

MEDICINAL CHEMISTRY-I

UNIT 3 NOTES

DRUGS ACHING ON ANS

- CHOLINERGIC NEUROTRANSMITTERS
- PARASYMPATHOLYTIC AGENTS
- CHOLINERGIC BLOCKING AGENTS



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PARASYMPATHETIC SYSTEM

- The Parasympathetic Nervous System is part of Autonomic Nervous System.
- It's often called the 'rest & digest' system because it slows down the heart rate, increases digestion & promotes activities that occurs when body is at rest.

KEY FUNCTIONS

- Slows Heart Rate
- Stimulates Digestion
- Promotes Gland Secretion
- Constricts Pupils
- Contracts the bladder
- Stimulates sexual arousal
- Constricts bronchi

Note: Parasympathetic System is also known as 'Cholinergic System'

CHOLINERGIC NEUROTRANSMITTERS

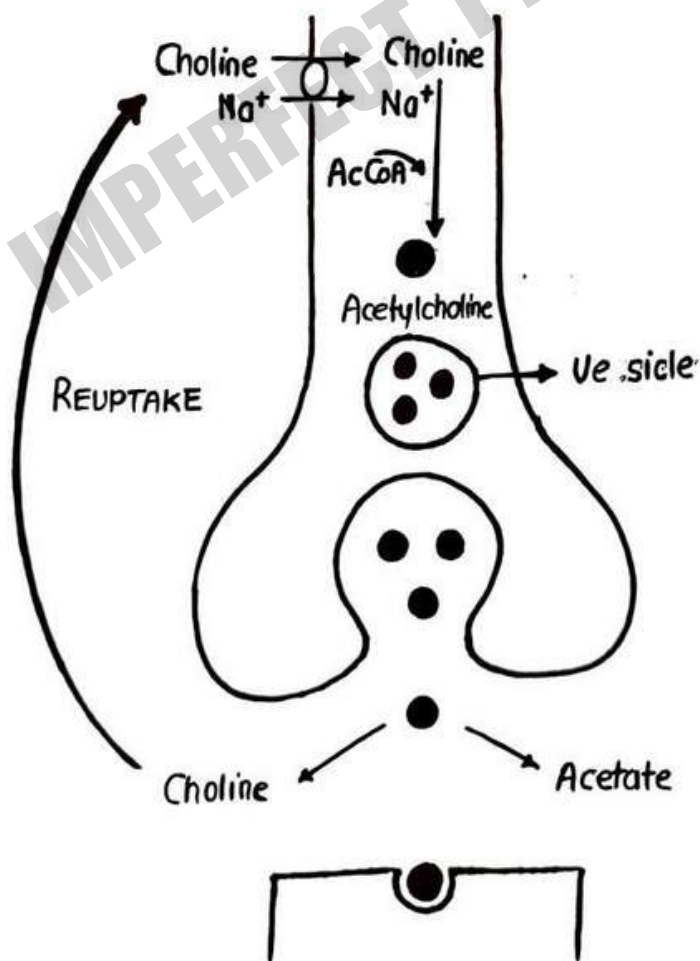
- A Cholinergic Neurotransmitter is a chemical messenger that transmits signals across a synapse & bind to Cholinergic receptors on the target cell & produce a response.
- Acetylcholine is the major Cholinergic Neurotransmitter.

ACETYLCHOLINE

- Acetylcholine is the primary neurotransmitter in the Cholinergic System which is responsible for transmitting signals between nerve cells.
- It plays a crucial role in :
 - Activating muscles (at neuromuscular junction)
 - Regulating Involuntary body functions (like heart rate & digestion)
 - Supporting brain functions (such as memory, attention & arousal in the Central Nervous System)

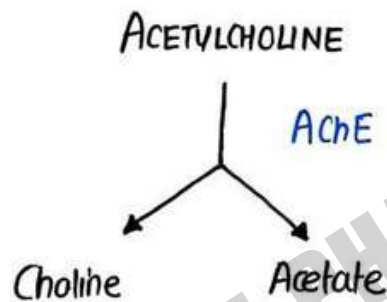
BIOSYNTHESIS OF ACETYLCHOLINE

- Biosynthesis of Acetylcholine refers to the biological process by which the neurotransmitter Acetylcholine (ACh) is produced.
- It occurs mainly in the nerve terminals of Cholinergic Neurons.
- The reaction is catalyzed by the enzyme choline acetyltransferase (ChAT)
- Choline (obtained from the diet or recycled from ACh breakdown) combines with Acetyl-CoA (produced in the mitochondria) to form Acetylcholine.
- The reaction is :



CATABOLISM OF ACETYLCHOLINE

- Catabolism of Acetylcholine refers to the breakdown of Acetylcholine after it has carried out its function at a synapse.
- It mainly happens in the synaptic cleft & involves:
- The enzyme acetylcholinesterase (AChE) rapidly breaks down acetylcholine



- The choline is taken back into the neuron to be reused for making new acetylcholine.
- This breakdown occurs very fast (within milliseconds)

CHOLINERGIC RECEPTORS

- Cholinergic Receptors are specialized proteins located on the surface of cells (mainly neurons, muscles & glands) to which Acetylcholine bind & mediate its effect.
- Cholinergic Receptors are broadly classified into two types:
 - ① Nicotinic Receptors
 - ② Muscarinic Receptors

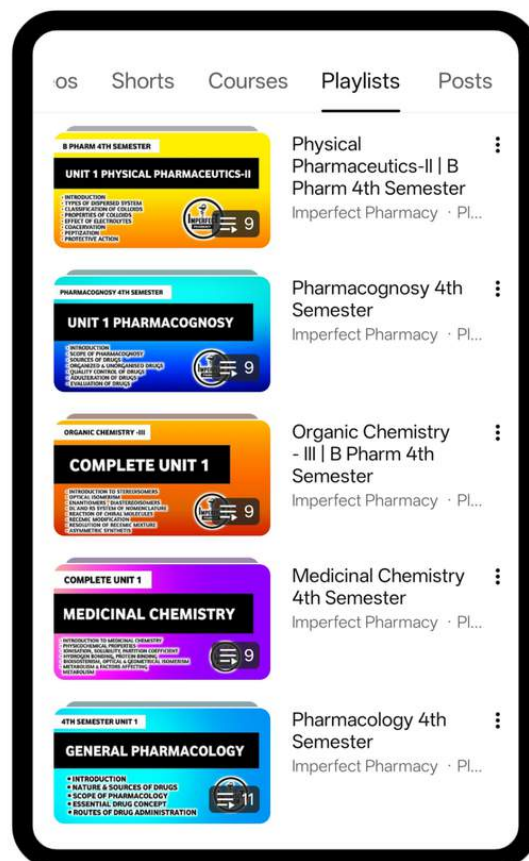
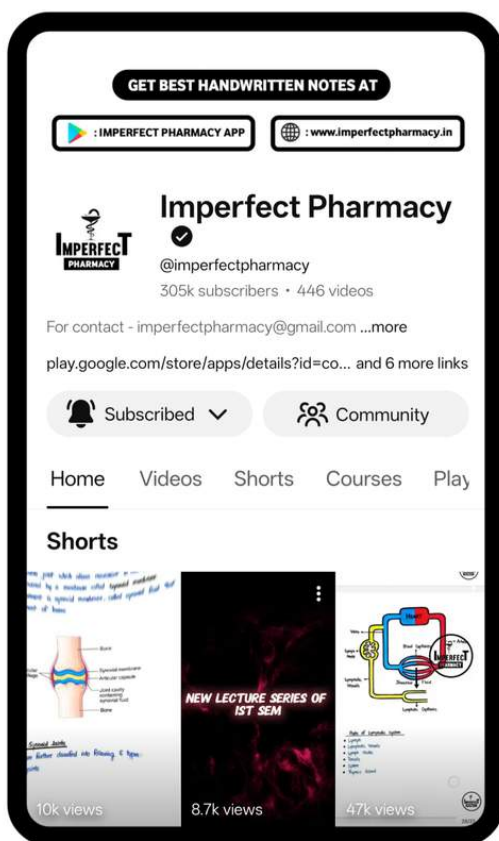
① MUSCARINIC RECEPTORS

- It belongs to G-Protein coupled receptors family.
- It is further divided into five subtypes:
 - (a) M₁ Receptors
 - (b) M₂ Receptors
 - (c) M₃ Receptors
 - (d) M₄ Receptors
 - (e) M₅ Receptors

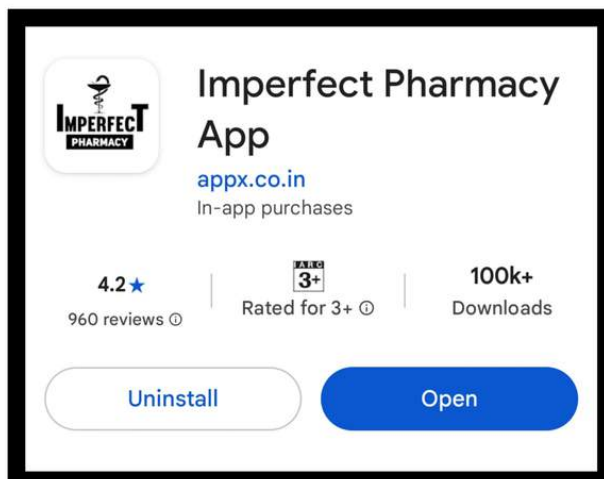
② NICOTINIC RECEPTORS

- They are ligand gated ion channels.
- It is of further two types:
 - (a) N_M Receptors
 - (b) N_N Receptors

FOR LECTURE VIDEOS VISIT OUR  CHANNEL



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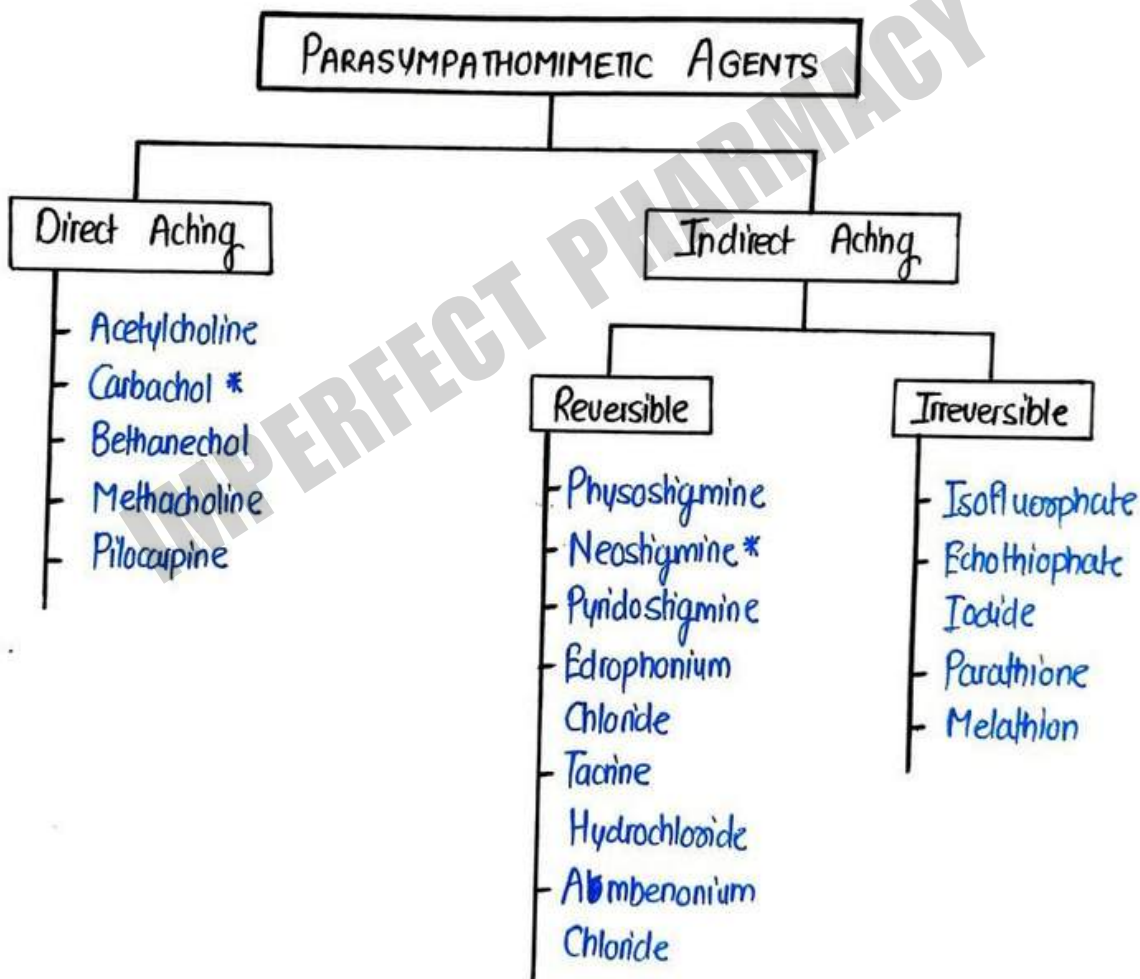


DISTRIBUTION OF CHOLINERGIC RECEPTORS

RECEPTORS	GI- PROTEIN	DISTRIBUTION	FUNCTION
M ₁	G _q	CNS , Autonomic Ganglia Gastric Parietal Cells	Memory Enhancement Gastric Acid Secretion Neuronal Excitation
M ₂	G _i	Heart , CNS	Slows Heart Rate Decreases conduction ↓ Neurotransmitter release
M ₃	G _q	Smooth Muscles , Exocrine Glands, Eye	Smooth Muscle Contraction Gland Secretion (saliva tears) , pupil constriction
M ₄	G _i	CNS	Inhibits Neurotransmitter Release
M ₅	G _q	CNS	May Modulate dopamine pathways .
N _N	Ion Channel (Na ⁺ /K ⁺)	Autonomic Ganglia (Sympathetic & Parasympathetic) Adrenal Medulla	Postganglionic neuron activation , catecholamine release
N _M	Ion Channel (Na ⁺ /K ⁺)	Skeletal Muscle Neuromuscular Junction	Skeletal Muscle Contraction

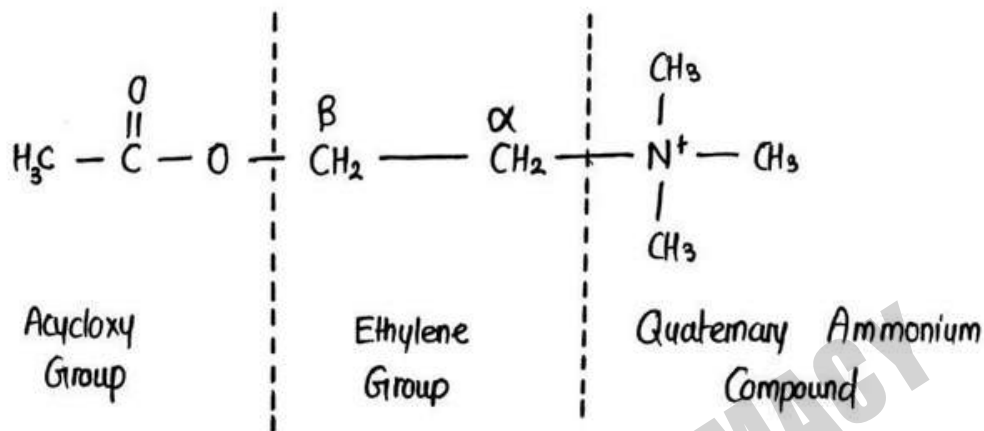
PARASYMPATHOMIMETIC AGENTS

Parasympathomimetic Agents are drugs that stimulate or mimic the effect of Parasympathetic Nervous System by either directly activating Cholinergic Receptors (Muscarinic / Nicotinic) or by increasing Acetylcholine levels.



SAR OF PARASYMPATHOMIMETIC AGENTS

The general structure of Parasympathomimetic agents is as follow:



① Substitution On Acyloxy Group

- Replacement of Acetate Group with carbamate Group, increases activity & stability
- Replacement of ester group by ether & ketone group give chemically stable & potent compound

② Substitution on Ethylene Group

- Increase in chain length will lead to decrease in activity.
- Branching on β substitution leads to reduction in nicotinic activity but increase muscarinic activity.

③ Substitution On Quaternary Ammonium Compound

- Placement of Primary, secondary or tertiary amines leads to decrease in activity.
- Replacement of more than 1 methyl group of Quaternary Ammonium group leads to complete loss of Cholinergic activity.
- Quaternary Ammonium Group is essential for activity.

① DIRECT ACTING PARASYMPATHOMIMETIC AGENTS

Direct Acting Parasympathomimetic Agents are drugs that directly stimulate cholinergic receptors by mimicking the effect of Acetylcholine.

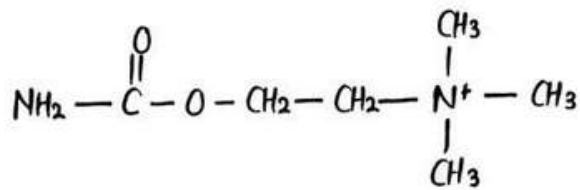
MOA

- These agents bind directly to cholinergic receptors (Nicotinic & Muscarinic) found in organs like heart, lungs, eyes, GIT.
- Once the receptor is activated, it triggers intracellular pathways leading to:
 - Smooth Muscle Contraction
 - Increased Secretion
 - Decreased Heart Rate
 - Pupil Constriction etc.

DRUGS

- Acetylcholine
- Carbachol *
- Bethanechol
- Methacholine
- Pilocarpine

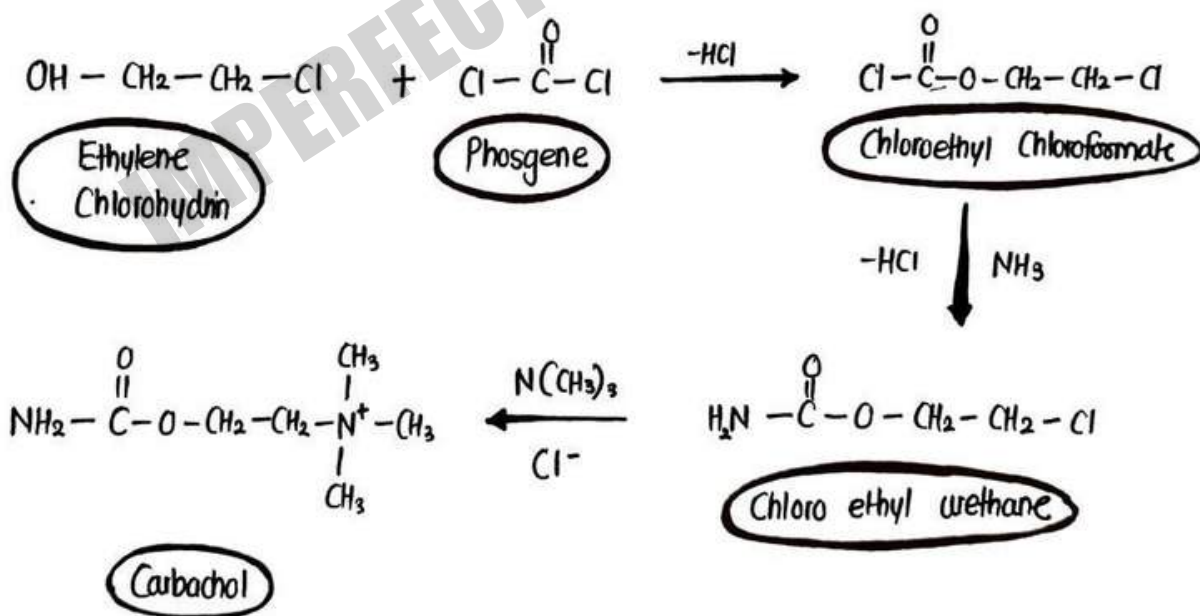
① CARBACHOL



MOA

- Carbachol binds with both Muscarinic & Nicotinic receptors.
- It is not inactivated by Cholinesterase so its action are more prolonged.

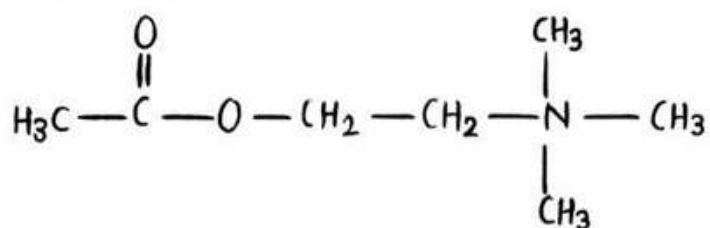
SYNTHESIS



USES

Use in case of severe chronic glaucoma

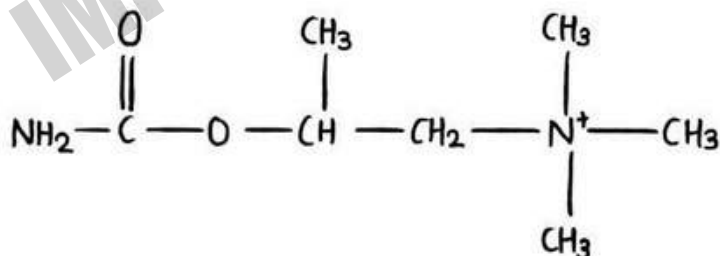
② ACETYLCHOLINE



Uses

- Used as eye drop to cause miosis.
- Used as vasodilator & cardiac depressant.

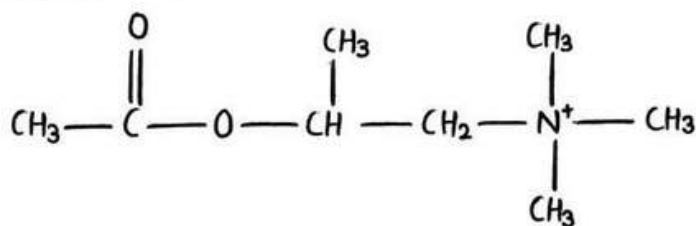
③ BETHANECHOL



Uses

- Used to stimulate GI tract & Urinary Bladder.
- It gives prolonged effect than Acetylcholine.

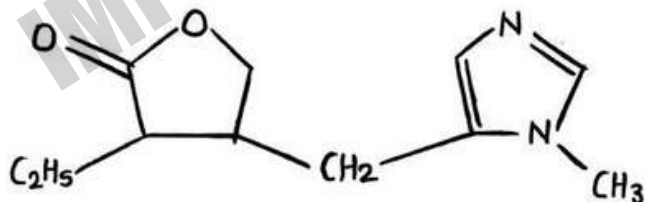
④ METHACHOLINE



Uses

- Treatment of Glaucoma
- Treatment of Tachycardia.

⑤ PILOCARPINE



Uses

- Treatment of Glaucoma.
- Treatment of dry eye / dry mouth.

② INDIRECT ACTING PARASYMPATHOMIMETIC AGENTS

- It is also known as Anticholinesterases.
- These are drugs that increase the activity of parasympathetic system by preventing the breakdown of Acetylcholine (ACh)

MOA

- They inhibit acetylcholinesterase (the enzyme that breaks down Acetylcholine)
- This causes an accumulation of Acetylcholine at synapses, hence increases the life of acetylcholine & duration of action.

TYPES

They are of two types :

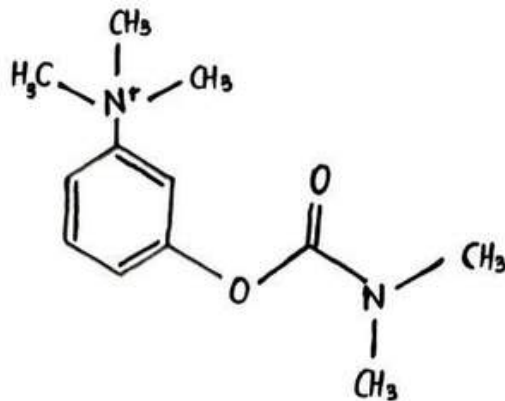
- ① Reversible
- ② Irreversible

① REVERSIBLE

These are those drugs which binds reversibly to Acetyl Cholinesterase enzyme & includes :

- Physostigmine
- Neostigmine *
- Pyridostigmine
- Edrophonium Chloride
- Tacrine Hydrochloride
- Ambenonium Chloride

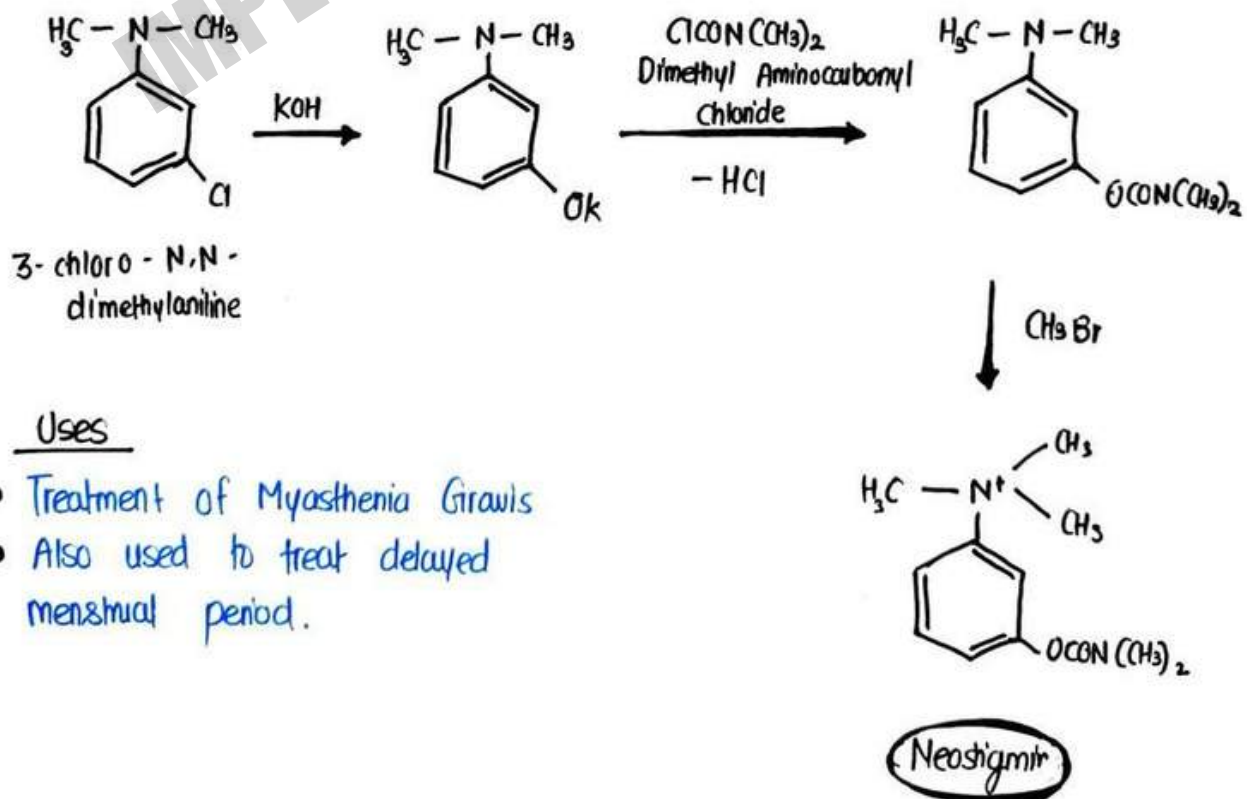
① NEOSTIGMINE *



MOA

Neostigmine reversibly binds with the enzyme Acetylcholinesterase & thus indirectly stimulates both Nicotinic & Muscarinic receptors.

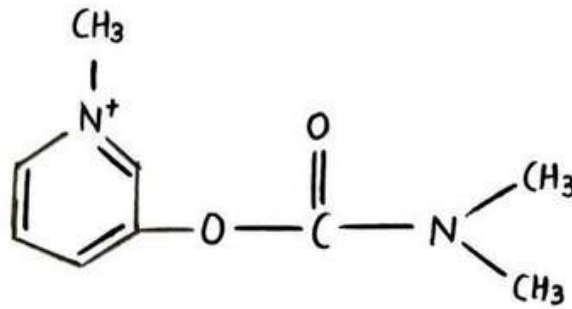
SYNTHESIS



Uses

- Treatment of Myasthenia Gravis
- Also used to treat delayed menstrual period.

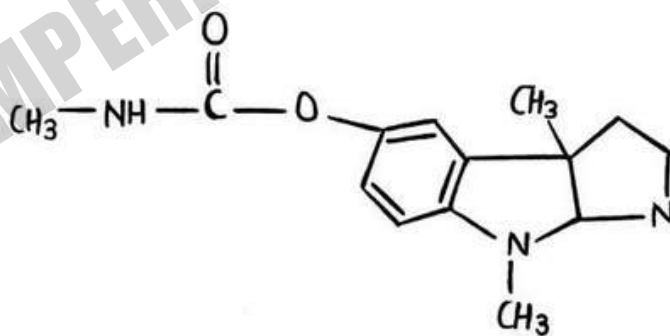
② PYRIDOSTIGMINE



Uses

- Myasthenia Gravis
- Treatment of nerve gas poisoning

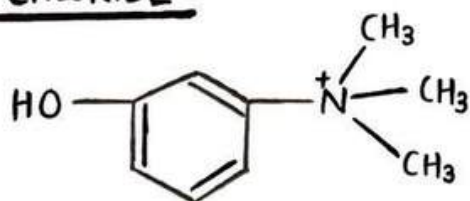
③ PHYSOSTIGMINE



Uses

- Treatment of Glaucoma
- Treatment of severe Anticholinergic Toxicity.

④ EDROPHONIUM CHLORIDE



Uses

- Treatment of Myasthenia Gravis
- Treatment of snake poisoning

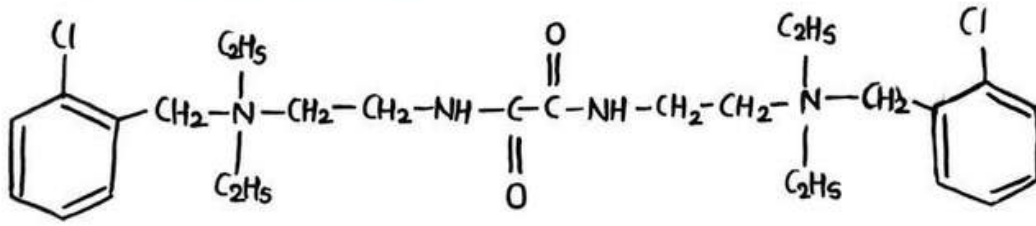
⑤ TACRINE HYDROCHLORIDE



Uses

- Treatment of Alzheimer's Disease

⑥ AMBENONIUM CHLORIDE



Uses

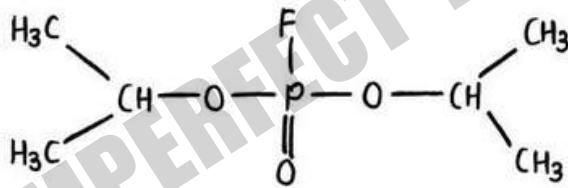
- Treatment of Myasthenia Gravis

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② Irreversible

- These are those drugs which produces Irreversible inactivation of Acetylcholinesterase enzyme.
- They bind to Cholinesterase & form a permanent covalent bond.
- It includes :
 - Isofluorophate
 - Ecothiophate Iodide
 - Parathione
 - Malathion

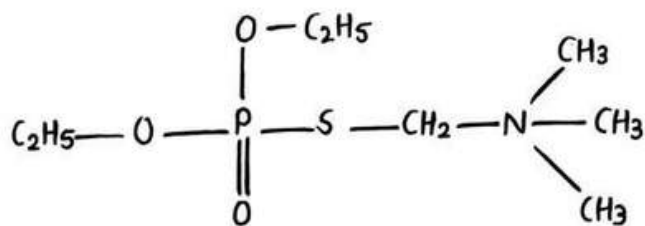
① ISOFLUORPHATE



Uses

- Treatment of Glaucoma

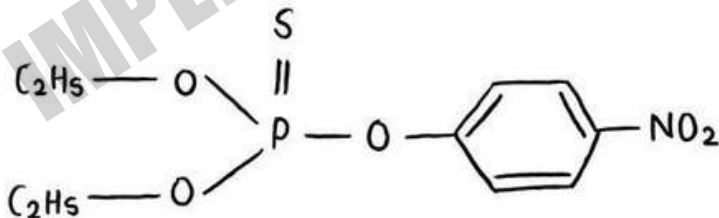
② ECHOTHIOPHATE IODIDE



Uses

- Treatment of Glaucoma

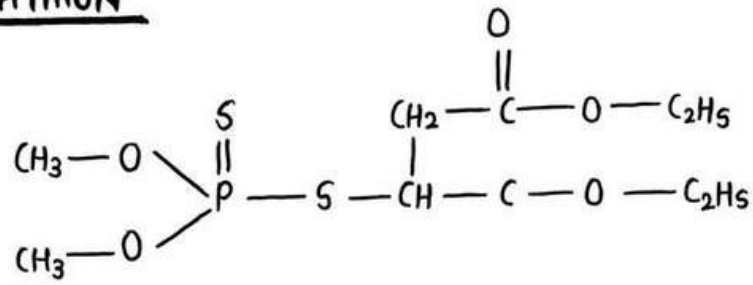
③ PARATHIONE



Uses

- Used as insecticide in agriculture

④ MALATHION



Uses

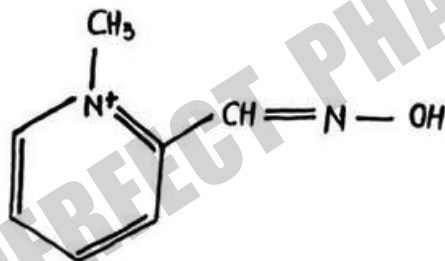
- Treatment of scabies
- Used as Insecticide

IMPERFECT PHARMACY

CHOLINESTERASE REACTIVATOR

- A Cholinesterase Reactivator is a type of drug specifically designed to restore the activity of Cholinesterase enzymes (Acetylcholinesterase) that have been inhibited by Organophosphate or carbamate compounds.
- These reactivators are mainly used as Antidotes in cases of poisoning by pesticides (Organophosphates) or nerve agents.

PRALIDOXIME CHLORIDE



MOA

Pralidoxime Chloride is a specific antidote that reactivates Acetylcholinesterase and allows normal nerve function to resume.

Uses

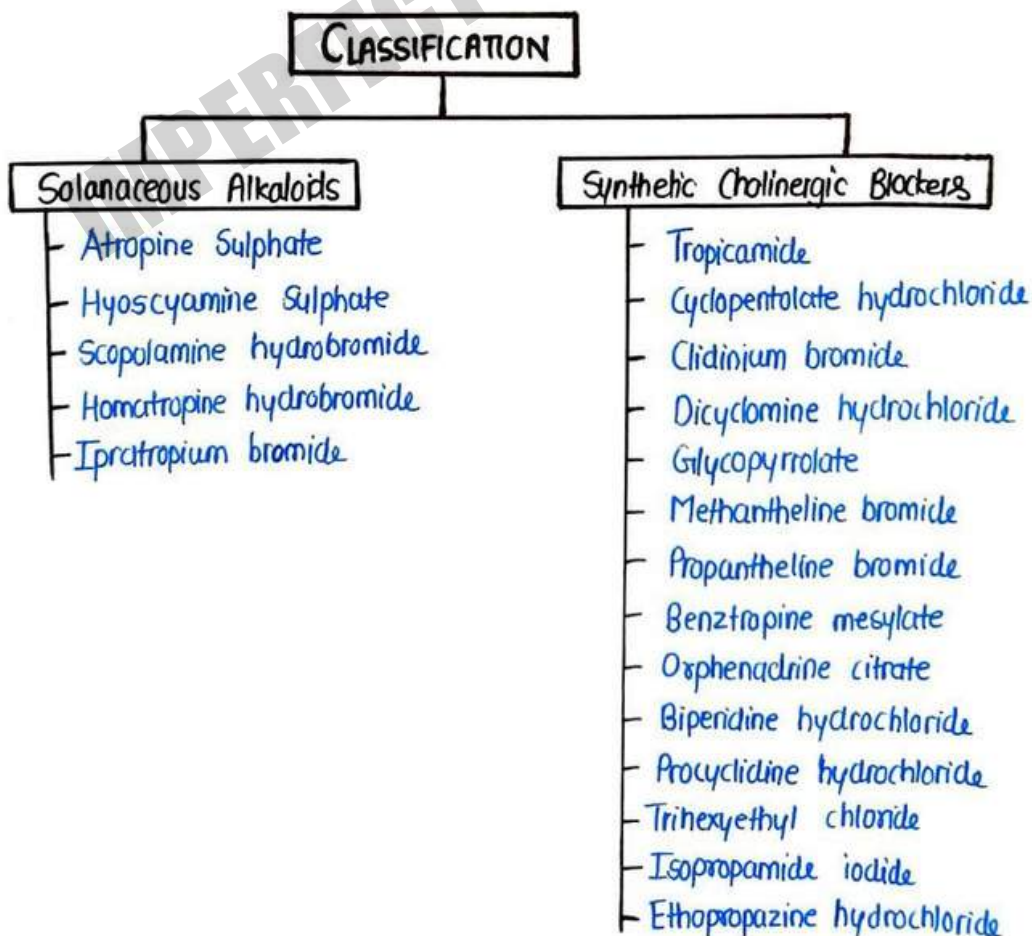
Used for the treatment of poisoning from organophosphorus compounds.

CHOLINERGIC BLOCKING AGENTS

They are also known as

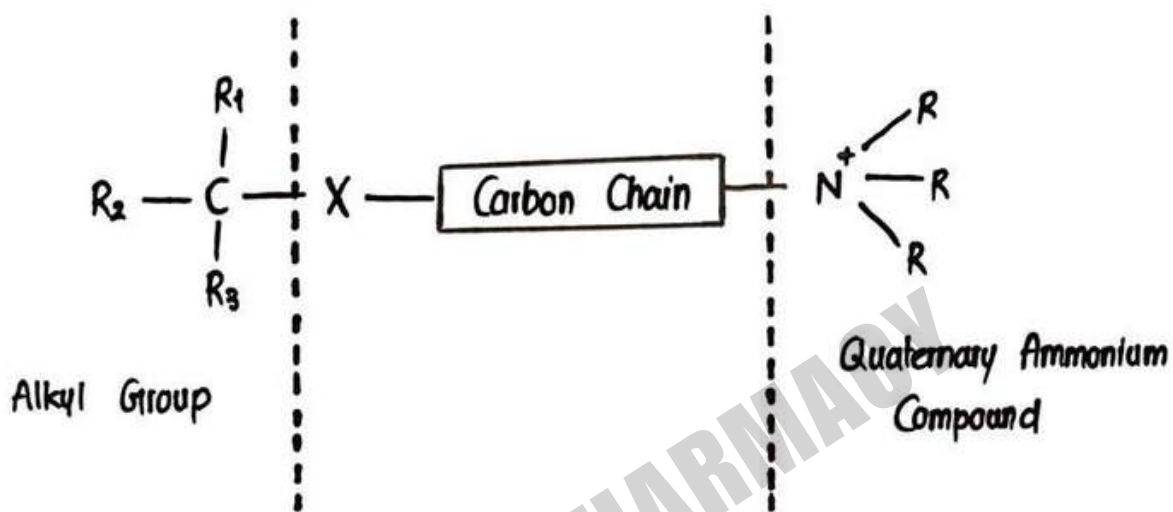
- Cholinolytic Agents
- Anticholinergic Agents
- Cholinergic Antagonist
- Parasympatholytic Agents
- Antimuscarinic Agents

These are those drugs or Agents which inhibit the effect of Acetylcholine or Parasympathomimetic Agents by blocking the cholinergic receptors.



SAR OF CHOLINERGIC BLOCKING AGENTS

The general structure of Cholinergic Blocking Agents is as follow :



① Substitution On Alkyl Group

- Substituent R_1 & R_2 must be carbocyclic or heterocyclic ring for maximal antagonist activity.
- Replacement of heterocyclic ring with Aromatic Ring decreases activity
- The ring could be identical but the most potent compounds are found to have different ring substitution.

② Substitution On Carbon Chain

- The length of carbon chain can be from two to 4 carbons but most potent anticholinergic agents have two methylene units in this chain.
- The substitution may be ester, ether or alcohol amine.
- The nature of group X effects the duration of action, physicochemical properties & side effect but have no effect on drug's ability to bind with receptors

③ Quaternary Ammonium Compound

- Quaternary Ammonium compound possess most potent Anticholinergic activity.
- Replacement of Quaternary to the tertiary, primary or secondary cause decrease in activity.

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① SOLANACEOUS ALKALOIDS

- Solanaceous Alkaloids are naturally occurring compounds primarily derived from the plants of Solanaceae Family (like Atropa, Datura, Belladonna)
- These Alkaloids such as Atropine, Hyoscyamine act as Anticholinergic Agents by competitively inhibiting the action of Acetylcholine at Muscarinic Receptors.

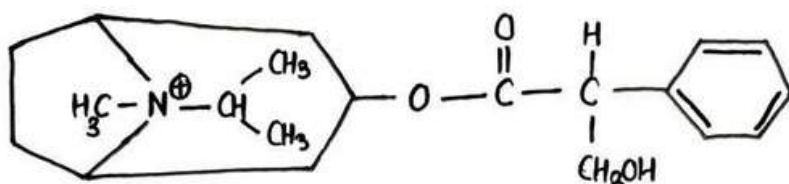
MOA

- Solanaceous Alkaloids like Atropine, Scopolamine & Hyoscyamine act mainly by competitive Antagonism at Muscarinic receptors (M_1 , M_2 , M_3) in the parasympathetic system.
- As a result, parasympathetic effects are inhibited, leading to Sympathetic effects like :
 - Pupil Dilation
 - Increased heart rate
 - Decreased secretions.
 - Relaxation of smooth Muscles.

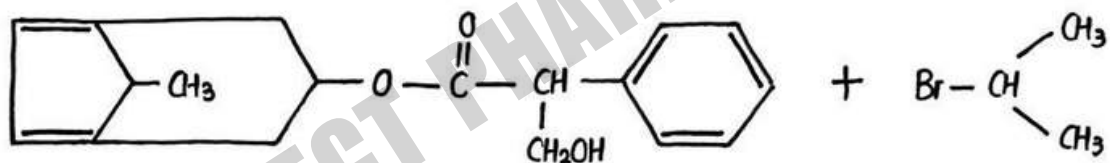
DRUGS

- Atropine Sulphate
- Hyoscyamine Sulphate
- Scopolamine Hydrobromide
- Homatropine Hydrobromide
- Ipratropium Bromide

① IPRATROPIUM BROMIDE *

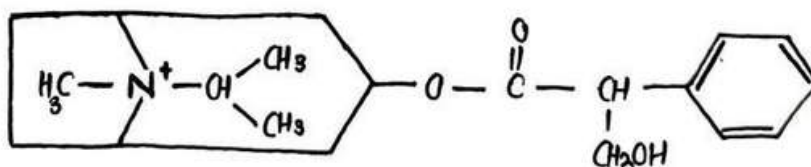


SYNTHESIS



Atropine

Isopropyl Bromide

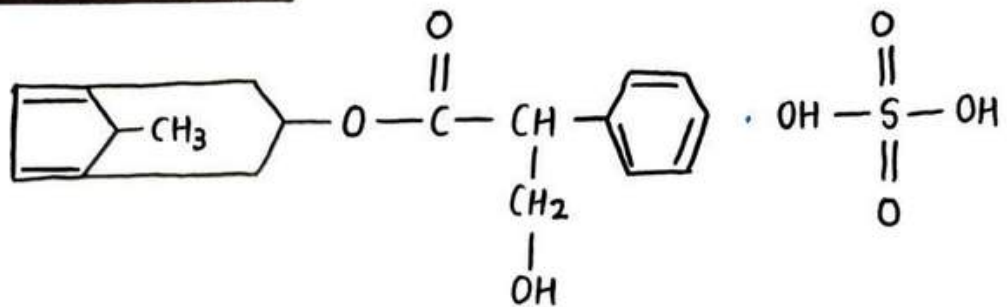


Ipratropium Bromide

Uses

- It is used in the treatment of Asthma.
- Treatment of COPD

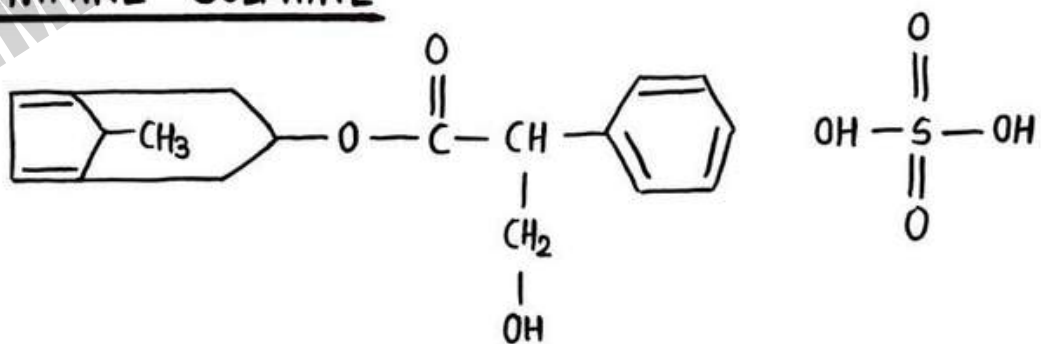
② ATROPINE SULPHATE



Uses

- Treatment of Gastric & Duodenal Ulcers.
- Treatment of smooth muscle spasm

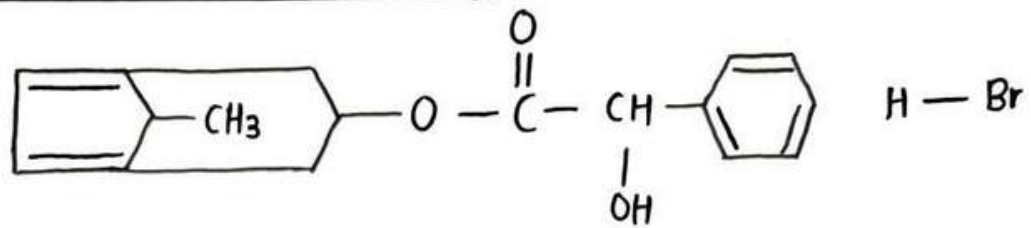
② HYOSCYAMINE SULPHATE



Uses

- Used in the treatment of gastric and duodenal ulcers.
- Used in the treatment of parkinson's disease.
- Prevent motion sickness

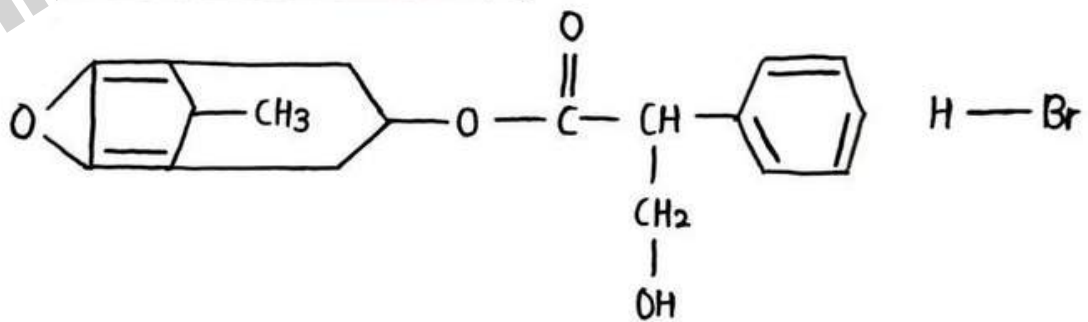
④ HOMATROPINE HYDROBROMIDE



Uses

- It is used to dilate or enlarge pupils in eye.

⑤ SCOPOLAMINE HYDROBROMIDE



Uses

- It is used in the treatment of motion sickness.
- Sometimes it is used to decrease saliva before surgery.

② **SYNTHETIC CHOLINERGIC BLOCKERS**

Synthetic Cholinergic Blockers are synthesized in laboratories & inhibits the action of acetylcholine at cholinergic receptors

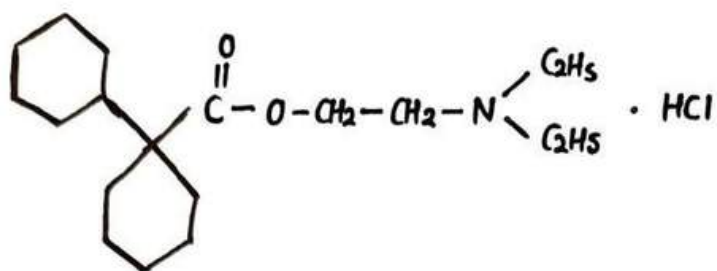
MOA

Synthetic Cholinergic blockers work by competitively inhibiting acetylcholine at muscarinic receptors in various organs controlled by the Parasympathetic Nervous System.

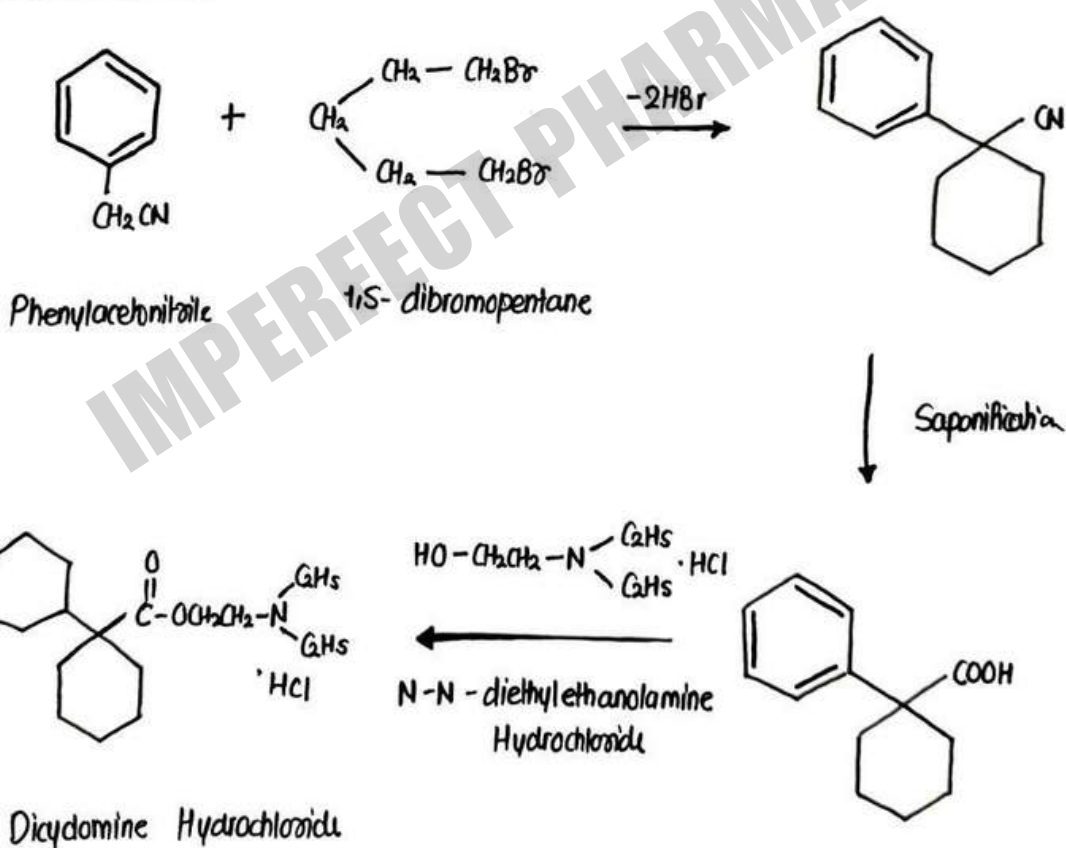
DRUGS

- Tropicamide
- Cyclopentolate hydrochloride
- Clinidium bromide
- Dicyclomine hydrochloride
- Glycopyrrolate
- Methantheline bromide
- Propantheline bromide
- Benztropine mesylate
- Orphenadrine citrate
- Biperidine hydrochloride
- Procyclidine hydrochloride
- Tridihexethyl chloride
- Isopropamide iodide
- Ethopropazine hydrochloride

① DICYCLOMINE HYDROCHLORIDE *



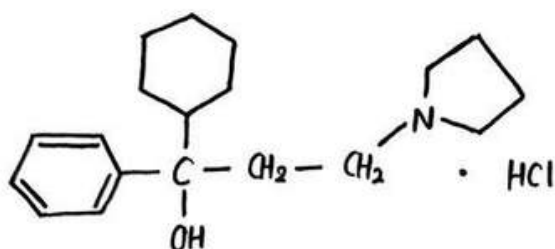
SYNTHESIS



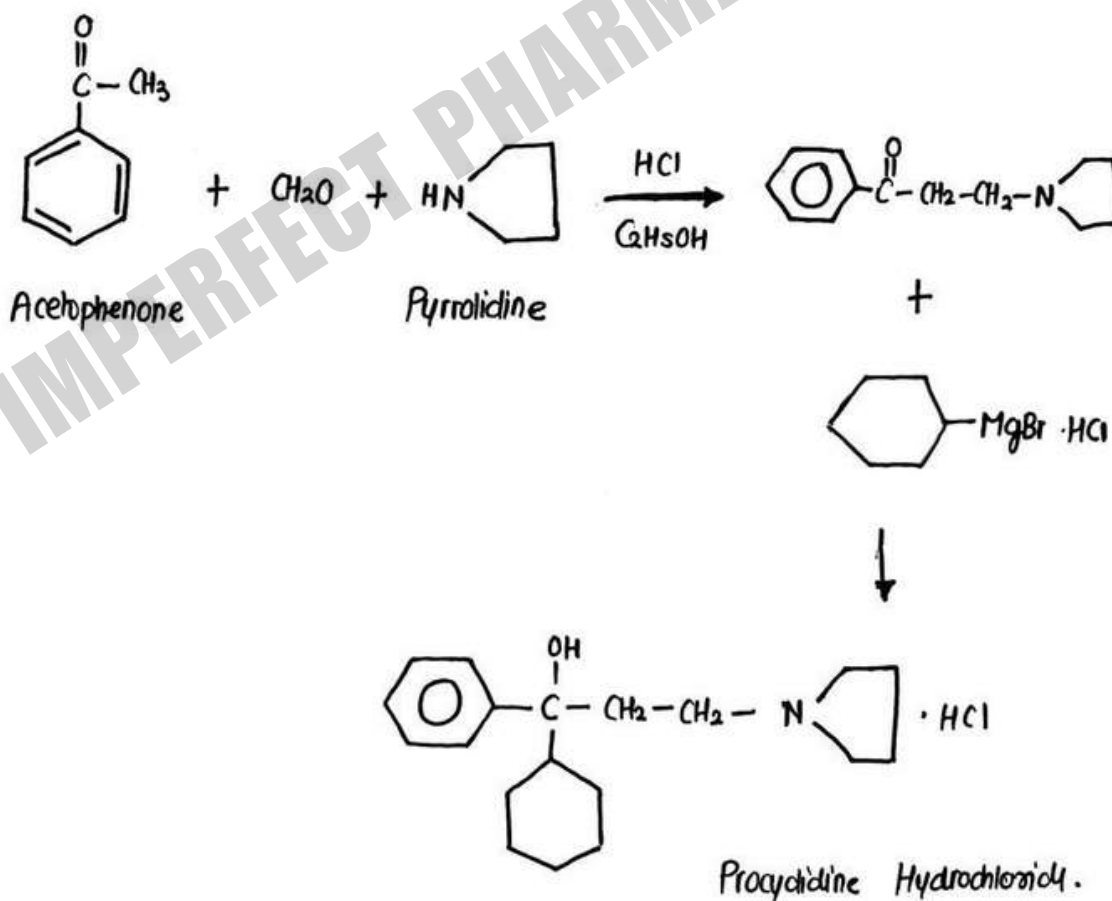
Uses

- Used in the treatment of IBS.
- Used in treatment of Gastric & Duodenal Ulcer.

② PROCYCLIDINE HYDROCHLORIDE *



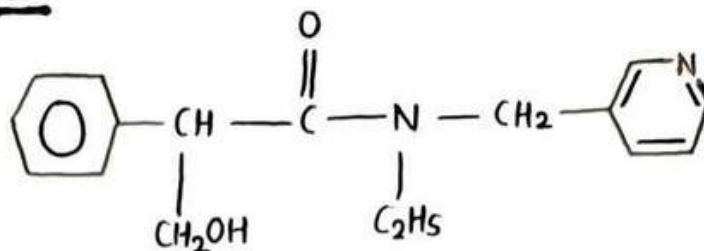
SYNTHESIS



Uses

- Parkinson's Disease

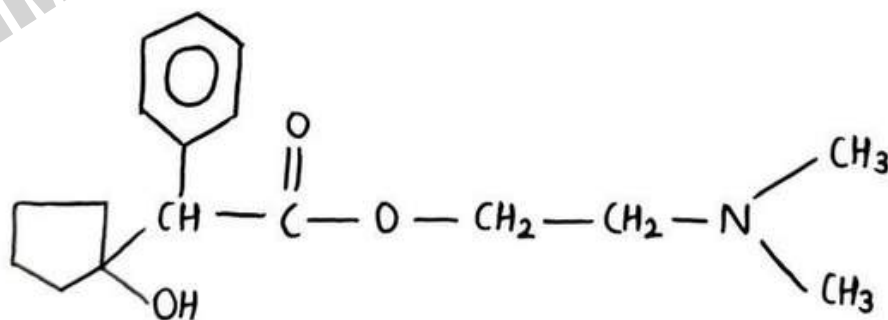
③ TROPICAMIDE



Uses

- Treatment of Mydriasis (pupil dilation)

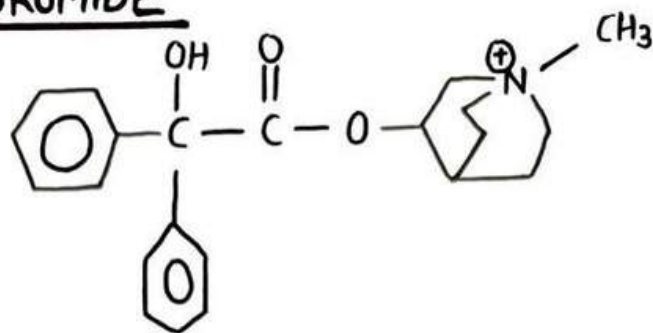
④ CYCLOPENTOLATE HYDROCHLORIDE



Uses

- Used in a eye drop for mydriasis.

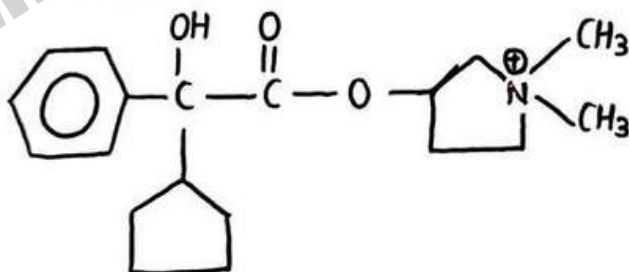
⑤ CLIDINIUM BROMIDE



Uses

- Treatment of Peptic Ulcer.
- Relieving Abdominal Pain
- Treatment of IBS.

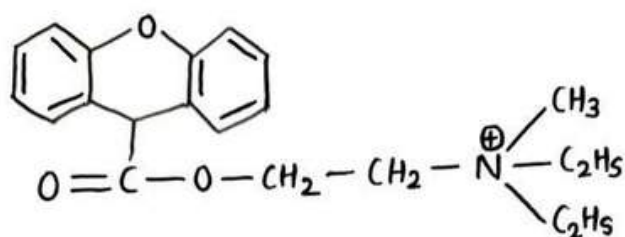
⑥ GLYCOPYRROLATE



Uses

- Treatment of COPD

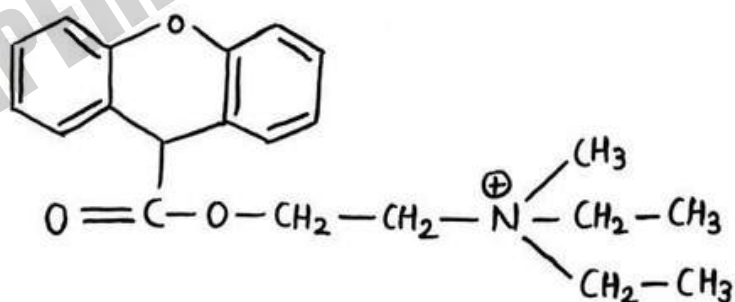
⑦ METHANTHELINE BROMIDE



Uses

- It is given in the combination of antacid to treat peptic ulcer.

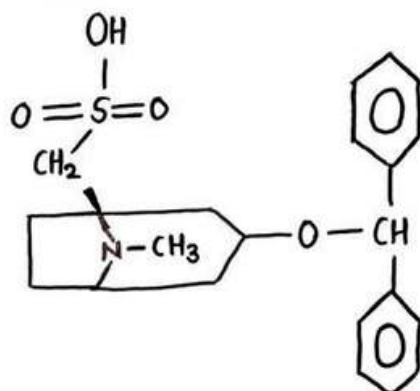
⑧ PROPANTHELINE BROMIDE



Uses

- It is used in the treatment of excess sweating.
- Used to treat spasm of the stomach, intestine & bladder.

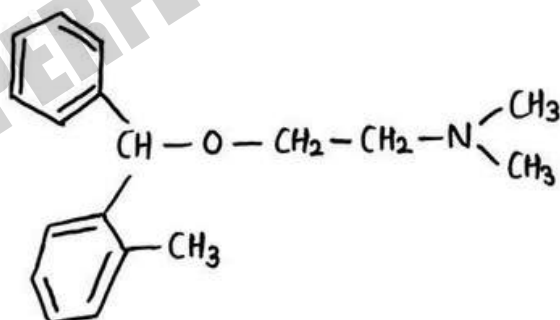
⑨ BENZTROPINE MESYLATE



Uses

- Used in the treatment of parkinson's disease.
- Used anticholinergic, antihistaminic and local anesthetic activity.

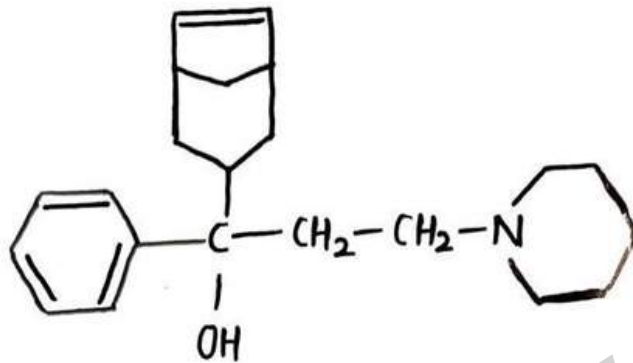
⑩ ORPHANDINE CITRATE



Uses

- It is used as skeletal muscle relaxant.
- Used in the treatment of parkinson's disease.

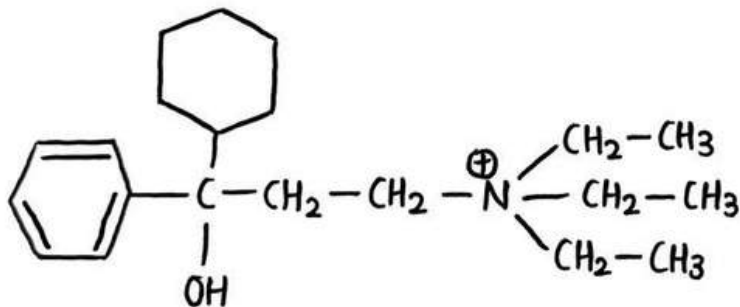
⑪ BIPERIDINE HYDROCHLORIDE



Uses

- It is used in all types of parkinson's disease.
- It have strong musculotropic action.

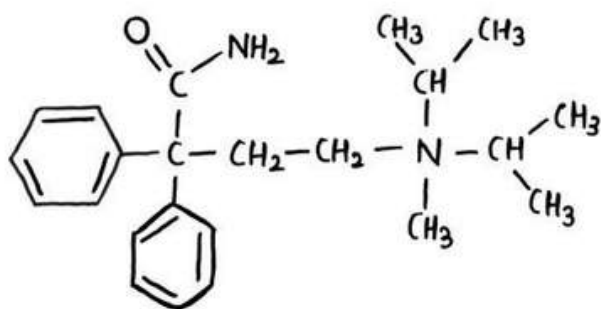
⑫ TRIDIHEXETHYL CHLORIDE



Uses

- It is used as antispasmodic and anti-parkinson's disease.

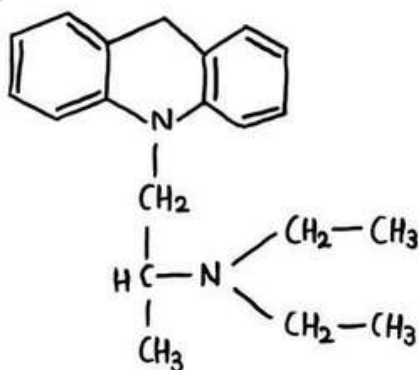
⑬ ISOPROPAMIDE IODIDE



Uses

- Used in the treatment of peptic ulcer.
- Used as potent anticholinergic, antispasmodic and antisecretory effects.

⑭ ETHOPROPAZINE HYDROCHLORIDE



Uses

- Used as adrenergic antagonist, Histamine antagonist and antiparkinson's drugs.

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER



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