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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.

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 noradrenalinel.

→ 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**: ↑ half-life by inhibiting MAO metabolism.
  - Substituents on **β-carbon**: ↑ β receptor activity (e.g., hydroxyl group).
  - Substituents on **amine group**: Larger groups → more β receptor selectivity; smaller groups → more α receptor activity.
  - Catechol hydroxyl groups → 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 β1 or β2 receptors).

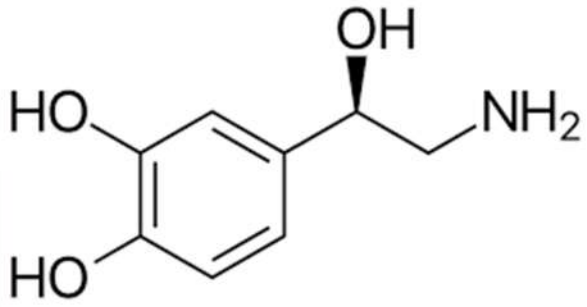
Example

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

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 α1-adrenergic receptors → produces vasoconstriction → increases blood pressure.
- ❖ Acts weakly on β1-receptors in the heart → increases force of contraction and heart rate (though reflex bradycardia may occur).
- ❖ Has little or no action on β2-receptors → so, unlike epinephrine, it does not cause bronchodilation.

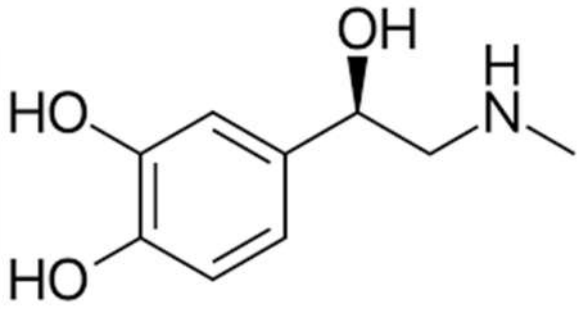
Uses

- ✓ 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 α1 receptors → vasoconstriction → ↑ blood pressure.
- Acts on β1 receptors → ↑ heart rate & cardiac contractility → ↑ cardiac output.
- Acts on β2 receptors → bronchodilation and vasodilation in skeletal muscles.
- Stimulates glycogenolysis → ↑ blood glucose.

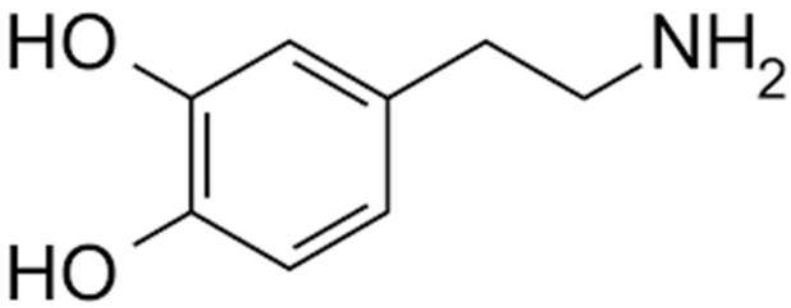
Uses

- Anaphylactic shock → drug of choice.
- Cardiac arrest → restores cardiac activity.
- Acute asthma attack (emergency bronchodilation).
- Used with local anesthetics → 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.

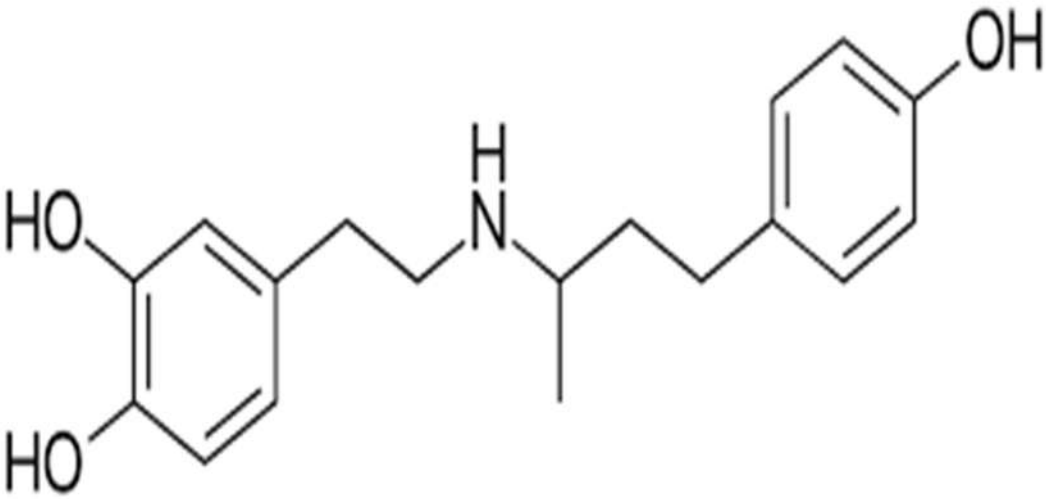
Uses

- 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 β1-receptor agonist → ↑ cardiac contractility and heart rate → ↑ cardiac output.
- Minimal effect on α1 receptors → slight or no change in blood pressure.
- Very little action on β2 receptors → no significant bronchodilation.

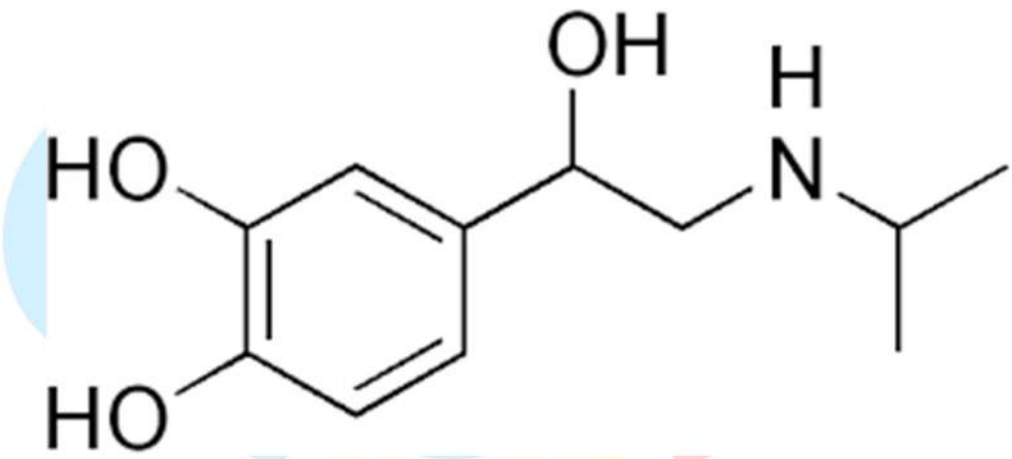
Uses

- Acute heart failure → short-term cardiac support.
- Cardiac surgery → to maintain cardiac output.
- Cardiogenic shock → 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 β1 and β2 agonist.
- β1 receptors → ↑ heart rate & cardiac contractility → ↑ cardiac output.
- β2 receptors → bronchodilation and vasodilation in skeletal muscles.
- Minimal α receptor activity → little effect on BP.

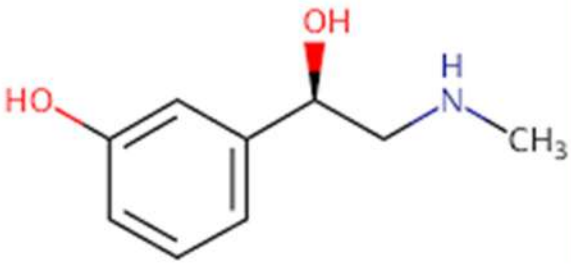
Uses

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

Phenylephrine

Structure

- Synthetic α1-adrenergic agonist.
- Contains benzene ring with –OH group and amine side chain.



Mechanism of Action (MOA)

- Selective α1 receptor agonist → vasoconstriction → ↑ blood pressure.
- Minimal action on β1 and β2 receptors → no significant bronchodilation or heart rate increase.

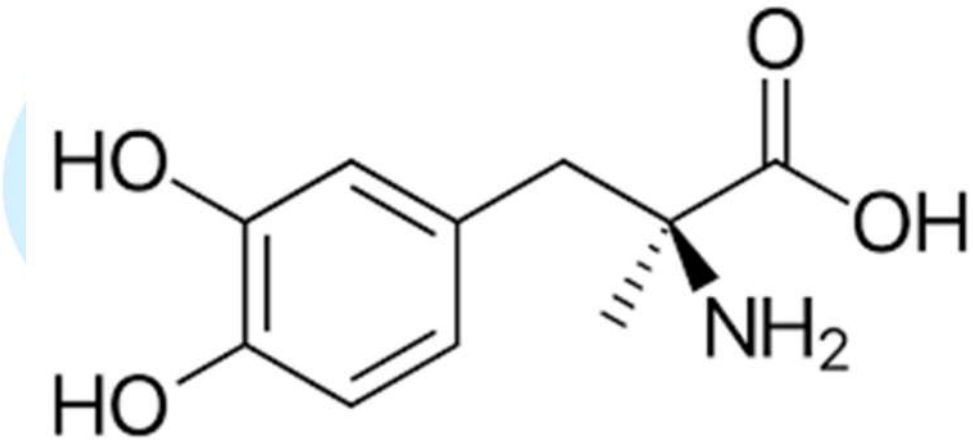
Uses

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

Methyldopa

Structure

- Synthetic α2-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 → stimulates central α2 receptors.
- ↓ Sympathetic outflow → ↓ peripheral vascular resistance → ↓ blood pressure.
- Minimal direct effect on heart rate.

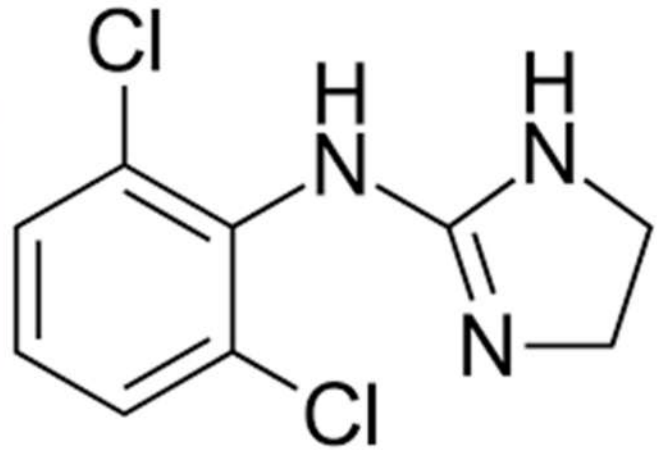
Uses

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

Clonidine

Structure

- Synthetic α2-adrenergic agonist.
- Contains imidazoline ring and amine side chain.



Mechanism of Action (MOA)

- Stimulates central α2 receptors → ↓ sympathetic outflow → ↓ peripheral vascular resistance → ↓ blood pressure.
- Reduces heart rate slightly.
- Minimal direct action on α1 or β receptors.

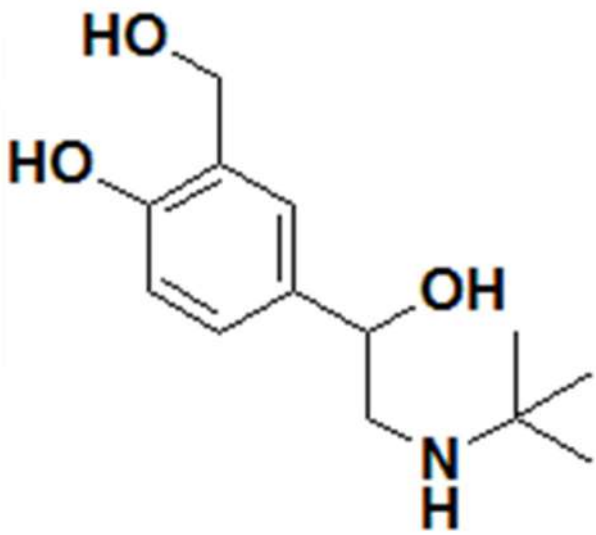
Uses

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

Salbutamol (Albuterol)

Structure

- Synthetic β2-adrenergic agonist.
- Contains benzene ring with –OH groups and amine side chain.



Salbutamol

Mechanism of Action (MOA)

- Selectively stimulates β2 receptors in the lungs → bronchodilation.
- Minimal effect on β1 receptors → little increase in heart rate.
- Relaxes smooth muscles of the airways → improves airflow.

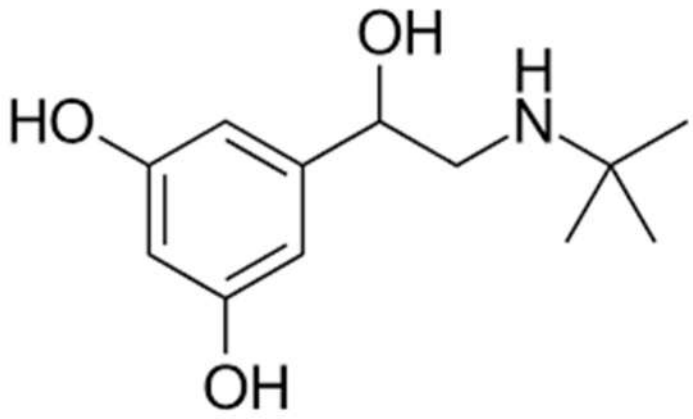
Uses

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

Terbutaline

Structure

- Synthetic β2-adrenergic agonist.
- Contains benzene ring with –OH groups and amine side chain.



Mechanism of Action (MOA)

- Selectively stimulates β2 receptors → bronchodilation.
- Minimal β1 activity → little effect on heart rate.
- Relaxes bronchial and uterine smooth muscles.

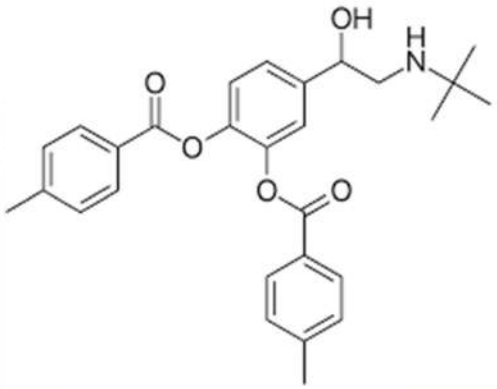
Uses

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

Bitolterol

Structure

- Synthetic β2-adrenergic agonist prodrug.
- Metabolized in the body to active form colterol.



Mechanism of Action (MOA)

- Stimulates β2 receptors → bronchodilation.
- Minimal effect on β1 receptors → little impact on heart rate.
- Relaxes bronchial smooth muscles, improving airflow.

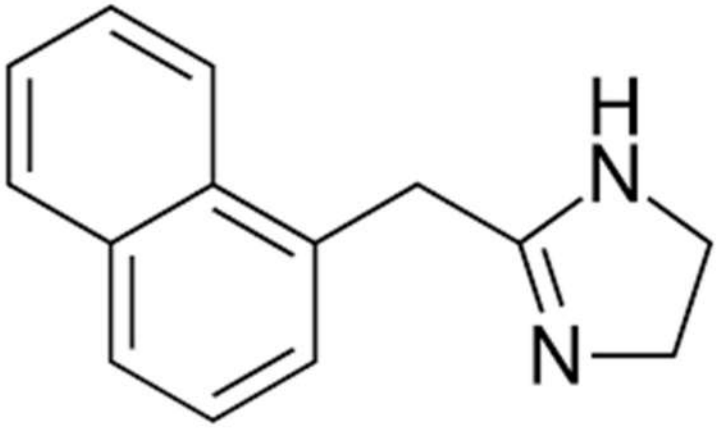
Uses

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

Naphazoline

Structure

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



Mechanism of Action (MOA)

- Stimulates α1 receptors → vasoconstriction of nasal and ocular blood vessels.
- Reduces mucosal edema and redness.
- Minimal effect on β receptors → negligible cardiac effects.

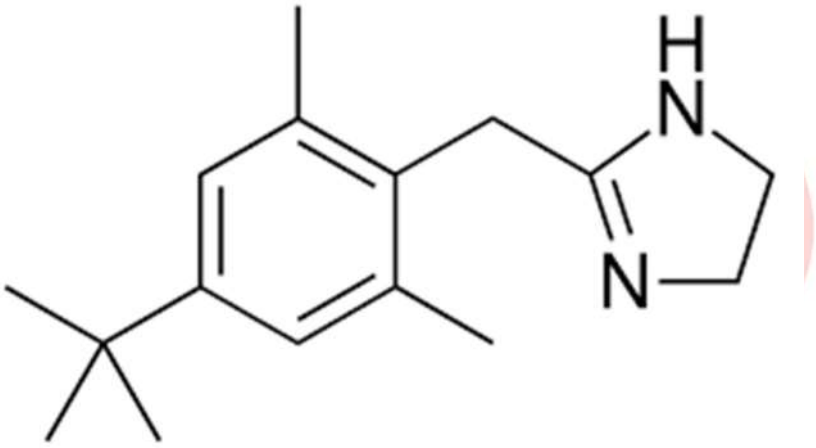
Uses

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

Xylometazoline

Structure

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



Mechanism of Action (MOA)

- Stimulates α1 receptors → vasoconstriction of nasal mucosa.
- Reduces mucosal swelling → eases airflow.
- Minimal effect on β receptors → little or no cardiac stimulation.

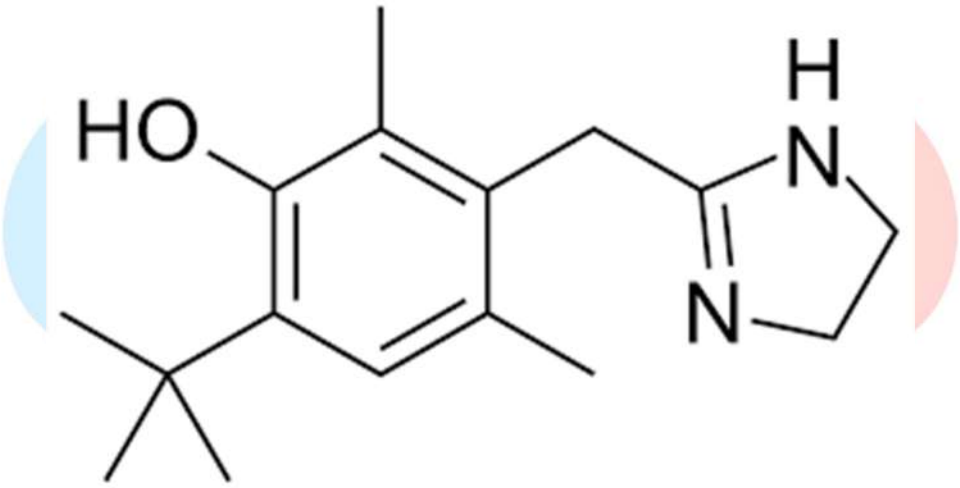
Uses

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

Oxymetazoline

Structure

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



Mechanism of Action (MOA)

- Stimulates α1 and partial α2 receptors → vasoconstriction of nasal mucosa.
- Reduces mucosal edema → eases nasal airflow.
- Minimal systemic effect → little impact on heart rate.

Uses

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

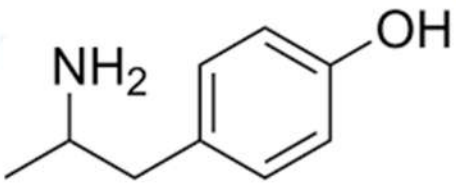
Indirect Acting Agents

- 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 α1 receptors → vasoconstriction and mydriasis.
- Minimal β receptor activity → negligible cardiac stimulation.

Uses

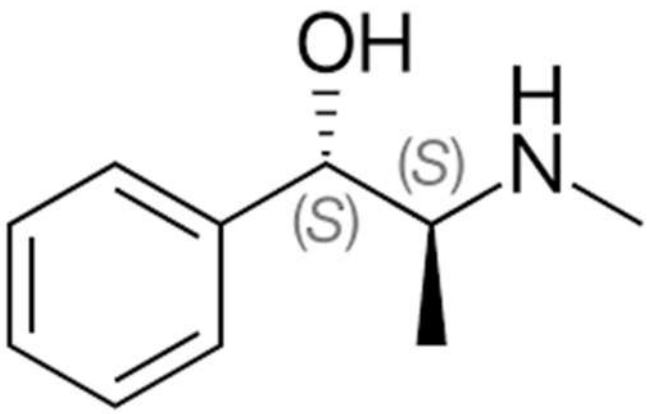
- Mydriasis → dilates pupil for ophthalmic examination.

- 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.
- α1 stimulation → vasoconstriction → reduces nasal congestion.
- β1 stimulation → mild ↑ heart rate & contractility.

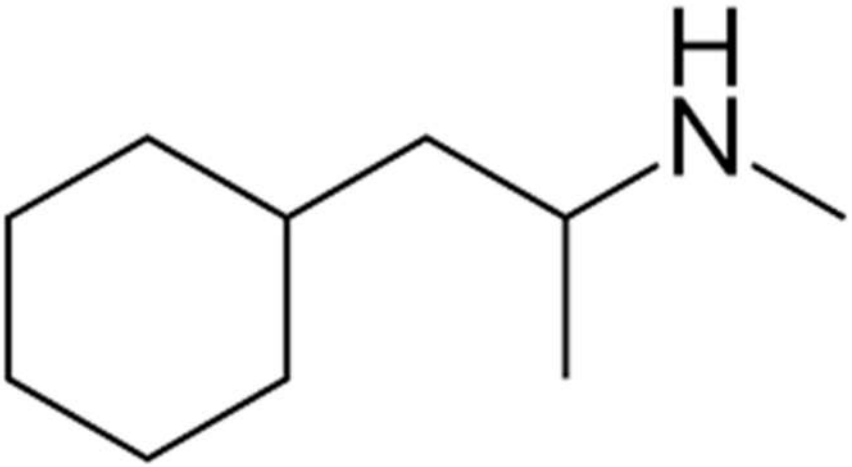
Uses

- Nasal congestion → rhinitis, sinusitis, common cold.
- Eustachian tube congestion → 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 α1 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 a-receptors while epinephrine has more pronounced effects at β-receptors.Also, the potency of both these drugs is different from each other.

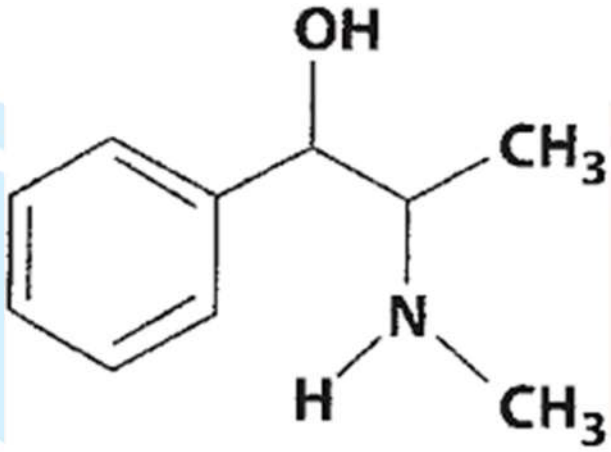
The drugs studied below are:

1) Ephedrine,
2) Metaraminol.

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 → vasoconstriction and mild cardiac stimulation.
- Indirect action: releases stored norepinephrine from sympathetic nerve endings.
- α1 stimulation → vasoconstriction → ↑ BP.
- β1 stimulation → ↑ heart rate & contractility.
- β2 stimulation → bronchodilation (mild).

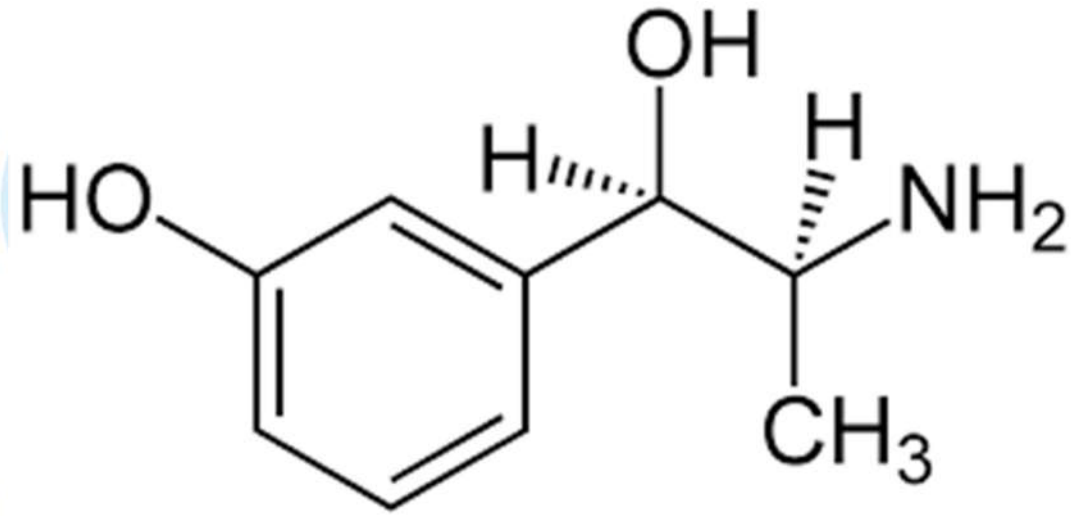
Uses

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

Metaraminol

Structure

- Synthetic direct-acting α1-adrenergic agonist.
- Contains a phenyl ring with amine and hydroxyl substituents.



Mechanism of Action (MOA)

- Stimulates α1 receptors → vasoconstriction → increases blood pressure.
- Minimal β1 or β2 activity → little effect on heart rate or bronchodilation.
- Sometimes causes reflex bradycardia due to ↑ BP.

Uses

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