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MEDICINAL CHEMISTRY – I

UNIT 2

TOPIC :

- **Sympathomimetic agents : SAR of Sympathomimetic agents**

Direct acting: Nor-epinephrine, Epinephrine, Phenylephrine*, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.

Indirect acting agents : Hydroxyamphetamine, Pseudoephedrine, Propylhexedrine.

Agents with mixed mechanism: Ephedrine, Metaraminol.

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Sympathomimetic Agents (Adrenergic Agonists)

- Adrenergic drugs or adrenergic agonists or sympathomimetic agents cause stimulation of the adrenergic receptors in the sympathetic nervous system.
- They are named so as they mimic the actions of major neurotransmitters of the sympathetic nervous system, i.e., epinephrine and norepinephrine.
- Adrenergic agents either directly or indirectly stimulate the adrenergic nerves.
- In direct stimulation, they mimic the actions of noradrenaline; while, indirect stimulation triggers the release of noradrenaline.
- The therapeutic application of these drugs is in the treatment of life threatening disorders like acute attacks of bronchial asthma, cardiac arrest, shock, and allergic reactions.
- These drugs are also used as nasal decongestants and appetite suppressants.

Structure-Activity Relationship (SAR) of Sympathomimetic Agents

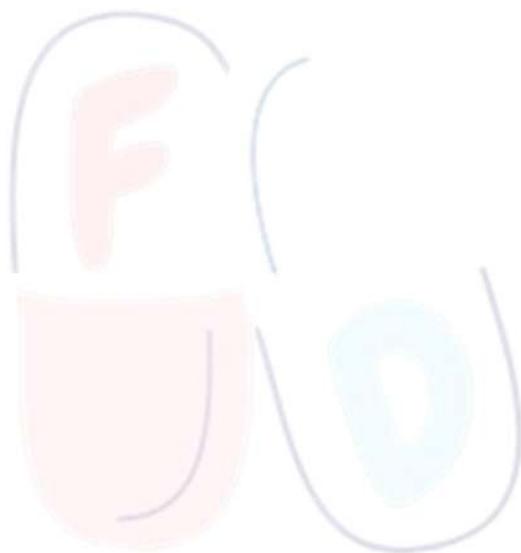
- **Basic nucleus:** β -Phenyl ethylamine.
- **Key modifications:**
 - Substituents on α -carbon: \uparrow half-life by inhibiting MAO metabolism.
 - Substituents on β -carbon: \uparrow β receptor activity (e.g., hydroxyl group).
 - Substituents on amine group: Larger groups \rightarrow more β receptor selectivity; smaller groups \rightarrow more α receptor activity.
 - Catechol hydroxyl groups \rightarrow required for direct agonist activity, but decrease oral bioavailability (due to COMT metabolism).

Direct Acting Agents

- The direct acting sympathomimetic agents directly bind and interact to activate the receptor. These agonists may have the property of receptor selectivity where in they can show selectivity (to act) either for any one particular class of receptors (like α - or β -receptors) or for any sub-class (e.g, specificity against β_1 or β_2 receptors).

Example

- Norepinephrine
- Epinephrine
- Dopamine
- Dobutamine
- Isoproterenol
- Phenylephrine
- Methyldopa
- Clonidine
- Salbutamol
- Terbutaline
- Bitolterol
- Naphazoline
- Xylometazoline
- Oxymetazoline

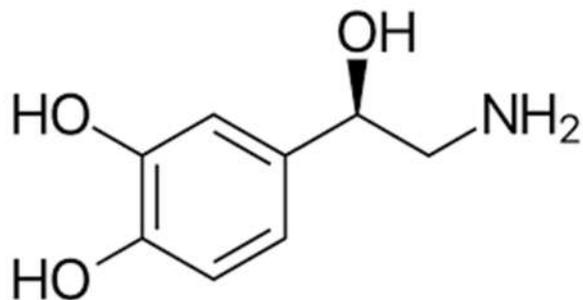


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Norepinephrine (Noradrenaline)

Structure

- A natural catecholamine neurotransmitter.
- Contains benzene ring with two -OH groups and an amine side chain.



Mechanism of Action (MOA)

- ❖ Acts mainly on α_1 -adrenergic receptors → produces vasoconstriction → increases blood pressure.
- ❖ Acts weakly on β_1 -receptors in the heart → increases force of contraction and heart rate (though reflex bradycardia may occur).
- ❖ Has little or no action on β_2 -receptors → so, unlike epinephrine, it does not cause bronchodilation.

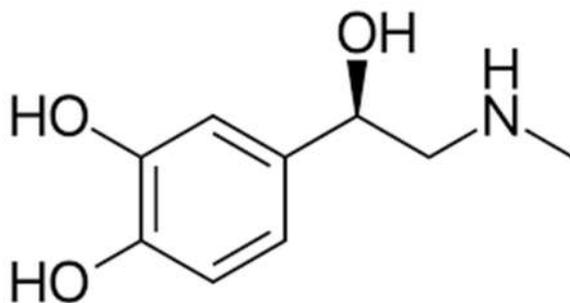
Uses

- ✓ To raise blood pressure in acute hypotension.
- ✓ In shock conditions (septic or cardiogenic) to maintain adequate blood circulation.
- ✓ As an adjunct in cardiac arrest to restore blood pressure.

Epinephrine (Adrenaline)

Structure

- Natural catecholamine hormone and neurotransmitter.
- Contains benzene ring with two -OH groups and an amine side chain.



Mechanism of Action (MOA)

- Acts on α_1 receptors \rightarrow vasoconstriction \rightarrow \uparrow blood pressure.
- Acts on β_1 receptors \rightarrow \uparrow heart rate & cardiac contractility \rightarrow \uparrow cardiac output.
- Acts on β_2 receptors \rightarrow bronchodilation and vasodilation in skeletal muscles.
- Stimulates glycogenolysis \rightarrow \uparrow blood glucose.

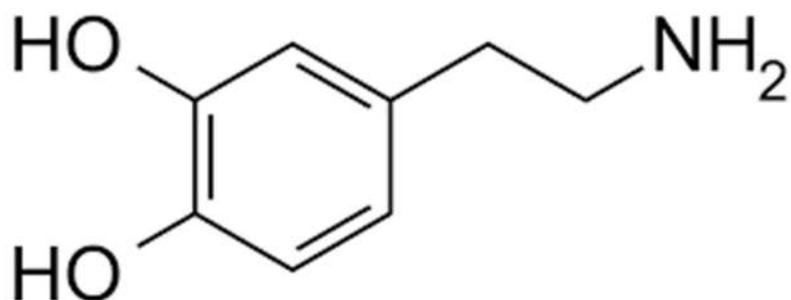
Uses

- Anaphylactic shock \rightarrow drug of choice.
- Cardiac arrest \rightarrow restores cardiac activity.
- Acute asthma attack (emergency bronchodilation).
- Used with local anesthetics \rightarrow prolongs action by vasoconstriction.
- Control of bleeding (local vasoconstriction).

Dopamine

Structure

- Natural catecholamine neurotransmitter.
- Immediate precursor of norepinephrine.
- Contains benzene ring with two -OH groups and an amine side chain.



Mechanism of Action (MOA)

- Low dose → D₁ receptors → renal & mesenteric vasodilation → ↑ renal blood flow & urine output.
- Moderate dose → β₁ receptors → ↑ heart rate & cardiac contractility → ↑ cardiac output.
- High dose → α₁ receptors → vasoconstriction → ↑ blood pressure.

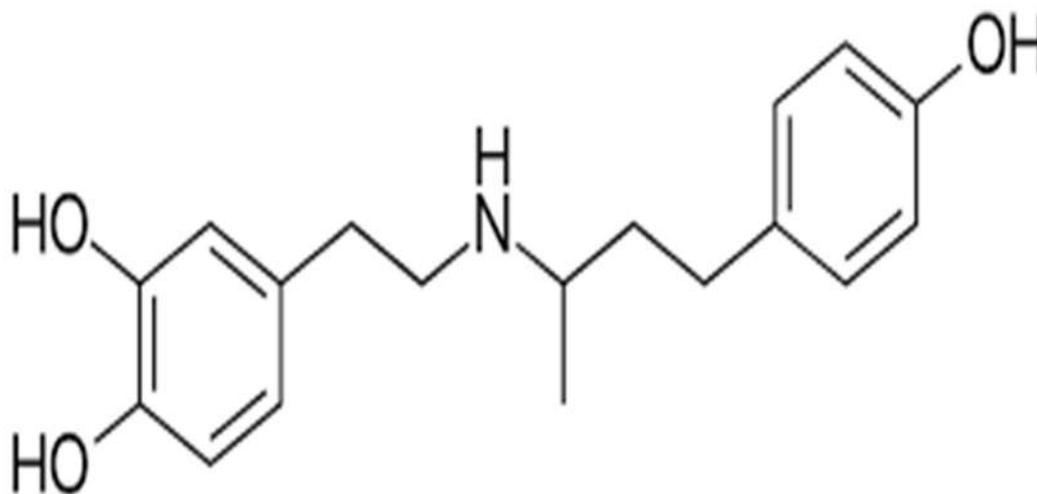
Uses

- Shock (septic or cardiogenic) → maintains BP & circulation.
- Acute heart failure → ↑ cardiac output.
- Early renal failure → improves renal perfusion & urine output.

Dobutamine

Structure

- Synthetic catecholamine.
- Contains benzene ring with two -OH groups and an amine side chain.



Mechanism of Action (MOA)

- Selective β_1 -receptor agonist \rightarrow \uparrow cardiac contractility and heart rate \rightarrow \uparrow cardiac output.
- Minimal effect on α_1 receptors \rightarrow slight or no change in blood pressure.
- Very little action on β_2 receptors \rightarrow no significant bronchodilation.

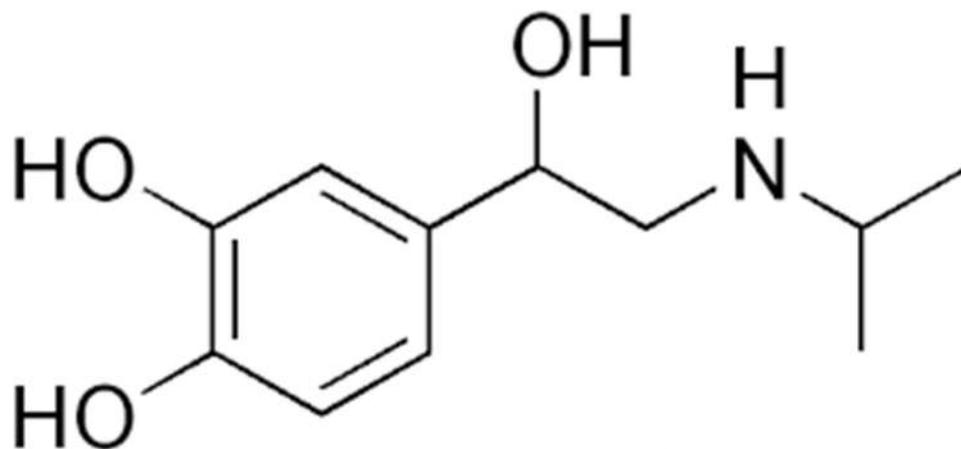
Uses

- Acute heart failure \rightarrow short-term cardiac support.
- Cardiac surgery \rightarrow to maintain cardiac output.
- Cardiogenic shock \rightarrow increases cardiac performance.

Isoproterenol

Structure

- Synthetic catecholamine.
- Contains benzene ring with two -OH groups and an amine side chain.



Mechanism of Action (MOA)

- Non-selective β_1 and β_2 agonist.
- β_1 receptors \rightarrow \uparrow heart rate & cardiac contractility \rightarrow \uparrow cardiac output.
- β_2 receptors \rightarrow bronchodilation and vasodilation in skeletal muscles.
- Minimal α receptor activity \rightarrow little effect on BP.

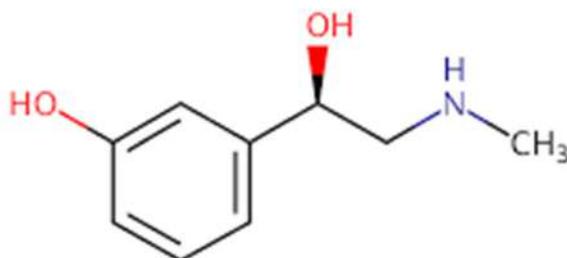
Uses

- Heart block \rightarrow to increase heart rate.
- Bradycardia \rightarrow temporary cardiac stimulation.
- Asthma (rarely now) \rightarrow bronchodilation in emergencies.

Phenylephrine

Structure

- Synthetic α_1 -adrenergic agonist.
- Contains benzene ring with -OH group and amine side chain.



Mechanism of Action (MOA)

- Selective α_1 receptor agonist → vasoconstriction → ↑ blood pressure.
- Minimal action on β_1 and β_2 receptors → no significant bronchodilation or heart rate increase.

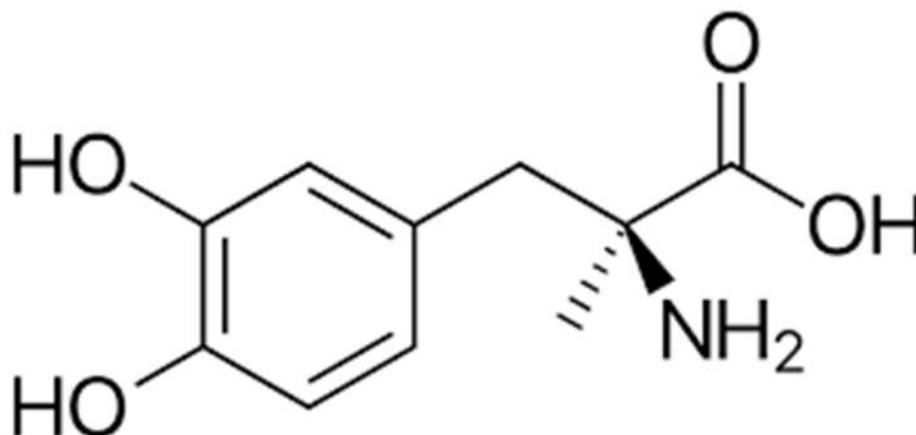
Uses

- Nasal decongestant → reduces mucosal swelling.
- Mydriatic → pupil dilation in eye exams.
- Hypotension → to raise blood pressure in shock or anesthesia.

Methyldopa

Structure

- Synthetic α_2 -adrenergic agonist.
- Analog of L-DOPA; contains benzene ring with -OH group and amine side chain.



Mechanism of Action (MOA)

- Converted in the CNS to α -methyl norepinephrine \rightarrow stimulates central α_2 receptors.
- \downarrow Sympathetic outflow \rightarrow \downarrow peripheral vascular resistance \rightarrow \downarrow blood pressure.
- Minimal direct effect on heart rate.

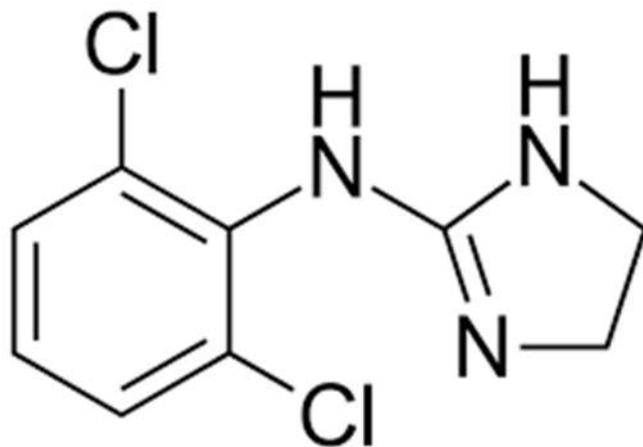
Uses

- Hypertension \rightarrow especially safe in pregnancy.
- Chronic hypertension management in patients who cannot tolerate other drugs.

Clonidine

Structure

- Synthetic α_2 -adrenergic agonist.
- Contains imidazoline ring and amine side chain.



Mechanism of Action (MOA)

- Stimulates central α_2 receptors \rightarrow \downarrow sympathetic outflow \rightarrow \downarrow peripheral vascular resistance \rightarrow \downarrow blood pressure.
- Reduces heart rate slightly.
- Minimal direct action on α_1 or β receptors.

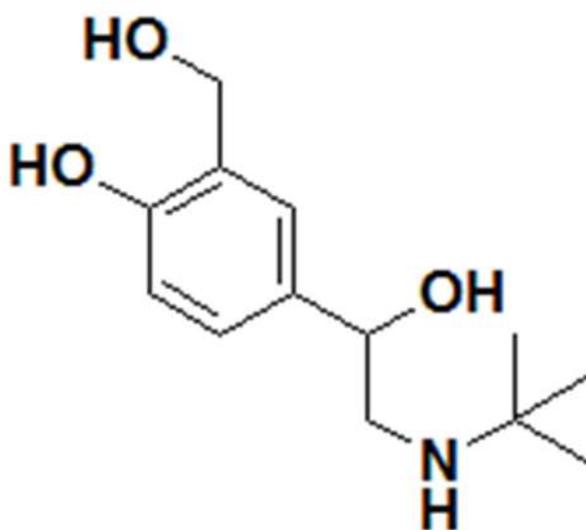
Uses

- Hypertension \rightarrow alone or in combination therapy.
- Withdrawal symptoms \rightarrow opioids, alcohol, and nicotine.
- Adjunct in chronic pain management.

Salbutamol (Albuterol)

Structure

- Synthetic β_2 -adrenergic agonist.
- Contains benzene ring with -OH groups and amine side chain.



Salbutamol

Mechanism of Action (MOA)

- Selectively stimulates β_2 receptors in the lungs → bronchodilation.
- Minimal effect on β_1 receptors → little increase in heart rate.
- Relaxes smooth muscles of the airways → improves airflow.

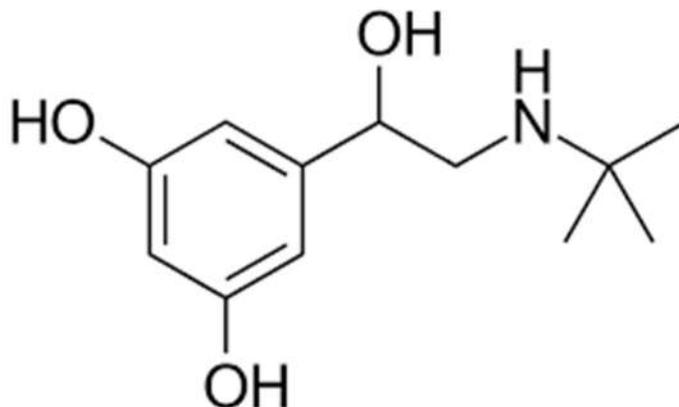
Uses

- Acute asthma attack → rapid bronchodilation.
- Chronic asthma & COPD → maintenance therapy.
- Exercise-induced bronchospasm → prevention.

Terbutaline

Structure

- Synthetic β_2 -adrenergic agonist.
- Contains benzene ring with -OH groups and amine side chain.



Mechanism of Action (MOA)

- Selectively stimulates β_2 receptors → bronchodilation.
- Minimal β_1 activity → little effect on heart rate.
- Relaxes bronchial and uterine smooth muscles.

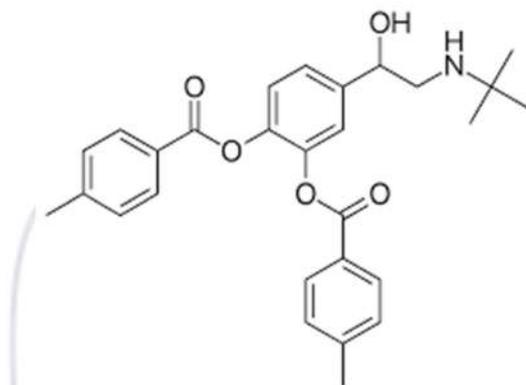
Uses

- Asthma & COPD → acute relief and maintenance.
- Preterm labor → uterine relaxation (tocolysis).
- Exercise-induced bronchospasm → prevention.

Bitolterol

Structure

- Synthetic β_2 -adrenergic agonist prodrug.
- Metabolized in the body to active form colterol.



Mechanism of Action (MOA)

- Stimulates β_2 receptors \rightarrow bronchodilation.
- Minimal effect on β_1 receptors \rightarrow little impact on heart rate.
- Relaxes bronchial smooth muscles, improving airflow.

Uses

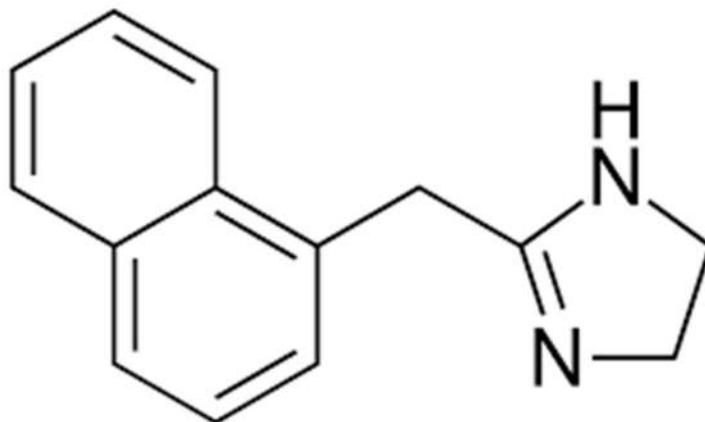
- Asthma & COPD \rightarrow short-term relief of bronchospasm.
- Prevention of exercise-induced bronchospasm.

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Naphazoline

Structure

- Synthetic α -adrenergic agonist.
- Contains imidazoline ring and amine side chain.



Mechanism of Action (MOA)

- Stimulates α_1 receptors \rightarrow vasoconstriction of nasal and ocular blood vessels.
- Reduces mucosal edema and redness.
- Minimal effect on β receptors \rightarrow negligible cardiac effects.

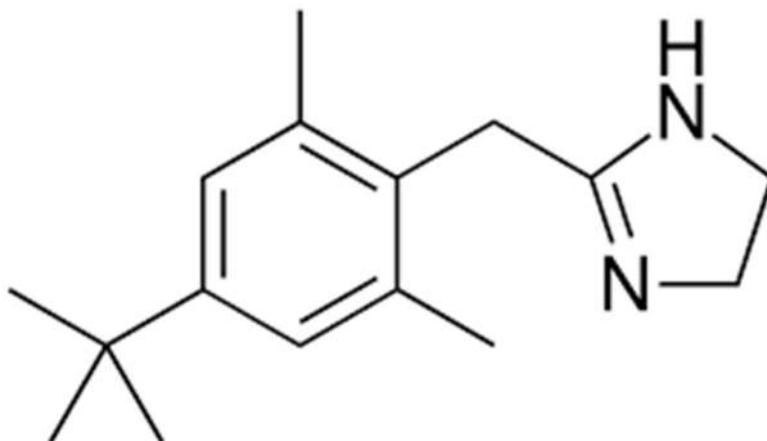
Uses

- Nasal congestion \rightarrow decongestant in rhinitis.
- Red eyes \rightarrow ocular vasoconstrictor in conjunctival irritation.

Xylometazoline

Structure

- Synthetic α -adrenergic agonist.
- Contains imidazoline ring and amine side chain.



Mechanism of Action (MOA)

- Stimulates α_1 receptors \rightarrow vasoconstriction of nasal mucosa.
- Reduces mucosal swelling \rightarrow eases airflow.
- Minimal effect on β receptors \rightarrow little or no cardiac stimulation.

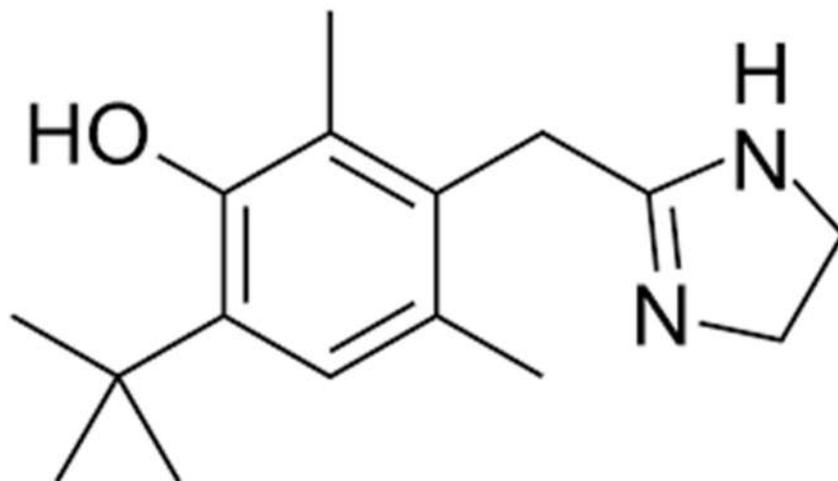
Uses

- Nasal congestion \rightarrow decongestant in rhinitis and sinusitis.
- Eustachian tube dysfunction \rightarrow temporary relief.

Oxymetazoline

Structure

- Synthetic α -adrenergic agonist.
- Contains imidazoline ring and amine side chain.



Mechanism of Action (MOA)

- Stimulates α_1 and partial α_2 receptors \rightarrow vasoconstriction of nasal mucosa.
- Reduces mucosal edema \rightarrow eases nasal airflow.
- Minimal systemic effect \rightarrow little impact on heart rate.

Uses

- Nasal congestion \rightarrow rhinitis, sinusitis.
- Redness of eyes \rightarrow ocular vasoconstrictor in conjunctival irritation.
- Eustachian tube congestion \rightarrow temporary relief.

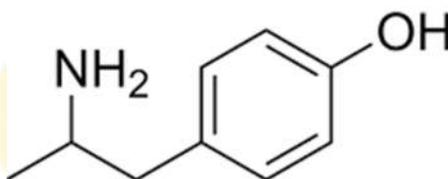
Indirect Acting Agents

- Indirect acting sympathomimetic agents stimulate the release of a stored neurotransmitter from within the adrenergic nerve terminals. The main neurotransmitter involved here is nor-epinephrine, which on being released stimulates the adrenergic receptors on the effector organs.
- The drugs studied below are:
 - 1) Hydroxyamphetamine,
 - 2) Pseudoephedrine.
 - 3) Propylhexedrine

Hydroxyamphetamine

Structure

- Synthetic indirect-acting sympathomimetic.
- Structurally related to amphetamines; stimulates release of norepinephrine.



Mechanism of Action (MOA)

- Indirect-acting → releases stored norepinephrine from sympathetic nerve endings.
- Stimulates α_1 receptors → vasoconstriction and mydriasis.
- Minimal β receptor activity → negligible cardiac stimulation.

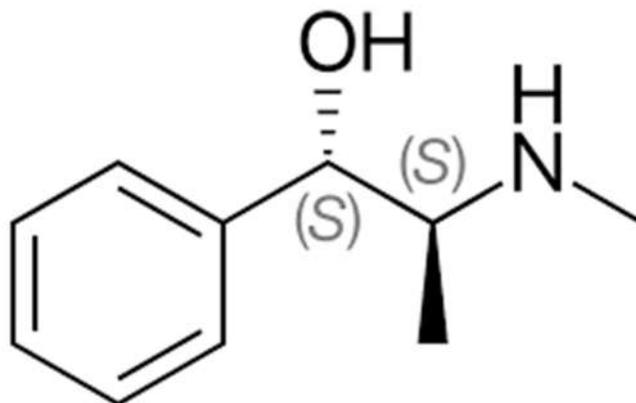
Uses

- Mydriasis → dilates pupil for ophthalmic examination.
- Diagnostic testing → to differentiate pre- and post-ganglionic sympathetic denervation (Horner's syndrome).

Pseudoephedrine

Structure

- Synthetic mixed-acting sympathomimetic.
- Structurally related to ephedrine; contains amine and hydroxyl groups.



Mechanism of Action (MOA)

- Direct action: weakly stimulates α and β receptors.
- Indirect action: releases stored norepinephrine from sympathetic nerve endings.
- α_1 stimulation \rightarrow vasoconstriction \rightarrow reduces nasal congestion.
- β_1 stimulation \rightarrow mild \uparrow heart rate & contractility.

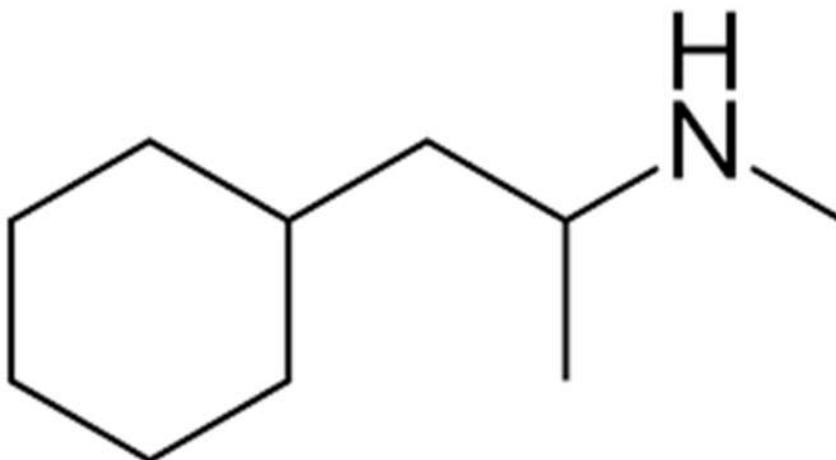
Uses

- Nasal congestion \rightarrow rhinitis, sinusitis, common cold.
- Eustachian tube congestion \rightarrow temporary relief.
- Sometimes used for hypotension in anesthesia (rare).

Propylhexedrine

Structure

- Synthetic indirect-acting sympathomimetic.
- Structurally related to amphetamines; contains amine and alkyl groups.



Mechanism of Action (MOA)

- Indirect action → releases norepinephrine from sympathetic nerve endings.
- Stimulates α receptors → vasoconstriction → reduces nasal congestion.
- Minimal β receptor activity → little effect on heart rate.

Uses

- Nasal congestion → short-term relief in rhinitis and common cold.
- Occasionally used in topical decongestant preparations.

Agents with Mixed Mechanism

- Some sympathomimetic agents (e-g ephedrine, metaraminol, and pseudoephedrine) have a mixed action.
- They act by releasing a neurotransmitter, and also have a direct-agonist activity.
- Amongst the adrenergic agonists, epinephrine and nor-epinephrine are the least specific.
- Both α - and β -receptors can be stimulated by nor- epinephrine and epinephrine, but due to the difference in their chemical structures, nor-epinephrine has more pronounced effects at α -receptors while epinephrine has more pronounced effects at β -receptors. Also, the potency of both these drugs is different from each other.

The drugs studied below are:

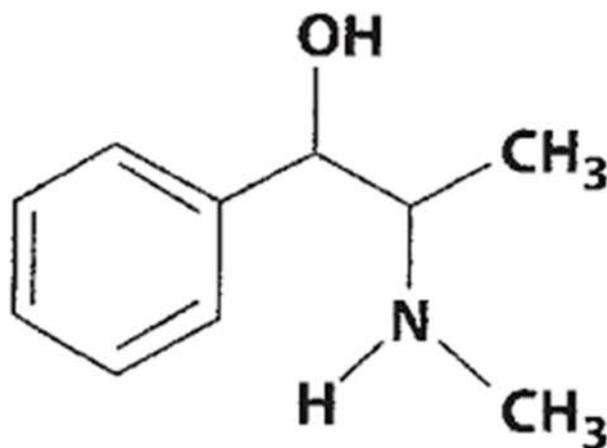
- 1) Ephedrine,
- 2) Metaraminol.

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Ephedrine

Structure

- Synthetic mixed-acting sympathomimetic.
- Contains benzene ring, hydroxyl group, and amine side chain.



ephedrine

Mechanism of Action (MOA)

- Direct action: stimulates α and β receptors \rightarrow vasoconstriction and mild cardiac stimulation.
- Indirect action: releases stored norepinephrine from sympathetic nerve endings.
- α_1 stimulation \rightarrow vasoconstriction \rightarrow \uparrow BP.
- β_1 stimulation \rightarrow \uparrow heart rate & contractility.
- β_2 stimulation \rightarrow bronchodilation (mild).

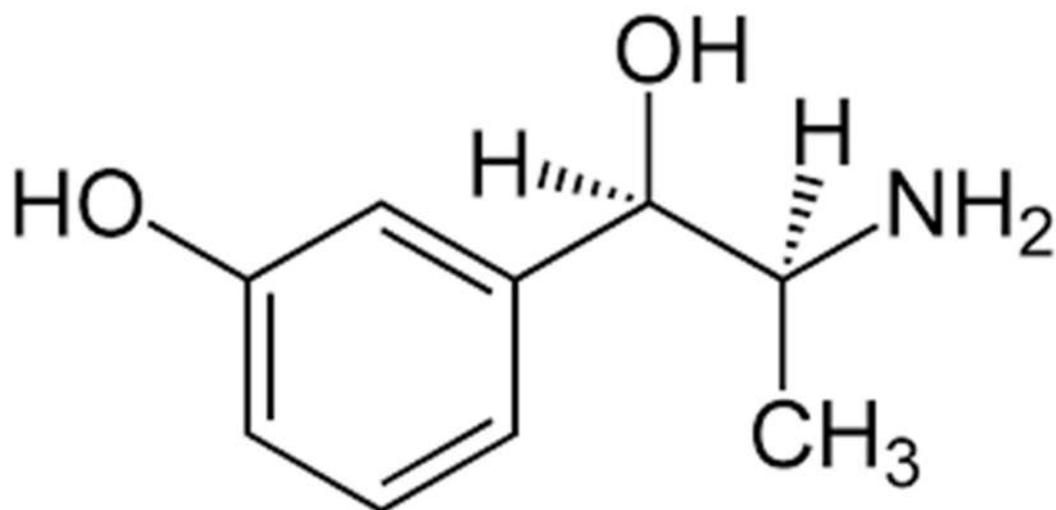
Uses

- Nasal congestion \rightarrow rhinitis, sinusitis.
- Hypotension \rightarrow especially in anesthesia.
- Bronchospasm \rightarrow mild relief in asthma (less preferred now).
- Urinary incontinence \rightarrow sometimes used for sphincter tone.

Metaraminol

Structure

- Synthetic direct-acting α_1 -adrenergic agonist.
- Contains a phenyl ring with amine and hydroxyl substituents.



Mechanism of Action (MOA)

- Stimulates α_1 receptors → vasoconstriction → increases blood pressure.
- Minimal β_1 or β_2 activity → little effect on heart rate or bronchodilation.
- Sometimes causes reflex bradycardia due to \uparrow BP.

Uses

- Hypotension → especially during anesthesia or shock.
- Acute management of low blood pressure in hospital settings.