MEDICINAL CHEMISTRY-I

B. PHARM IV TH SEM

UNIT-III

Shailesh Pathak

*CHOLINERGIC NEUROTRANSMITTERS

Drugs and chemicals that cause the parasympathetic division to react are termed parasympathomimetic, whereas those blocking the action are called parasympatholytics

- Parasympathetic Nervous system is also known as cholinergic system or.

*Neurotransmission :—

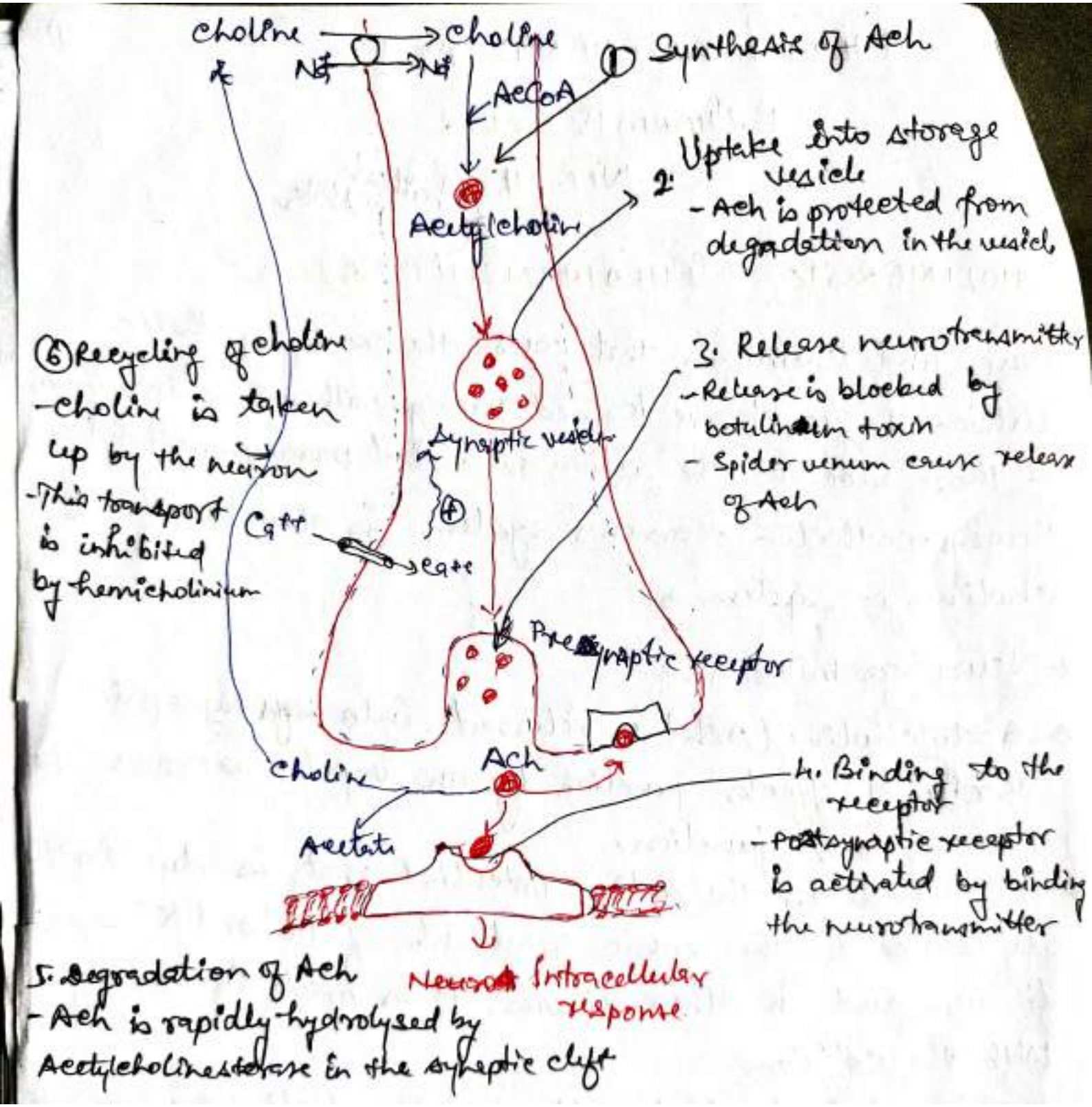
⇒ Acetylcholine (Ach) is released into synaptic vesicles of effector junction by an impulse across the neuroeffector junction.

⇒ This lead to the action potential that is due to the difference in the ionic gradients of Na^+ and K^+ equilibrium and in other tissues, it is mediated along with the Ca^{++} ion

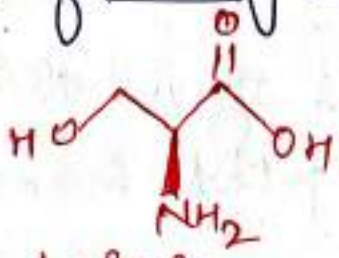
⇒ Ach is synthesized locally in the cholinergic nerve ending by ATP dependent system

⇒ Choline is actively taken by the axonal membrane and acetylated with the help of ATP and coenzyme A by the choline acetylase.

⇒ Choline is the limiting substrate for the synthesis of Ach

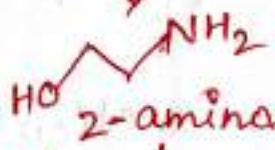

choline
choline
Na+
Na+
1. Synthesis of Ach
AcCoA
Acetylcholine
2. Uptake into storage vesicle
- Ach is protected from degradation in the vesicle
6. Recycling of choline
- choline is taken up by the neuron
- This transport is inhibited by hemicholinium
3. Release neurotransmitter
- Release is blocked by botulinum toxin
- Spider venum cause release of Ach
Synaptic vesicle
Ca++
Ca++
Presynaptic receptor
Ach
Choline
4. Binding to the receptor
- postsynaptic receptor is activated by binding the neurotransmitter
Acetate
Intracellular response
5. Degradation of Ach
- Ach is rapidly hydrolysed by Acetylcholinesterase in the synaptic cleft

* Biosynthesis of Acetylcholine (Ach) ⇒



L-Serine

↓ Serine decarboxylase



2-aminoethanol

↓ S-adenosyl methionine

Choline-N-methyl transferase

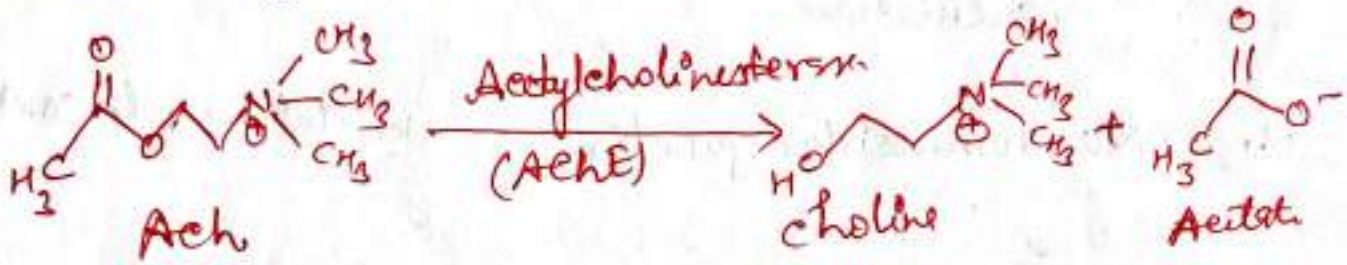
choline

↓ Acetyl CoA

Choline acetyl transferase

Acetylcholine

* Metabolism of Acetylcholine ⇒



Ach → choline + Acetate

* Cholinergic receptors and their distribution ⇒

* These receptors comprises of G-protein coupled with muscarinic and ligand gated channeled nicotinic receptor.

Cholinergic receptor

1. Muscarinic receptors (M)
2. Nicotinic receptors (N)

- M_1
- M_2
- M_3
- M_4
- M_5
- N_1
- N_2

Receptor	Location
M- M_1	Striatum, cortex, hippocampus.
M- M_2	Forebrain, thalamus, heart, pupil, spinal cord, Exocrine.
M- M_3	Brain, hypothalamus, pupils, exocrine, peripheral arteries.
M- M_4	Striatum, cortex, hippocampus, spinal cord
M- M_5	Dopaminergic neurons, basal ganglia, brain vasculature
N- N_1	Neuromuscular junction. → skeletal muscle contraction
N- N_2	Autonomic ganglia, CNS, Adrenal medulla

* Muscarinic Receptor (M):-

Receptor	Location	function
M_1:	CNS, gastric & salivary gland autonomic ganglia enteric nerve	- ↑ Cognitive function - ↑ Seizure activity - ↑ Autonomic ganglia
M_2:	Autonomic nerve terminal, CNS, heart, smooth muscle	↑ Smooth muscle contraction, Neural inhibition in periphery ↓ ganglionic transmission Neural inhibition ↓ heart rate ↑ Tremors hypothermia & analgesia
M_3:	CNS, heart smooth muscle, gland	- ↑ Smooth muscle contraction (bladder - ↑ Salivary gland secretion - ↑ food intake, body fat deposits. - Inhibits dopamine release - Synthesis of nitric oxide.
M_4:	CNS-	- Inhibition of autoreceptor and hetero receptor mediated transmitter release in CNS. - Analgesia - Facilitate dopamine release
M_5=	Low level of CNS & periphery	- Mediate dilation of cerebral arteries - Facilitates dopamine release - drug seeking behavior and reward.

* Cholinergic receptors and their distribution ⇒

* These receptors comprises of G. Protein coupled with muscarinic and ligand gated channeled nicotinic receptor

Cholinergic receptor

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M_1 M_2 M_3 M_4 M_5 N_1 N_2

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M- M_5	Dopaminergic neurons, basal ganglia, brain, vasculature
N- N_1	Neuromuscular junction. → skeletal muscle contraction
N- N_2	Autonomic ganglia, CNS, Adrenal medulla

* Parasympathomimetic agents:

⇒ Drugs and chemicals that cause the parasympathetic division are termed as parasympathomimetic.

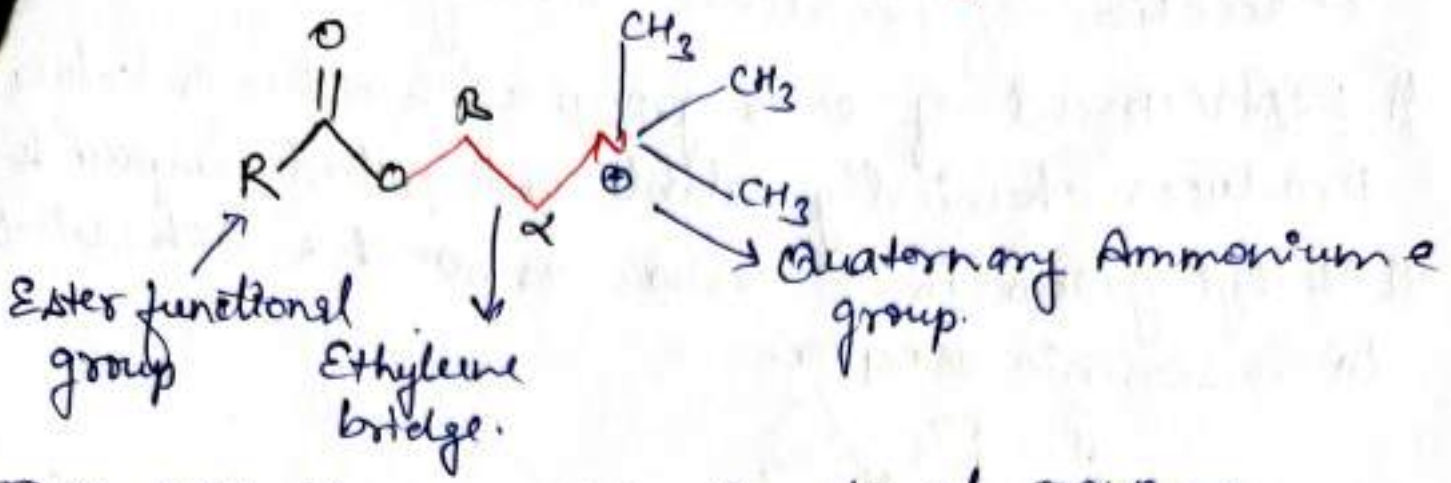
⇒ The cholinomimetic or parasympathomimetic or cholinergic drugs are those which cause a muscarinic action on the the receptors of effector organ provided by the post ganglionic cholinergic nerves.

⇒ Acetylcholine receptor stimulants and cholinesterase inhibitors together comprise a large group of drugs called as cholinergic drugs that mimic the action of Ach

CLASSIFICATION of Parasympathomimetic agent ⇒

1. Direct acting drugs
   - a) Choline Ester
     - Acetylcholine
     - Methacholin
     - Bethacholine
     - *Carbachol**
   - b. cholinomitic alkaloids
     - Pilocarpin
     - Muscarine
     - Arecholin
2. Indirect acting (AChE inhibitors)
   - a) Reversible inhibitors
     - i) Carbamates
       - Physostigmine
       - Neostigmin*
       - Pyridostigmine
       - Tacrine HCl
       - Rivastigmine
     - ii) 4° Ammonium compounds
       - Edrophonium Chloride
       - Ambenonium cholid
       - Demecarium
   - b) Irreversible inhibitors
     - Organophosphates
       - Isofluorphate
       - Echothiopate Iodid
       - Parathion
       - Malathion

SAR of Parasympathomimetic agents :-



① Modification of Ester functional group —

a) Ester group of Ach contributes to the binding of the compound to the muscarinic receptor

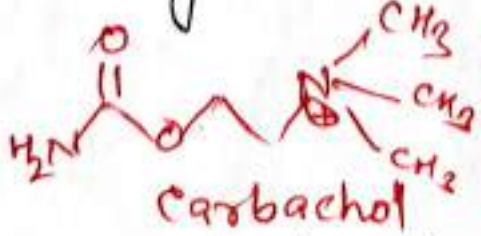
b) Replacement of methyl group by ethyl or large alkyl group produce inactive compounds

c) Ester of aromatic or higher molecular weight acids posses cholinergic antagonist activity

d) Essential for affinity.

② Modification of Ethylene bridge :-

a) Methyl ester is rapidly hydrolysed by cholinesterase. To reduce susceptibility to hydrolysis, methyl ester is replaced by carbamate esters, were found to be more stable than carboxylate.



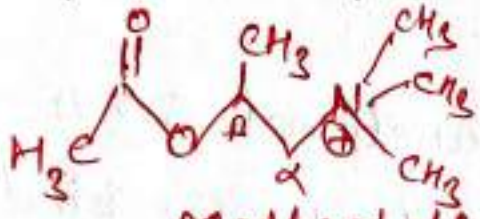
Carbachol

b) Placement of α- substitution in choline moiety a results in a reduction of both nicotinic and muscarinic activity.

c) Incorporation of β-substitution lead to reduction of nicotinic activity.

d) Replacement of ester group with ether or ketone produces chemically stable and potent compounds.

e) Methyl group in β-carbon as potent as Ach selective to muscarinic receptor.



Methacholine.

(3) Modification of Quaternary Ammonium Group-

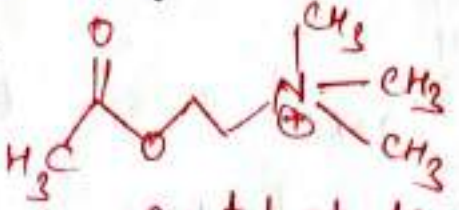
a) The Quaternary Ammonium group is essential for intrinsic activity and contributes to the affinity of the molecule for the receptors.

b) The trimethyl ammonium group is the optimal functional moiety for the activity.

c) Placement of 1°, 2° & 3° amines leads to decrease in activity

① Directly Acting drugs -

① Acetylcholine -

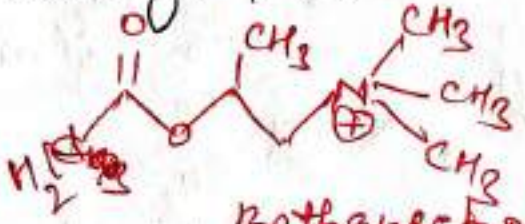


Acetyl choline

*MOA - It exerts agonistic effect on muscarinic M_3-receptor, causing contraction of ciliary muscle

Uses - Cataract surgery.
- Iridectomy (removal of small portion of iris)
- Miosis (dilation of pupil)

② Bethanechol -



Bethanechol

MOA - Directly stimulates muscarinic receptors. Causing increased intestinal motility & tone.

Uses - Relief of urinary retention
- Abdominal distention (swelling of abdomen)

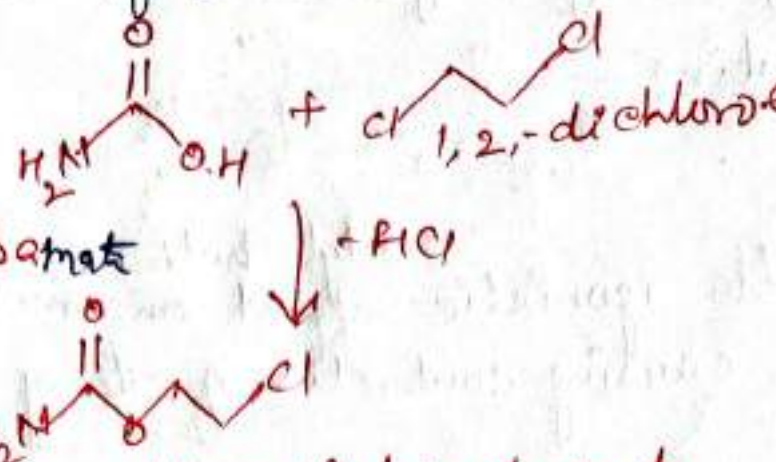
③ *Carbachol ⇒

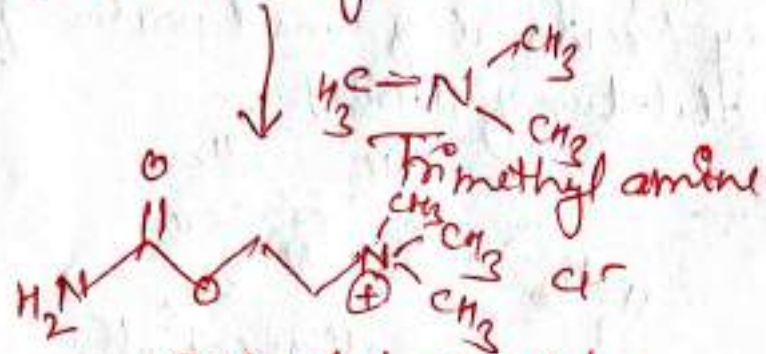
2-[(aminocarbonyl)oxy]-N,N,N,trimethyl ethanaminium

*MOA ⇒ It is an ester of choline and thus posses both muscarinic and nicotinic properties. Action like ACh.

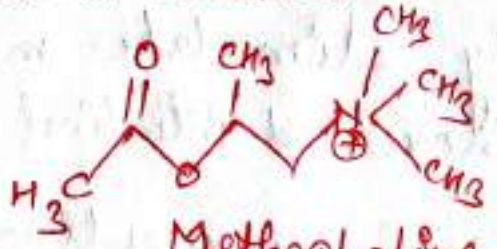
Uses ⇒ - Glaucoma (damage of optical nerve, vision loss)
- Ocular surgery

* Synthesis of * Carbachol :—





④ Methacholine ⇒



*MOA ⇒ Binds with muscarinic receptor and induces bronchoconstriction

*Uses - - Diagnosis of BHR (bronchial Hyperreactivity)
- Asthma.

⑤ Pilocarpine ⇒

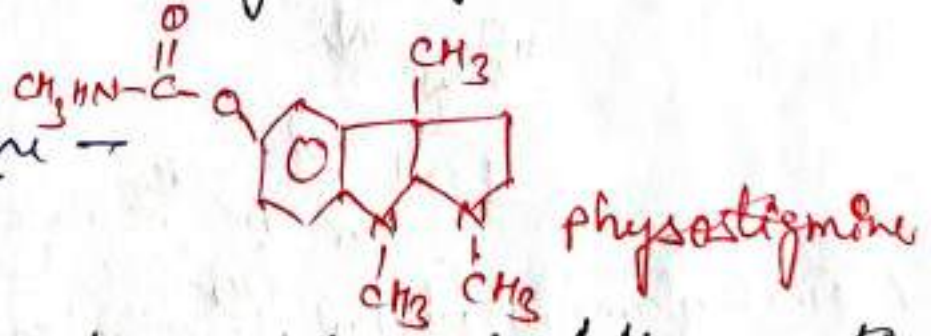
*MOA ⇒ It act on M.3 receptor in smooth muscles and cause contractions in gut, trachea & eye.

*Uses ⇒ - Glaucoma
- Sjogren syndrome (dry mouth and lack of tears).

Indirect / cholinesterase Inhibitors –

- There are two types of cholinesterases in humans. AChE and butyrylcholinesterase (BuChE)
- BuChE (pseudocholinesterase) is located in human plasma. Although its biological function is not clear, it has catalytic properties similar to those of AChE.
- Inhibition of AChE prolongs the duration of the neurotransmitter in the junction and produces pharmacological effect similar to those observed when AChE is administered.
- These Inhibitors are Indirect-acting cholinergic agonist. AChE Inhibitor have been used in the treatment of myasthenia gravis, glaucoma. and atony in G.I tract.

① Physostigmine –



physostigmine

MOA – Indirectly act as cholinergic by preventing the degradation of AChE. this results in an accumulation of AChE in the synaptic cleft. Therefor drug produce response. It bind both muscarinic and nicotinic receptor.

Uses –

↳ Glaucoma

- antidote for atropine poisoning

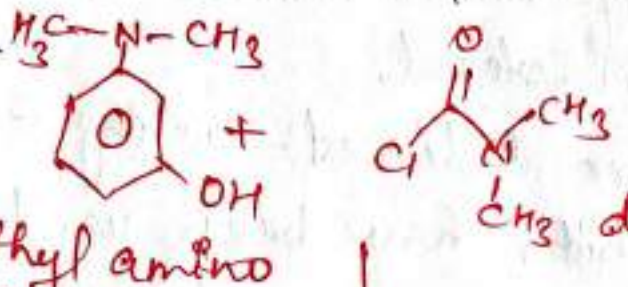
(2) Neostigmine ⇒

Neostigmine.

MOA - Inhibit the hydrolysis of AchE by competing with acetylcholine for attachment to acetylcholinesterase at site of cholinergic transmission.
- It enhances cholinergic action by facilitating the transmission of impulses across neuromuscular junctions.

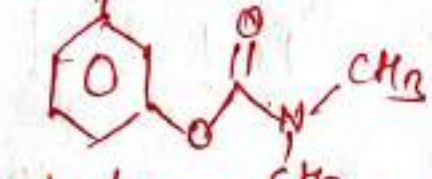
Uses - Improve muscle strength
- Myasthenia Gravis (certain muscle disease)
- Stimulate bladder & G.I. tract.

Synthesis -



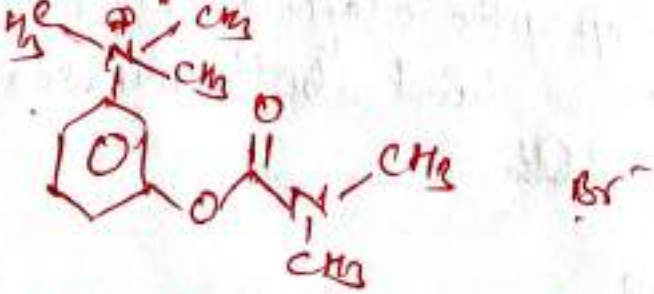
3-dimethyl amino phenol

dimethyl carbamoyl chloride.



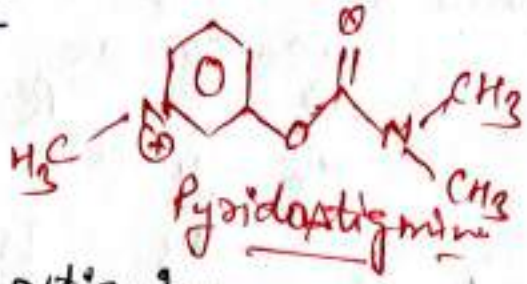
3-(dimethylamino) phenyl dimethyl carbamate

CH_3Br



Neostigmine bromide.

④ Pyridostigmine –

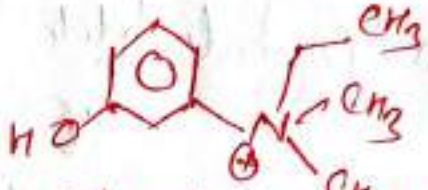


Pyridostigmine

*MOA ⇒ Same as neostigmine

*Uses - Myasthenia Gravis (muscles weakness & fatigue)

⑤ Edrophonium chloride ⇒

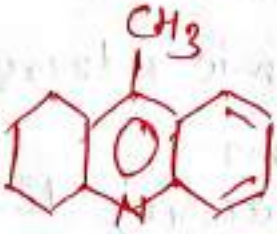


Edrophonium chloride

*MOA Indirectly provide a cholinergic action by preventing the degradation of Ach

*Uses ⇒ Myasthenia Gravis
- Anti arrhythmic.

⑥ Tacrine ⇒HCl



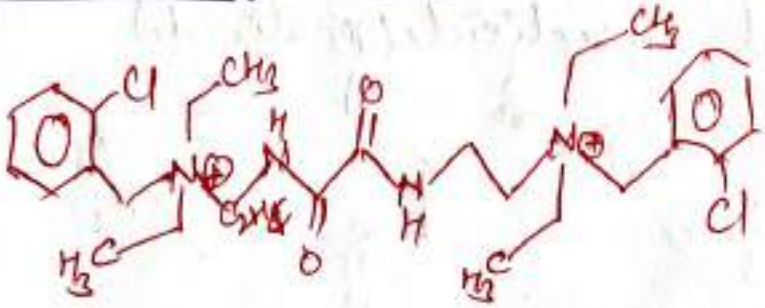
Tacrine HCl

MOA – It is reversible inhibition of AchE which thereby slow the breakdown of the chemical messenger Ach in the brain

Uses - Alzheimer disease (neurodegenerative disorders that affect memory, thinking & reasoning)

⑦ Ambenonium chloride –

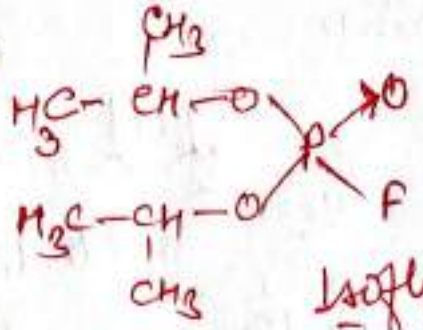
MOA – suppressing the activity of AchE.



Uses - Myasthenia Gravis

Ambenonium chloride.

⑧ Isoflurophate →

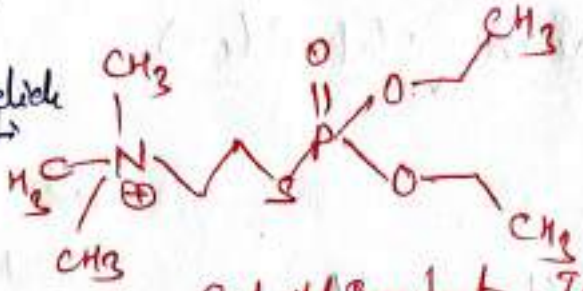


Isoflurophate

*MOA - It is act as an irreversible cholinesterase inhibitor

Uses - Glaucoma.

⑨ Echothiophate Iodide →

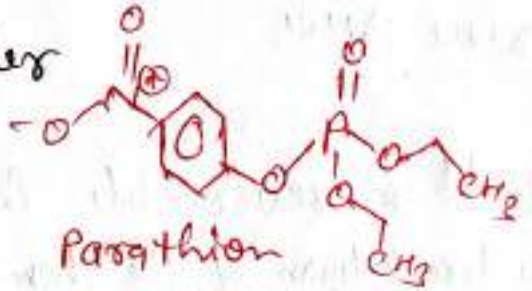


Echothiophate Iodide

*MOA - Echothiophate potentiate the action of Ach at cholinergic synapse.

Uses - ophthalmic redness
- Glaucoma
- eye focusing disorder

⑩ Parathion :-

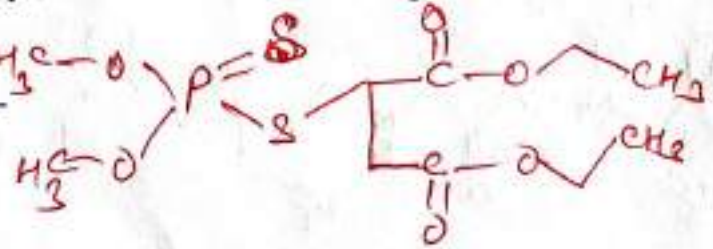


Parathion

*MOA - It blocking the degradation of Ach & It is relatively weak inhibitor of cholinesterase.

Uses - Agricultural Insecticide (Pesticide).

⑪ Malathion :-



MOA & Uses same as Parathion

* Cholinesterase reactivator :-

⊙ Pralidoxime chloride :-

Pralidoxime Cl

* MOA - It is a reactivate cholinesterase (mainly out-side of N.S.) which has been inactivated by phospho-rylation due to an organophosphate pesticide
* Uses
  - ↳ Act antidote for poisoning by parathion
  - Myasthenia Gravis

MEDICINAL CHEMISTRY-II

B. Pharm - IV th Sem

UNIT-III (B)

Khatkar Pathak

* CHOLINERGIC BLOCKING AGENT :⇒

- It is also known as Anticholinergic agent or parasympatholytic agent or antimuscarinic agent
- Anticholinergic action by drugs and chemical apparently depends on their ability to reduce the no. of free receptors that can interact with ACh.
- Drugs that block or inhibit the action of Ach in the nervous system (PSNS). Parasympathetic

* Classification :- Anticholinergic drugs

① Natural alkaloid
- Atropine
- Hyoscine (Scopolamine)
- Hyoscyamine

② Semisynthetic derivatives
- Atropine methanitrate
- Hyoscine butyl bromide
- Homatropine
- Ipratropium bromide
- Tiotropium bromide.

③ Synthetic compound

a) Mydriatic
- Cyclopentolate
- Tropicamide.

② Antisecretory & Antispasmodic.

I) Tertiary compound
- Dicyclomine
- Valethamate, Pipenzepine

II) Quaternary compound
- Propantheline, clinidium
- Oxypheronium, Isopropamide
- Glycopyrrolate, Pipenzolate

③ Vasicoselective
- Oxybutynin
- Flavoxate
- Tolterodine

④ Antiparkinsonism
- Trihexyphenidyl
- Procyclidine
- Biperiden

classification of Anticholinergic drug -

① Solanaceous alkaloid & analogs
- Atropine sulphate
- Hyoscyamine sulphate
- Scopolamine HBr
- Homotropine HBr
- Ipratropium bromide.

(b) Amino alcohol Ether -
- Benztropine mesylate
- Orphenadrin citrate

(c) Amino alcohol -
- Biperiden HCl
- Procyclidine HCl
- Trihexethyl chloride.
- Tolterodine

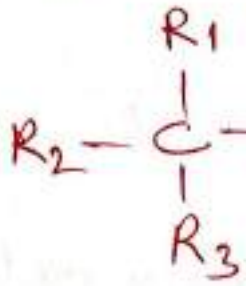
② Synthetic Cholinergic blocking agent

a) Aminoalcohol Esters
- clinidium bromide.
- Cyclopentolate HCl
- Dicyclomine HCl
- Glycopyrrolate
- Mepenzolate
- Methantheline bromide.
- Oxyphencyclimine. brom
- Propantheline bromide.
- Oxybutinin
- Soligenacin

(d) Aminamide -
- Isopropamide Iodide
- Tropicamide
- Darifenacin.

(e) Miscellaneous -
- Diphemanil
- Ethopropazine HCl
- Papaverine.

SAR of Anticholinergic agent ⇒



(1) R_1 or R_2 group must be carbocyclic or heterocyclic.

(2) R_3 group can be H, -OH, $-CH_2OH$, amide.

(3) X is mostly Ester in most potent derivatives but it can be ether oxygen or absent completely.

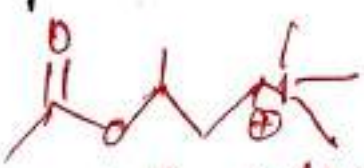
(4) The N substituent can be both quaternary ammonium salt or tertiary amine with different alkyl groups

(5) The distance between the ring substituted carbon and nitrogen is not fixed but maximum potency requires about 2 carbon units

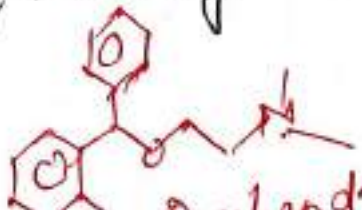
A) Nitrogen group —

- It agonist the N can only be quaternary but antagonist N can be both quaternary or tertiary.

Eg



Methacholine



Orphendrine

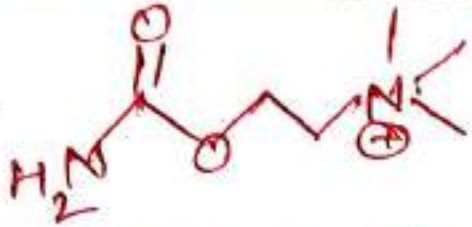
(B) Ethylene bridge —

- In agonist the no ethylene is fixed at only 2

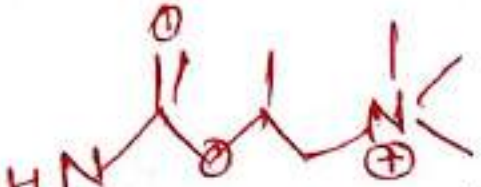
but

- In antagonist no. of ethylene can range from 2-4

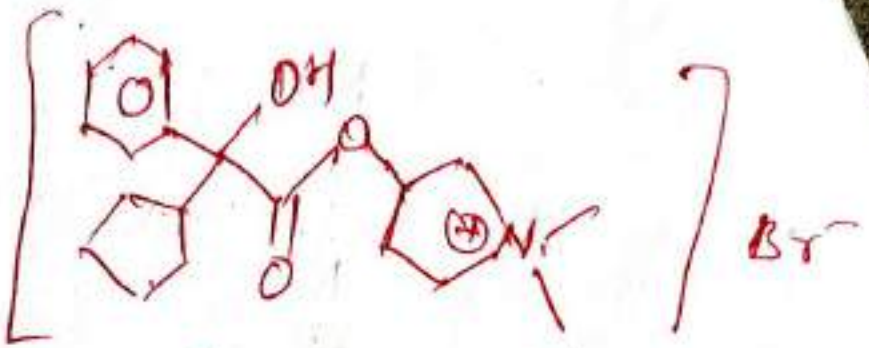
Eg



Carbamate



Bethanecol



Glycopyrrolate

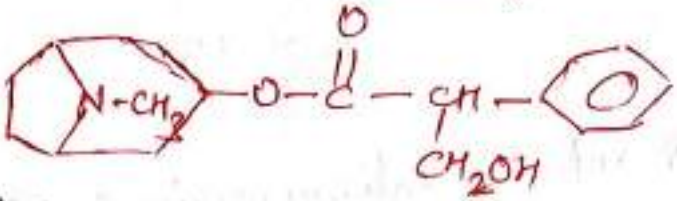
© Selectivity -

- In agonist the methyl substitution in ethylene group controls selectivity of muscarinic or nicotin
- In antagonist no such feature is present. Still it only antagonize eg methacholine

Methacholine.

* Solanaceous alkaloids and analogues -

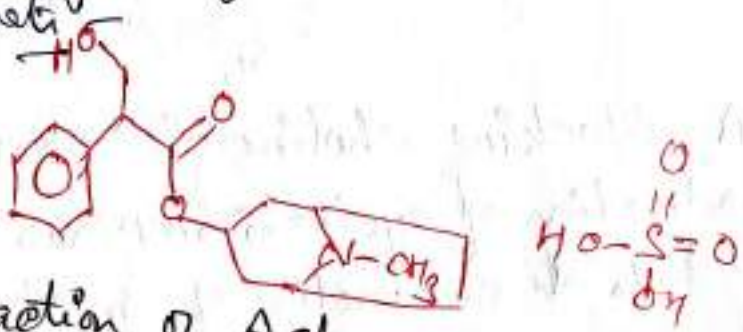
(1) Atropine :-



* MOA ⇒ It is competitively binds to muscarinic receptor and antagonizes it thus blocking all cholinergic effect

* Uses - Bradycardia
- Reduce secretion before surgery
- Treat Iritis (painful inflammation of eye)

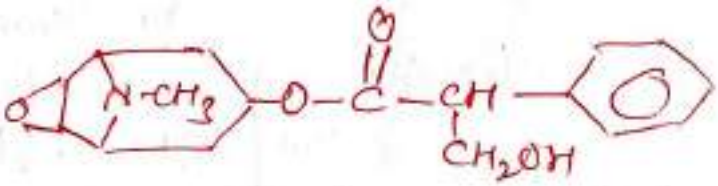
(2) Hyoscyamine sulphate



MOA - Inhibit the action of Ach

Uses - Anti emetic
Anti spasmodic
Parkinsonism, mania & delirium (confused thinking)

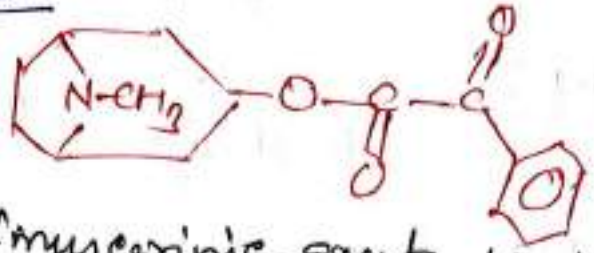
(3) Scopolamine HBr -



* MOA - It is competitively binds to muscarinic receptor and antagonizes it thus blocking all cholinergic effect

* Uses - It depress CNS
- Treat iritis (Eye inflammation)
- Treat Parkinsonism (neurodegenerative disorder) — Tremors, stiffness slowness movement
- Treat motion sickness (nausea, dizziness & vomiting)

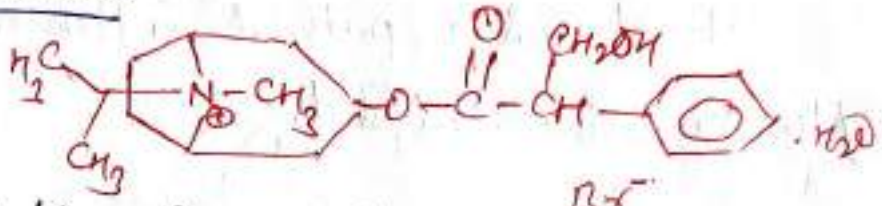
④ Homotropine HBr –



*MOA ⇒ act as antimuscarinic agent, blocking the effect of Ach, a neurotransmitter in PSNS.

*Uses ⇒ -Mydriatic
Suppress cough

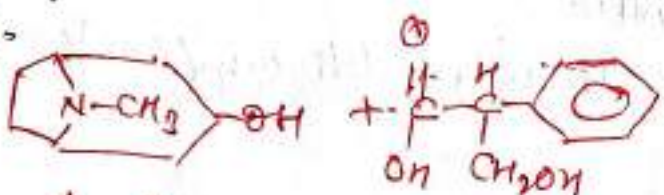
⑤ Ipratropium bromide –



MOA – Blocking cholinergic receptors decreases the production of cyclic GMP (Guanosine mp) → in lung airway leads to the contraction of smooth muscle.

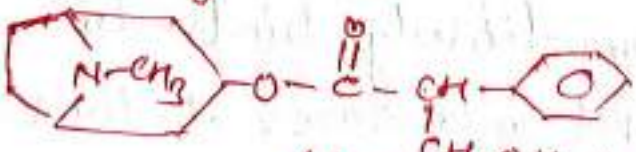
Uses – COPD (Chronic obstructive Pulmonary disease)
– runny nose (rhinorrhea)

Synthesis –

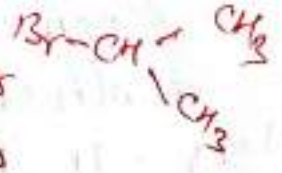


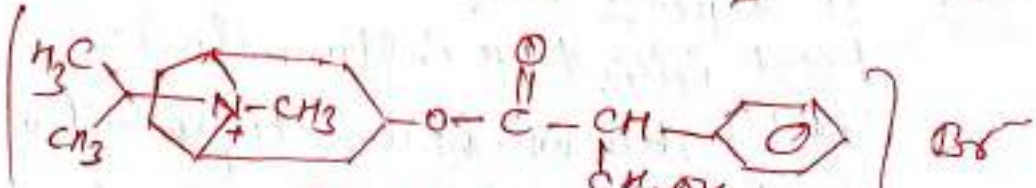
Tropine + Tropic acid

$-H_2O$ | Esterification with HCl



Atropine

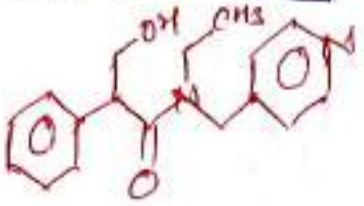




Ipratropium bromide

Synthetic cholinergic blocking agent -

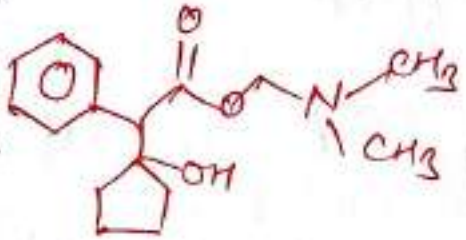
1) ~~Physostigmine~~ - Tropicamide ⇒



MoA ⇒ It antagonize M4 receptor

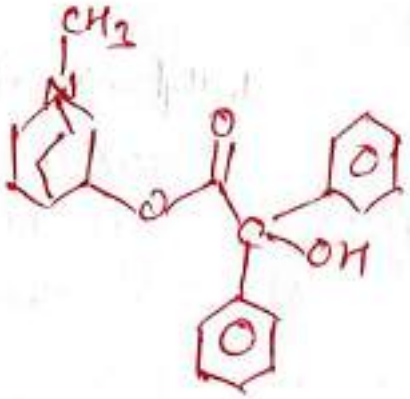
Uses ⇒ - Mydriatic (abnormal dilation of pupils)
- cycloplegia (paralyzes the eye's ciliary muscle which control the pupil)

2) Cyclopentolate hydrochloride ⇒



*MoA - Competitively inhibits the binding of Acetylcholine to muscarinic

Uses - Spasmodic activity
- Mydriatic
- Cycloplegia

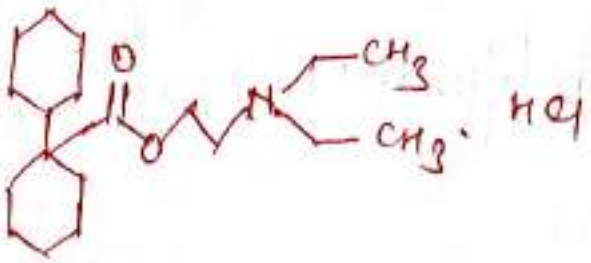


3) Clinidium Bromide ⇒

MoA - Same above.

Uses - Peptic ulcer, hyperchlorhydria, ulcerative colitis, GIT disturbance

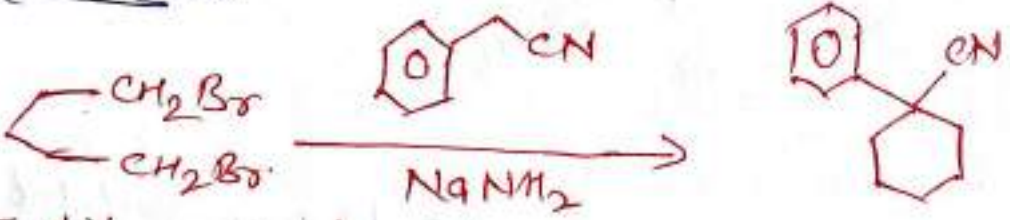
(4) Dicyclomine HCl :-



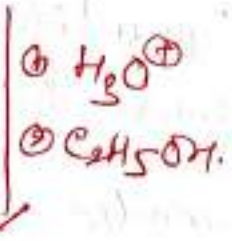
*MOA- It is binds more firmly to M_1 & M_3 than to M_2 & M4 receptor.

*Uses ⇒
- Smooth muscles Spasm
- biliary dysfunction
- dysmenorrhea (cramps & pelvic pain with Menstruation)
- Neurotropic effect

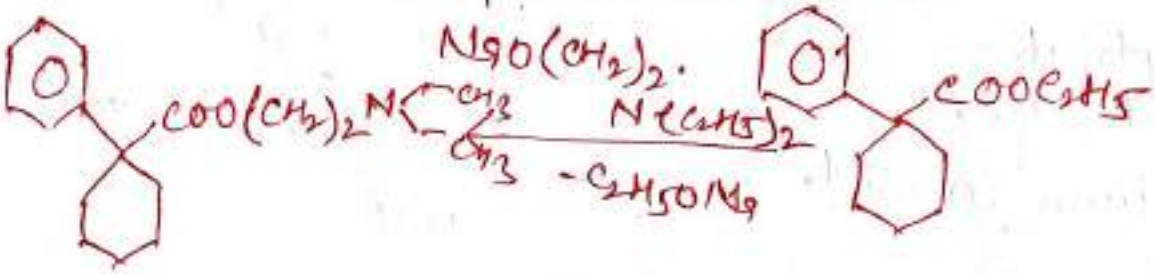
*Synthesis ⇒

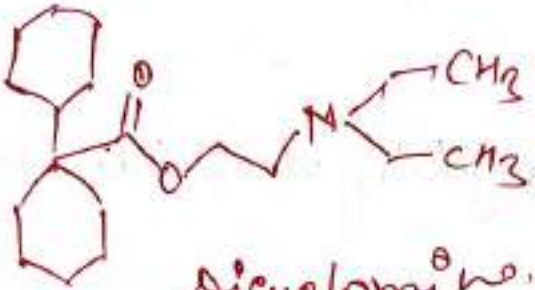


1,5- dibromo pentane



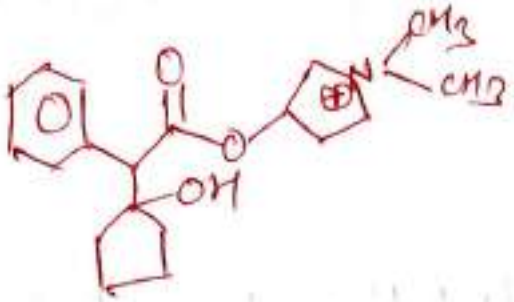
diethylamin sod. ethoxide





Dicyclomine.

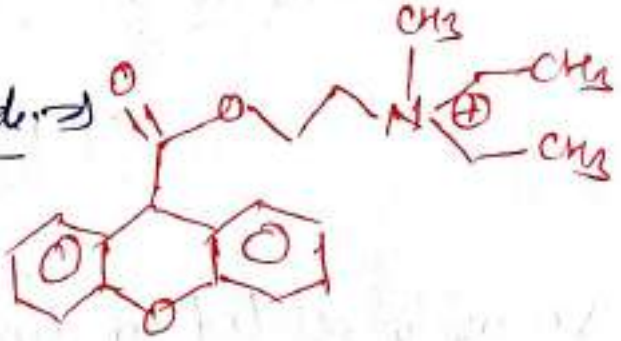
(5) Glycopyrrolate →



MOA → Its block the M_2 and M_3 receptor. M_1 have low affinity

Uses → Peptic ulcer
- GI, spasm
- hyperacidity

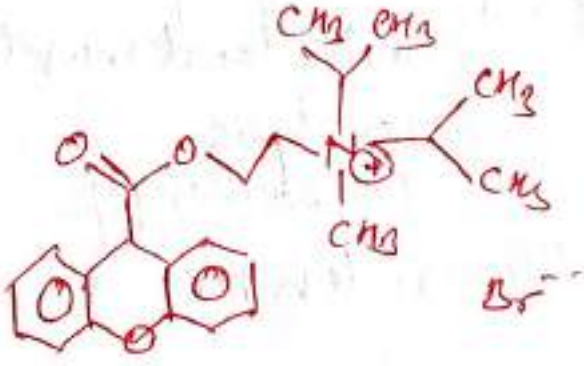
(6) Methantheline bromide →



MOA → Block the nicotinic receptor

Uses → - Peptic ulcer.
- bladder irritability.

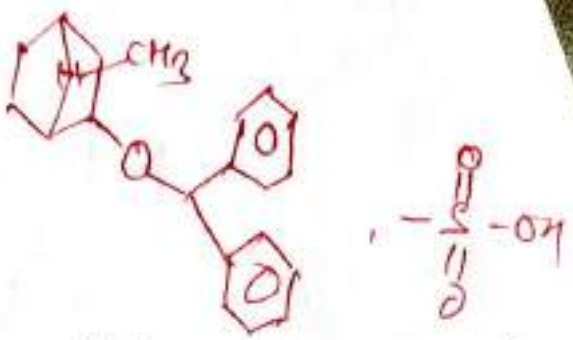
(7) Propantheline Bromide →



MOA → ganglionic blocking activity to muscarinic activity

Uses → Peptic ulcer.
Antispasmodic.

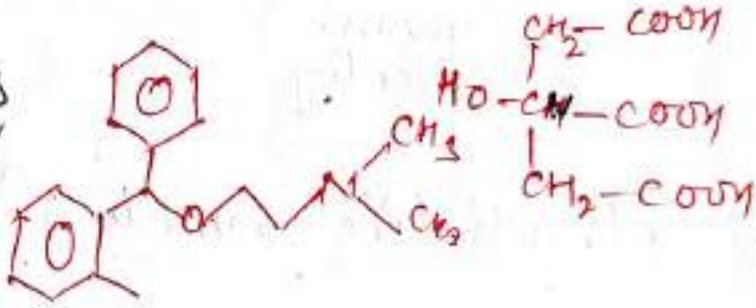
⑧ Benztropine mesylate :-



MoA ⇒ It has anticholinergic, antistaminic & local anaesthetic properties.

Uses ⇒ as atropin.

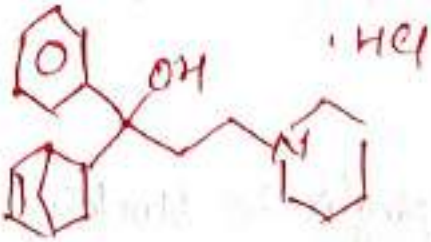
⑨ Orphendrine citrate ⇒



*MoA ⇒ closely related to diphenhydramine structurally but has much lower antihistaminic activity and much higher anticholinergic activity

Uses ⇒
- pain local muscle spasm
- paralysis
- physiotherapy.

⑩ Biperiden HCl ⇒

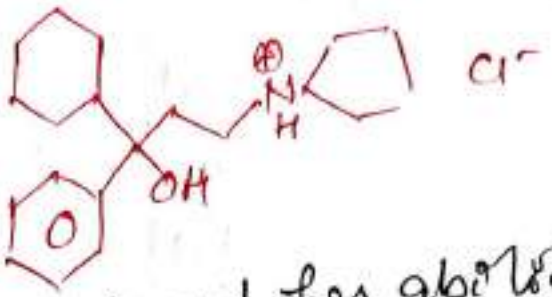


* MoA ⇒ Block the nicotinic receptor

* Uses ⇒ Spinal cord injury, Epilepsy
- Parkinsonism

(11) Procyclidine.HCl ⇒

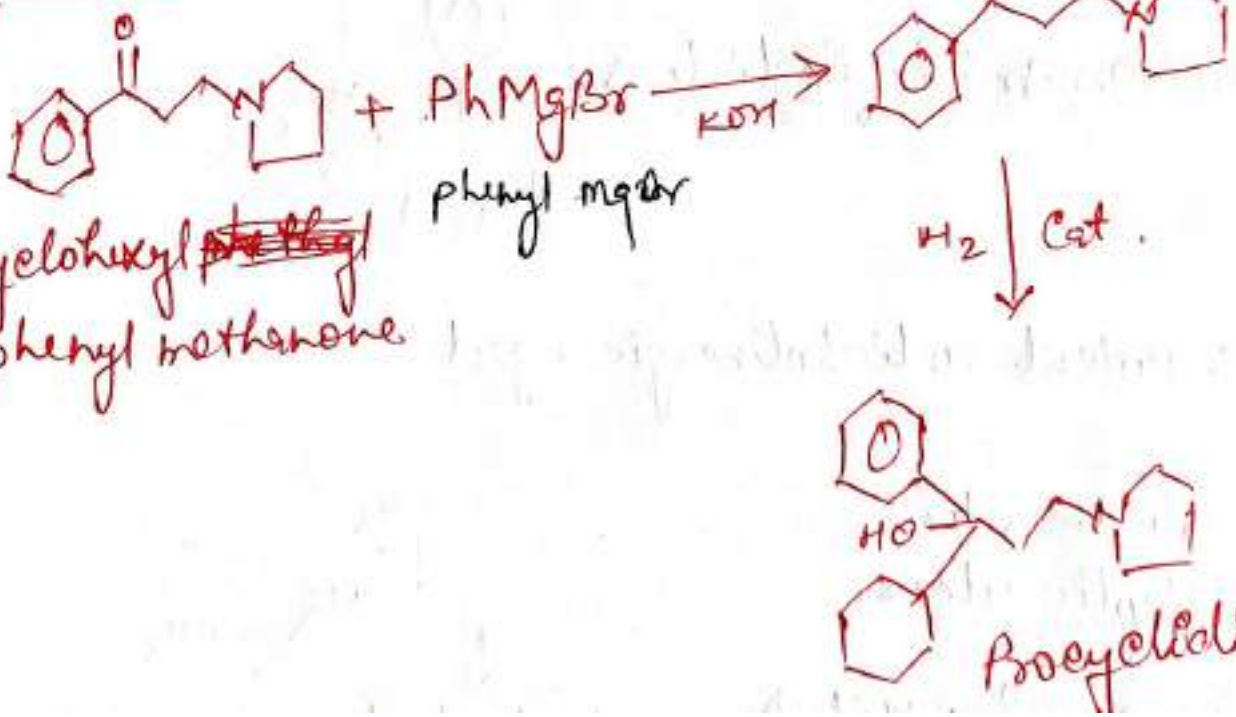
(11)



MOA ⇒ Peripheral anticholinergic and has ability to relieve voluntary muscle spasticity (involuntary spasm and pain caused by damage or disruption to the brain & spinal cord

Uses ⇒ Parkinson syndrome. (nerve cell damage in the brain cause loss of balance)

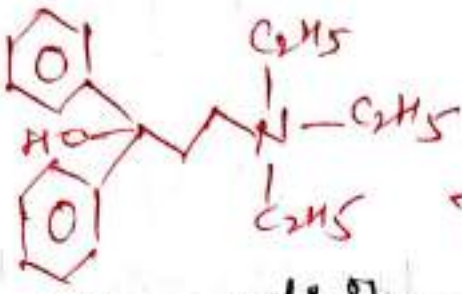
Synthesis ⇒



Cyclohexyl phenyl methanone

Procyclidine.

(12) Tri/di hexethyl chloride:-

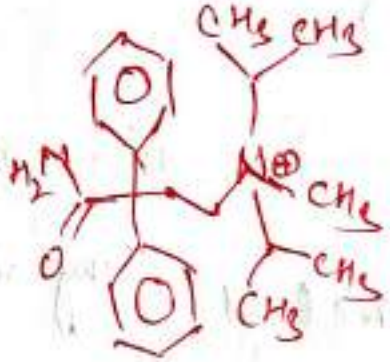


Trihexethyl cl.

* MOA ⇒ Ganglion blocking activity.

* Uses ⇒ G.I. disease.
- Peptic ulcer.
- Hyper acidity
- Diarrhea.

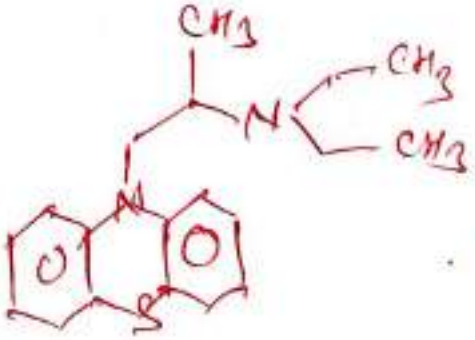
(13) Isopropamide Iodide ⇒



* MOA ⇒ Potent anticholinergic agent

* Uses ⇒ GI disorder.
Peptic ulcer.

(14) Ethopropazine HCl ⇒



MOA ⇒ block muscarinic receptor.

Uses ⇒ Parkinsonism