitable for subcutaneous, intra muscular or undiluted iv injection – danger of necrosis

Norepinephrine



- Potent stimulant of both α and β adrenoceptors
- Limited therapeutic value
- Used to maintain blood pressure in acute hypotensive states
- Substrate for MAO and COMT, not effective orally
- Undergoes oxidation in prolonged exposure to air. Sodium bisulfite used as antioxidant in NE preparations

Dopamine

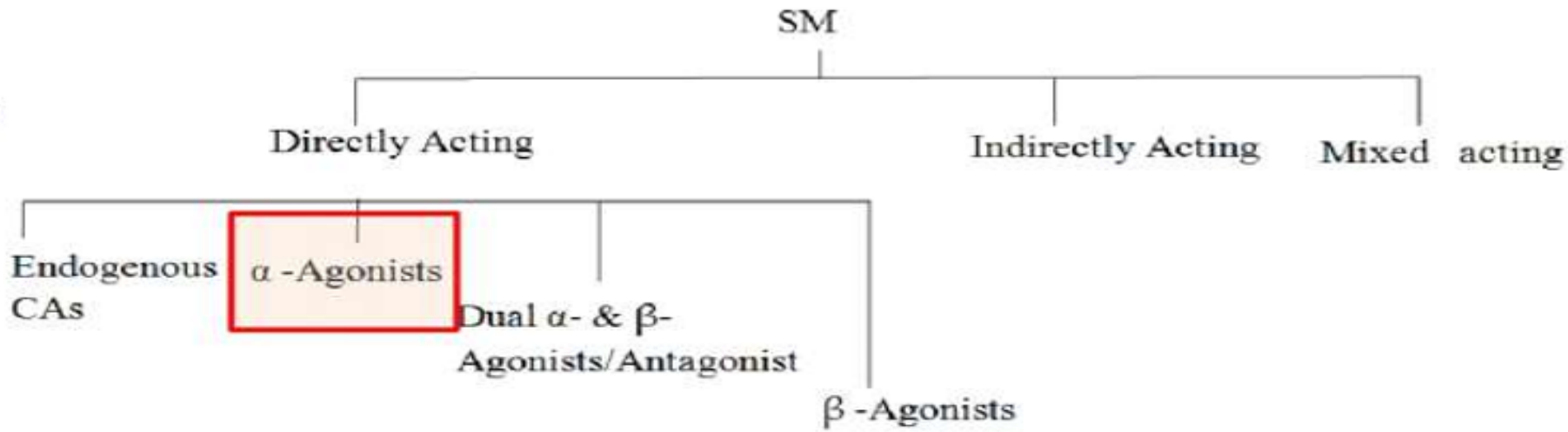


- Not strictly an adrenergic drug, acts on dopamine receptors.
- Stimulates cardiac β_1-AR through both direct and indirect mechanisms.
- Used to correct hemodynamic, or congestive heart failure
- Rapidly metabolized by MAO and COMT. Not effective orally.

CLASSIFICATION

α -Agonists

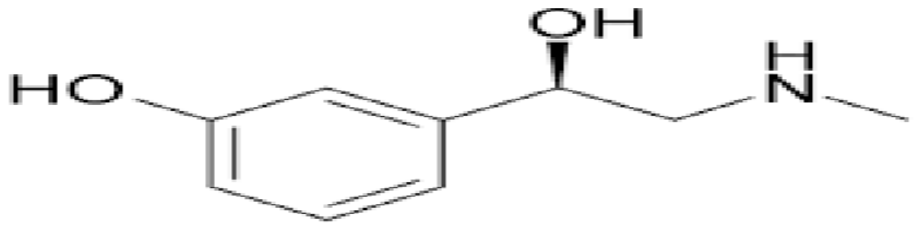
- Phenylethanolamines
  1. Phenylephrine
  2. Methoxamine
  3. Midodrine
- 2-Arylimidazoline
  1. Naphazoline
  2. tetrahydrozoline
  3. xylometazoline
  4. oxymetazoline
- 2-Aminoimidazolines
  1. Clonidine
  2. Apraclonidine
  3. Brimonidine
- Open-Ring Imidazolidines
  1. Guanabenz
  2. Guanfacine
- Methyldopa



α Agonists

(a) Phenylethanolamines

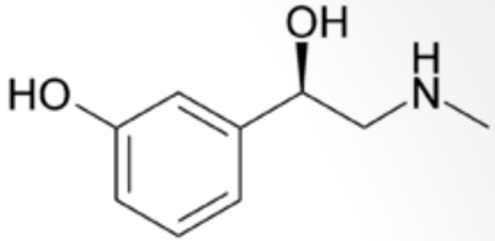
Phenyl ephrine



It is a potent vasoconstrictor which is active orally and its duration of action is twice than that of ephinephrine

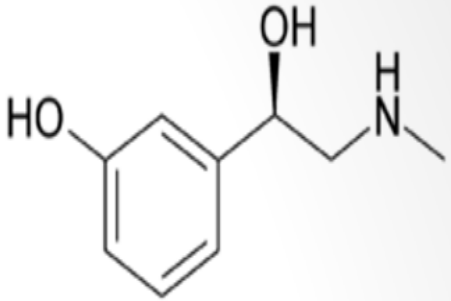
It is non toxic mainly used as nasal decongestion and also dilation of pupil in glaucoma.

Phenylephrine



- Phenylephrine is a selective α1-adrenergic receptor agonist of the phenethylamine class used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure.
- Phenylephrine can also cause a decrease in heart rate through reflex bradycardia
- Phenylephrine can be used topically to prevent symptoms of hemorrhoids. Since phenylephrine is a vasoconstrictor, the blood vessels are narrowed, reducing the pain associated with hemorrhoids.
- Phenylephrine is used as an eye drop to dilate the pupil to facilitate visualization of the retina.
- Phenylephrine is commonly used as a vasopressor to increase the blood pressure in unstable patients with hypotension

Phenylephrine



Mechanism of action

- Oral phenylephrine is extensively metabolized by monoamine oxidase, an enzyme that is present on the outside of cells, throughout the body. Compared to intravenous pseudoephedrine, phenylephrine has a reduced and variable bioavailability; only up to 38%.
- Phenylephrine is a sympathomimetic drug, which means that it mimics the actions of epinephrine (commonly known as adrenaline) or norepinephrine.
- Phenylephrine selectively binds to alpha receptors which cause blood vessels to constrict.
- Phenylephrine may cause side effects such as headache, reflex bradycardia, excitability, restlessness and cardiac arrhythmias.

CLASSIFICATION

2-Arylimidazoline

- All are α_1-agonists
- Used for their vasoconstrictive effects as nasal decongestant and ophthalmic decongestant

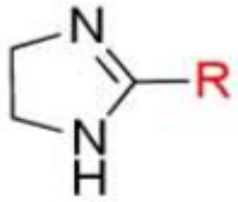
(1) Naphazoline

(2) Tetrahydrozoline

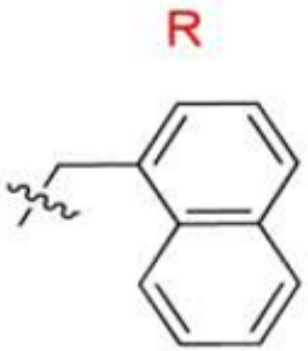
(3) Xylometazoline

(4) Oxymetazoline

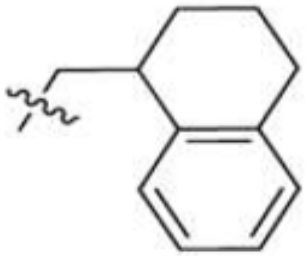
2-Arylimidazoline



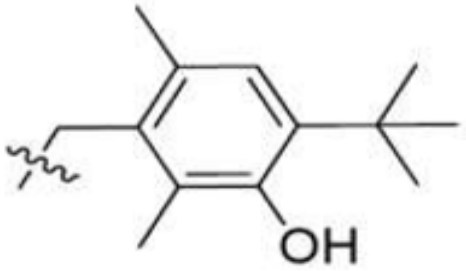
Naphazoline



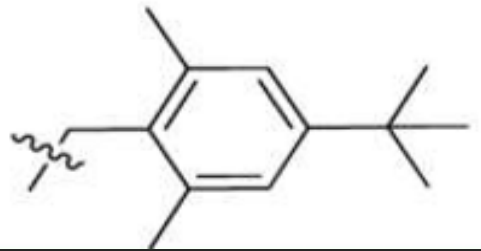
Tetrahydrozoline



Oxymetazoline



xylometazoline

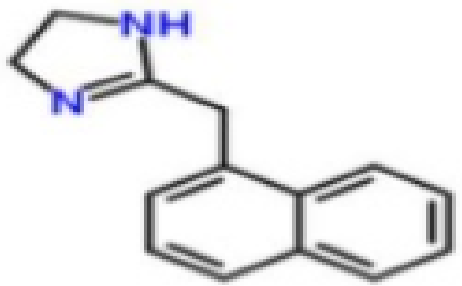


Imidazoline moity
pKa 9-10
Limited access to the CNS

- one-carbon bridge between imidazoline ring and a phenyl ring, and thus has a phenylethylamine structure

- lipophilic substituents on the phenyl ring may be important for the α_1-selectivity

NAPHAZOLINE

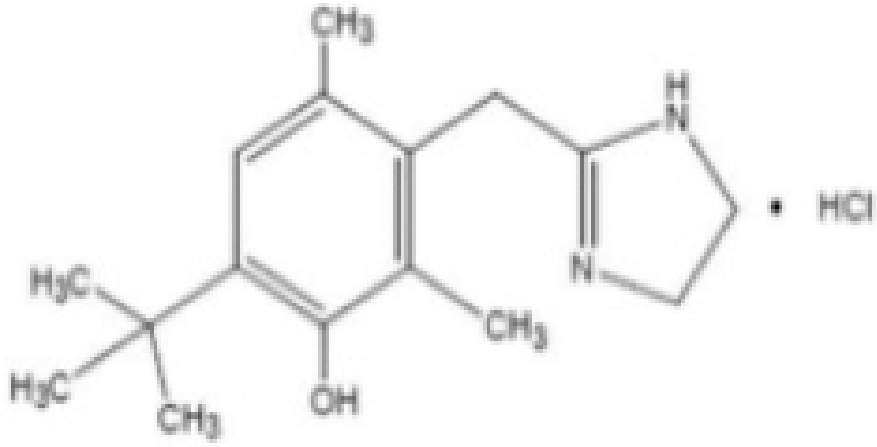


- Uses: 1. α-receptor agonist

2. Naphazoline is a decongestant used to relieve redness, puffiness, and itchy/watering eyes due to colds, allergies, or eye irritations.

- Direct-acting α 1 agonists.
- Used as topical decongestants because of promoting the constriction of the nasal mucosa.

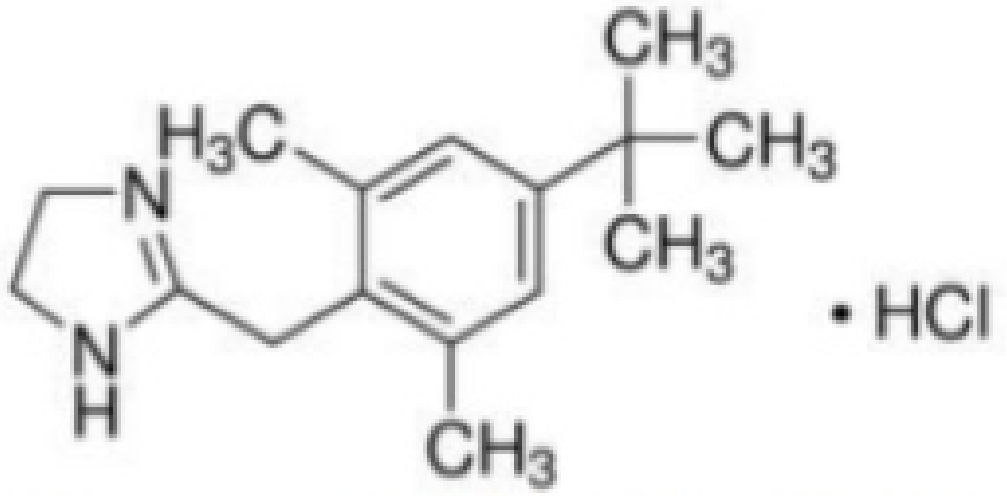
OXYMETAZOLINE



Uses: 1. Oxymetazoline nasal spray is used to relieve nasal discomfort caused by **colds**, **allergies**, and hay fever.

2.It is also used to relieve sinus **congestion** and pressure.

XYLOMETAZOLINE



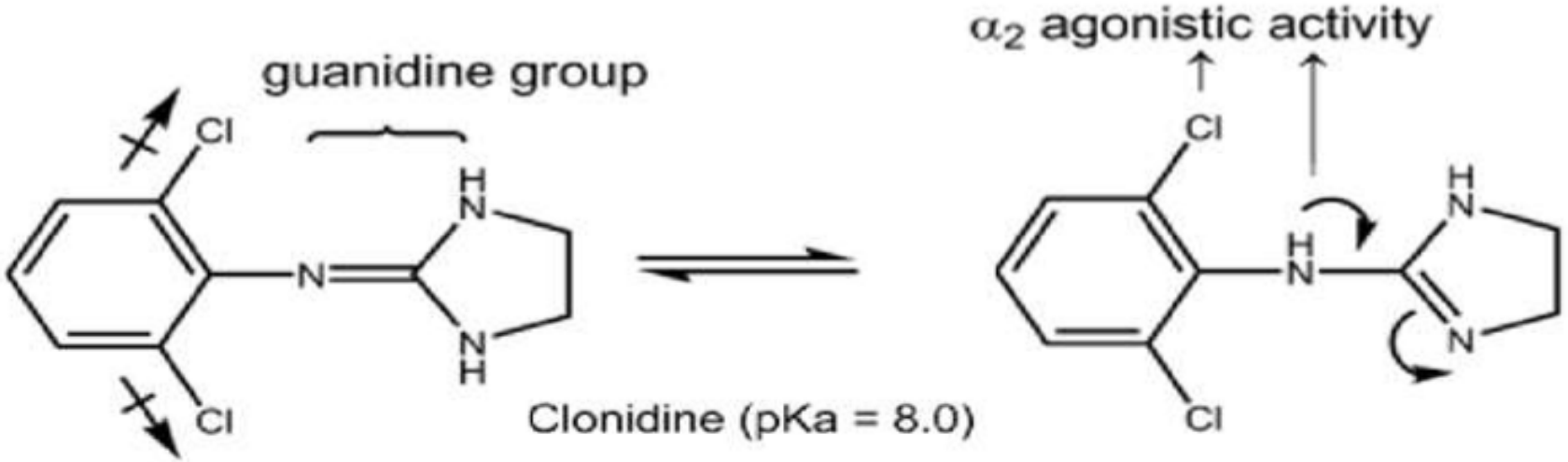
Uses: 1.Xylometazoline nasal is a decongestant that shrinks blood vessels in the nasal passages.

2.Dilated blood vessels can cause **nasal congestion (stuffy nose)**. Xylometazoline nasal (for use in the **nose**) is used to treat **stuffy nose** caused by **allergies**, sinus irritation, or the **common cold**.

2-Aminoimidazolines

- presence of O-chlorine groups and NH bridge.

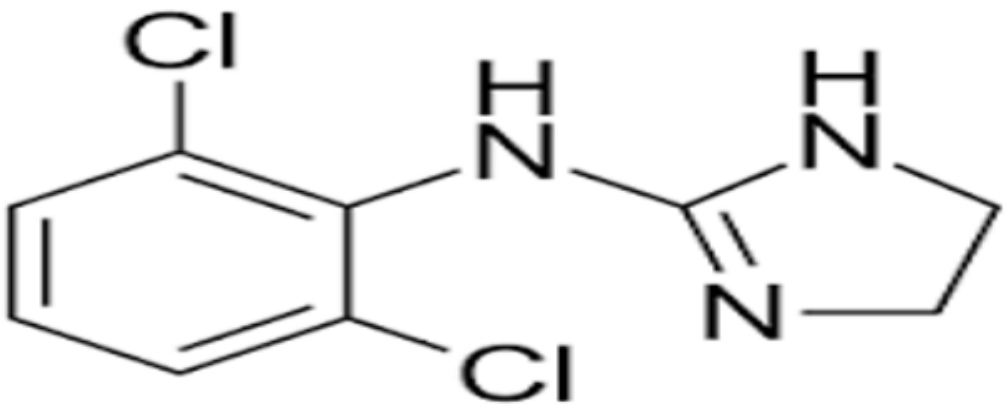
(1) Clonidine



inductive and resonance effects of the dichlorophenyl ring decrease pKa of clonidine

- [nasal decongestant to hypotensive]
- PNS → α_1-agonist → nasal decongestants + hypertension
- Low pKa → remains nonionized → crosses the BBB
- CNS → α_{2A}-adrenergic agonist → causing inhibition of sympathetic output → vasodilation → ↓ HR → hypotension

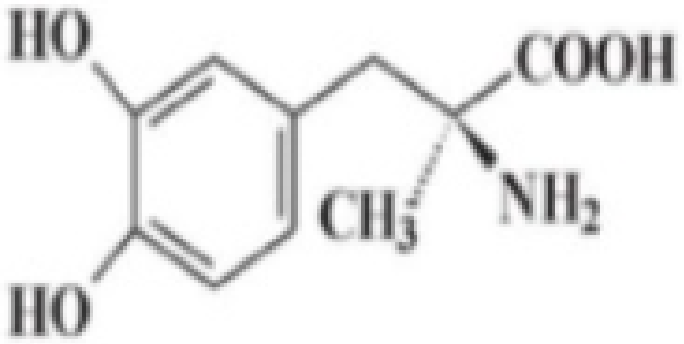
Clonidine



- It has selective α2 adrenergic agonist activity
- Used in the treatment of hypertension

STRUCTURE AND ITS USES:

METHYL DOPA



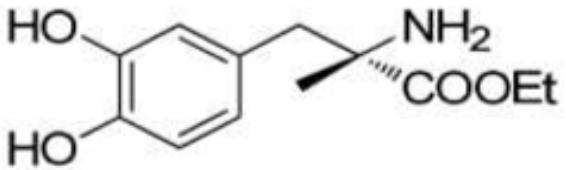
Uses: 1.selective α2 receptor agonist

2.Antihypertensive agent in pregnancy

3.Relaxes blood vessels for smooth blood flow during hypertension.

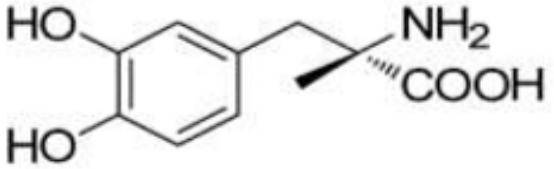
Side effects:Sedation, drowsiness,drymouth,depression

Methyldopa



Methyldopate

Esterase



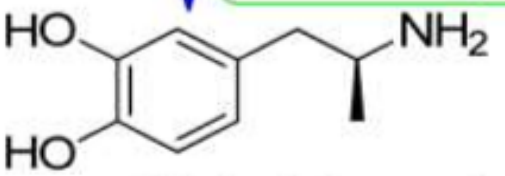
L- α -Methyldopa

Chemistry : L-α-Methyldopa is a pro-drug
zwitterion

M/A:

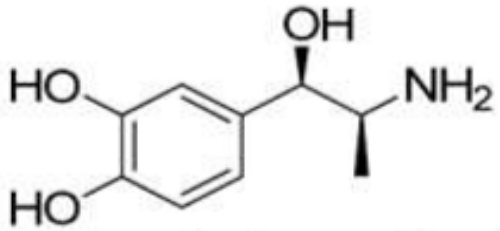
- originally designed as DOPA DC inhibitor but it is metabolized by enzymes and gives active metabolite α-methylnorepinephrine which is α_2-agonist acting in the CNS → decrease sympathetic outflow → lower blood pressure.
- only oral dosage from are possible
- Its ester form Methyldopate in i.v. formulation

Step_2 ↓ DOPA decarboxylase



α -Methyldopamine

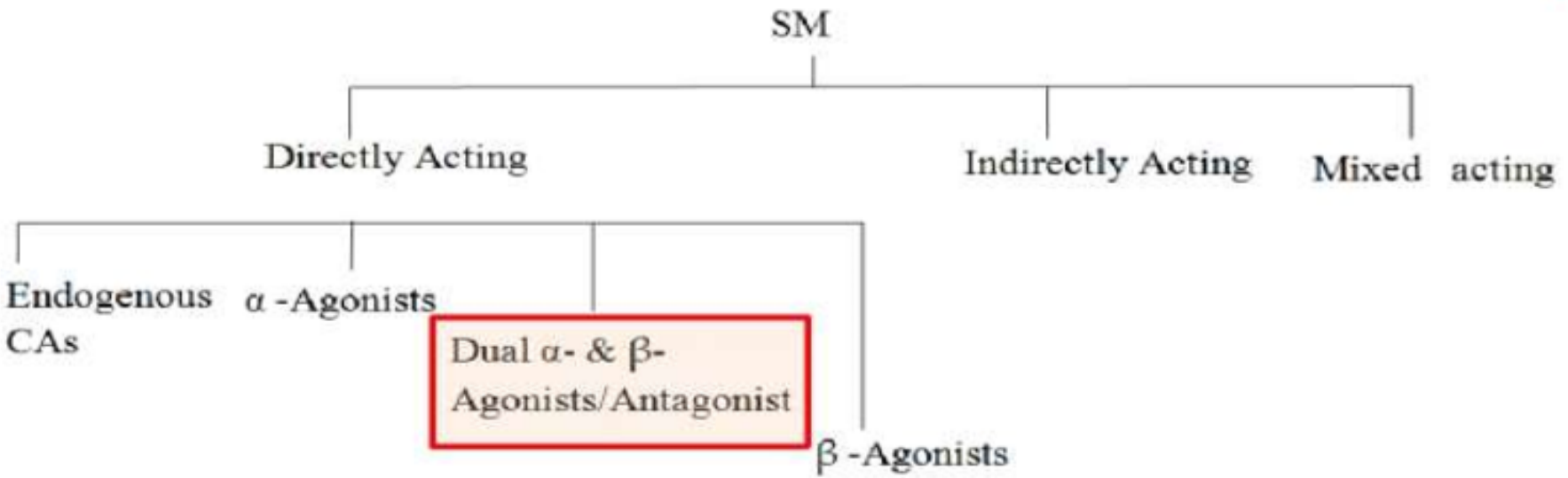
Step_3 ↓ dopamine β-hydroxylase



(1*R*,2*S*)- α-methylnorepinephrine
selective α_2-agonist

Use : antihypertensive

CLASSIFICATION

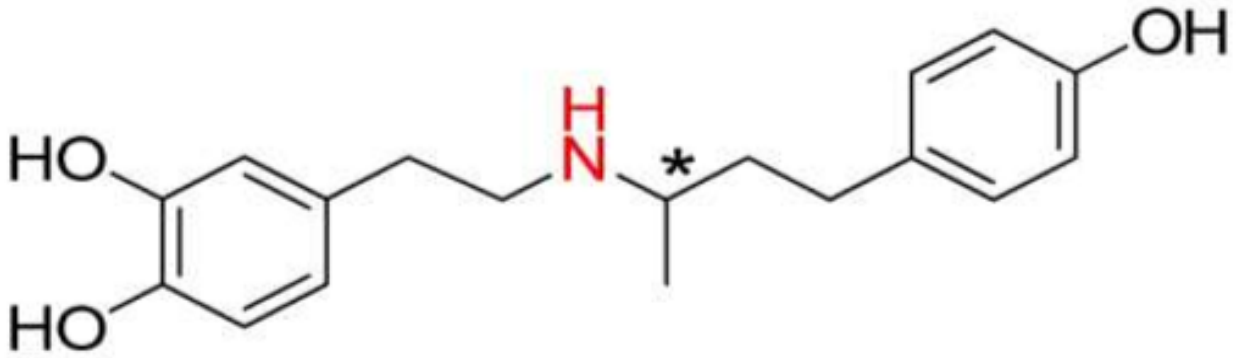


Dual α- & β-Agonists/Antagonists

1. Dobutamine

Dual α- & β-Agonists/Antagonists

(1) Dobutamine

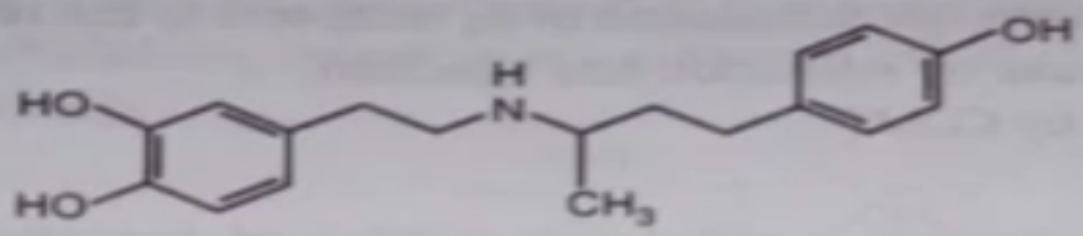


Chemistry:

- (-) isomer is a potent α_1-agonist
- (+) isomer is a potent α_1-antagonist
- isomers are β_1-agonist [(+) > (-)]
- thus, when the racemate is used clinically, the α-effects of the enantiomers cancel each other, leaving primarily the β_1-effects.

Use: used as a cardiac stimulant after surgery or congestive heart failure (CHF)

1. Dobutamine:



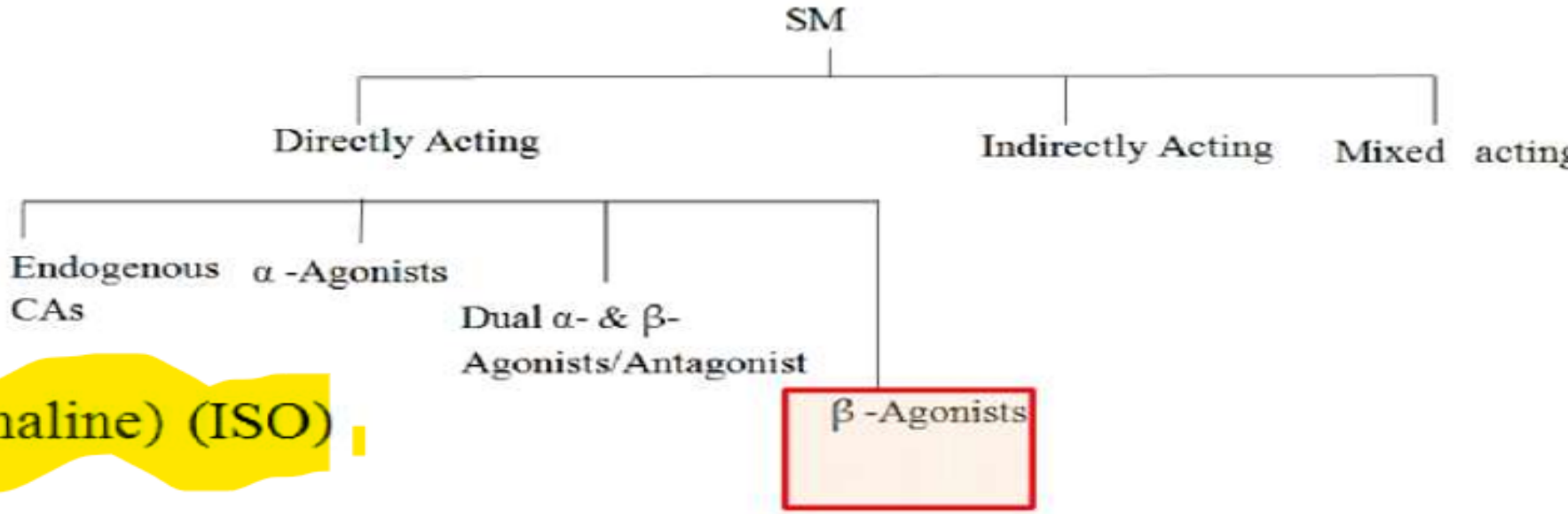
Dobutamine

- Dobutamine is chemically 3,4-dihydroxy-N-[3-(4-hydroxyphenyl)-1-methylpropyl]-b-phenylethylamine.
- It is a synthetic catecholamine derivative.
- It is given by intravenous infusion, since it is not effective orally.
- It gets metabolized by COMT and conjugation, but not by MAO.
- It resembles dopamine chemically, but possesses a bulky aromatic residue on the amino group i.e. 1-(methyl)-3-(4-hydroxyphenyl) propyl and absence of a β-OH group.
- It is a selective β_1 receptor agonist and has only slight indirect actions.
- It increases cardiac output without any effect on heart rate and blood pressure.
- It is a racemic mixture of two enantiomeric forms. The (+) isomer has potent β-agonistic actions. The (–) isomer has potent α_1 agonistic and poor β-agonistic actions.
- Racemic dobutamine increases the inotropic activity of the heart to a much greater extent than chronotropic activity.
- It does not act as an agonist at the dopaminergic receptors that mediate renal vasodilation.

Uses:

- Dobutamine is used in patients of heart failure associated with myocardial infarction, open heart surgery and cardiomyopathy.

CLASSIFICATION

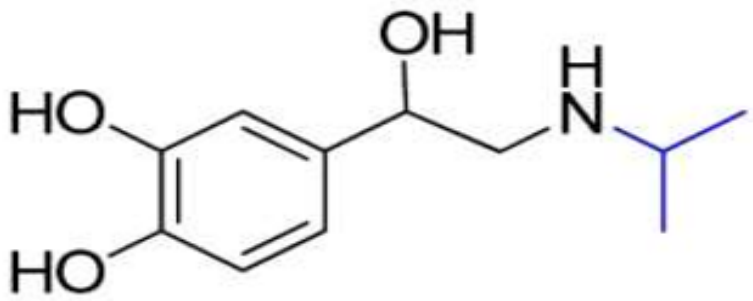


β-Agonists

1. Isoproterenol (Isoprenaline) (ISO)
2. Metaproterenol } Resorcinol bronchodilators
3. terbutaline
4. Albuterol (Salbutamol)
5. pirbuterol
6. salmeterol
7. Formoterol
8. Isoetharine
9. Bitolterol
10. Ritodrine

CLASSIFICATION

(1) Isoproterenol

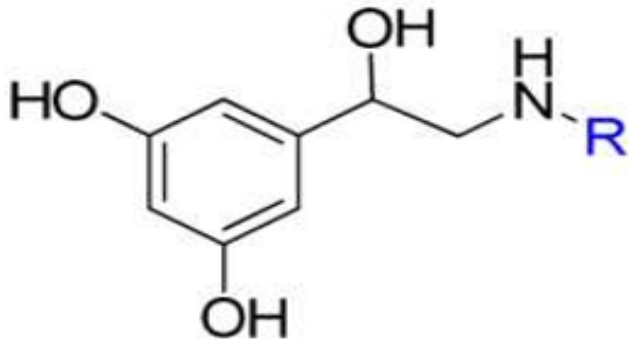


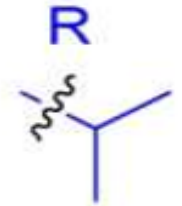
β_1 agonist → ↑ HR → use for treatment of heart block

β_2 agonist → bronchodilation → asthma , COPD

resorcinol bronchodilators

(2) Metaproterenol (3) terbutaline



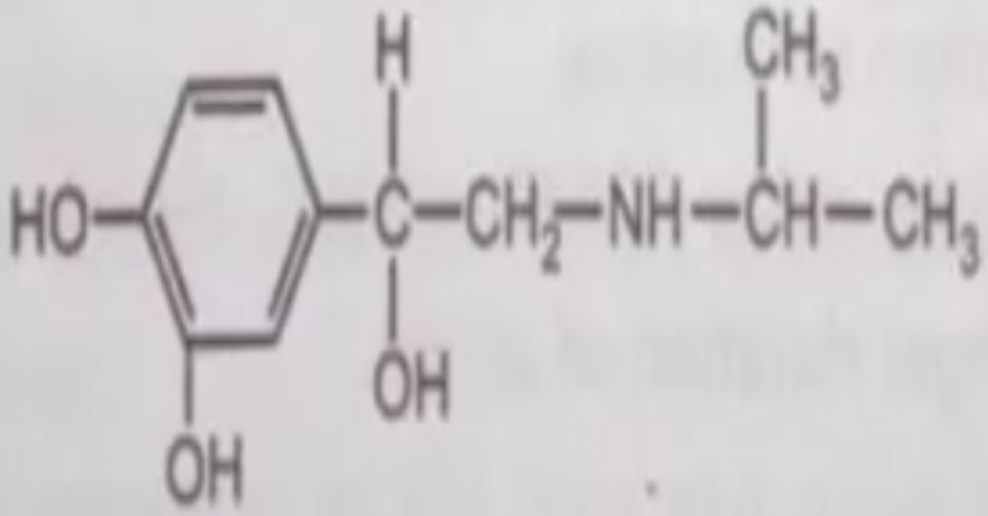


Metaproterenol :

Terbutaline :

- Resorcinol moiety → selective β2 agonist + not metabolized by COMT

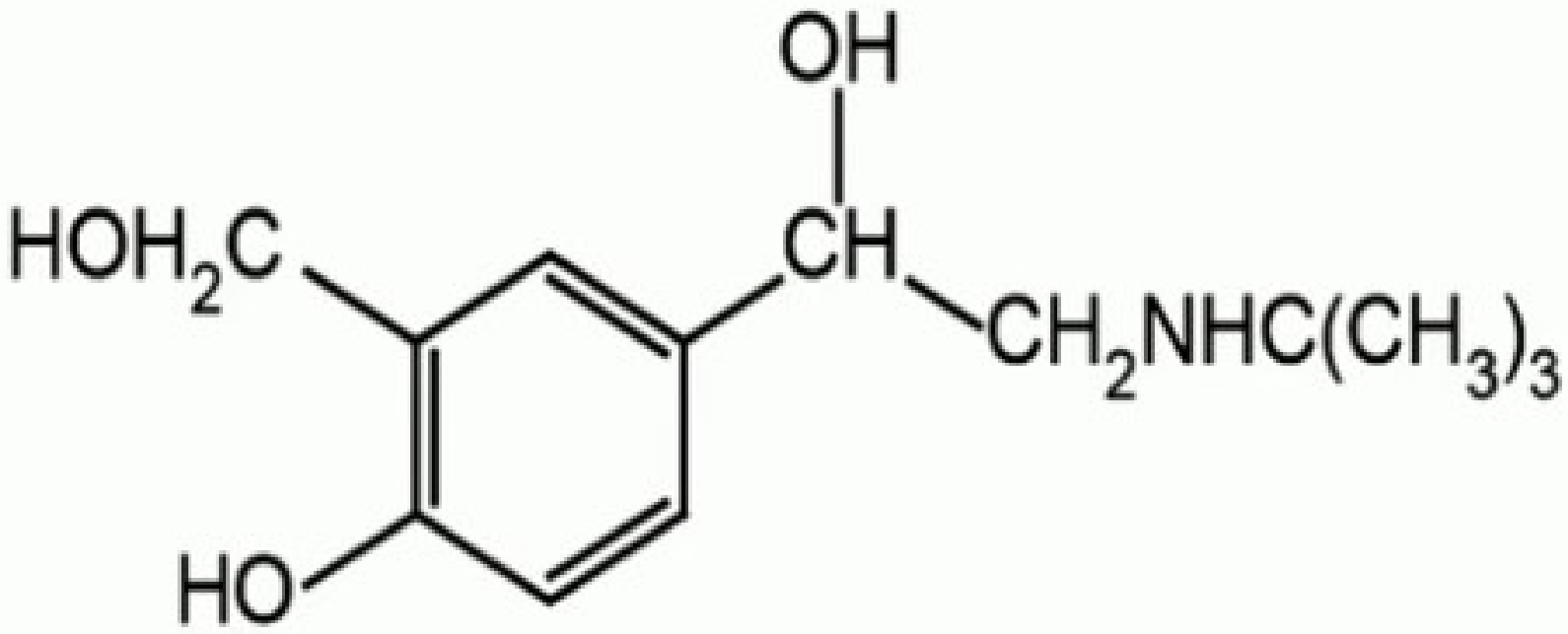
1. Isoproterenol:



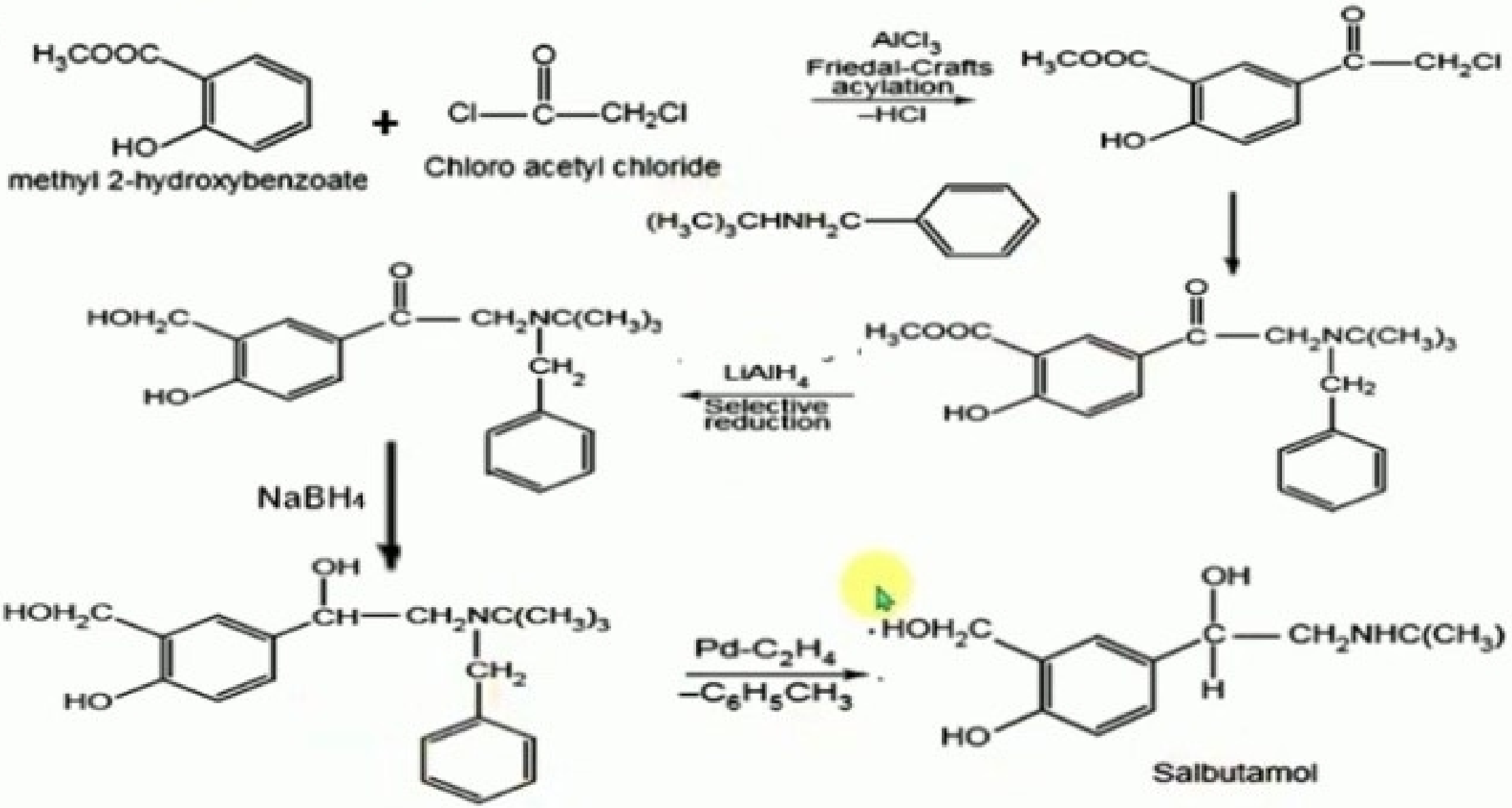
Isoproterenol

- Isoproterenol is chemically, 4-[1-hydroxy-2-[isopropylaminoethyl]-1,2-benzenediol.
- It acts on both β_1 and β_2 receptors.
- As it contains an isopropyl substitution on the nitrogen atom, it has virtually no effect on α–receptors.

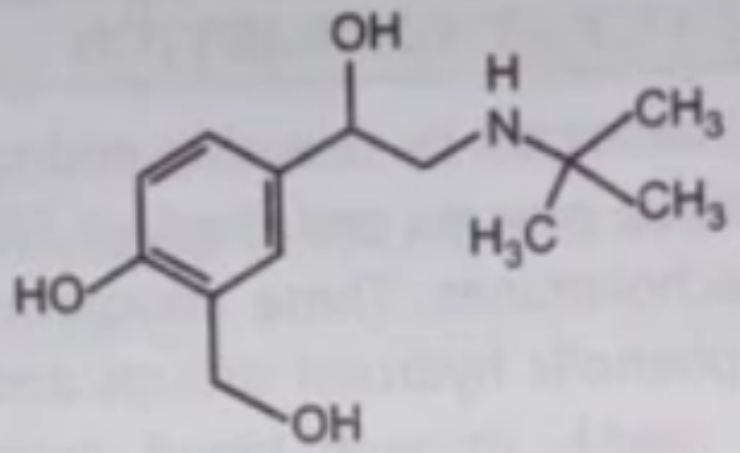
Structure of Salbutamol



Synthesis of Salbutamol



3. Salbutamol (Albuterol):



Salbutamol (Albuterol)

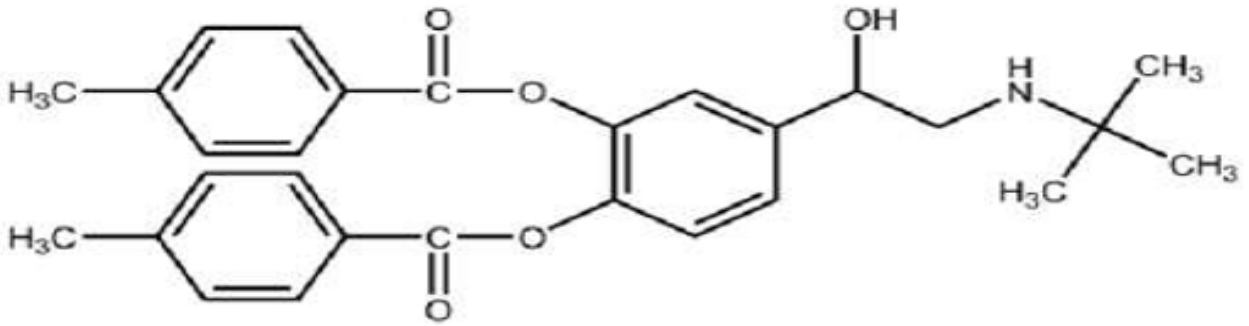
- Salbutamol is chemically, 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(tert-butylamino) ethanol.
- It is a selective β_2 receptor agonist whose selectivity results from replacement of the meta-hydroxyl group of the catechol ring with a hydroxyl methyl moiety.
- It is not metabolized by either COMT or MAO.
- It is active orally and they exhibit a longer duration of action.

Uses:

- Metaproterenol, Terbutaline and Salbutamol (albuterol) possess strong β_2 agonistic properties.
- They are used in the treatment of bronchial asthma.

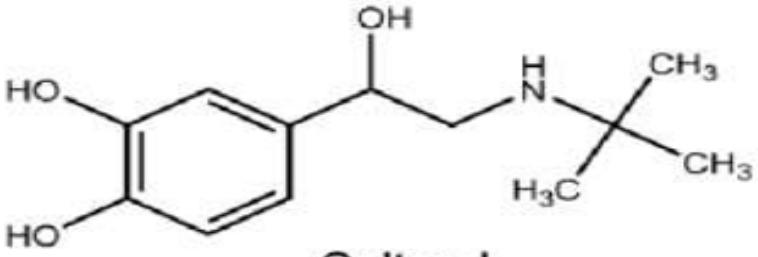
CLASSIFICATION

(9) Bitolterol



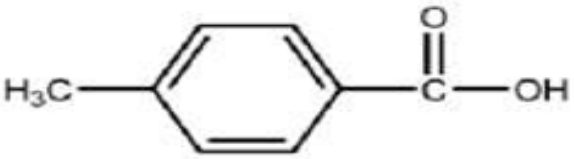
Bitolterol (a prodrug of Colterol)

esterases in the lung and other tissues



Colterol

\+ 2



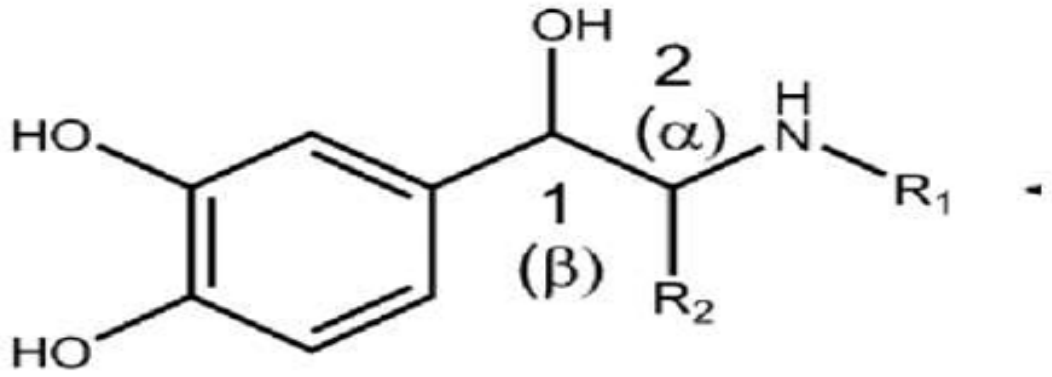
p-Toluic Acid

- N-*tert-butyl* group
  → selective β2 + not metabolized by MAO
- Prodrug resist to metabolism by COMT

SAR (phenylethylamine)

Structure required for activity:

1. β-Phenylethylamine
2. Catechol ring
3 (1R)-OH

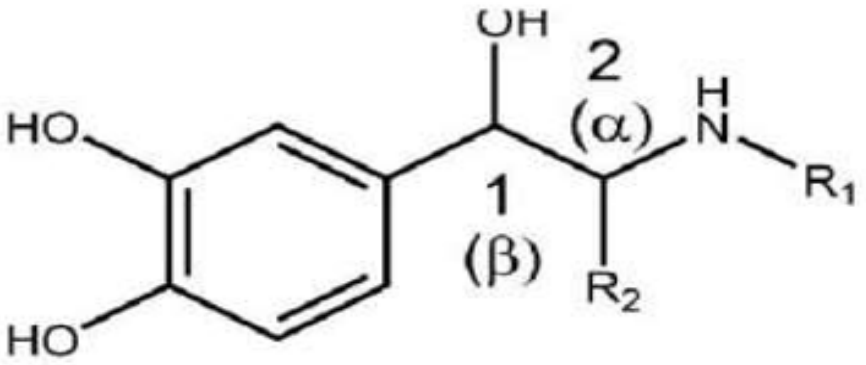


1. Optical Isomerism

- For CAs, the more potent enantiomer has the (1*R*) configuration. This enantiomer is typically several 100-fold more potent than the enantiomer with the (1*S*) configuration.

2. R_1, Substitution on the Amino Nitrogen

- Determines α or β - Receptor Selectivity.
- Primary and secondary amines have good adrenergic activity, whereas tertiary amines and quaternary ammonium salts do not.



R_1-Substitution on N

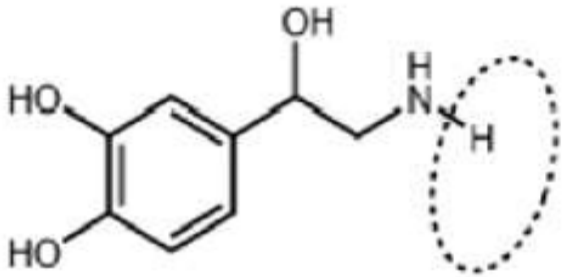
↑ the size of R_1 → ↑ β activity
↓ α activity
↓ degradation by MAO

t-butyl: ↑ β_2 activity
e.g. Colterol

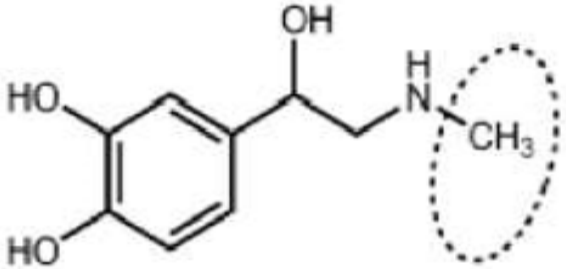
SAR (phenylethylamine)

2. R_1, Substitution on the Amino Nitrogen

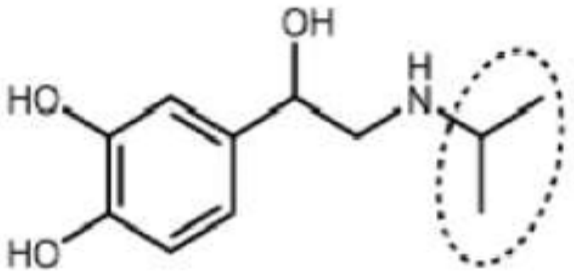
- As the size of the nitrogen substituent increases, α -receptor agonist activity generally decreases and β -receptor agonist activity increases
  + protect the amino group from undergoing metabolism by MAO



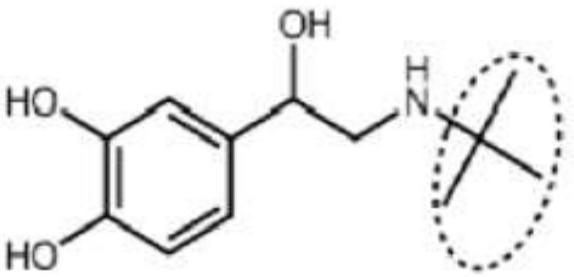
Norepinephrine (NE)
α > β agonist
α agonist



Epinephrine (E)
α, β_1 and β_2 agonist
nonselective α and β agonist



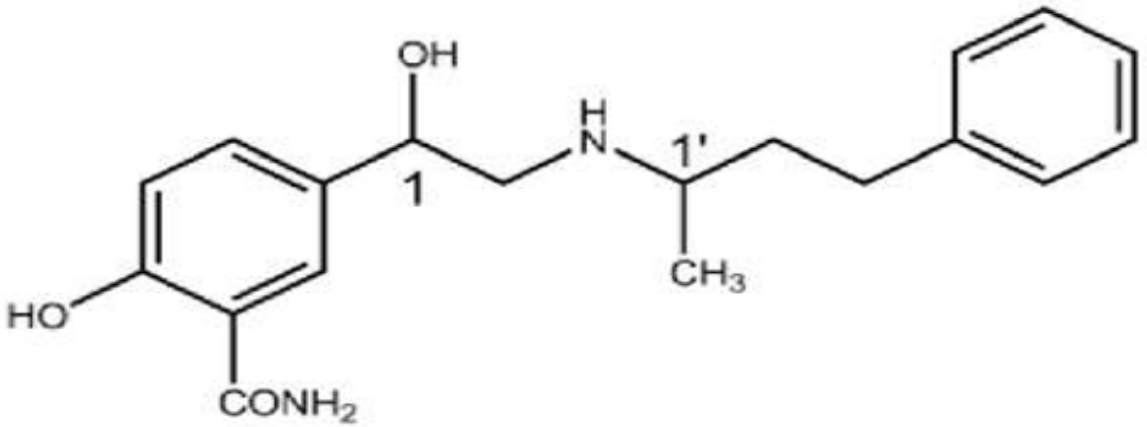
Isoproterenol (ISO)
β_1 and β_2 agonists
nonselective β agonist



N-*t*-Butylnorepinephrine (Colterol)
selective β_2 agonist

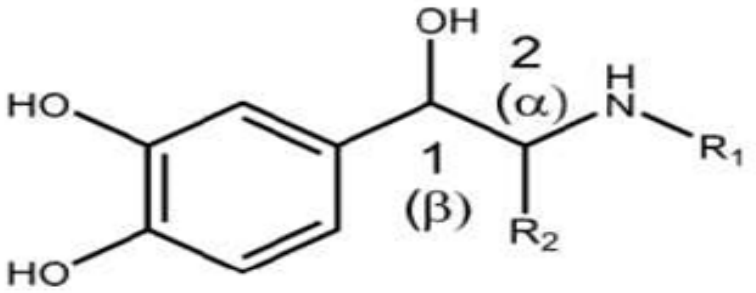
2. R_1, Substitution on the Amino Nitrogen

- large lipophilic (LPL) groups have can α_1-blocking activity e.g. labetalol



Labetalol

3. R_2, Substitution on the α –Carbon



R_2-Sustitution on C_2

small alkyl groups (Me, Et) tolerated

↓ degration by MAO

still substrates for COMT → little effect on DOA

Et group:

↓ α >> β (more β–selective, e.g., ethylnorepinephrine)

↑ CNS activity

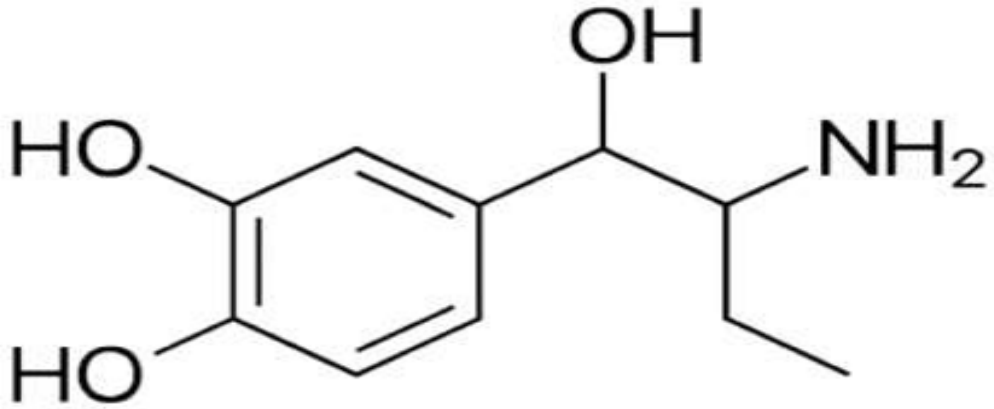
↑ oral activity & DOA

(2S) methyl group: ↑ α_2 activity

SAR (phenylethylamine)

3. R_2, Substitution on the α –Carbon

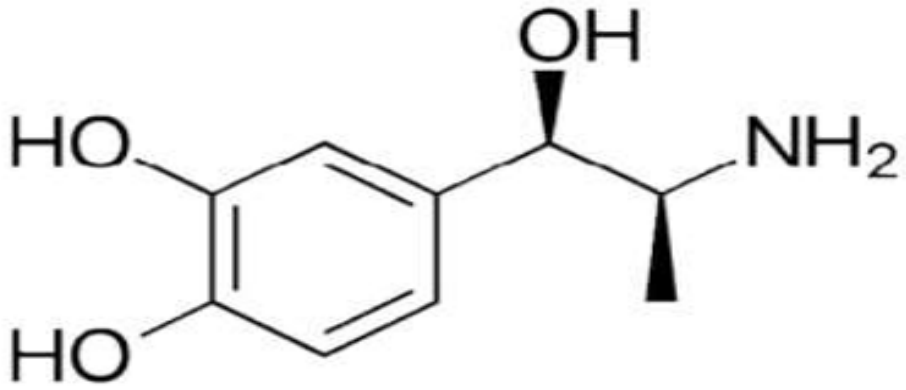
- Substitution by small alkyl group slows metabolism by MAO with little effect on DOA
- Lipophilicity of R_2 substituted compounds often exhibit enhanced oral effectiveness and greater CNS activity.
- An ethyl group in this position diminishes α -activity far more than β -activity, affording compounds with β - selectivity (e.g., ethylnorepinephrine and isoetharine).



SAR (phenylethylamine)

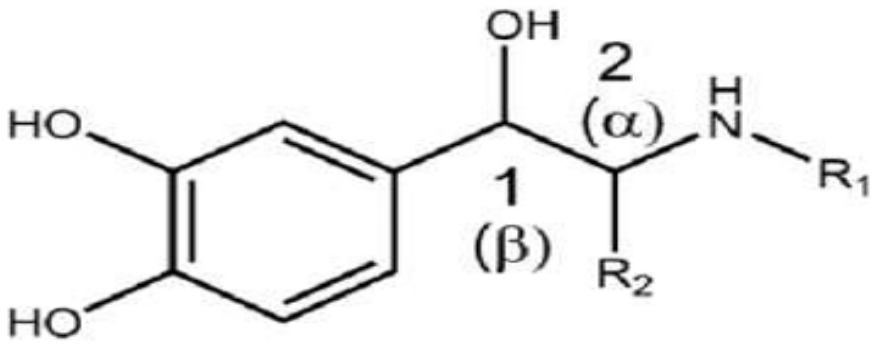
3. R_2, Substitution on the α –Carbon

- α - methylnorepinephrine, it is the erythro (1R,2S) isomer that possesses significant activity at α_2-receptors



SAR (phenylethylamine)

4. *OH substitution on the β –carbon*



- Essential
- generally decreases CNS activity largely because it lowers lipid solubility
- Compounds lacking the -OH group (e.g. DA) have a greatly reduced adrenergic receptor activity.

5. *Substitution on the Aromatic Ring*

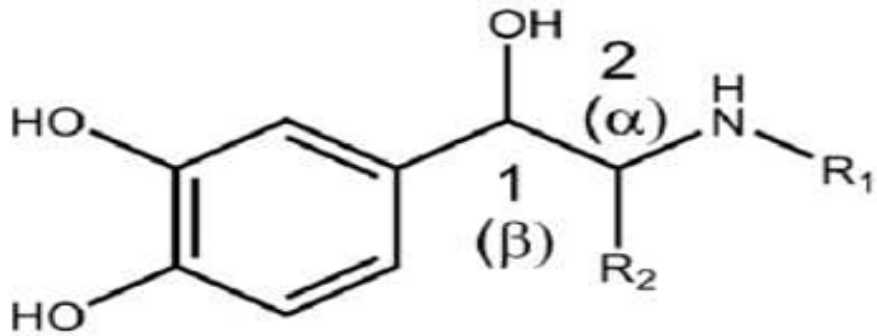
Aromatic substituents

3', 4'-diOH for both α & β agonist activity
metabolized by COMT→
poor oral activity and short DOA
hydrophilic → poor CNS activity

3', 5'-diOH (e.g., metaproterenol)
3'-CH_2OH, 4'-OH (e.g., albuterol)
↑ β_2 activity
↓ degradation by COMT →
↑ absorption, oral activity, & DOA

4'-OH is more important for β activity
3'-OH is more important for α activity
(e.g., phenylephrine: α-agonist)

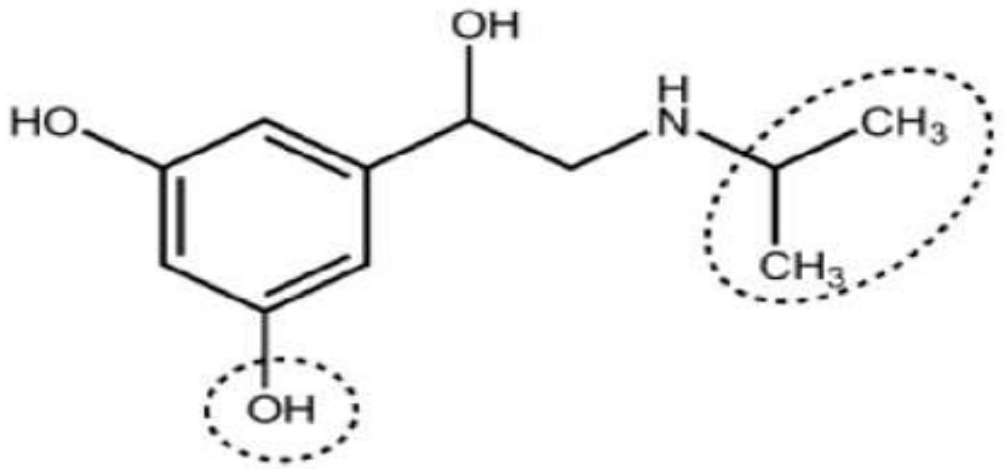
No phenolic substitution:
↓both α and β activity
direct or indirect activity



SAR (phenylethylamine)

5. Substitution on the Aromatic Ring

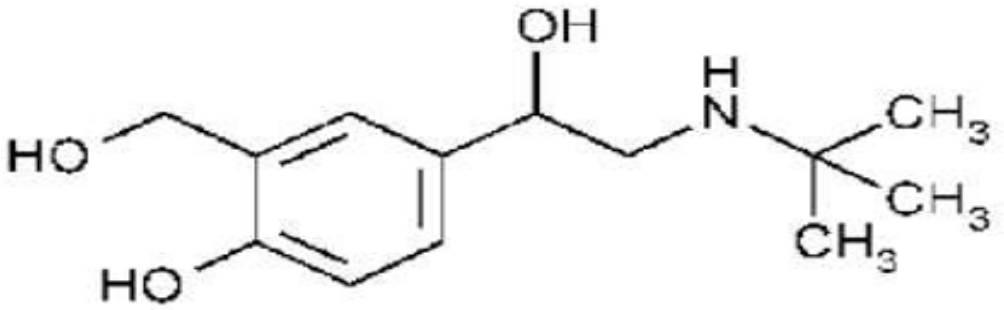
- replacement of the catechol function of ISO with the resorcinol structure gives a selective β_2-agonist, e.g. metaproterenol
- It will longer the DOA as because the resorcinol ring is not a substrate for COMT



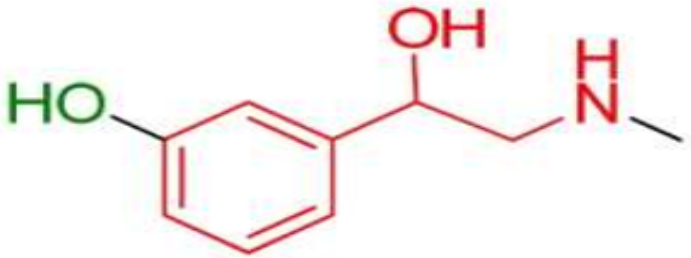
SAR (phenylethylamine)

5. Substitution on the Aromatic Ring

- replacement of the meta-OH of the catechol structure with a hydroxymethyl group gives agents, such as albuterol selective β 2-agonist



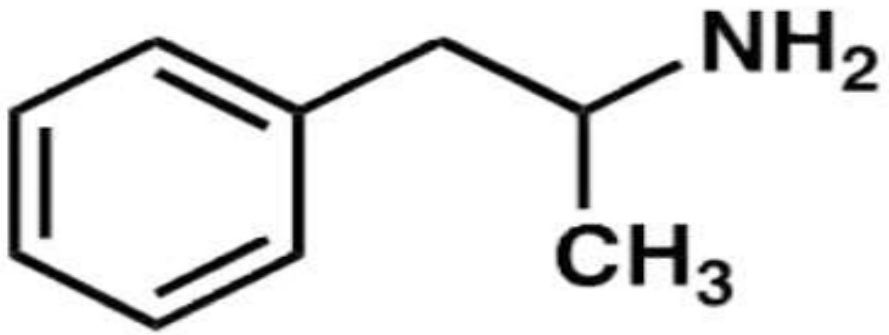
- removal of the *p*-OH group from E gives phenylephrine which lacks β action but has less α_1-agonist property



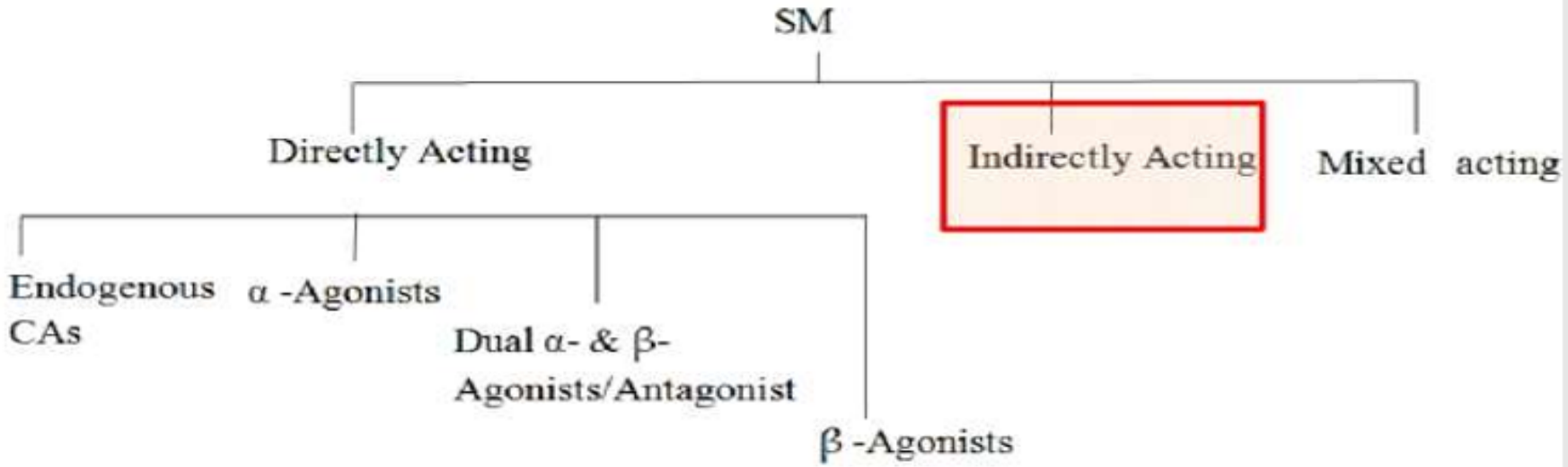
SAR (phenylethylamine)

6. *CAs without OH Groups*

- loss of direct sympathomimetic activity becomes indirectly sympathomimetics
- not metabolized by COMT, and they are orally active and have longer DOA
- e.g. amphetamine



CLASSIFICATION



Indirect-Acting Sympathomimetics

Phenylisopropylamines

1. Amphetamine
2. Methamphetamine
3. Hydroxyamphetamine

Phenylpropanolamines

1. (+)-Pseudoephedrine

M/A

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

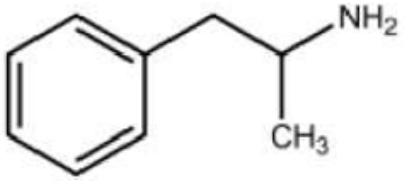
Phenylisopropylamines

(1) Amphetamine (2) methamphetamine

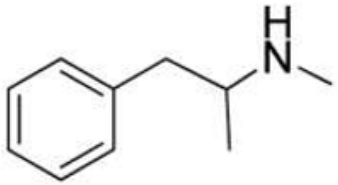
- By mimicking the release of the CAs NTs, NE , DA + serotonin action → CNS stimulant and central appetite suppressant effects

(3) Hydroxyamphetamine

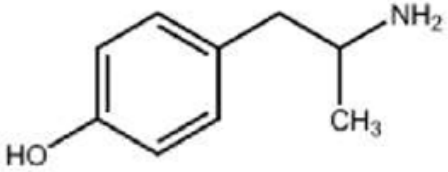
- presence of *p*-OH group → no CNS stimulant action
- used to dilate the pupil diagnosis / surgical procedures on the eye.



Amphetamine
Log P = 2.81

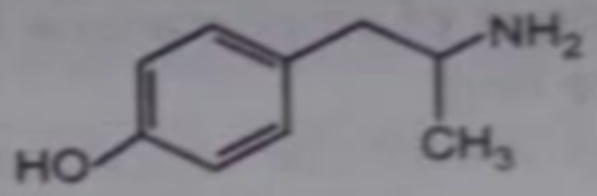


Methamphetamine



Hydroxyamphetamine
Log P = 1.07
pKa = 10.71

2. Hydroxyamphetamine:



Hydroxyamphetamine

- Hydroxyamphetamine is chemically, 4-(2-aminopropyl)phenol or 1-(4-hydroxy-phenyl)-propan-2-amine.
- It possesses α-receptor stimulant activity, but lacks CNS activity.
- It is a powerful vasoconstrictor.

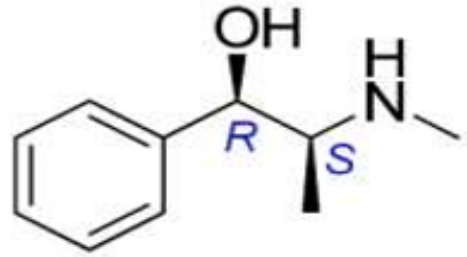
Uses:

- Hydroxyamphetamine is used as an anorexiant in the treatment of obesity.
- It is used to dilate the pupil for diagnostic eye examinations and for surgical procedures on the eye.
- It is used sometimes with cholinergic blocking drugs like atropine to produce a mydriatic effect.
- It is used in hyperkinetic syndrome in children.
- It is used in narcolepsy (sudden attack of sleep in completely inappropria situations).

Phenylpropanolamines

(1) L-(+)-Pseudoephedrine

- β-OH has *S*- stereochemistry ,Thus no directly acting mechanism
- Causes indirect vasoconstriction →Use: nasal decongestant



(-) Ephedrine

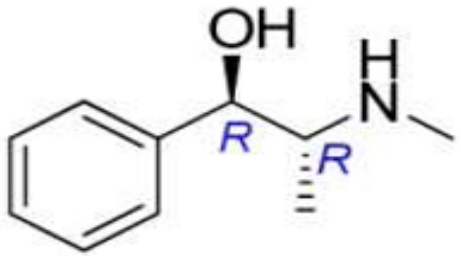
Enantiomers

(+) Ephedrine

Ephedrine
(threo racemate)
Mix acting drug

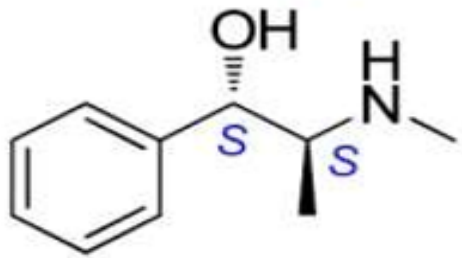
Diastireomers

Diastireomers



(-) Pseudoephedrine

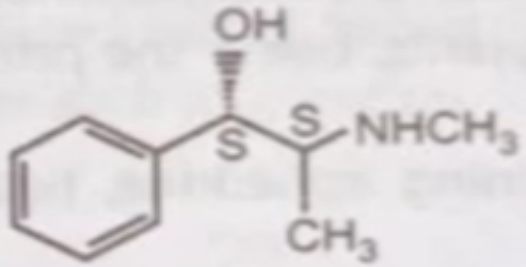
Enantiomers



(+) Pseudoephedrine

Pseudoephedrine
(Erythro racemate)
Indirectly acting drug

3. Pseudoephedrine:



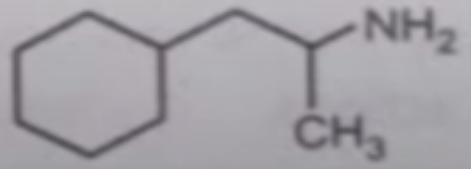
L-(+)-Pseudoephedrine

- *L-(+)*-Pseudoephedrine is chemically, *(1S,2S)*-2-(methylamino)-1-phenylpropan-1-ol.
- It is the (*S,S*) diastereoisomer of ephedrine in which β-OH group is having S-configuration.
- It is a naturally occurring alkaloid from the *Ephedra* species.
- Ephedrine has a mixed mechanism of action whereas pseudoephedrine acts predominantly by an indirect mechanism.

Uses:

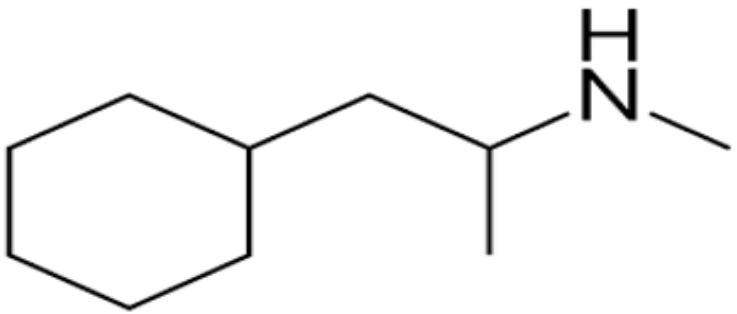
- It is used as nasal decongestant and in treatment of cold.
- It can also be used in the treatment of hypertension.

4. Propylhexedrine:



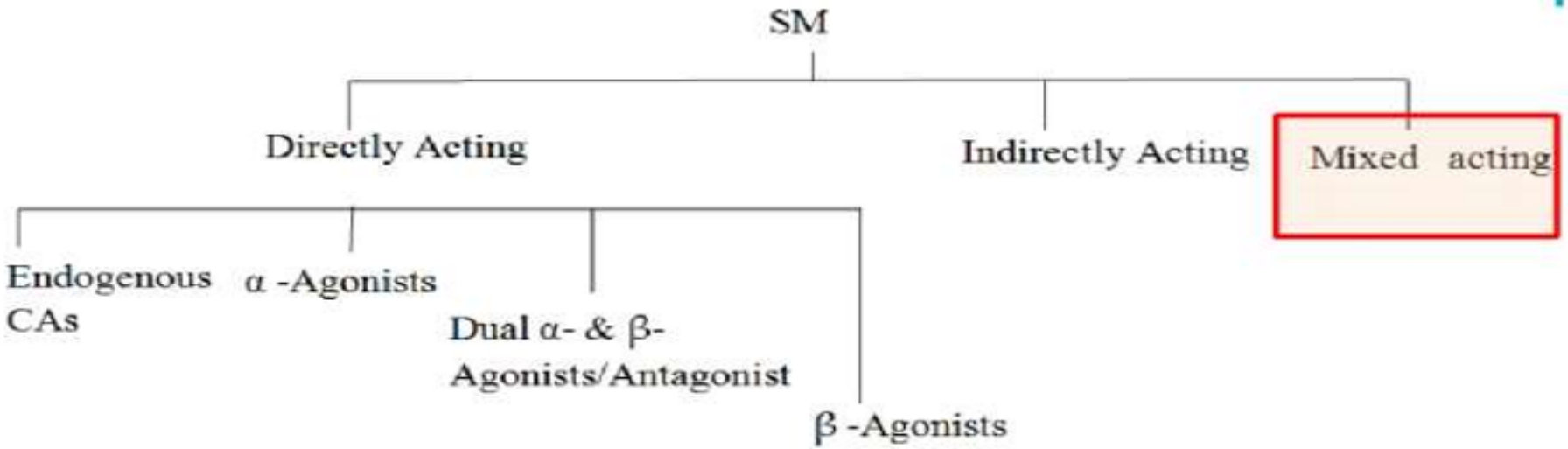
Propylhexedrine

Propylhexedrine



- Propylhexedrine binds to and activates **alpha**-adrenergic receptors in the mucosa of the respiratory .This results in vasoconstriction and reduces swelling and inflammation of the mucous membrane lining, therefore relieving nasal and sinus congestion.

CLASSIFICATION

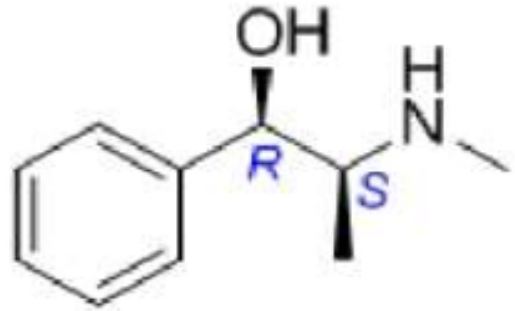


Mixed-Acting Sympathomimetics

1. (-) Ephedrine

Phenylpropanolamines

(1) D-(-)-Ephedrine

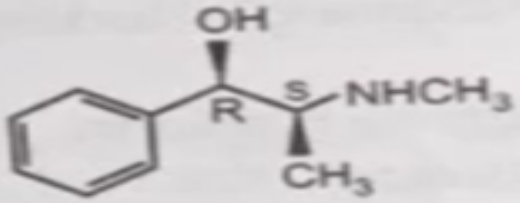


(-) Ephedrine

- *(1R,2S)-D-(-)*-ephedrine is most active from all four isomers

- An α- and β -adrenergic agonist (*β*-OH has *R*- stereochemistry) and also enhance release of NE
- As it is mix acting , it has Ephedrine can be used for a variety of purposes, a bronchodilator, vasopressor, cardiac stimulant, and nasal decongestant

1. Ephedrine:



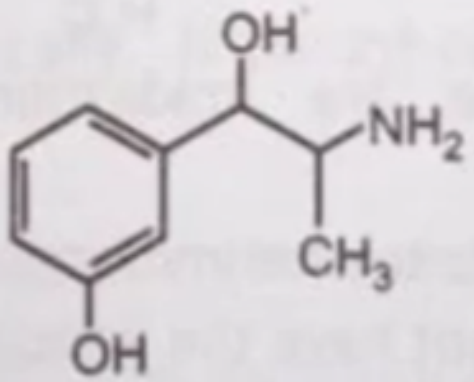
D-(–)-Ephedrine

- Ephedrine is chemically, *(1R, 2S)*-2-(methylamino)-1-phenylpropan-1-ol.
- It occurs naturally in many plants, being the principal alkaloid obtained from various species of *Ephedra*.
- *Ma Huang*, the plant containing ephedrine, has been used in China for over 2000 years.
- It contains two asymmetric carbon atoms, thus there are four optically active forms.
- The *erythro* racemate is called as ephedrine, whereas *threo* racemate is known as pseudoephedrine.
- Among four compounds available, *D(–)* isomer is clinically most active.
- It has agonist activity at both α and β-receptors.
- Ephedrine decomposes gradually and darkens when exposed to light.
- It is not metabolized by either MAO or COMT.

Uses:

- The pharmacological activity of ephedrine resembles with epinephrine.
- Ephedrine differs from adrenaline mainly by its
  (a) effectiveness after oral administration,
  (b) longer duration of action,
  (c) more pronounced central actions,
  (d) much lower potency.
- It produces a sharp rise in systolic, diastolic and pulse pressures, with a reflex bradycardia, similar to adrenaline, but lasting for 10 times as long.

3. Metaraminol:



Metaraminol

- Metaraminol is chemically, 3-[(1R,2S)-2-amino-1-hydroxypropyl]phenol.
- It is an isomer of phenylephrine.
- It possesses a mixed mechanism of action.
- It's direct-acting effects mainly on α-adrenergic receptor.

Uses:

- Metaraminol is used for its vasopressor action for maintaining blood pressure during spinal anaesthesia and hemorrhage.
- It has also been used to treat severe hypotension brought on by other traumas that induce shock.

Therapeutic classification of drugs

I. Pressor agents

- Noradrenaline
- Ephedrine
- Dopamine
- Methoxamine
- Phenylephrine
- Amphetamine
- Mephentermine

II. Cardiac stimulants

- Adrenaline
- Isoprenaline
- Dobuatmine

III. Bronchodilators

- Adrenaline
- Isoprenaline
- Salbutamol
- Terbutaline
- Salmeterol
- Formoterol

IV. Nasal decongestants

- Phenylephrine
- Naphazoline
- Xylometazoline
- Pseudoephirine
- Oxymetazoline
- Phenyl propanolamine

V. CNS stimulants

- Amphetamine
- Methamphetamine
- Dexamphetamine

VI. Anorectics

- Fenfluramine
- Sibutramine
- Dexfenfluramine

VII. Uterine relaxants and vasodilators

- Ritodrine
- Salbutamol
- Isoxsuprine
- Terbutaline

THANK YOU