UNIT-II

Drugs acting on Autonomic nervous system

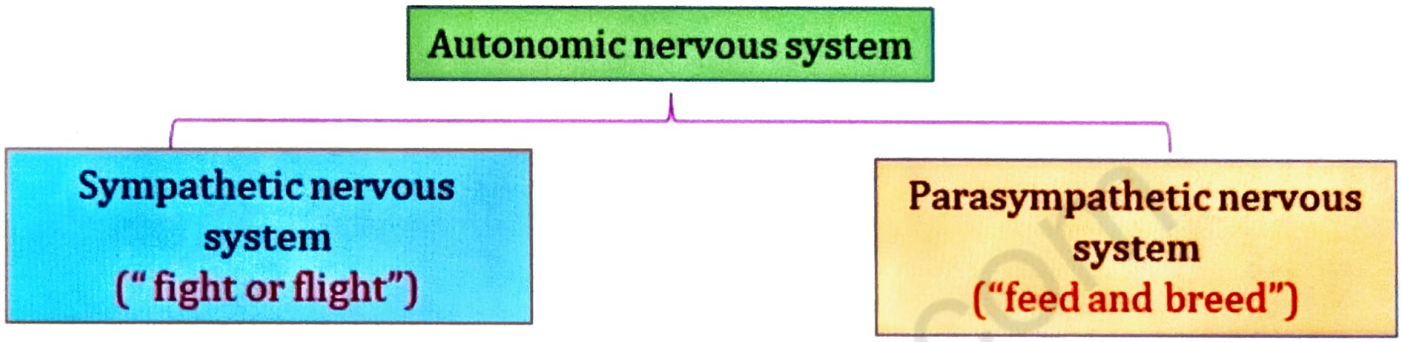
Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ ADRENERGIC NEUROTRANSMITTER
- ❑ SYMPATHOMIMETIC AGENTS
- ❑ ADRENERGIC ANTAGONIST

❑ INTRODUCTION

❖ Autonomic nervous system (ANS)

- It is a **complex set of neurons** that mediate **internal homeostasis without conscious intervention or voluntary control**.
- The ANS maintains **blood pressure, regulates the rate of breathing, influences digestion, urination, and modulates sexual arousal.**

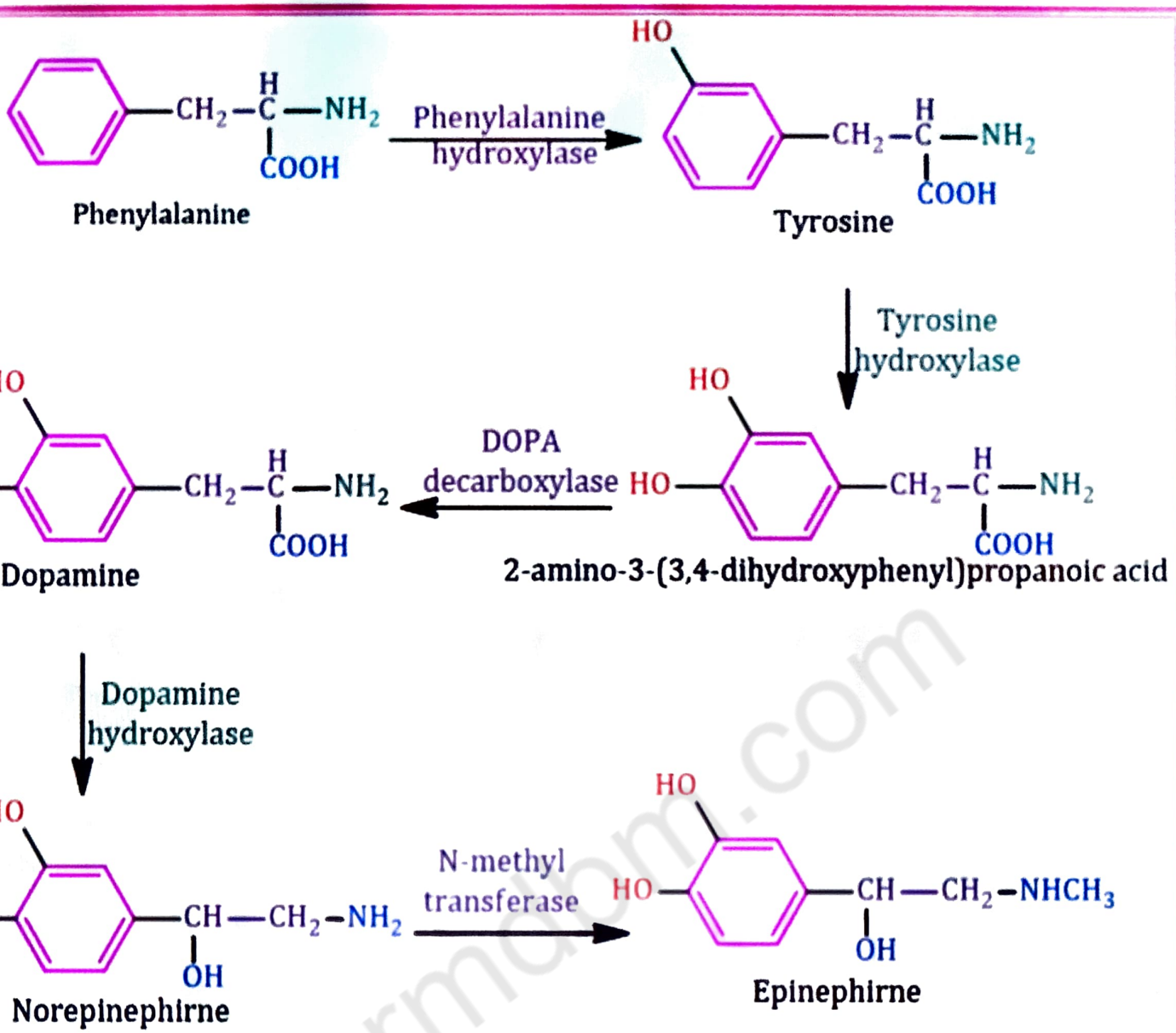


❑ ADRENERGIC NEUROTRANSMITTER

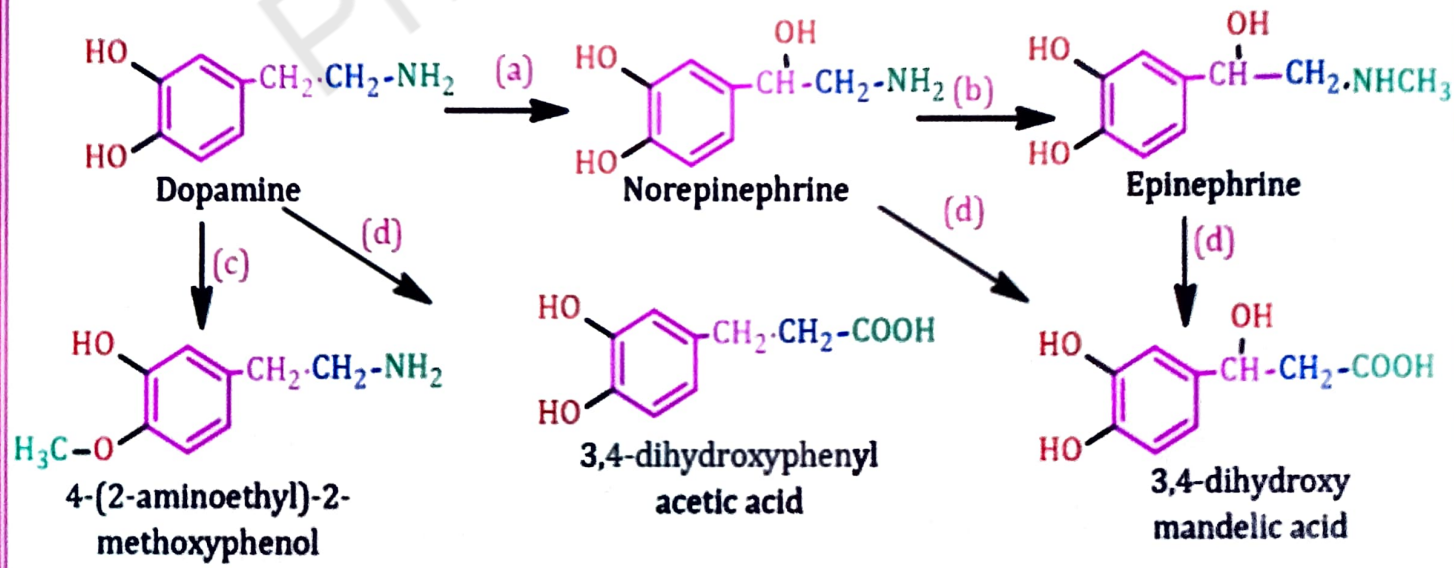
- An adrenergic nerve fiber is a neuron for which **the neurotransmitter is either adrenaline (epinephrine), noradrenaline or dopamine**.
- These neurotransmitters are released at a location known as the synapse, which is a **junction point between the axon of one nerve cell and the dendrite of another.**
- **Dopamine** (pleasure) → **feeling of pleasure, also addiction, movement and motivation.**
- **Nor epinephrine** (concentration) → **It affect attention and responding action in the brain.**
- **Epinephrine** (Adrenaline) → **It produced in stressful situation, increase heart rate & blood flow.**

❖ Biosynthesis of catecholamines

- The biosynthesis takes place in adrenergic and dopaminergic neurons in the CNS, sympathetic neurons in the ANS and in the adrenal medulla.



❖ Catabolism of catecholamines

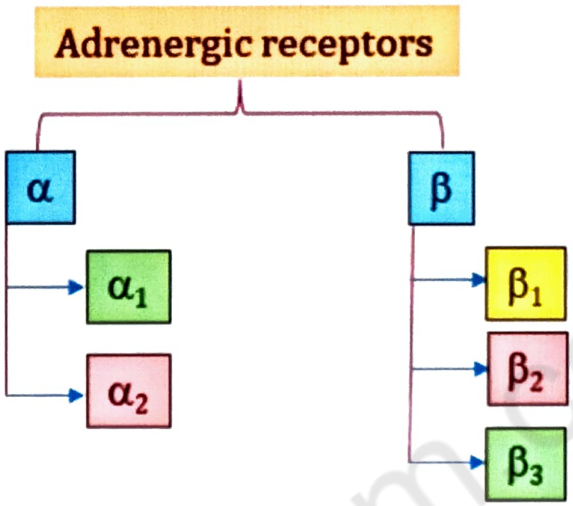


(a) Dopamine-β-monooxygenase (c) catechol-o-methyltransferase

(b) Phenyl ethanolamine-N- methyltransferase (d) monoamine oxidase

❖ Adrenergic receptors (alpha & beta) and their distribution :-

- Adrenergic receptor are those receptor in which adrenergic drugs/neurotransmitter will **bind directly to induce various action/responses.**
- Adrenergic receptors are **membrane bound G-Protein Coupled receptors.**



❖ Distribution Adrenergic receptors with their action:-

Receptor	Location
α_1	Arterioles (coronary, visceral, cutaneous), veins, internal sphincters, Iris dilator muscle.
α_2	Presynaptic membrane, pancreas, veins, adipose tissue, GIT sphincters, salivary glands.
β_1	Heart (SA node, atrial muscle, AV node, ventricles), kidney (JG apparatus), Adipose tissue.
β_2	Arterioles(muscular), veins, bronchi (muscles), liver, pancreas, uterus, Iris constrictor muscle
β_3	Adipose tissue, urinary bladder.

- These receptor **belongs to a large family of cell membrane receptor** which are liked to the **Carrier protein through the one or more GTP activated protein for producing response.**

❑ SYMPATHOMIMETIC AGENTS

- Sympathomimetic drugs **(also known as adrenergic drugs and adrenergic amines)** are stimulant compounds which **mimic the action of sympathetic nervous system.**
- Sympathomimetic drugs are used to **treat cardiac arrest and low blood pressure, or even delay premature labor, among other things.**

Classification of adrenergic drugs

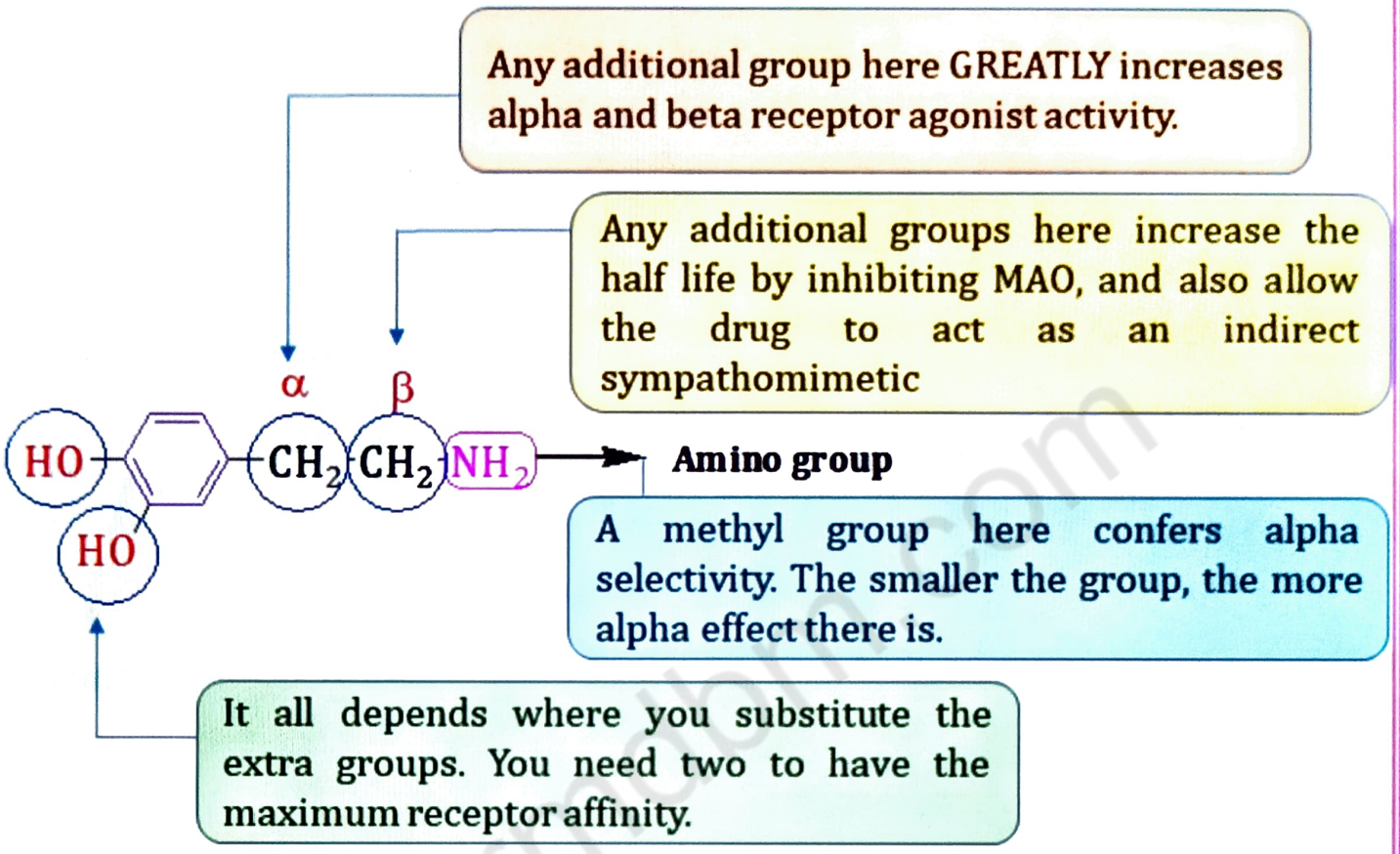
- **Direct acting**
  - **α agonist**
    - **Nonselective**
      - Epinephrine
      - Norepinephrine
    - **Selective**
      - **α_1 agonists**
        - Phenylephrine
        - Methoxamine
      - **α_2 agonists**
        - Clonidine
        - Guanfacine
        - Guanabenz
        - Detomidine
        - Romifidine
        - Medetomidine
  - **β agonist**
    - **Nonselective**
      - Isoproterenol
      - Epinephrine
    - **Selective**
      - **β_1 agonists**
        - Dobutamine
      - **β_2 agonists**
        - Terbutaline
        - Salbutamol (Albuterol)
        - Mtaproterenol
        - Ritodrine
- **Mixed acting**
  - Ephedrine
  - Mephentermine
  - Metaraminol
- **Indirect acting**

❖ Mechanism of action:-

- Sympathomimetic drugs are agents which in **general mimic responses due to stimulation of sympathetic nerves.**

- These agents are able to **directly activate adrenergic receptors** or to **indirectly activate them by increasing nor epinephrine and epinephrine** (mediators of the sympathoadrenal system) levels.

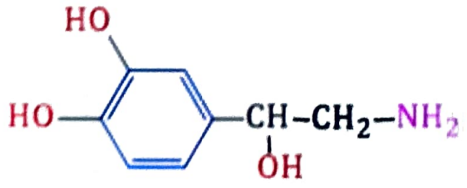
❖ SAR of sympathomimetic agents



❖ Drugs acting on sympathomimetic agents:-

➢ **Direct acting** :-These are those drugs/agents which directly bind with adrenergic receptors (Both α & β) and gives its pharmacological action. The action produced are of rapid onset and of short duration.

1) Norepinephrine



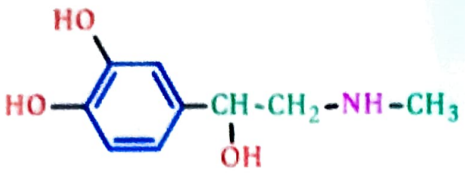
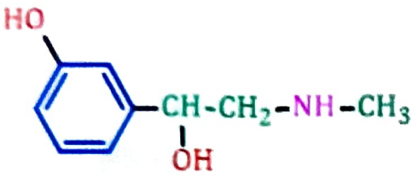
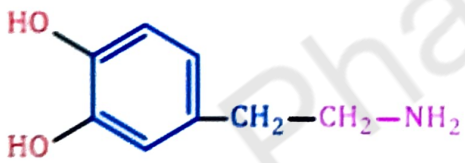
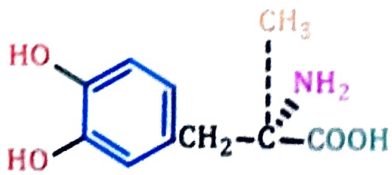
4-(2-amino-1-hydroxyethyl) benzene-1,2-diol

✓ Mechanism of action

- Potent at α-receptor [less potent than adrenaline.
- Also effect on β1-receptor but no effect on β2 receptor.

✓ Uses →

- Strong vasoconstriction properties.
- localize the effects of local anesthetics.

2) Epinephrine  4-(1-hydroxy-2-(methylamino) ethyl)benzene-1,2-diol	✓ **Mechanism of action** • **Directly bind with α, β_1 and β_2 receptor.** • For **oral route it is given in the form of prodrug** (Pivalic acid) **to prevent from first pass metabolism.** ✓ **Uses →** • Used in **treatment of asthma** • **Relaxes bronchial muscles.**
3) Phenylephrine  3-(1-hydroxy-2-(methylamino)ethyl)phenol	✓ **Mechanism of action** • **Bind at α- receptor, no action on β-receptors** ✓ **Uses** • **Increase blood pressure** in acute hypotension. • **Used as mydriatic agent** during eye surgery.
4) Dopamine  4-(2-aminoethyl) benzene -1,2-diol	✓ **Mechanism of action** • **Directly** bind with **β- receptor.** • **Indirectly** on **α- receptor** ✓ **Uses** • Used in **congestive heart failures** where it **increase BP and urine.** • Used in **patient of shock.**
5) Methyldopa  2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid	✓ **Mechanism of action** • Methyldopa **converted into x-methyl norepinephrine** by enzyme dopamine beta hydroxylase and **bind with α_2- receptor** ✓ **Uses** • Used as **antihypertensive.** • Prevent **heart attack and kidney problem.**

6) Clonidine

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

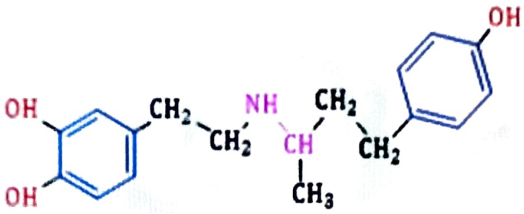
✓ Mechanism of action

- It is centrally on α_2 receptor.

✓ Uses

- Used as hypertension
- Also used as mild sedative

7) Dobutamine



4-(2-((4-(4-hydroxyphenyl)butan-2-yl)amino)ethyl)benzene-1,2-diol

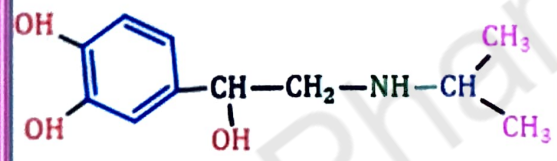
✓ Mechanism of action

- It is directly stimulate β_1 & α_1, receptor. (dual acting drugs).

✓ Uses

- It is used to treat heart failure problem occurring during Cardiac surgery.
- Treatment of congestive heart failure.

8) Isoproterenol



4-(1-hydroxy-2-(isopropylamino)ethyl)benzene-1,2-diol

✓ Mechanism of action

- Act on both β_1 & β_2 receptors.
- β_1 (increase cardiac output)
- β_2 (increase Broncho dilation)

✓ Uses

- Used for treatment of bronchial asthma.
- Used in treatment of bradycardia.

9) Terbutaline

5-(2-(tert-butylamino)-1-hydroxyethyl)benzene-1,3-diol

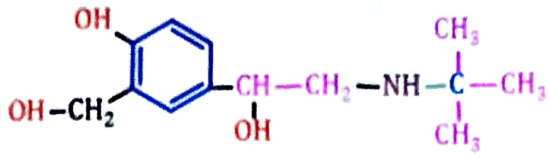
✓ Mechanism of action

- Bind with β_2- receptor better than Isoprenaline.

✓ Uses

- Given orally for the treatment of asthma.
- Also use as an aerosol/inhalation.

10) Salbutamol



4-(2-(tert-butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol

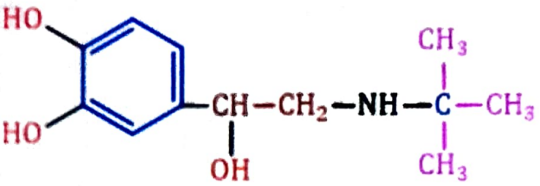
✓ **Mechanism of action**

- **Directly** bind with **β_2- receptor.**

✓ **Uses**

- Used to **relax uterine Smooth muscles** and **to delay premature labour.**
- Orally for **relief of bronchospasm.** (narrowing of bronchi).

11) Bitolterol



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

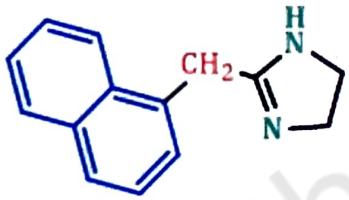
✓ **Mechanism of action**

- Bind with **β_2- receptor.**

✓ **Uses**

- Prodrug of colterol
- Bronchodilator (used to treat asthma).

12) Naphazoline



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

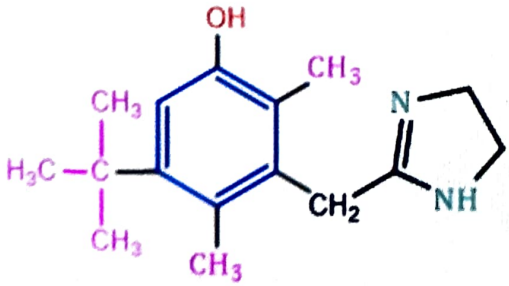
✓ **Mechanism of action**

- **Powerful α-receptor** which stimulant (α_1 & α_2)

✓ **Uses**

- Used as a **vasoconstrictor.**
- **Reduced swelling.**
- Relief of **rhinitis and sinusitis.**

13) Oxymetazoline



5-(tert-butyl)-3-((4,5-dihydro-1H-imidazol-2-yl)methyl)-2,4-dimethylphenol

✓ **Mechanism of action**

- Partially **agonist at α_2 and selective agonist at α_1 receptor.**

✓ **Uses**

- Due to their vasoconstriction properties, it is used to **treat nose bleeding** and redness of eye due to irritation.

14) Xylometazoline

2-(3-(tert-butyl)-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazole

✓ Mechanism of action

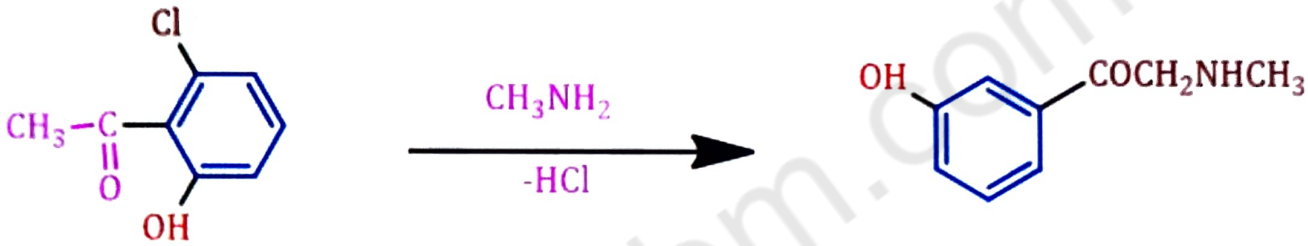
- **Bind** with both α_1 & α_2 receptor.

✓ Uses

- Produces **constriction of large veins in nose.**
- Treat symptoms of **nasal congestion, allergies** e.g.- NASAL DROPS.

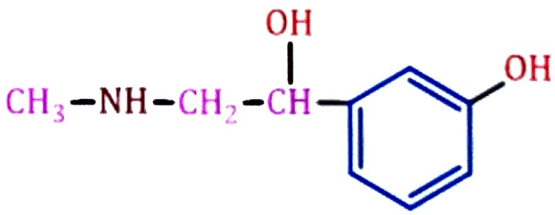
❖ Synthesis of Phenylephrine:-

➢ From: 3-Chloro acetyl phenol



3-chloro acetyl phenol

(i) H2/Catalytic reduction
(ii) Resolved with d-camphor sulphonate



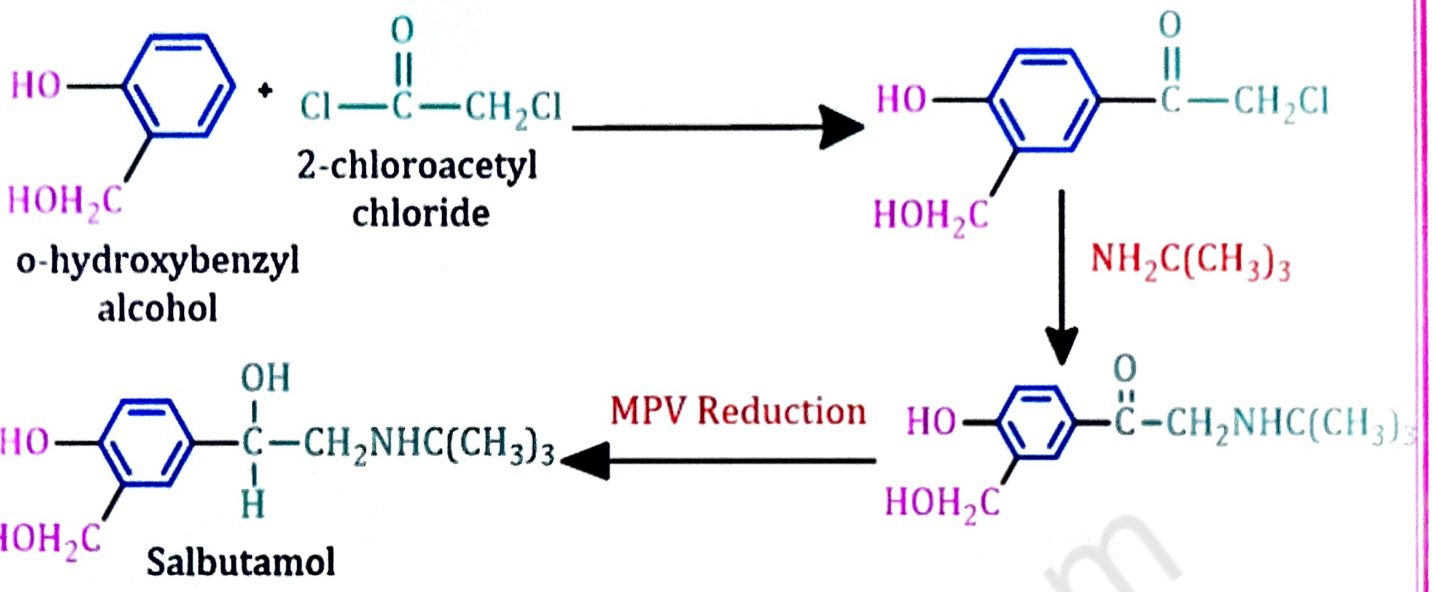
Phenylephrine

✓ Properties

- It is a **white or almost white crystalline powder**, **freely soluble in ethanol and water.**
- It **resistant to COMT** and has **predominantly α1 agonist effect.**

❖ Synthesis of salbutamol:-

➢ From:- o-Hydroxy benzyl alcohol

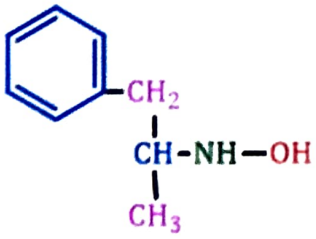


✓ Properties

- It is **a white or almost white crystalline powder**, **sparingly soluble in water, but freely soluble in ethanol**.
- It has strong β2 adrenergic activity.

➢ **Indirect acting :-** Those **drugs which act indirectly to increase the concentration of neurotransmitter** by causing its release.

1) Hydroxyamphetamine



(R)-N-(1-phenylpropan-2-yl)hydroxylamine

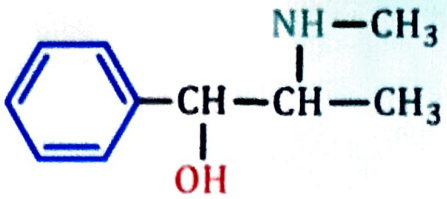
✓ Mechanism of action

- Cause **release of nor-adrenaline**.
- from nerve synapse and causes dilation of pupil.

✓ Uses

- Used an eye drop to **dilate the pupil**.
- Used as a **Horner syndrome diagnostic agents for testing** (damage of nerve of eye).

2) Pseudoephedrine



2-(methylamino)-1-phenylpropan-1-ol

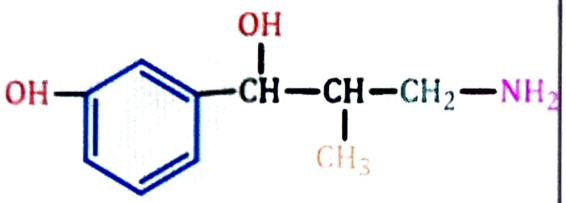
✓ **Mechanism of action**

- It **stimulates** both α_1 & α_2 **receptor.**
- It stimulate central nervous system.

✓ **Uses**

- It **increase the blood pressure** (hypertension) by **increasing cardiac output and causing vasoconstriction**.

3) Propylhexedrine



3-(3-amino-1-hydroxy-2-methylpropyl)phenol

✓ **Mechanism of action**

- **Activates α-receptor** in the **mucosa of respiratory tract.**

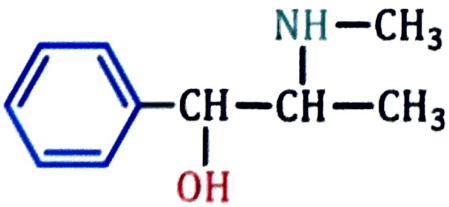
✓ **Uses**

- Used to **relief of congestion due to cold, allergies, rhinitis** (inflammation of mucous membrane of nose) **due to any virus infection** (common cold)or any **allergic reaction.**

➢ **Mixed acting:-** These are those **drugs which act on adrenergic receptors** and also **effect the release of noradrenaline**.

- Act both as **direct acting and indirect acting**.

1) Ephedrine



2-(methylamino)-1-phenylpropan-1-ol

✓ **Mechanism of action**

- It **stimulates** both α_1 & α_2 **receptor.**
- It **stimulate central nervous system.**

✓ **Uses**

- Used as **nasal decongestant** in the **form of nasal drops & nasal spray**.
- Used in **various allergic disease** like **hay fever and urticaria.**

2) Metaraminol

3-(2-amino-1-hydroxypropyl)phenol

✓ Mechanism of action

- Act on both α_1 & α_2 receptor.
- Stimulates noradrenaline.

✓ Uses

- Used in the treatment of hypotension.

❑ ADRENERGIC ANTAGONIST

- Adrenergic blockers are also called as antiadrenergic drugs or sympatholytic.
- Drug that inhibits the function of adrenergic receptors.

1. Adrenergic receptors:- which are divided into two groups.

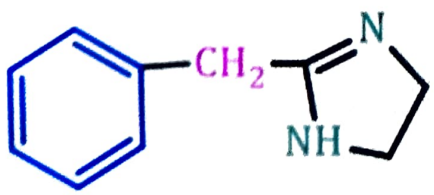
- The first group of receptors are the beta (β) adrenergic receptors. There are β1, β2, and β3 receptors.
- The second group contains the alpha (α) adrenoreceptors. There are only α1 and α2 receptors

❖ Mechanism of action of α-Adrenergic receptor blockers:-

- Adrenergic antagonists have inhibitory or opposing effects on the receptors in the adrenergic system.
- Administration of an adrenergic antagonist that specifically targets the β-receptors, results decrease in blood pressure by reducing cardiac output.

❖ Drugs acting on Adrenergic blockers :-

1) Tolazoline



2-benzyl-4,5-dihydro-1H-imidazole

✓ Mechanism of Action (Reversible)

- It is Structurally similar as α-agonists, so they blocks the α-receptor and, stop α-agonists to produce effects.

✓ Uses

- Used as Vasodilator.
- It Causes stimulation of gastric acid secretion.

2) Phentolamine

3-(((4,5-dihydro-1H-imidazol-2-yl)methyl)(p-tolyl)amino)phenol

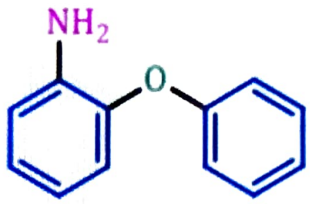
✓ Mechanism of action

- It **blocks** both **α_1 & α_2 receptor**.

✓ Uses

- **Used as a vasodilators, inhibit catecholamines effects** (vasoconstriction).
- Used to **control hypertensive conditions**.

3) Phenoxybenzamine



2-phenoxyaniline

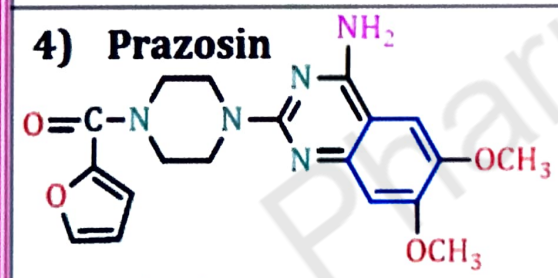
✓ Mechanism of action

- It **blocks** both **α_1 & α_2 receptor**.
- **Irreversible α-blocker.**

✓ Uses

- Used in the **treatment in urinary retention**.
- Used in the **treatment of hypertension caused by Pheochromocytoma.**

4) Prazosin



(4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl)(furan-2-yl)methanone

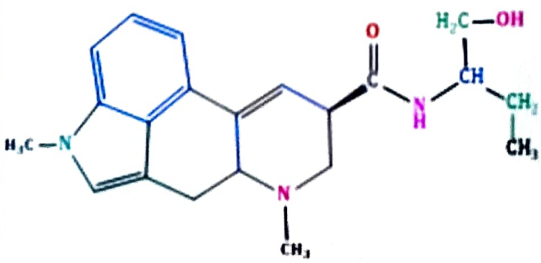
✓ Mechanism of action

- It has **affinity for α_1- receptor**, so it **blocks α_1- receptor.**

✓ Uses

- It is used to **treat heart failure and Raynaud syndrome**

5) Methysergide



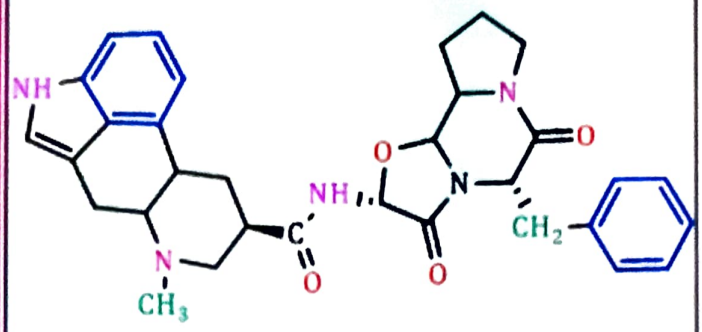
✓ Mechanism of action

- It is an antagonist of **α-adrenergic receptor.**
- **Potent serotonin antagonist**

✓ Uses

- Used as **prophylactic** in the **treatment of severe migraine.**

6) Dihydroergotamine



✓ Mechanism of action

- It is **an antagonist** of α-adrenergic receptor.

✓ Uses

- Used as **vasoconstriction.**
- Used in the **treatment of migraine.**

❖ Synthesis of Tolazoline :-

➢ From: Phenyl acetonitrile

2-Phenyl acetonitrile

Tolazoline

❖ Adverse effects of Adrenergic Antagonists

- Cold feet and hands.
- Fatigue.
- Nausea, weakness, and dizziness.
- Dry mouth, skin, and eyes.
- Slow heartbeat.

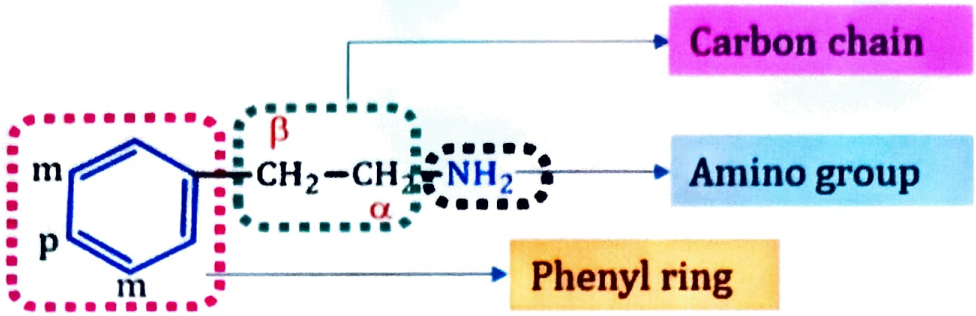
2. β-Adrenergic blockers:

- A class of drug, **that blocks β-adrenergic substances** such as adrenaline (epinephrine).
- **It antagonizes** the **effects produced by the drug acting on β- receptor.**

❖ Mechanism of action of β-Adrenergic blockers:

- It **reduces your blood pressure.**
- Beta blockers work **by blocking the effects of the hormone epinephrine,** also known as adrenaline.
- Beta blockers **cause your heart to beat more slowly and with less force, which lowers blood pressure**

❖ SAR of β-blockers



➢ Phenyl ring

- Aromatic ring and its substituent is the primary determinant of β_1 antagonistic activity.
- Alkenyl and Alkanyloxy group when present in o-position on phenyl ring, give good B-antagonist activity.
- If phenyl ring is replaced by naphthyl or substituted than they are non-selective (e.g. propranolol).
- Addition of -OH group in phenyl ring lead to removal of antagonist activity.
- N, N–disubstitution decreases the β blocking activity, and the activity is maintained by the addition of phenyl ethyl or hydroxy phenyl ethyl to amine as a part of the molecule.

• Substitution of the carbon chain

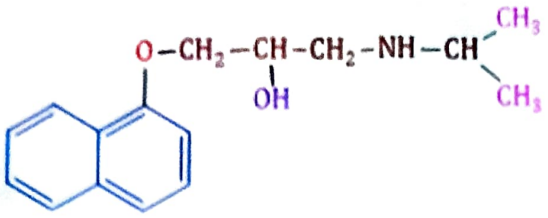
- The –OCH2 group is placed between the aromatic ring ethyl amine side chain increase activity or essential for the activity.
- Two carbon chain are essential for the activity.

➢ Substitution on amino group

- If isopropyl and t-butyl are present an amino group, then it provides nucleophilicity to the amino group.

❖ Drugs acting on Beta Adrenergic blockers :-

1) Propranolol



1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol

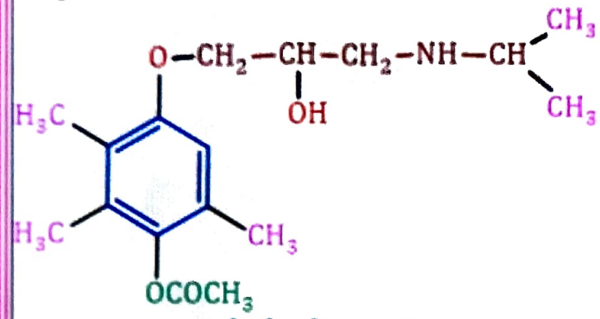
✓ Mechanism of action

- It act **due to decrease renin release** and **reduced cardiac output.**
- It is **non selective β-adrenergic blocker.**

✓ Uses

- Used in the **treatment of hypertension.**
- Used in the **treatment of cardiac arrhymia.**

2) Metibranolol



4-(2-hydroxy-3-(isopropylamino)propoxy)-2,3,6-trimethylphenyl acetate

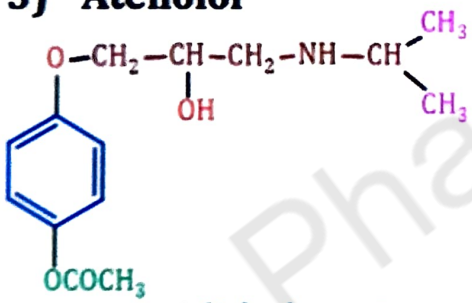
✓ Mechanism of action

- It is **non selective β-adrenergic blocker.**

✓ Uses

- Used in **eye drop and the treatment of glaucoma.**

3) Atenolol



4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl acetate

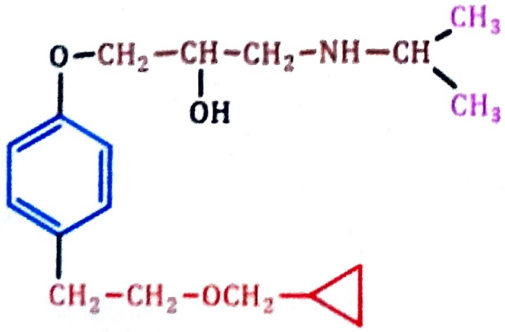
✓ Mechanism of action

- It is **non β_1-selective antagonist.**

✓ Uses

- Used in the **treatment of hypertension.**
- Used in the **emergency treatment of cardiac arrhythmia.**

4) Betazolol



1-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)-3-(isopropylamino)propan-2-ol

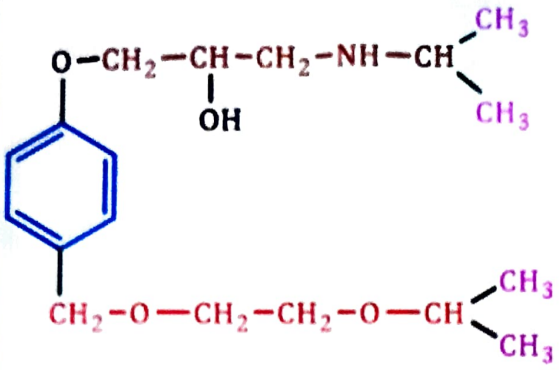
✓ Mechanism of action

- It is **non β_1-selective blocker.**

✓ Uses

- Used in the **treatment of hypertension.**
- Used in **eye drop and the treatment of glaucoma.**

5) Bisoprolol



1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-(isopropylamino)propan-2-ol

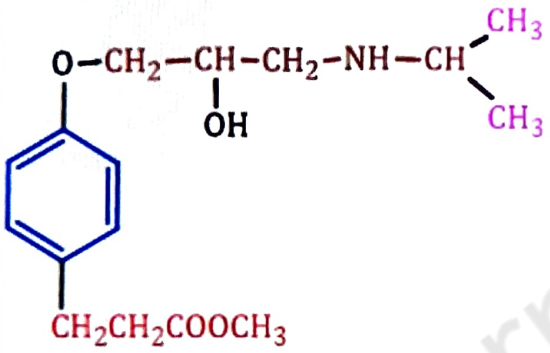
✓ Mechanism of action

- It is **non β_1-selective blocker**.

✓ Uses

- Used as **hypertension.**
- Used in the **treatment of heart disease e.g. cardiac arrhythmia, myocardial infraction.**

6) Esmolol



methyl 3-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)propanoate

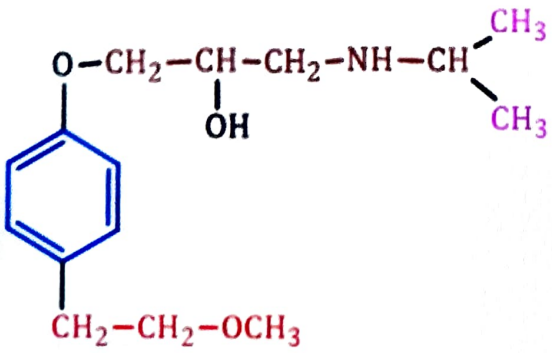
✓ Mechanism of action

- It is **non β_1-selective blocker.**

✓ Uses

- Used as **short acting hypertension.**
- Used in the **early treatment of myocardial infraction.**

7) Metoprolol



1-(isopropylamino)-3-(4-(2-methoxyethyl)phenoxy)propan-2-ol

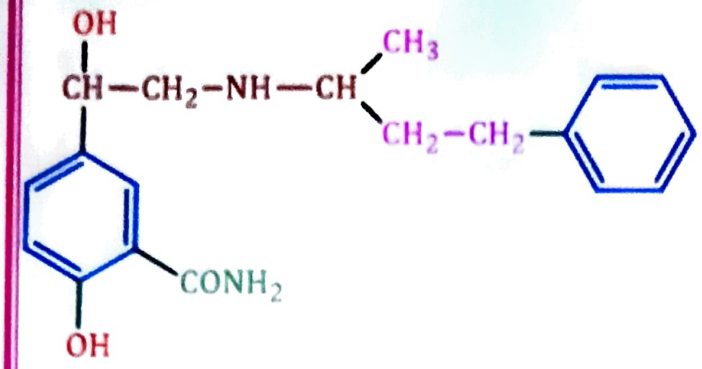
✓ Mechanism of action

- It is **non β_1-selective blocker.**

✓ Uses

- Used in the **treatment of hypertension.**
- Helpful in the **treatment of heart failure.**

8) Labetalol



2-hydroxy-5-(1-hydroxy-2-((4-phenylbutan-2-yl)amino)ethyl)benzamide

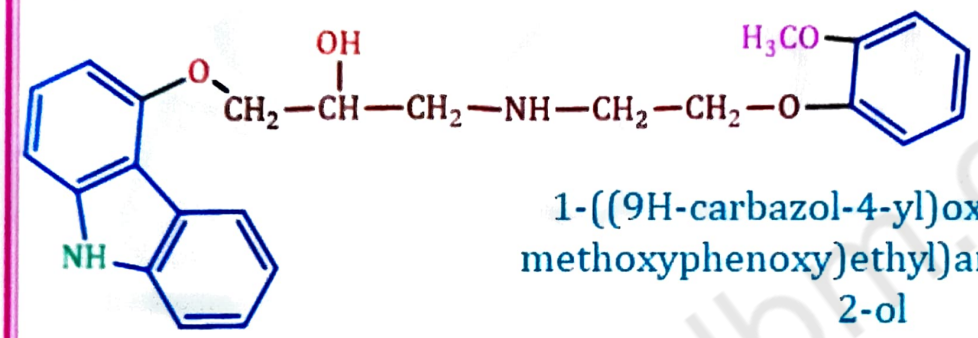
✓ Mechanism of action

- It is **non β_1-selective blocker**.
- Act as **competitive blocker on both α_1 and β-receptor**.

✓ Uses

- Used as **antihypertensive agent**.
- Given **intravenously in sever hypertension**.

9) Carvedilol



1-((9H-carbazol-4-yl)oxy)-3-((2-(2-methoxyphenoxy)ethyl)amino)propan-2-ol

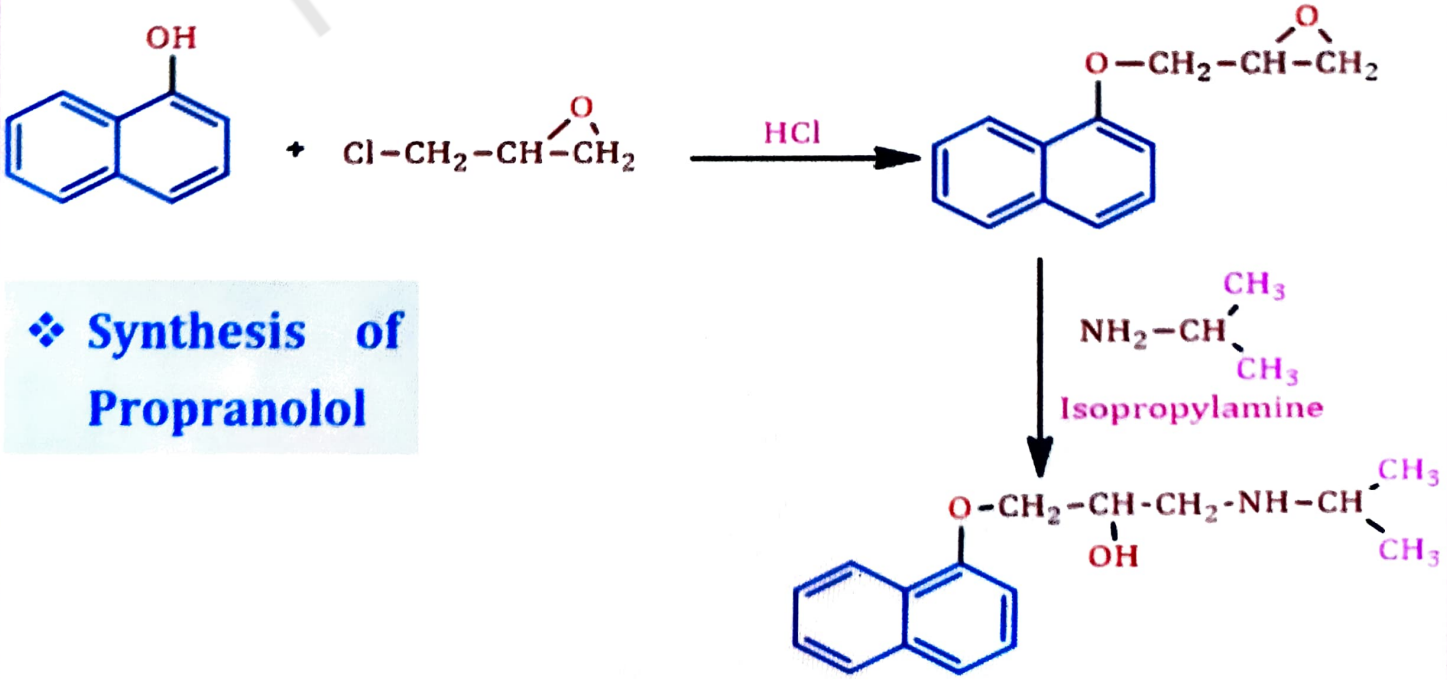
✓ Mechanism of action

- **Non selective β- blocker**. Act on **both α_1 and β-receptor**.
- Due to **α_1- blocker it relax blood vessels, and reduce BP**.

✓ Uses

- Used as **antihypertensive agent**.
- Given **intravenously in sever hypertension**.

❖ Synthesis of Propranolol



❖ Adverse effects of Beta- adrenergic blockers

- Cold feet and hands.
- Fatigue.
- Nausea, weakness, and dizziness.
- Dry mouth, skin, and eyes.
- Slow heartbeat.
- Swelling of the hands and feet.
- Weight gain