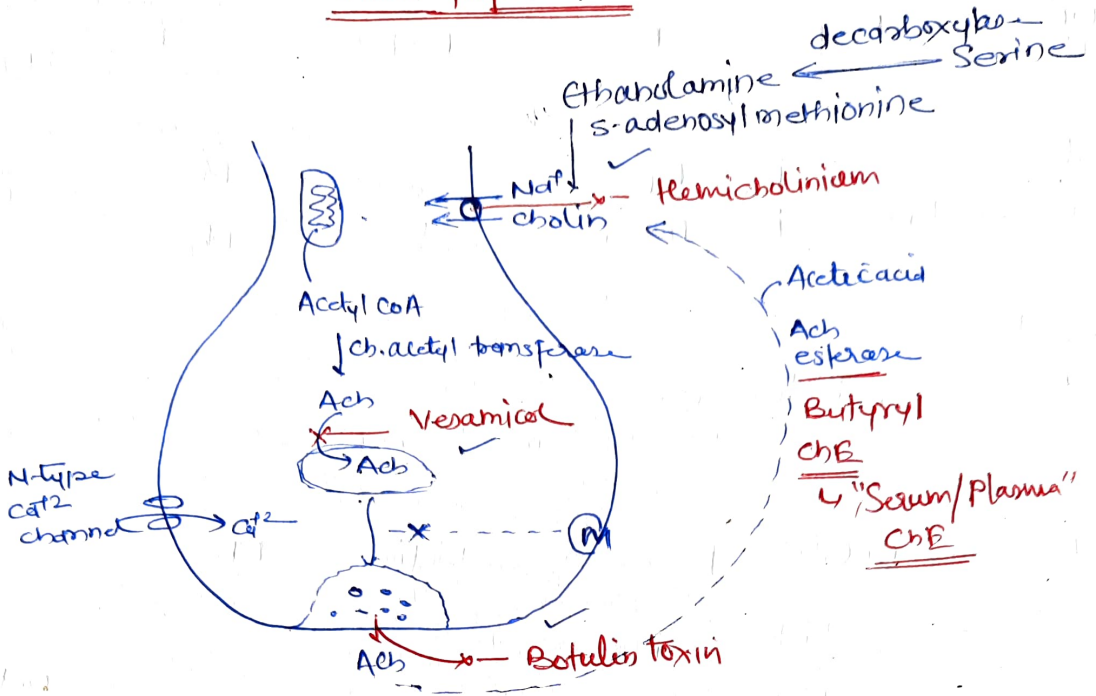


# Para Sympathetic



Receptors - M<sub>1</sub>, M<sub>3</sub>, M<sub>5</sub> = G<sub>q</sub> & NM - LG Na<sup>+</sup> channel  
 M<sub>2</sub>, M<sub>4</sub> - G<sub>s</sub> & NN

| R              | Location   | Agonist                            | Antagonist                            |
|----------------|--|------------------------------------|---------------------------------------|
| M <sub>1</sub> | Neuronal, GI gland   | Acetyl cholin carbachol            | Atropin<br>Pirenzepine<br>Dicyclomine |
| M <sub>2</sub> | Heart SA & AV node<br>(→ chrono, ions, & dromotropic effect) | ACh                                | Gallamine<br>Tropetamine              |
| M <sub>3</sub> | Exocrine glands<br>Smooth muscle<br>eye                      | ACh<br>carbachol                   | Difenidol                             |
| M <sub>4</sub> | Fore brain<br>(Autoreceptor) → e                             |                                    |                                       |
| M <sub>5</sub> | S. nigra (brain) -   | cerebral artery ↑ dopamine release |                                       |
| NN             | Autonomic ganglia  | Nicotin Lebolin<br>ACh, DMPP       | Hexamethonium                         |
| NM             | Sk. mus  | PTMA, Nicotine<br>ACh              | D-Tubocurarine                        |

# Parasympatho mimetics

**I choline Esters** : - Acetylcholine  
 Methacholine  
 Carbachol  
 Bethanechol - 4<sup>o</sup> Ammonium  
 ↳ GI. bladder atony

glaucoma - } 4<sup>o</sup> diagnosis of Asthenia ppt

**II Natural Alkaloid** : - (+) muscarine (Amanita muscaria)

Pilocarpus microphyllus

← Pilocarpine ↳ Isolated in 1869 by  
 Asecholine "Schmiedeleberg"

↳ Areca catechu Other = Nicotin

**III Choline Esterase Inhibitors**

Oxotremorine  
 Tremorine  
 Lebeline

(A) Reversible

Carbamates :



Physostigmine

Neostigmine

Pyridostigmine

Rivastigmine

Edrophonium

Donepezil

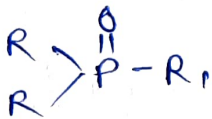
- Carbamoyl or  
 Carbamate ester

Acedine : - Tacrine

(B) Irreversible

Carbamate : - Carbaryl, Propoxure

Organophosphates :



Isoflurophate

Echothiophate

Parathion

Malathion

Tabun

Sarin

Soman

} used in glaucoma

} - as Insecticide

} - Nerve gases for warfare

**Therapeutic use** : -

- ① Glaucoma - Physostigmine, Pilocarpine, Carbachol, Isoflurophate
- ② Myasthenia Gravis - Neostigmine, Pyridostigmine
- ③ Diagnosis - Edrophonium - M.G.
- ④ Alzheimer - Rivastigmine, Tacrine, Donepezil, Galantamine
- ⑤ Post-operative ileus - Bethanechol, Neostigmine, Pyridostigmine

\* NM - DMPP - Dimethyl phenyl pyridazinium

NM - PTMA - Phenyl trimethyl Ammonium

# Pharmacological Action

## Muscarinic Action :-

- ① Heart → HR ↓ (Hyperpolarisation SA Node, ↓ Automaticity)  
 (M<sub>2</sub>) (-) chronotropic  
 (G<sub>i</sub>) → ↓ force of contraction (-) inotropic  
 ↓  
 ⊕ AC → ↓ conduction velocity (AV node) - (-) dromotropy  
 ⊕ K<sup>+</sup>

- ② Blood Vessels :- Relaxation by eDRA (NO) (M<sub>3</sub>)  
 ↳ At high dose - constrict by sympathetic activation

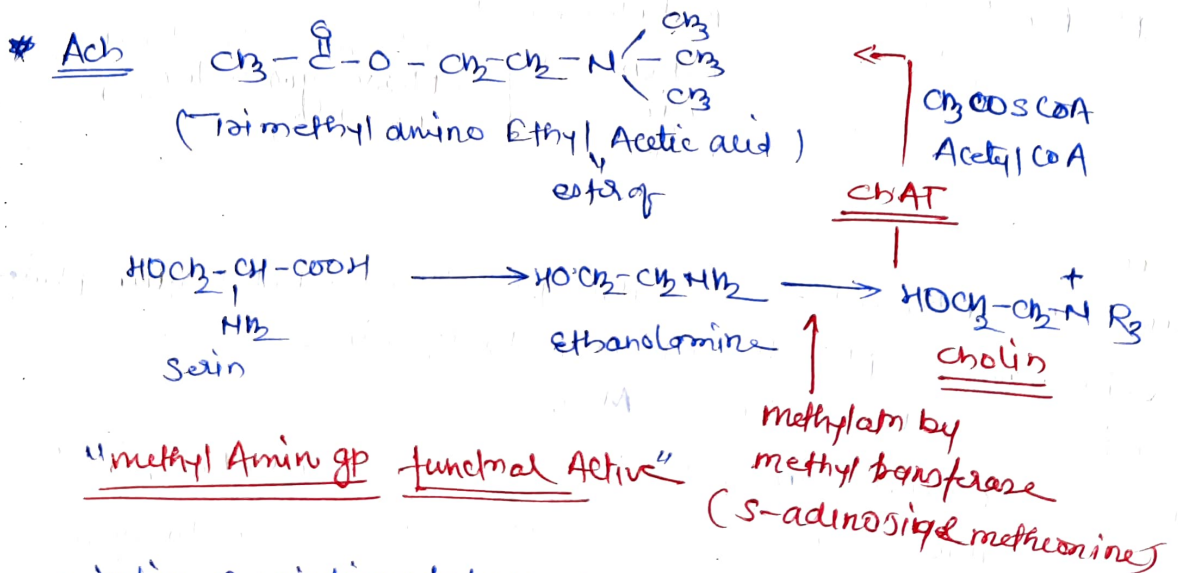
- ③ Smooth muscles :- all are constrictor except  
 (Sphincter) (M<sub>3</sub>)

- ④ GI Secretion (M<sub>1</sub>) & other Secretion (M<sub>3</sub>) - ↑

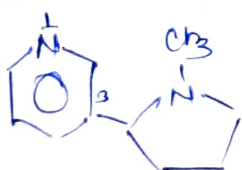
- ⑤ Eye (M<sub>3</sub>) - Constriction of radial & ciliary muscle  
 → Accommodation for Near Vision (miosis)  
 → Constrict ciliary mus - ↑ outflow for glaucoma

## Nicotinic Action NN - stimulation

NM = sk. muscle contraction



## \* Nicotin (Nicotiana tabacum)



(-) Nicotine

3-(1-methylpyrrolidine-2yl) pyridine



# MEDICHEM-I, U-3, PARASYMPATHETIC SYSTEM

## Parasympathomimetic Agents

↳ SAR

↳ Direct Acting Agents - Acetylcholine, Carbachol\*, Bethanachol, Methacholine, Pilocarpine

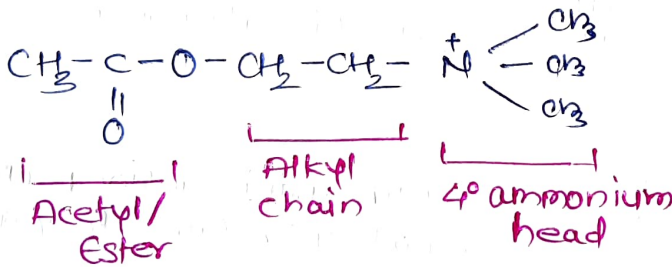
↳ Indirect-Acting / cholinesterase Inhibitor

A. Reversible : → Carbamate Derivatives → Physostigmine, Neostigmine\*, Pyridostigmine, Edrophonium, ~~Ta~~ Ambenonium, Acedine - Tacrine

B. Irreversible - Organophosphates - Isoflurophate, Echothiophate, Parathione, Malathione

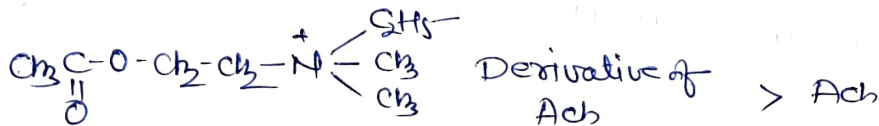
↳ Choline Esterase Reactivator - Pralidoxime

## SAR OF PARASYMPATHOMIMETIC AGENTS

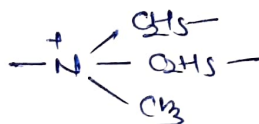


### A. 4° Amm. Head

- # 4° Ammonium group  $-\text{N}^+ \begin{array}{l} \diagup \\ | \\ \diagdown \end{array}$  required for binding with cholinergic receptor, other onium (Sulfonium & phosphonium) cause less activity
- # other 1°, 2°, 3° amines - ↓ Activity
- # replace  $\text{N}^+ \begin{array}{l} \diagup \text{CH}_3 \\ | \text{CH}_3 \\ \diagdown \text{CH}_3 \end{array}$  by  $\text{SH}_3$  or large alkyl group → ~~↓~~ activity ↑



- # replace more than 1 methyl group on  $-\text{N}^+ \begin{array}{l} \diagup \\ | \\ \diagdown \end{array}$  leads to complete loss of cholinergic activity



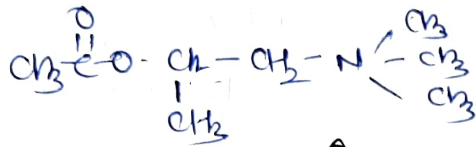
## B. Alkyl chain — CH<sub>2</sub>-CH<sub>2</sub>—

# Alkyl chain maintains the distance b/w ester and 4<sup>o</sup> Ammonium group

# Increase length → ↓ activity

# branching of ethylene — ↑ the potency to M receptor

Methacholine > Ach → potency & resistance to chE



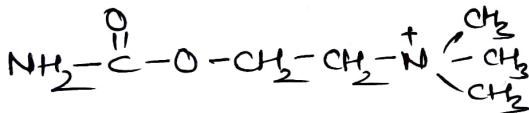
methacholine

3 (+) isomers 240 times more active

## C. Ester Group ? — $\overset{\text{O}}{\parallel}\text{C}-\text{O}$

# Ester group helps in hydrogen bonding formation with the receptor

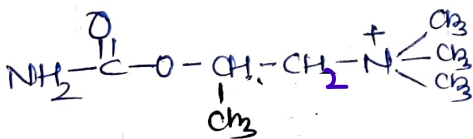
# Acetate ester (CH<sub>3</sub>— $\overset{\text{O}}{\parallel}\text{C}-\text{O}$ ) of Ach replaced by a carbamate ester (NH<sub>2</sub>— $\overset{\text{O}}{\parallel}\text{C}-\text{O}$ ) — enhance activity and resistance to choline esterase and also enhance nicotinic action



Carbachol

→ N > MR

→ used in Glaucoma

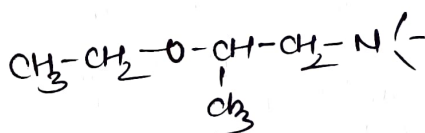


Bethanachol

→ Muscarinic action mainly

→ post-operative atony of GI & Bladder

# Ester group replaced by keton (R-OR) or ether give compound which chemically stable & have ~~some~~ cholinergic action (MR)

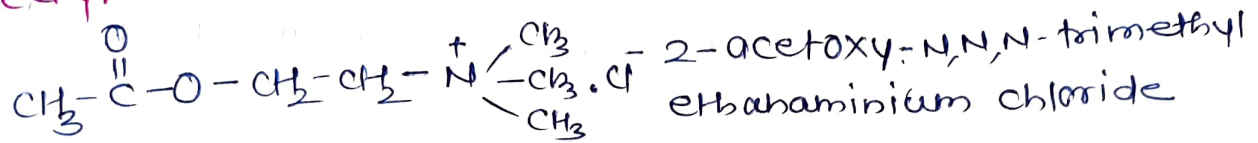


β-methyl choline ethyl ether

# Aromatic Ester — Antagonist

# A. DIRECT ACTING CHOLINERGIC DRUGS

## 1. Acetylcholine



(Trimethyl amino ethyl ester of Acetic acid)

MOA = MIR & NR

Use  $\Rightarrow$  clinically not used, easily metabolised by AChE & BuChE.

Effect  $\Rightarrow$  # miotic action =  $\downarrow$  Post operative rise in IOP

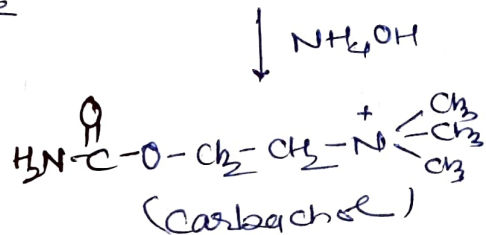
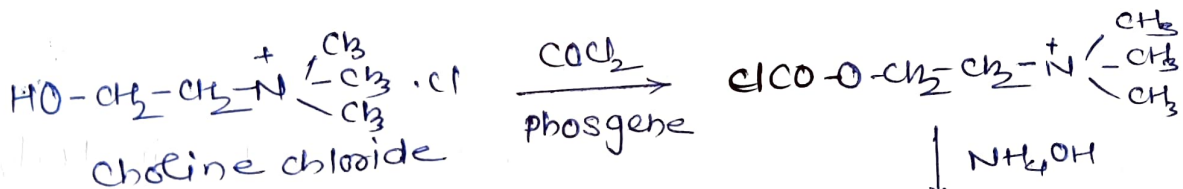
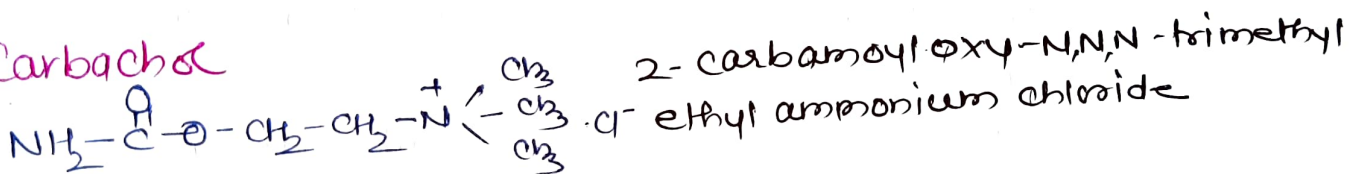
# vasodilation by GPRF

# cardiac depression

#  $\uparrow$  tone of all smooth muscle

#  $\uparrow$  Glandular secretion

## 2. Carbachol

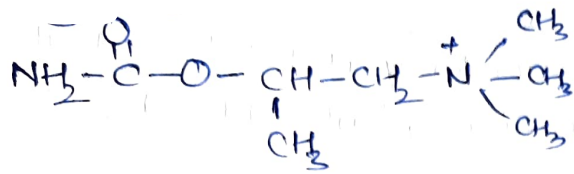


MOA - N & MIR

Uses - # used as alternative to pilocarpine in the management of Glaucoma

# It may be used for treatment of decreased airmotility

### 3. Bethanechol

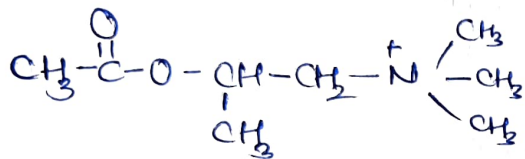


2-carbamoyloxy-1-(N,N,N-trimethyl)propyl ammonium chloride

MOA :- Mainly MR action

Uses - # post operative ileus  
#

### 4. Methacholine



2-acetoxy-N,N,N-trimethylpropan-1-ammonium chloride

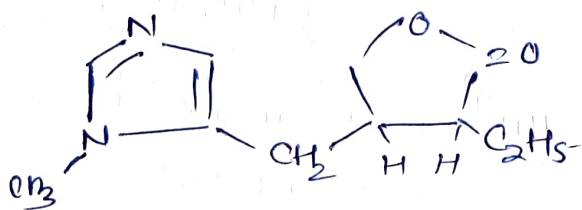
MOA - Main Muscarinic (MR) action

Uses - # Glaucoma

# Used to diagnosis bronchial hyperactivity and asthmatic reaction

# also used in peripheral vascular disease

### 5. Pilocarpine (Pilocarpus microphyllus)



3-ethyl-4-(1-methyl-5-imidazol-2-ylmethyl) tetrahydrofuran-2-one

MOA - MR

Use - # Glaucoma (1-5% solution)

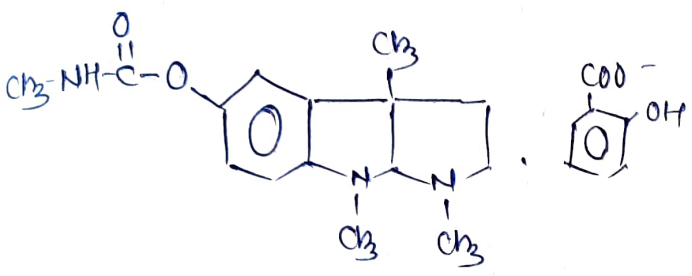
# treatment of dry eyes & dry mouth



# B. CHOLINESTERASE INHIBITORS

## I. Reversible

### 1. Physostigmine Salicylate



- Eserine Alkaloid
- Carbamate salicylate
- "Physostigma venenosum"

1,3,8-trimethyl-2,3,8,9-tetrahydropyrido [2,3-b] -indole  
-5-yl-N-methyl carbamate

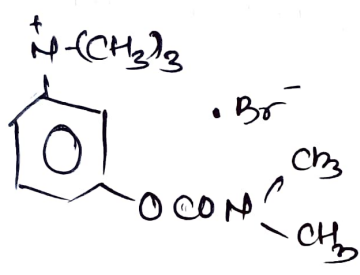
↓ Hydrolysis  
methyl carbamic a +

Eserine  
↓ oxidation  
Rubreserine (Red color compound)

MOA - ↑ the availability of Ach at synaptic junction by inhibiting ChE (Cholinesterase enzyme). MR action mainly.

- Uses - # Glaucoma (0.25 - 0.5% topical)  
# 0.6 - 1.2 mg parenterally - treatment of Atropine or Belladonna poisoning and Tricyclic antidepressants  
# as mitotic action

### 2. Neostigmine bromide

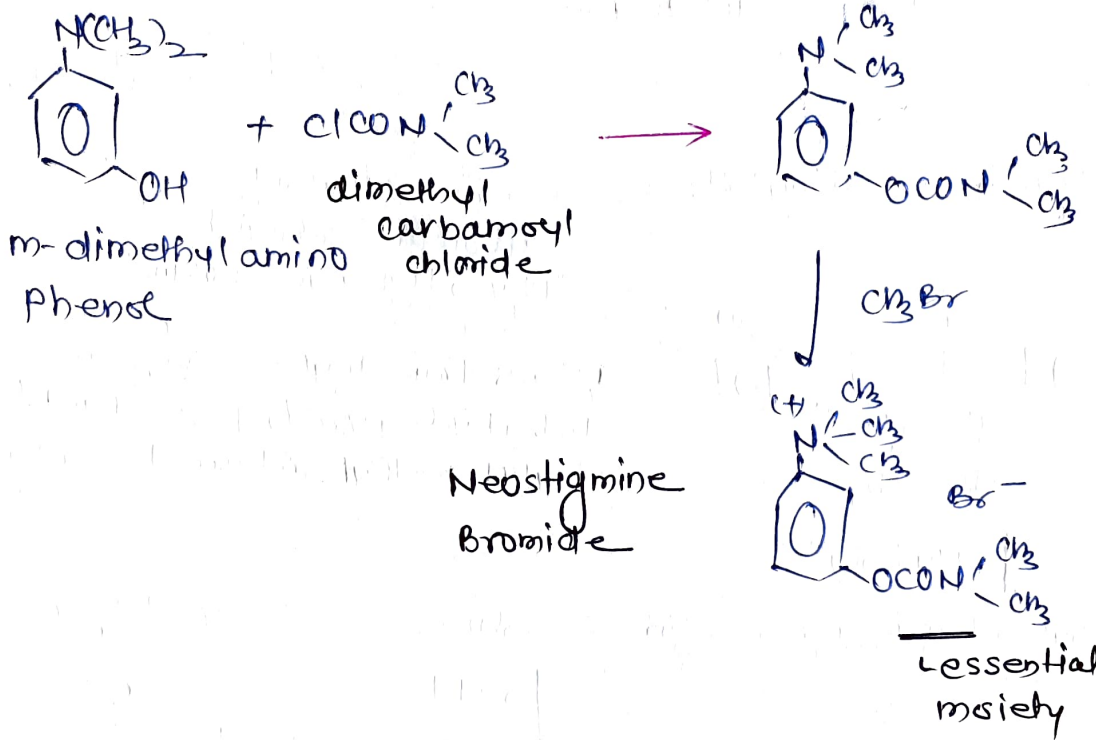


- # 4<sup>o</sup> Ammonium Comp - water soluble
- # Dimethyl carbamoyl ester
- # MOA → Mainly Nm Receptor (Indirectly)

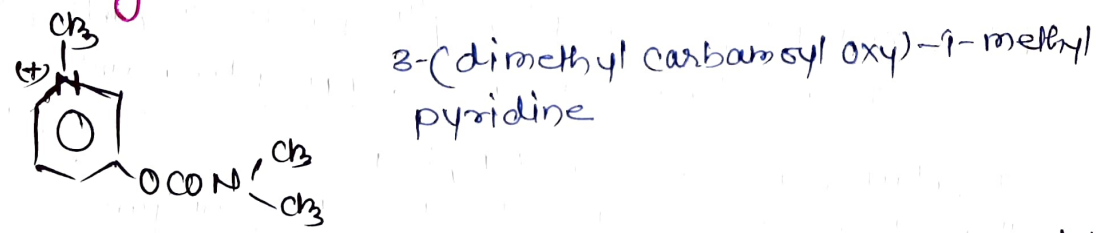
- Uses - # Myasthenia Gravis  
# also used in post operative urinary retention & GI ileus

↳ 3-(dimethyl carbamoyl oxy) trimethyl anilinium bromide  
↳ N,N,N-trimethyl- meta- (dimethyl carbamoyl oxy) benzammonium bromide





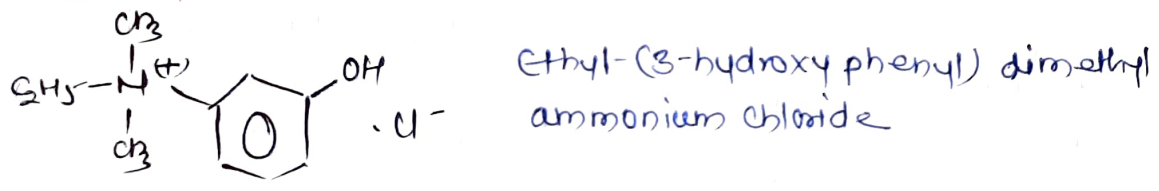
### 3. Pyridostigmine



MOA :- Inhibit cholinesterase enzyme → ↑ ACh → NMJ mainly

- Use -
- # Myasthenia Gravis
  - # prophylaxis against the neuromuscular effects of nerve gas poisoning
  - # It has been used to management of post operative urinary retention

### 4. Edrophonium chloride

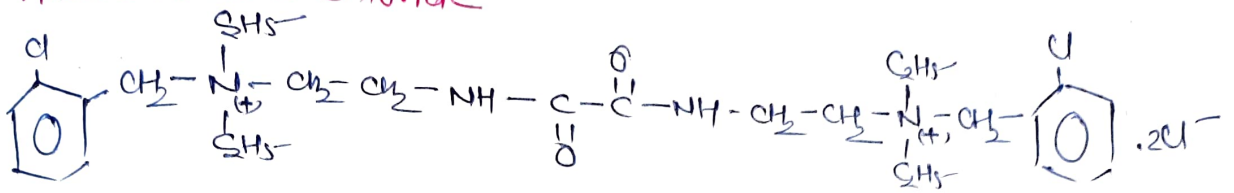


# Lack of carbamoyl group - ↓ potency & duration

MOA - Anticholinesterase → NMJ mainly

- Use =
- # Diagnosis of Myasthenia Gravis
  - # also used in Snake bite

## 5. Ambenonium chloride

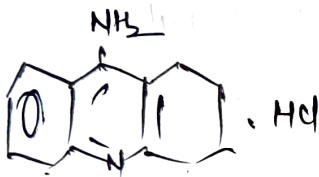


2,2'-[C 1,2-dioxoethane-1,2-diyl] diimino] bis [N-(2-chlorobenzyl)-N,N'-diethyl ethanaminium] chloride

MOA - ↓ ChE - NM/R

Uses - Myasthenia Gravis

## 6. Tacrine hydrochloride



1,2,3,4-tetrahydroacridin-9-amine

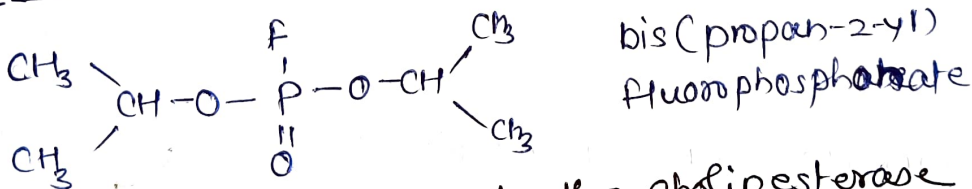
MOA :- ↓ ChE

Uses - # Dementia in Alzheimer's disease

# Analeptic agent to promote mental alertness

## II IRREVERSIBLE

### 1. Isoflurofate



bis(2-propan-2-yl) fluorophosphate

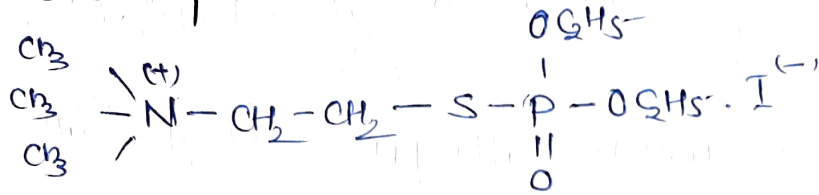
MOA - Irreversible inactivate the cholinesterase enzyme

Uses = # used as ~~mitotic~~ ~~agent~~ ~~mitotic~~ agent in the treatment of glaucoma

# used in civilian laboratory to mimic lethal nerve gas exposure or organophosphate toxicity

# Also shows protease inhibition properties, so useful for additive for protein or cell isolation procedure

## 2. Ecothiophate iodide

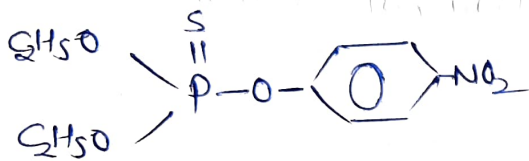


2-(diethoxy phosphoryl sulfanyl)-ethyl-N,N,N-trimethyl azanium iodide

MOA :- ↓ ChE

Uses - # Glaucoma

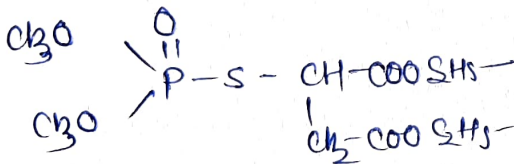
## 3. Parathion



O,O-diethyl-O-(p-nitrophenyl) phosphorothioate

# used as insecticide in farming

## 4. Malathion



Diethyl-2-[(Dimethoxy phosphorothioyl) Sulfanyl] butan-dioate

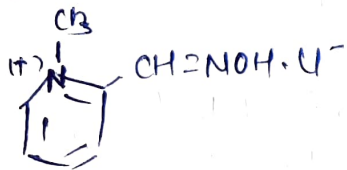
# Insecticide

# treatment of Scabies

# o.s.f. - head lice

## CHOLINESTERASE REACTIVATOR

### Pralidoxime chloride



2-[(hydroxyamino) methyl]-1-methyl Pyridinium chloride

# Reactivate ChE enzyme rapidly and used in the treatment of overdose of Organophosphate poisoning by binding to anionic site of enzyme & displace the phosphate from the Serine residue

# also used in inorganic phosphorus & phosphate poisoning