MEDICINAL CHEMISTRY-I

UNIT 2 NOTES

DRUGS ACHING ON ANS

- ADRENEGIC NEUROTRANSMITTERS
- SYMPATHOMIMETIC AGENTS
- ADRENEGIC ANTAGONIST

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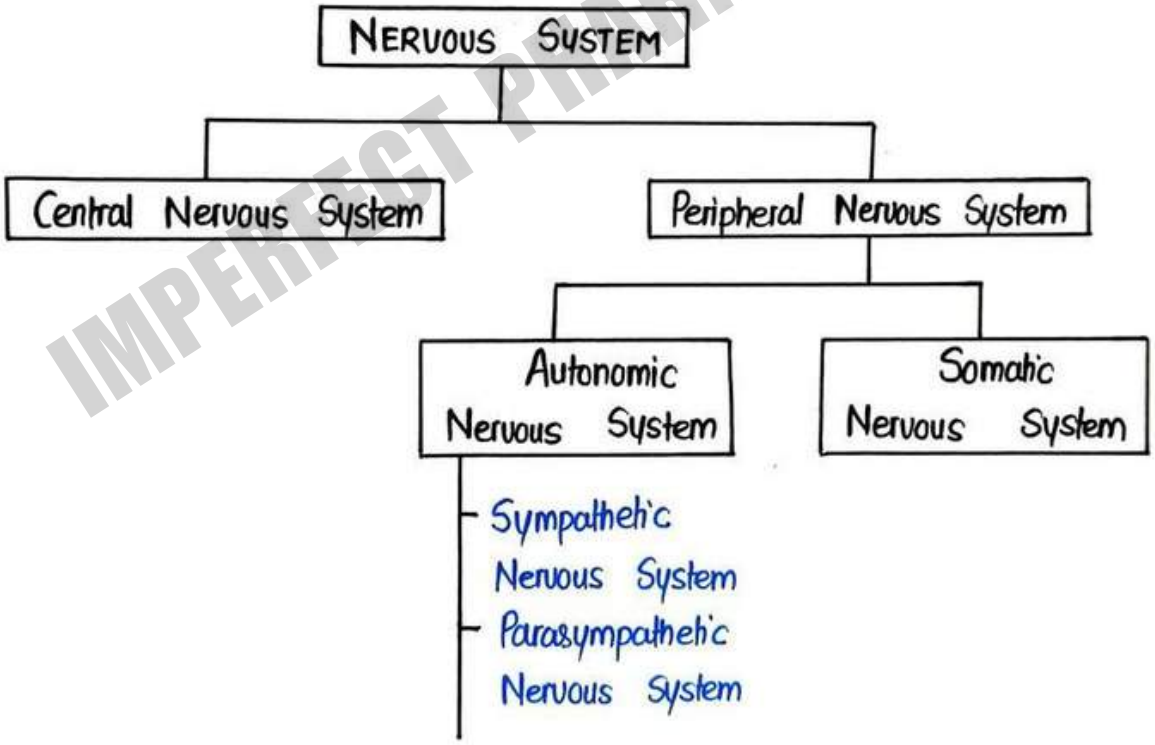
DRUGS ACTING ON ANS

Drugs acting on the Autonomic Nervous System (ANS) are medications that affect the functions of Sympathetic & Parasympathetic branches of ANS, which control involuntary body functions like heart rate, digestion, respiratory rate, pupil size & glandular activity.



① SYMPATHETIC NERVOUS SYSTEM

- It is known as "Fight or Flight" system.
- This system prepares the body to face stressful or emergency situations.

KEY FUNCTIONS

- Increases Heart Rate
- Dilates Broonchi (Improves Airflow)
- Dilates Pupil (Mydriasis)
- Inhibits Digestion
- Inhibits Salivation
- Stimulates Glucose release from Liver
- Relaxes Bladder (Urine retention)
- Causes vasoconstriction (raises BP)
- stimulates sweating

NEUROTRANSMITTERS

- Preganglionic : Acetylcholine (ACH)
- Post Ganglionic : Norepinephrine or Epinephrine

ADRENERGIC NEUROTRANSMITTERS

- Adrenergic Neurotransmitters are chemical messengers released by Adrenergic Neurons, which primarily act on adrenergic receptors (alpha & beta receptors) in the Sympathetic Nervous System.
- These neurotransmitters are involved in "Fight or Flight" responses like increasing heart rate, blood pressure & energy availibility.
- They are also known as Catecholamines.
- The three main adrenergic neurotransmitters are :

① Dopamine
② Norepinephrine
③ Epinephrine

① DOPAMINE

- It is the first catecholamine in the synthesis chain.
- It acts on dopaminergic receptors (D_1, D_2).
- It has mild action on β_1 & α_1 receptors at higher doses.
- It plays important role in renal vasodilation, CNS functions (mood, movement) & precursor to norepinephrine.

② NOR- EPINEPHRINE

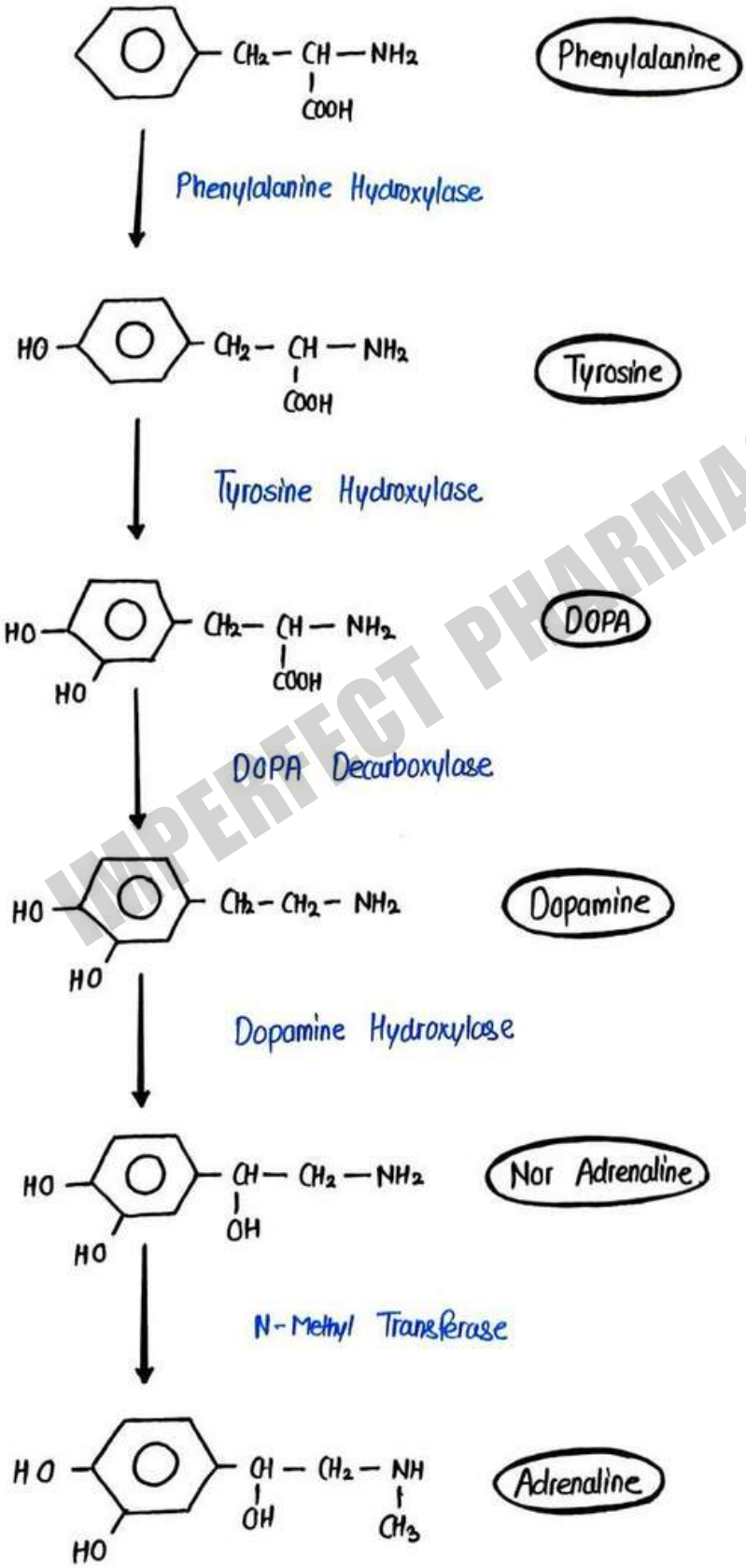
- They are also known as Noradrenaline.
- It is the primary neurotransmitter released by sympathetic postganglionic neurons.
- It acts mainly on α_1, α_2 & β_1 receptors.
- Primary functions include :
  - Increases heart rate & contractility. (β_1)
  - Vasoconstriction (α_1) - increases BP.

③ EPINEPHRINE

- It is also known as Adrenaline.
- It acts on α_1, α_2 β_1 & β_2 receptors.
- Functions :
  - Increases Heart Rate & Cardiac Output (β_1)
  - Bronchodilation (β_2)
  - Vasoconstriction (α_1) & vasodilation in skeletal muscles (β_2)
  - Raises blood glucose levels (stimulates glycogenolysis)

BIOSYNTHESIS OF CATECHOLAMINES

Phenylalanine
↓ Phenylalanine Hydroxylase
Tyrosine
↓ Tyrosine Hydroxylase
DOPA
↓ Dopa Decarboxylase
Dopamine
↓ Dopamine Hydroxylase
Nor- Epinephrine
↓ N- Methyl transferase
Epinephrine



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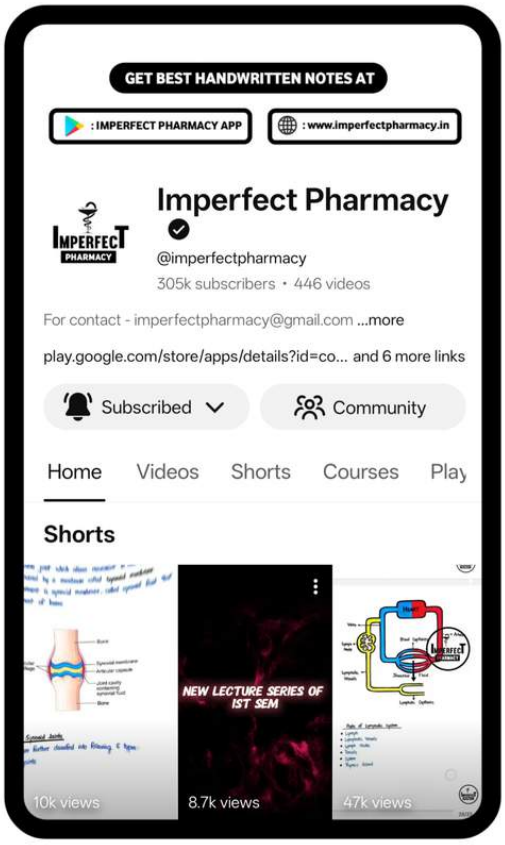

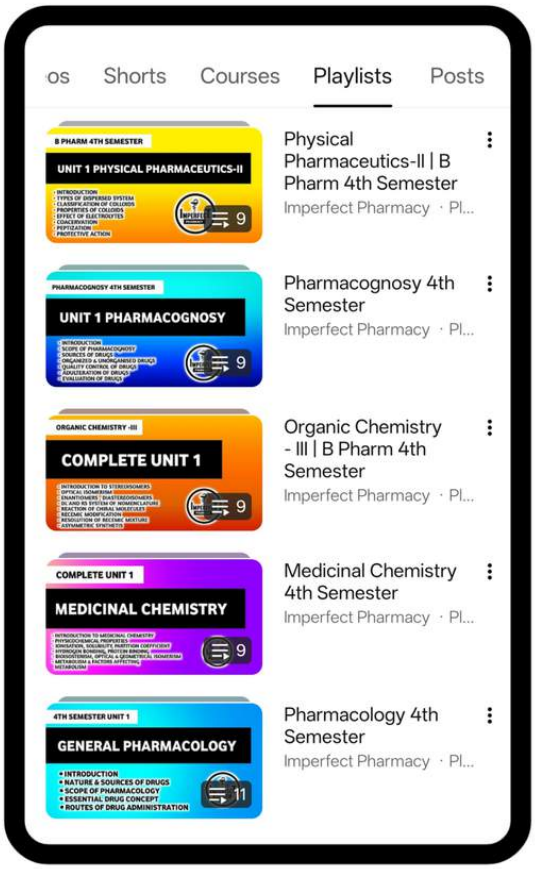

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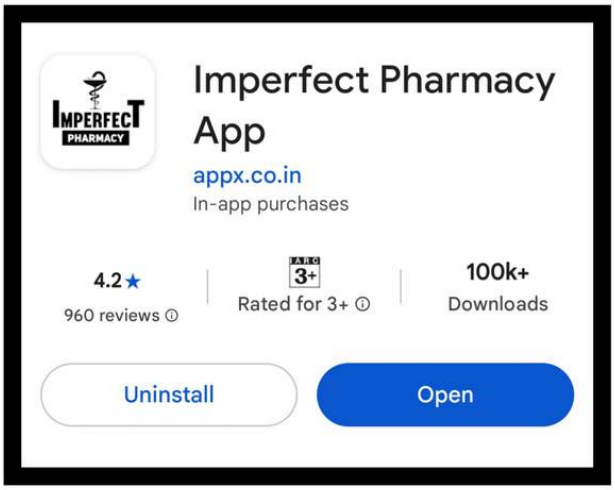


STEPS

- First Phenyalanine is converted into Tyrosine by the enzyme 'Phenylalanine Hydroxylase'
- Tyrosine is converted into DOPA by the enzyme 'tyrosine hydroxylase'
- DOPA is then converted to Dopamine by the enzyme 'DOPA decarboxylase'
- Dopamine is then converted to Norepinephrine by the enzyme 'Dopamine β- hydroxylase'
- Nor- Epinephrine is then finally converted to Epinephrine by the enzyme 'N- methyl transferase'.

CATABOLISM OF CATECHOLAMINES

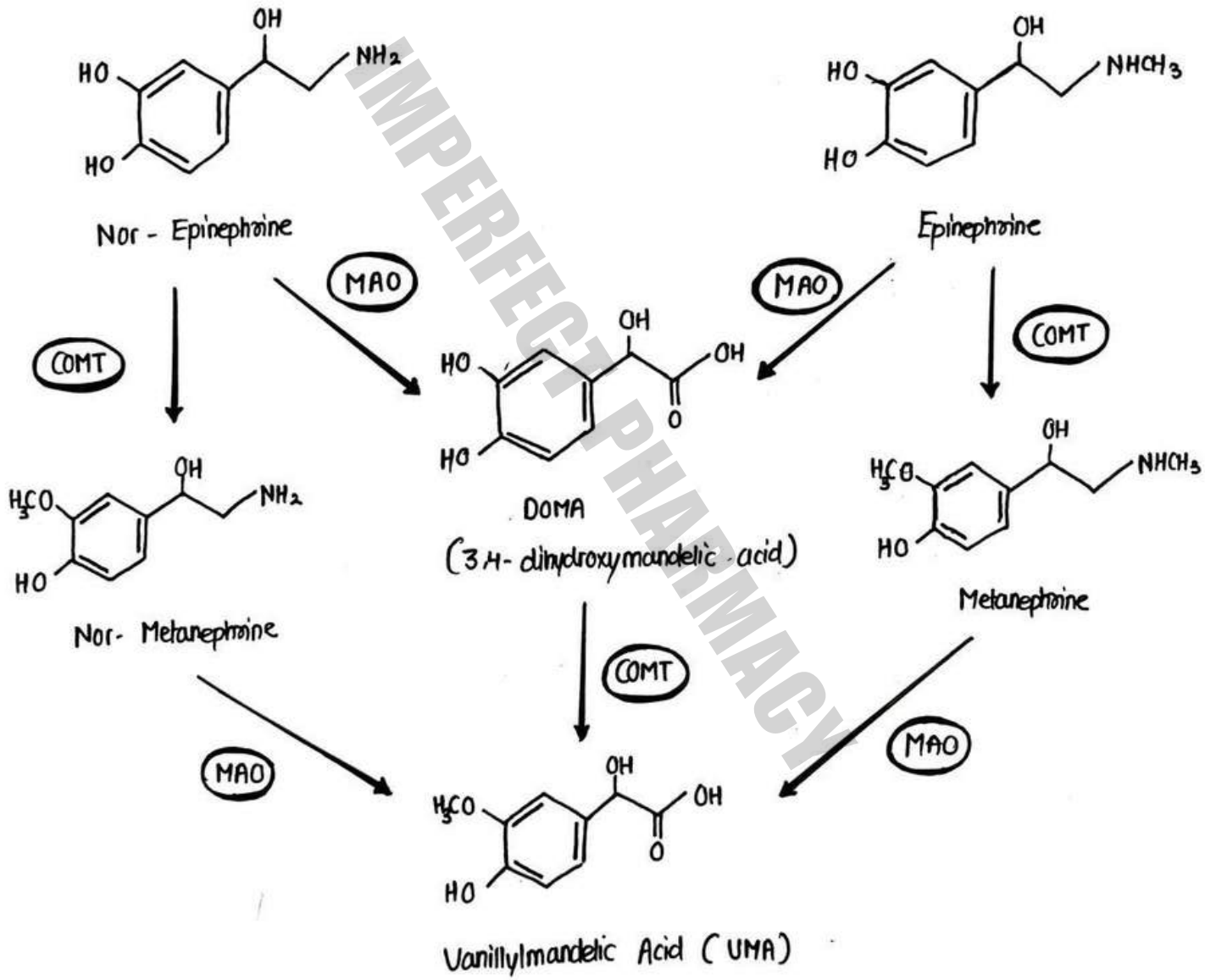
- Catabolism of catecholamines refers to breakdown or degradation of catecholamines like Dopamine, Norepinephrine and Epinephrine after they have performed their functions in body.
- This breakdown is mainly done by two enzymes:

① Monoamino Oxidase (MAO)

- found in almost all body tissues.
- It breaks down catecholamines by removing the amine ($-NH_2$) group.

② Catechol - O- Methyltransferase (COMT)

- Found in Liver & kidneys.
- Adds a methyl group to catechol ring.



ADRENERGIC RECEPTORS

- Adrenergic Receptors are class of G-Protein-Coupled Receptors (GPCRs) that are targeted by the catecholamines i.e. norepinephrine and Epinephrine.
- These receptors mediate the physiological response of sympathetic nervous system & are involved in wide range of processes including heart rate regulation, smooth muscle contraction or relaxation etc.

TYPES OF ADRENERGIC RECEPTORS

Adrenergic Receptors are broadly classified into two main types:

① Alpha (α) adrenergic receptors
② Beta (β) adrenergic receptors

① α Adrenergic Receptors

- They are mainly responsible for smooth muscle contraction & vasoconstriction.
- They are of two types

(a) α_1 Receptors
(b) α_2 Receptors

② β Adrenergic Receptors

- They usually cause smooth muscle relaxation & increases heart activity.
- They are of 3 types:

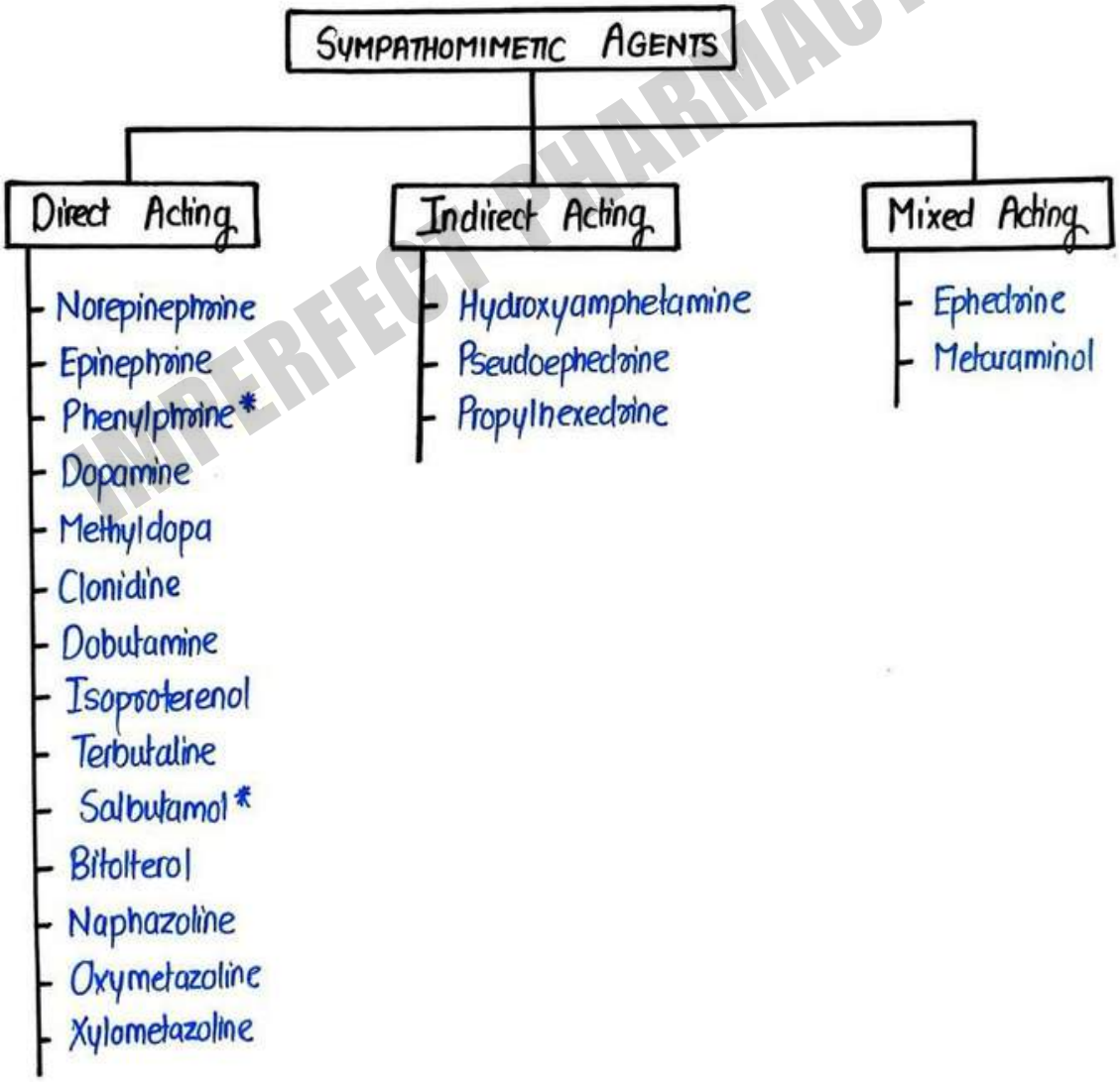
(a) β_1 Receptors
(b) β_2 Receptors
(c) β_3 Receptors

Distribution & Functions Of Adrenergic Receptors

Receptor	Location	Functions
α_1	Blood Vessels, Iris, Bladder Liver	Vasoconstriction, Mydriasis Urinary Retention
α_2	Presynaptic Terminals, Pancreas, Platelets CNS	Inhibits NE ↓ Insulin ↓ BP
β_1	Heart, kidney	↑ HR, ↑ Contractility ↑ renin
β_2	Lungs, Uterus, Blood Vessels Liver	Bronchodilation, Vasodilation Tocolysis, Glycogenolysis
β_3	Adipose Tissue, Bladder	Thermogenesis, Bladder Relaxation

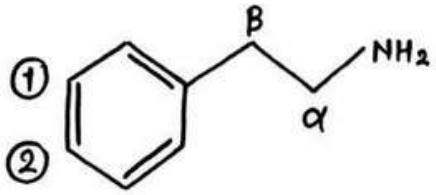
SYMPATHOMIMETIC AGENTS

- Sympathomimetic Agents are drugs or substances that mimic the effects of the sympathetic nervous system by stimulating adrenergic receptors (α & β receptors)
- They either directly activate these receptors or increase the levels of natural neurotransmitters like norepinephrine or epinephrine.



SAR OF SYMPATHOMIMETIC AGENTS

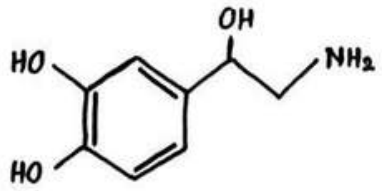
The general structure of Sympathomimetic Agents is β- Phenyl ethylamine.



β- Phenyl Ethylamine

- Any additional group on β carbon atom greatly increases alpha & beta receptor agonist activity.
- Any additional group on α carbon atom increases half life by inhibiting MAO and also allow the drug to act as an indirect sympathomimetic agent.
- Presence of amino group on phenyl ethylamines is essential for direct agonist activity.
- Presence of methyl group on amine increases alpha selectivity. The smaller the group, the more alpha effect is there.
- Presence of -OH groups on ① & ② position increases potency at both α & β receptors.

① NOR- EPINEPHRINE



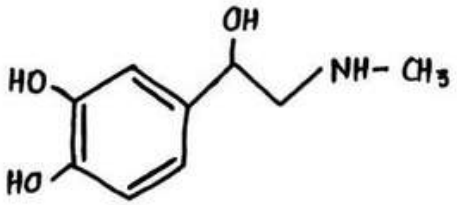
MOA

- Norepinephrine mainly acts on α_1 receptors to increase blood pressure by causing vasoconstriction.
- It also acts a little on β_1 receptors in the heart to increase heart rate & strength.

Uses

- It raises blood pressure & helps the heart pump better.

② EPINEPHRINE



MOA

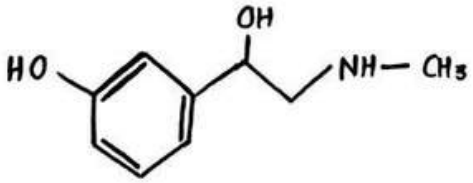
It acts on alpha & beta receptors in the body.

- α_1 : narrows blood vessels to raise blood pressure.
- β_1 : increases heart rate & strength.
- β_2 : relaxes airway muscles to make breathing easier.

Uses

- Epinephrine helps the heart beat stronger, open the lungs & raises blood pressure.

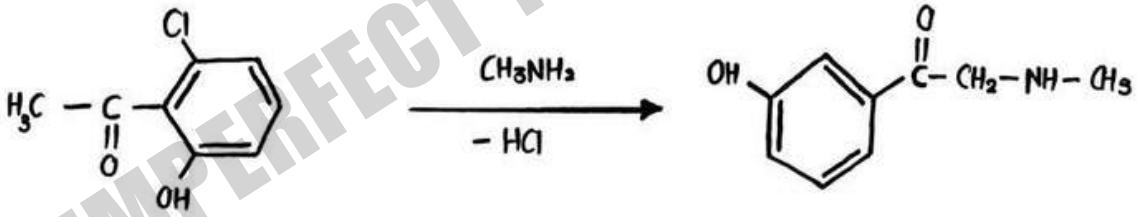
③ PHENYLPHRINE *



MOA

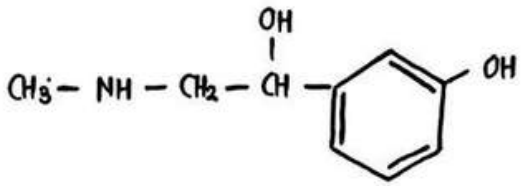
- It acts on α_1 receptors only.
- It causes vasoconstriction (tightening of blood vessels)
- Has little or no effect on heart or lungs

SYNTHESIS



3- chloro acetyl phenol

Catalytic reduction



Phenylphrine

Properties

- It is a white crystalline powder.
- It is freely soluble in ethanol & water.
- It is resistant to COMT.

Uses

- It increases blood pressure in acute hypotension.
- It also used sometimes for treating nasal decongestion & shock.

④ DOPAMINE

MOA

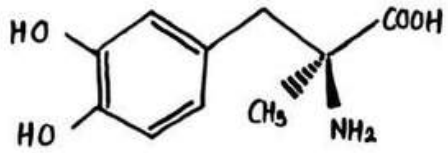
Dopamine works by improving blood flow & helping the heart pump better, depending on the dose.

- Low Dose : Increases kidney blood flow (acts on dopamine receptors)
- Medium Dose : Strengthens heartbeat (acts on β_1 receptors)
- High Dose : Vasoconstriction – ↑ Blood Pressure (acts on α_1 receptors)

Uses

- Acute congestive Heart failure & Shock
- Pancreatitis.

⑤ METHYLDOPA



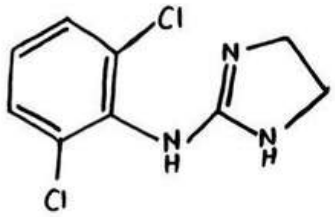
MOA

- Methyldopa converted into α-methyl norepinephrine by enzyme dopamine beta hydroxylase & bind with α_2- receptors.
- This reduces nerve signals that normally increase blood pressure.
- As a result, - blood vessels relax & blood pressure drops.

Uses

- Used as antihypertensive agents
- Prevent heart attack & kidney problem.

⑥ CLONIDINE



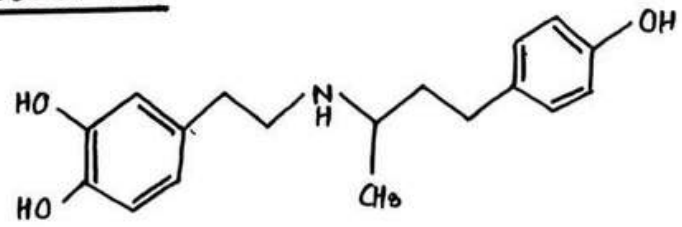
MOA

- Clonidine lowers blood pressure by stimulating α_2 receptors in the brain, which reduces nerve signals that cause blood vessels to tighten.
- In short it relaxes blood vessels by reducing nerve signals from the brain.

Uses

- Used as Antihypertensive Agents.
- It is also used as mild sedative agents.

⑦ DOBUTAMINE



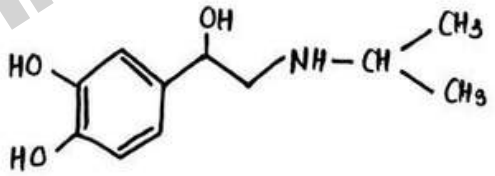
MOA

- Dobutamine mainly stimulate β_1 receptors in the heart
- This increases heart rate & heart muscle strength

Uses

- Used in treatment of Heart failure during cardiac surgery

⑧ ISOPROTERENOL



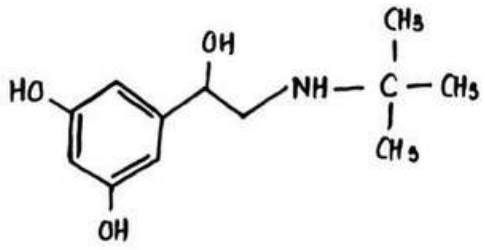
MOA

- It activates β_1 receptors to increase heart rate & strength.
- It activates β_2 receptors to relax airway muscles & lower blood pressure.

Uses

- Used in treatment of Bronchial Asthama
- Used in treatment of Bradycardia

⑨ TERBUTALINE



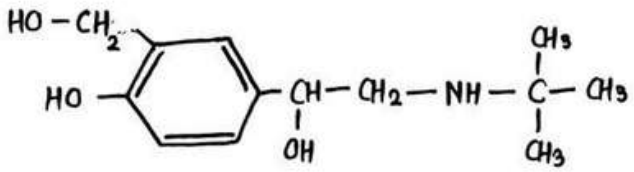
MOA

- It mainly stimulates β_2 receptors.
- This causes airway muscles to relax
- It also relaxes Uterine smooth muscles.

Uses

- It is given orally in the treatment of Asthama.
- It is also used in treatment of COPD.

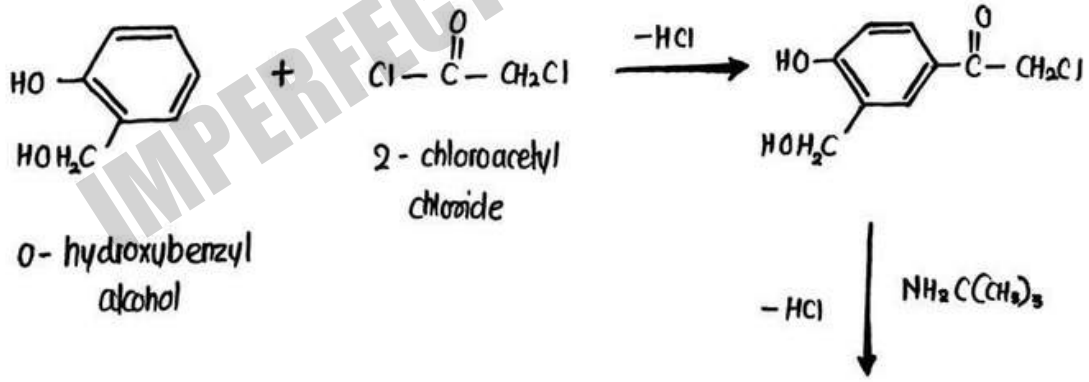
(10) SALBUTAMOL *

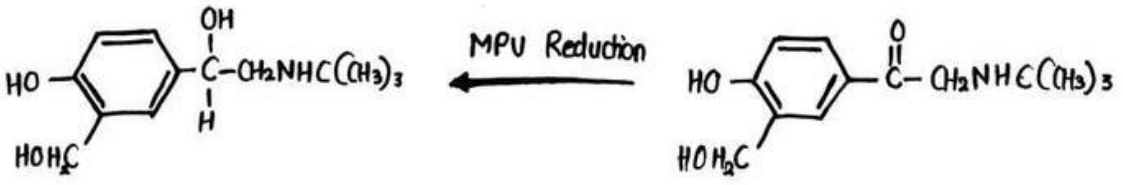


MOA

- Salbutamol works by relaxing the muscles in the airway to make breathing easier :
- It shimulates β_2 receptors in the lungs, which relaxes the airways.

SYNTHESIS





Salbutamol

PROPERTIES

- It is a white or almost white crystalline powder
- It is sparingly soluble in water but freely soluble in ethanol.

Uses

- It is used to relax uterine smooth muscles
- It is used in bronchial asthama.
- It is also used in prevention of premature labour

(H) BITOLTEROL

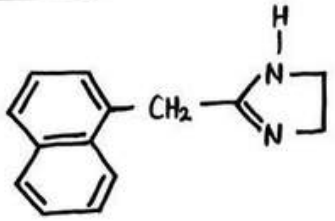
MOA

- It works by relaxing the muscles in the airway to help you breath easier.
- It activates β_2 receptors in the lungs.
- This causes the airways to open up.

Uses

- Used in the treatment of bronchial asthama

(12) NAPHAZOLINE



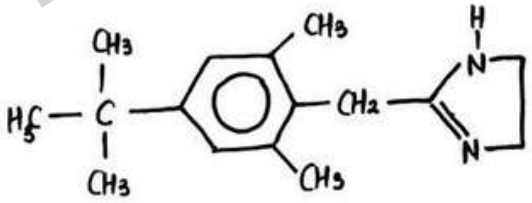
MOA

- Naphazoline acts on alpha (α_1, α_2) adrenergic receptors.
- It causes vasoconstriction.

Uses

- It is used as a vasoconstrictor
- It reduces swelling.

(13) OXYMETAZOLINE



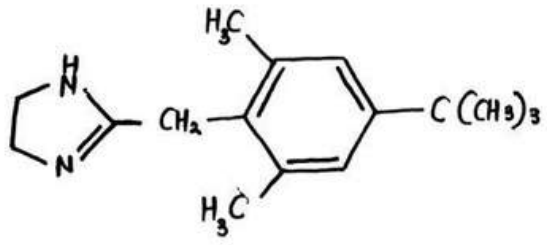
MOA

- It works by narrowing blood vessels in the nose to reduce swelling and congestion.
- It works on α-adrenergic receptors & causes vasoconstriction.

Uses

- It is used in treatment of nasal congestion & redness in eye.

(14) XYLOMETAZOLINE



MOA

- Xylometazoline works by narrowing blood vessels in the nose to reduce swelling & congestion.
- It activates α adrenergic receptors.
- This causes vasoconstriction.

INDIRECT ACTING SYMPATHOMIMETIC AGENTS

- Indirect Acting sympathomimetic agents are drugs that do not directly stimulate adrenergic receptors, but increase the activity of the sympathetic nervous system by :
- Releasing stored norepinephrine from nerve endings
- Inhibits the reuptake of norepinephrine
- Inhibiting its breakdown by enzymes like MAO or COMT.
- It includes :

① Hydroxyamphetamine
② Pseudoephedrine
③ Propyhexedrine

① HYDROXYAMPHETAMINE

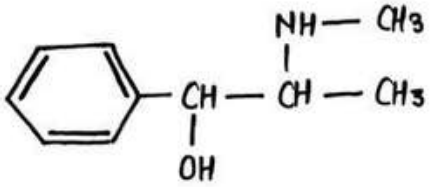
MOA

- Hydroxyamphetamine works by releasing norepinephrine from nerve endings in the eye
- This norepinephrine stimulates α receptors, causing the people to dilate (mydriasis).

Uses

- It is mainly used as eyedrop to dilate the pupil.

② PSEUDOEPHEDRINE



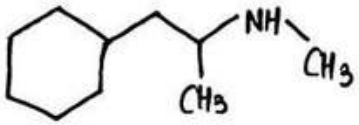
MOA

- It indirectly releases norepinephrine, which stimulates α receptors.
- This causes vasoconstriction & provide releaf in nasal congestion.

Uses

- It is used in allergic rhinitis, sinusitis etc.

③ PROPYLHEXEDRINE



MOA

- It helps to relelve nasal congestion by releasing norepinephrine which acts on α receptors to cause vasoconstriction.

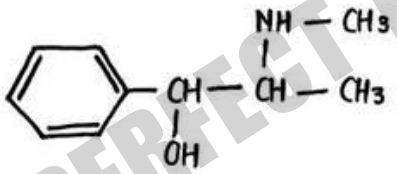
- Uses
- Used in nasal congestion & allergic rhinitis

MIXED ACTING SYMPATHOMIMETIC AGENTS

- Mixed acting sympathomimetic agents are drugs that work in two ways: Directly stimulate adrenergic receptors
- Indirectly increase norepinephrine levels by releasing it from nerve endings.
- It includes:

① Ephedrine
② Metaraminol

① EPHEDRINE



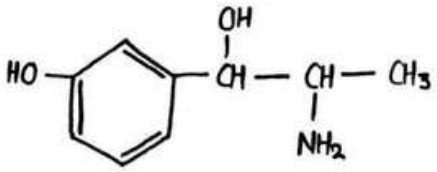
MOA

- Ephedrine works by both directly stimulating receptors and indirectly increasing norepinephrine.
- It acts on α_1, β_1 & β_2 receptors

Uses

- It is used as nasal decongestant.
- It is used in various allergic disease like hay fever & sometimes in apetite suppression.

② METARAMINOL



MOA

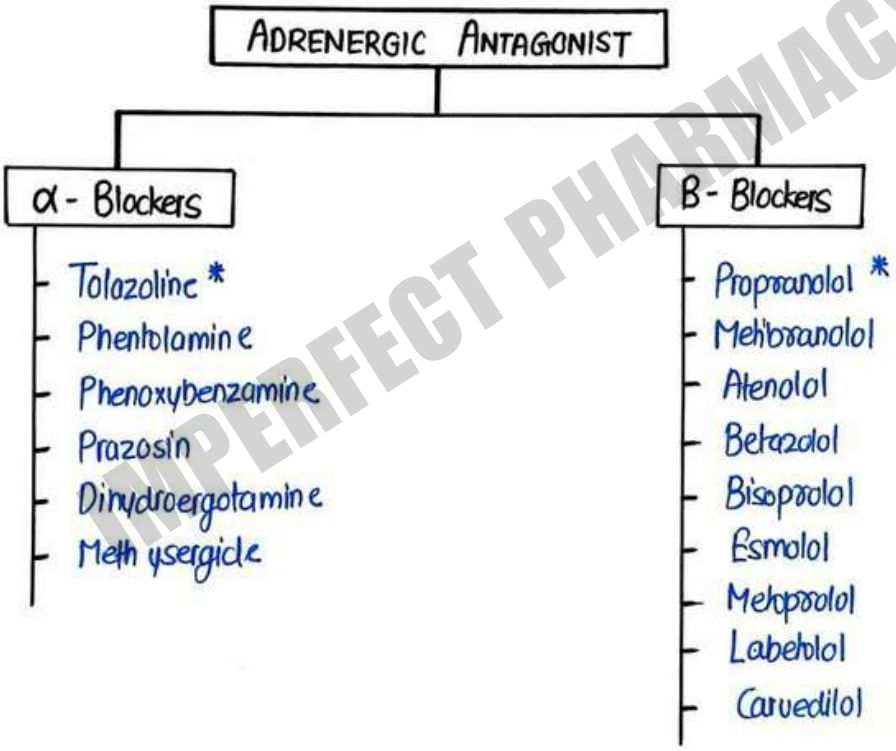
- Metaraminol acts by directly stimulating α-1 receptors & also by releasing norepinephrine & leads to vasoconstriction.

Uses

- It is used in the treatment of hypotension.

ADRENERGIC ANTAGONIST

- Adrenergic Antagonist are drugs that block the effect of adrenaline & noradrenaline on adrenergic receptors in the body.
- They work by binding to adrenergic receptors without activating them thus preventing stimulation by body's natural catecholamines.



① ALPHA- ADRENERGIC BLOCKERS

Alpha- Adrenergic blockers, also known as α- blockers, are drugs that inhibit the stimulation of α- adrenergic receptors by Adrenaline or Noradrenaline.

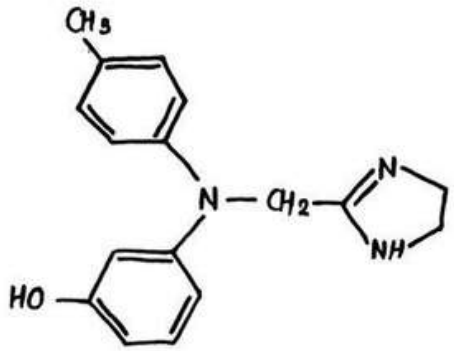
MOA

Alpha blockers prevent the constriction of blood vessels, leading to relaxation of smooth muscles & lowering of blood pressure.

DRUGS

① Tolazoline *
② Phentolamine
③ Phenoxybenzamine
④ Prazosine
⑤ Dihydroergotamine
⑥ Methysergide

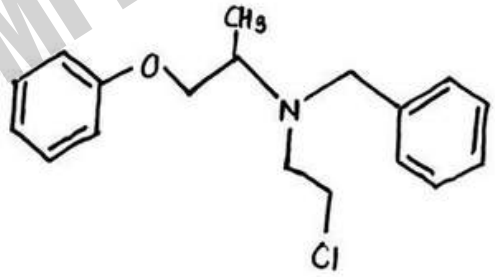
② PHENTOLAMINE



Uses

- It is used in treatment of Hypertension.
- It is also used in treatment of erectile dysfunction.

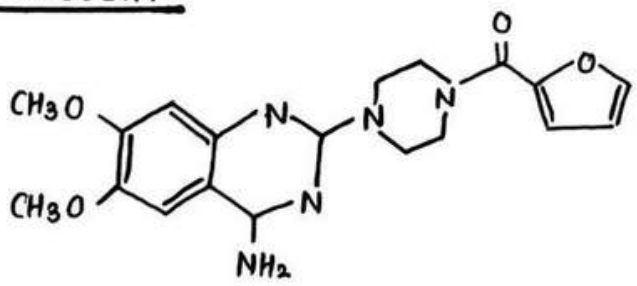
③ PHENOXYBENZAMINE



Uses

- It is used in treatment of urinary retention.
- It is used in treatment of hypertension.

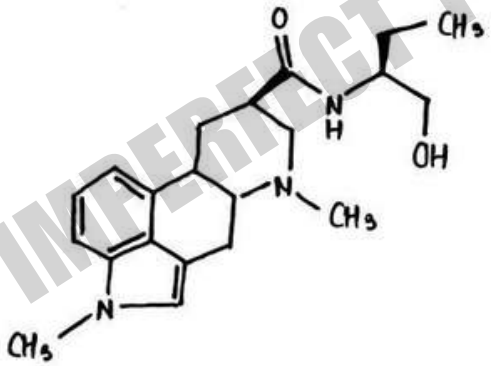
④ PRAZOSIN



Uses

- It is used in treatment of Heart failure.

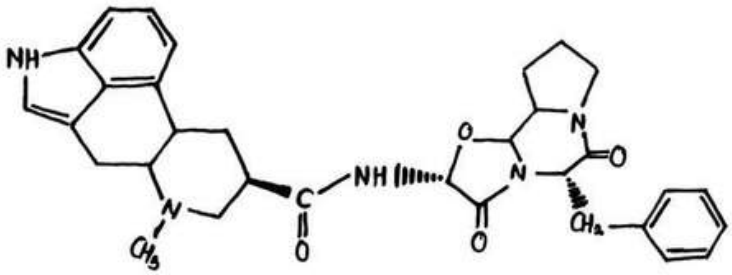
⑤ METHYSERGIDE



Uses

- It is used in the treatment of severe migraine.

⑥ DIHYDROERGOTAMINE



Uses

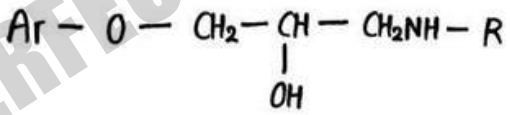
- It is used in the treatment of Migraine.

② β- ADRENERGIC BLOCKERS

- Beta Adrenergic blockers, also known as β- Blockers, are drugs that block the stimulation of β- adrenergic receptors by Adrenaline & Noradrenaline.
- They mainly block β_1 receptors & leads to
  - Slower heart rate
  - Reduced force of heart contraction
  - Lower blood pressure

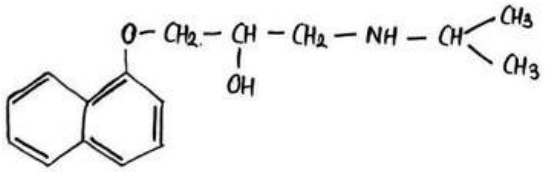
SAR Of β- BLOCKERS

The General structure of β- blockers is as follow:

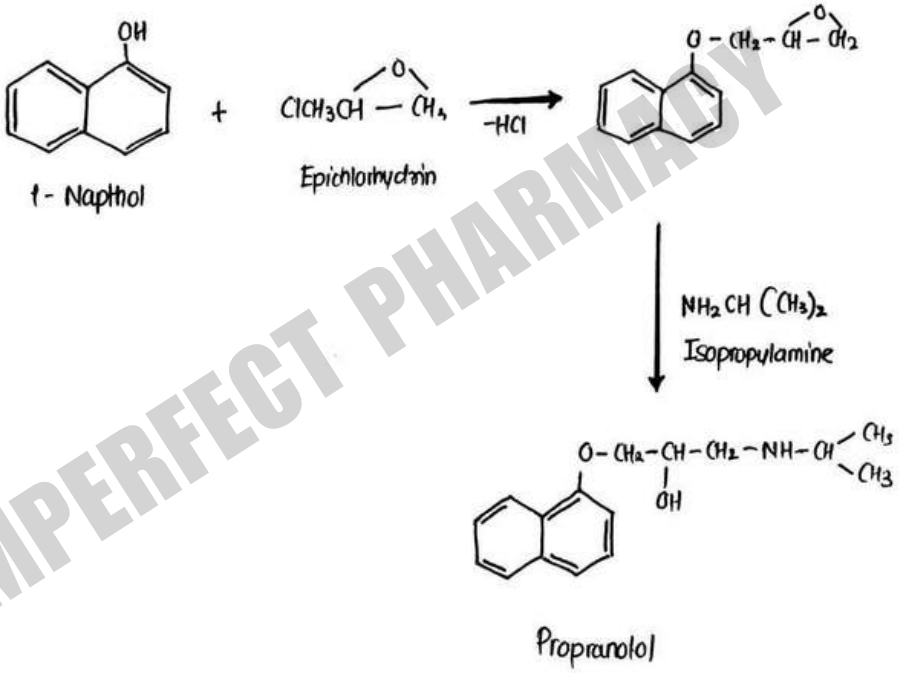


- The O-CH_2 group between the aromatic ring & ethylamino side chain is responsible for antagonistic property.
- The -OH group at β- position is essential for activity.
- Nitrogen atom should be of secondary amine for optimum β- blocking activity.
- The most effective substituents at amino group are isopropyl & tertiary butyl group.

① PROPRANOLOL *



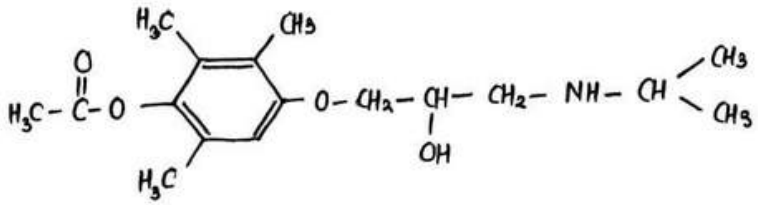
SYNTHESIS



Uses

- It is used in treatment of tremors, angina, hypertension.
- It is also used in prevention of heart attack.

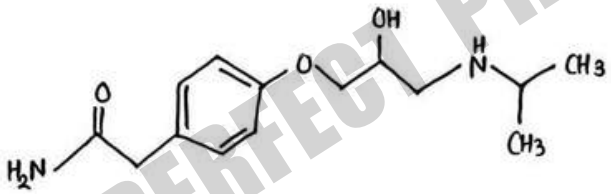
② METIBRANOLOL



Uses

- It is used as eye drop & treatment of glaucoma.

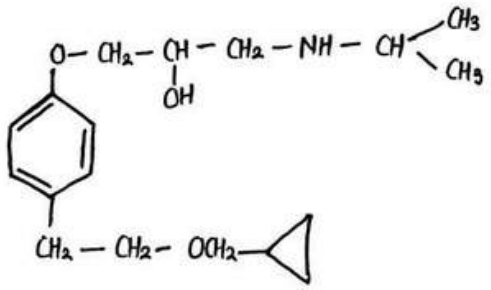
③ ATENOLOL



Uses

- It is used in long term treatment of angina pectoris & hypertension.

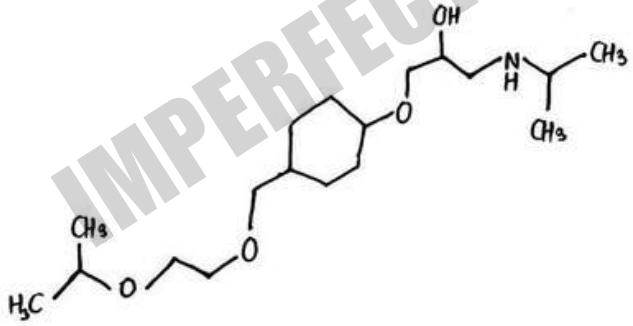
④ BETAZOLOL



Uses

- It is used in treatment of Hypertension.
- It is used in treatment of Glaucoma.

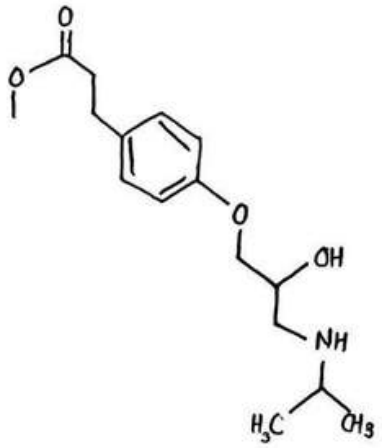
⑤ BISOPROLOL



Uses

- Heart failure
- Angina Pectoris

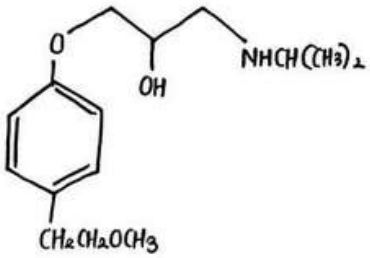
⑥ ESMOLOL



Uses

- It is used in early treatment of Myocardial Infarction.

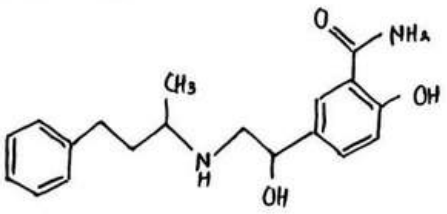
⑦ METOPROLOL



Uses

- Hypertension
- Heart failure

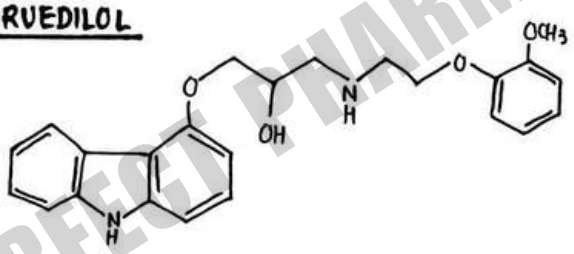
⑧ LABETOLOL



Uses

- Hypertension

⑨ CARVEDILOL



Uses

- Severe Hypertension

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

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