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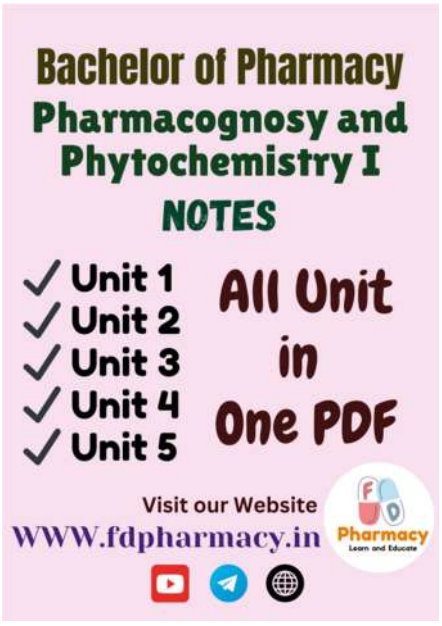
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MEDICINAL CHEMISTRY – I

UNIT 3

TOPIC :

- **Parasympathomimetic agents : SAR of Parasympathomimetic agents**
  Direct acting agents : Acetylcholine, Carbachol, *Bethanechol,* Methacholine, Pilocarpine.
  Indirect acting/ Cholinesterase inhibitors (Reversible & Irreversible): *Physostigmine, Neostigmine*, Pyridostigmine, Edrophonium chloride,
  Tacrine hydrochloride, Ambenonium chloride, Isofluorphate, Echothiophate iodide, Parathione, Malathion.
  Cholinesterase reactivator : Pralidoxime chloride.

Parasympathomimetic Agents (Cholinomimetics)

- Parasympathomimetic agents are drugs that stimulate or mimic the effects of the parasympathetic nervous system (PNS).
  - They act either by directly activating cholinergic receptors (muscarinic/nicotinic)
  - Or by increasing acetylcholine (ACh) levels at synapses.

Classification

A. Direct-Acting Cholinergic Agonists

- These drugs directly bind to and stimulate muscarinic or nicotinic receptors.
- Examples:
  - Acetylcholine
  - Carbachol
  - Bethanechol
  - Methacholine
  - Pilocarpine

B. Indirect-Acting Cholinergic Agonists

- These drugs inhibit acetylcholinesterase (AChE) → ↑ ACh concentration at synapse → prolonged stimulation of cholinergic receptors.

1. Reversible AChE Inhibitors

- Physostigmine
- Neostigmine
- Pyridostigmine
- Edrophonium chloride
- Tacrine hydrochloride
- Ambenonium chloride

2. Irreversible AChE Inhibitors (Organophosphates)

- Form covalent, long-lasting bonds with AChE → enzyme permanently inactivated.
- Require new enzyme synthesis for recovery.
- Examples:
  - Isoflurophate
  - Echothiophate
  - Diisopropyl fluorophosphate (DFP)
  - Malathion
  - Parathion

SAR of Parasympathomimetic Agents (Cholinergic Agonists)

The general structure of acetylcholine and its analogues can be divided into three key regions:

1. Acyl group (–COOR, e.g., acetyl group)
2. Ethylene bridge ($–CH_2–CH_2–$)
3. Quaternary ammonium group ($–N^+R_3$)

1. Substitution on Acyl Group

- Replacement of the acetyl group with carbamate group (–NH–COO–) → increases chemical stability against hydrolysis by acetylcholinesterase.
  - Example: Carbachol, Bethanechol.
- Replacement of ester group by ether linkage → gives chemically more stable and potent compounds.

2. Substitution on Ethylene Bridge

- Chain length modification:
  - Increasing the distance between quaternary nitrogen and acyl group (beyond 2 carbons) → decreases activity.
  - Optimal chain length = 2 carbons.
- β-Substitution (branching at β-carbon):
  - Leads to decreased nicotinic activity but increases muscarinic selectivity.
  - Example: Bethanechol (more muscarinic selective).

3. Substitution on Quaternary Ammonium Group

- Quaternary nitrogen (N^+R_3) is essential for cholinergic activity.
- Replacing with primary, secondary, or tertiary amines → results in loss of activity.
- Substituting more than one methyl group (on the trimethylammonium moiety) → causes marked loss of activity.
- At least one methyl group on quaternary nitrogen is essential for activity.

Direct-Acting Parasympathomimetic Agents (Cholinergic Agonists)

- Direct-acting parasympathomimetic agents are drugs that directly bind to cholinergic receptors (muscarinic or nicotinic) and mimic the effects of acetylcholine.

Mechanism of Action (MOA)

- These drugs bind directly to muscarinic (M1–M5) or nicotinic (NN, NM) receptors in organs such as the heart, lungs, eye, gastrointestinal tract, bladder, and glands.
- Once bound, they trigger intracellular signaling pathways that cause:
  - Smooth muscle contraction (bronchi, GIT, bladder).
  - Increased glandular secretion (saliva, sweat, tears).
  - Decreased heart rate (bradycardia).
  - Pupil constriction (miosis) and accommodation for near vision.

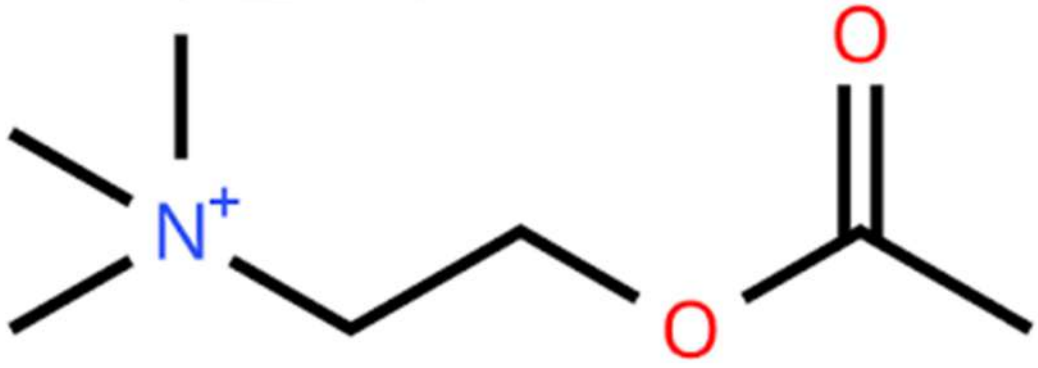
Examples

1. Acetylcholine
2. Carbachol
3. Bethanechol
4. Methacholine
5. Pilocarpine

Acetylcholine (ACh)

Structure

- A natural neurotransmitter of the parasympathetic nervous system.
- Chemically, it is an ester of acetic acid and choline.
- Structure:
  - Quaternary ammonium group ($-N^+(CH_3)_3$) → essential for activity.
  - Ethylene bridge ($-CH_2-CH_2-$).
  - Acetyl ester linkage ($-O-CO-CH_3$).
- Highly polar and hydrophilic, so it does not cross the blood–brain barrier.



Mechanism of Action (MOA)

- Acts as the prototype cholinergic neurotransmitter.
- Binds to:
  - Muscarinic receptors (M1–M5) → smooth muscle contraction, glandular secretion, decreased heart rate, pupil constriction.
  - Nicotinic receptors (NN, NM) → stimulation of autonomic ganglia & skeletal muscle contraction.
- Rapidly inactivated by acetylcholinesterase (AChE) in the synaptic cleft → very short duration of action.

Uses

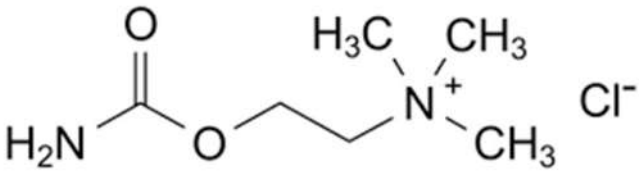
- Very limited clinical use due to rapid hydrolysis.
- Intraocular use:
  - Instilled during eye surgery to cause miosis (pupil constriction).
- Occasionally used in ophthalmology for short-term reduction of intraocular pressure.

Carbachol (Carbamylcholine)

Structure

- Synthetic carbamate ester of choline.
- Similar to acetylcholine but the acetyl group is replaced by a carbamyl group → makes it resistant to hydrolysis by acetylcholinesterase (AChE).
- Belongs to the group of direct-acting parasympathomimetic agents.

Carbachol



Mechanism of Action (MOA)

- Binds to both muscarinic and nicotinic cholinergic receptors.
- Causes:
  - Miosis (pupil constriction).
  - Increased aqueous humor outflow → lowers intraocular pressure.
  - Smooth muscle contraction in GIT and bladder (rarely used systemically).
- Prolonged action compared to acetylcholine, because it is not rapidly hydrolyzed by AChE.

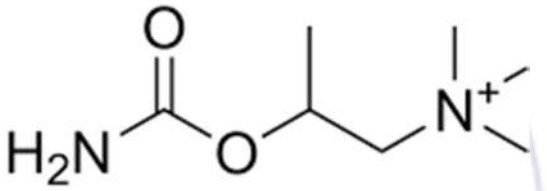
Uses

- Ophthalmology:
  - Treatment of glaucoma (reduces intraocular pressure).
  - Produces miosis during intraocular surgery.
- Rarely used systemically due to strong nicotinic effects (ganglionic stimulation, unwanted side effects).

Bethanechol

Structure

- Synthetic choline ester.
- Structurally similar to acetylcholine, but:
  - Has a carbamate group instead of acetyl → resistant to hydrolysis by acetylcholinesterase (AChE).
  - Has a β-methyl group substitution → increases selectivity for muscarinic receptors and reduces nicotinic activity.



Mechanism of Action (MOA)

- Selective muscarinic receptor agonist (little or no action on nicotinic receptors).
- Produces:
  - Contraction of bladder detrusor muscle → helps in urination.
  - Increased GI motility and secretion.
  - Miosis and increased aqueous humor outflow (mild ocular effect, not preferred for glaucoma).

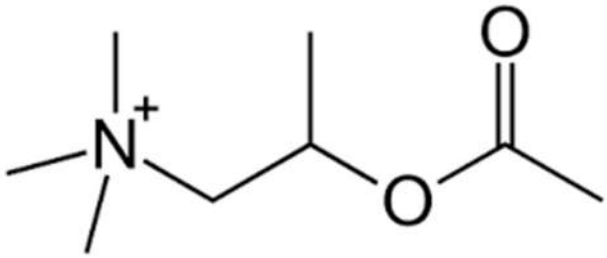
Uses

- Urinary retention (non-obstructive, postoperative, postpartum).
- Neurogenic bladder (atony of bladder).
- Postoperative ileus (to stimulate bowel movement).

Methacholine

Structure

- Synthetic choline ester.
- Similar to acetylcholine, but with:
  - A β-methyl substitution on the ethylene group.
  - This substitution → increases muscarinic selectivity and decreases nicotinic activity.
- Rapidly hydrolyzed by acetylcholinesterase → short duration of action.



Mechanism of Action (MOA)

- Direct-acting muscarinic receptor agonist (selective).
- Binds to muscarinic receptors → causes:
  - Bronchoconstriction.
  - Increased secretions (salivary, gastric, bronchial).
  - Mild cardiac effects (bradycardia).
- Nicotinic action negligible.

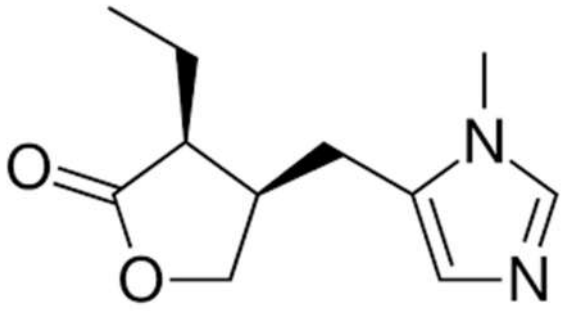
Uses

- Diagnosis of bronchial hyperreactivity / asthma (Methacholine Challenge Test).
  - Patient inhales aerosol → bronchoconstriction observed → confirms asthma.
- Rarely used therapeutically because of bronchoconstriction risk.

Pilocarpine

Structure

- A natural alkaloid obtained from the leaves of *Pilocarpus jaborandi*.
- Belongs to the imidazole alkaloid group.
- Non-selective muscarinic receptor agonist (direct acting).
- Unlike choline esters (ACh, Carbachol, Bethanechol, Methacholine), it is not an ester and is not hydrolyzed by acetylcholinesterase → longer duration of action.



Mechanism of Action (MOA)

- Binds directly to muscarinic receptors (M_1–M_3).
- Produces:
  - Contraction of iris sphincter muscle → miosis (pupil constriction).
  - Contraction of ciliary muscle → opens trabecular meshwork → ↑ outflow of aqueous humor → ↓ intraocular pressure.
  - Stimulation of exocrine glands → ↑ secretion of saliva, sweat, tears.
- Little effect on nicotinic receptors.

Uses

- Ophthalmic uses:
  - Treatment of glaucoma (reduces intraocular pressure).
  - Produces miosis during ocular surgery.
- Systemic uses:
  - Treatment of xerostomia (dry mouth) → in Sjögren's syndrome or after radiotherapy.
  - Stimulates salivary and sweat glands.

Indirect Acting Parasympathomimetic Agents (Anticholinesterases)

- These are drugs that inhibit acetylcholinesterase (AChE), the enzyme responsible for breaking down acetylcholine (ACh) in the synaptic cleft.
- By inhibiting AChE → increase the concentration and duration of action of ACh at cholinergic receptors.
- Enhance parasympathetic activity indirectly.

Mechanism of Action (MOA)

1. Normally: ACh is released → binds receptor → rapidly hydrolyzed by AChE.
2. Anticholinesterases block AChE → ACh accumulates in synapse.
3. Prolonged stimulation of muscarinic (smooth muscle, glands, heart) and nicotinic (neuromuscular junction, autonomic ganglia) receptors.

→ **Results in:**

- ↑ Secretions (saliva, sweat, tears, bronchial).
- ↑ Smooth muscle contraction (bronchoconstriction, GIT motility).
- ↓ Heart rate.
- Skeletal muscle stimulation (twitching, then paralysis at high dose).

Classification

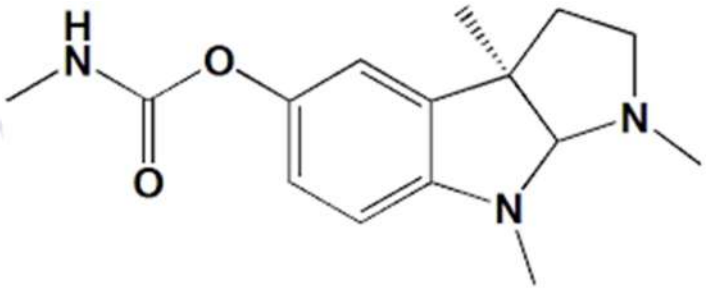
A. Reversible Anticholinesterases

- Bind reversibly to AChE.
- Duration: minutes to hours.
- Examples:
  - Physostigmine
  - Neostigmine
  - Pyridostigmine
  - Edrophonium chloride
  - Tacrine hydrochloride
  - Ambenonium chloride

Physostigmine

Structure

- A natural alkaloid obtained from the Calabar bean (*Physostigma venenosum*).
- Belongs to reversible carbamate anticholinesterases.
- Tertiary amine → lipid soluble, can cross the blood–brain barrier (BBB) (unlike neostigmine).



Physostigmine

Mechanism of Action (MOA)

- Inhibits acetylcholinesterase reversibly.
- Prevents breakdown of acetylcholine (ACh) → ↑ ACh at synaptic cleft.
- Enhances both:
  - Muscarinic effects → miosis, salivation, bradycardia, bronchoconstriction, ↑ GIT motility.
  - Nicotinic effects → stimulation of skeletal muscle (at neuromuscular junction).
- Because it crosses BBB → also enhances central cholinergic activity.

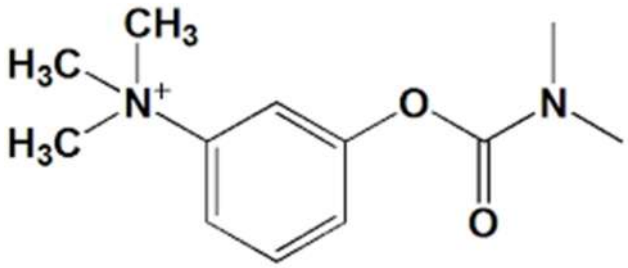
Uses

- Ophthalmic:
  - Treatment of glaucoma (reduces intraocular pressure by causing miosis and ↑ aqueous humor drainage).
- Neurological:
  - Treatment of anticholinergic drug poisoning (e.g., atropine, scopolamine overdose) because it crosses BBB.
- Alzheimer's disease:
  - Sometimes used to improve memory (not common now, replaced by safer drugs).

Neostigmine

Structure

- A synthetic carbamate derivative.
- Belongs to reversible anticholinesterases.
- Contains a quaternary ammonium group → polar, water-soluble, cannot cross BBB.
- More stable than physostigmine.



Neostigmine

Mechanism of Action (MOA)

- Reversibly inhibits acetylcholinesterase (AChE) → prevents breakdown of acetylcholine → ↑ ACh at cholinergic synapses.
- Enhances muscarinic (smooth muscle, glands, heart) and nicotinic (neuromuscular junction) actions.
- Additionally, it directly stimulates nicotinic receptors at neuromuscular junction → improves muscle contraction.
- Does not act on CNS (cannot cross BBB).

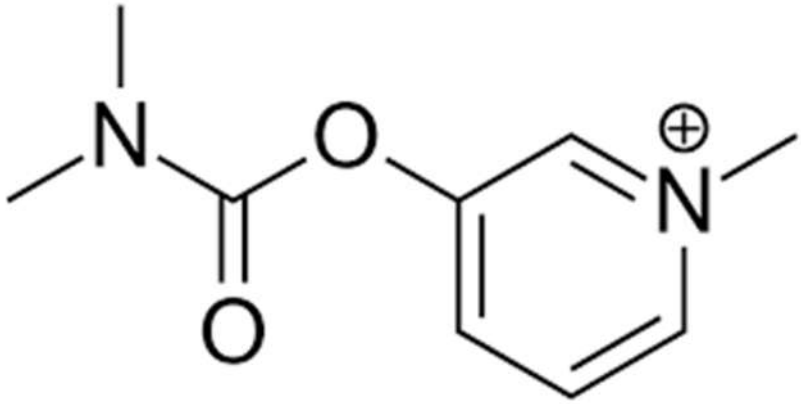
Uses

- Myasthenia gravis → improves muscle strength by enhancing neuromuscular transmission.
- Postoperative paralytic ileus & urinary retention → stimulates smooth muscle contraction.
- Reversal of non-depolarizing neuromuscular blocker (e.g., tubocurarine) after surgery.
- Glaucoma (rarely used now).

Pyridostigmine

Structure

- A synthetic carbamate derivative.
- Belongs to reversible anticholinesterases.
- Contains a quaternary ammonium group → water-soluble, does not cross BBB.
- Structurally similar to neostigmine, but with a pyridine ring → increases duration of action.



Mechanism of Action (MOA)

- Reversibly inhibits acetylcholinesterase (AChE) → accumulation of ACh at synapses.
- Enhances muscarinic actions (smooth muscle contraction, glandular secretion, bradycardia) and nicotinic actions (skeletal muscle contraction at neuromuscular junction).
- Compared to neostigmine: longer duration of action (3–6 hours vs. 2–4 hours).

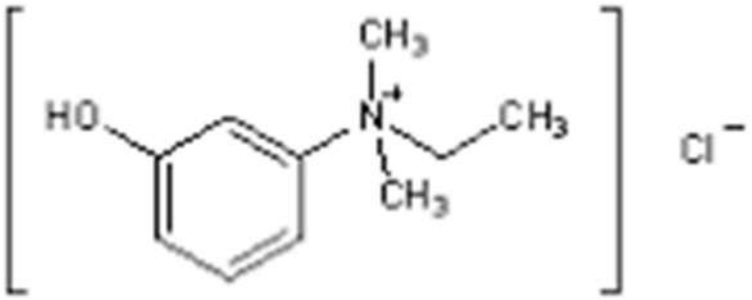
Uses

- Myasthenia gravis (drug of choice for long-term management) → improves muscle strength.
- Prophylaxis against nerve gas poisoning (military use).
- Reversal of non-depolarizing neuromuscular blockers after surgery.
- Treatment of paralytic ileus & urinary retention (less common).

Edrophonium Chloride

Structure

- A synthetic quaternary ammonium compound.
- Belongs to reversible anticholinesterases.
- Unlike neostigmine/pyridostigmine, it is not a carbamate → it binds only non-covalently (via electrostatic and hydrogen bonds) to acetylcholinesterase.
- Highly polar → does not cross BBB.



Mechanism of Action (MOA)

- Reversibly inhibits acetylcholinesterase (AChE) → prevents breakdown of ACh.
- Rapid onset and very short duration of action (5–15 minutes).
- Enhances both muscarinic and nicotinic effects.
- Because of short action → useful only for diagnostic and not therapeutic purposes.

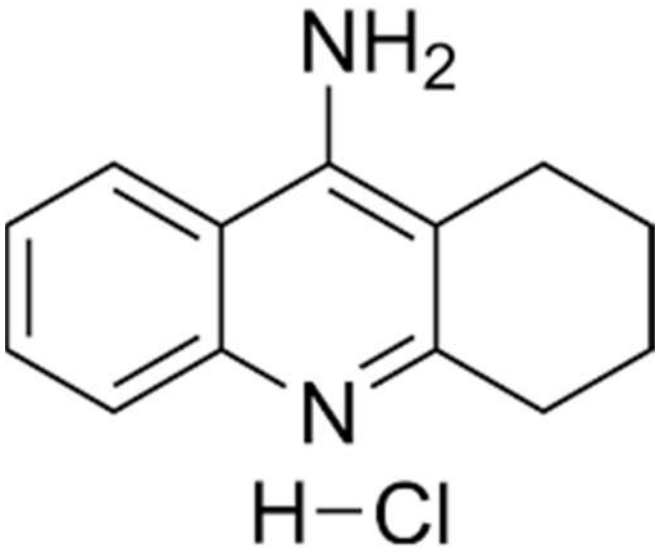
Uses

- Diagnostic test for myasthenia gravis (*Tensilon test*):
  - Increases muscle strength temporarily in MG patients.
- Differentiate between myasthenic crisis and cholinergic crisis:
  - Improvement after injection → myasthenic crisis.
  - Worsening of symptoms → cholinergic crisis.
- Reversal of non-depolarizing neuromuscular blockers (short procedures).

Tacrine Hydrochloride

Structure

- A synthetic acridine derivative.
- Belongs to centrally acting reversible anticholinesterases.
- Being a lipophilic tertiary amine, it crosses the blood–brain barrier (BBB).
- First drug developed for Alzheimer's disease.



Mechanism of Action (MOA)

- Reversibly inhibits acetylcholinesterase (AChE) in the CNS.
- Leads to increased acetylcholine levels in the brain → improves cholinergic neurotransmission.
- Provides symptomatic relief in Alzheimer's disease (improved memory, cognition).
- Also has some action as a muscarinic receptor agonist.

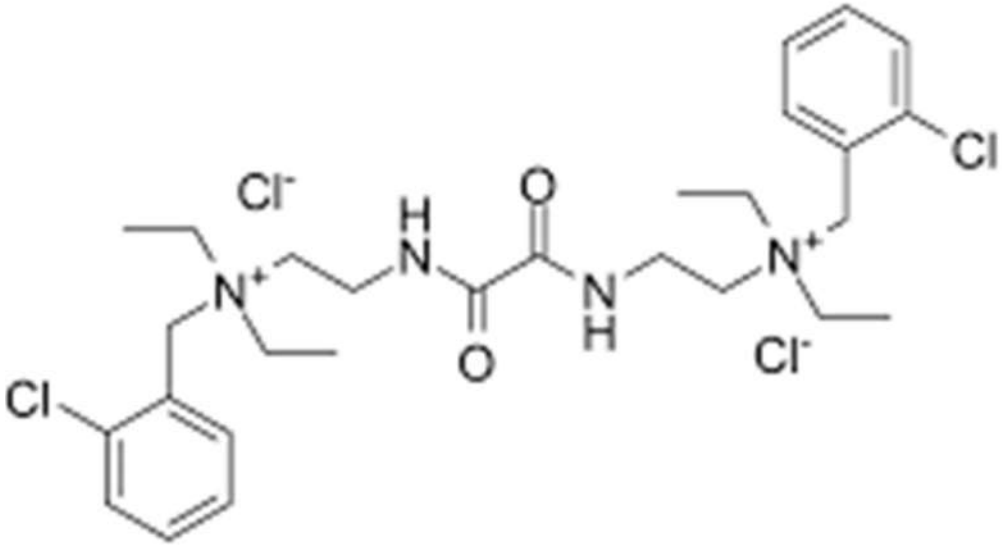
Uses

- Alzheimer's disease (first approved drug, now rarely used due to toxicity).
- Mild improvement in memory, attention, and learning ability.

Ambenonium Chloride

Structure

- A synthetic reversible anticholinesterase.
- Belongs to carbamate derivatives.
- Contains a quaternary ammonium group → water-soluble, cannot cross BBB.
- Structurally related to neostigmine/pyridostigmine but has two quaternary ammonium centers → higher potency.



Mechanism of Action (MOA)

- Reversibly inhibits acetylcholinesterase (AChE) at neuromuscular junction.
- Prevents hydrolysis of acetylcholine (ACh) → ↑ ACh concentration.
- Enhances stimulation of nicotinic receptors in skeletal muscle → improves neuromuscular transmission.
- More potent and longer-acting than neostigmine.

Uses

- Myasthenia gravis → improves muscle strength (used as an alternative when neostigmine/pyridostigmine not suitable).
- Reversal of non-depolarizing neuromuscular blockers (occasionally).
- Rarely used now due to availability of safer agents.

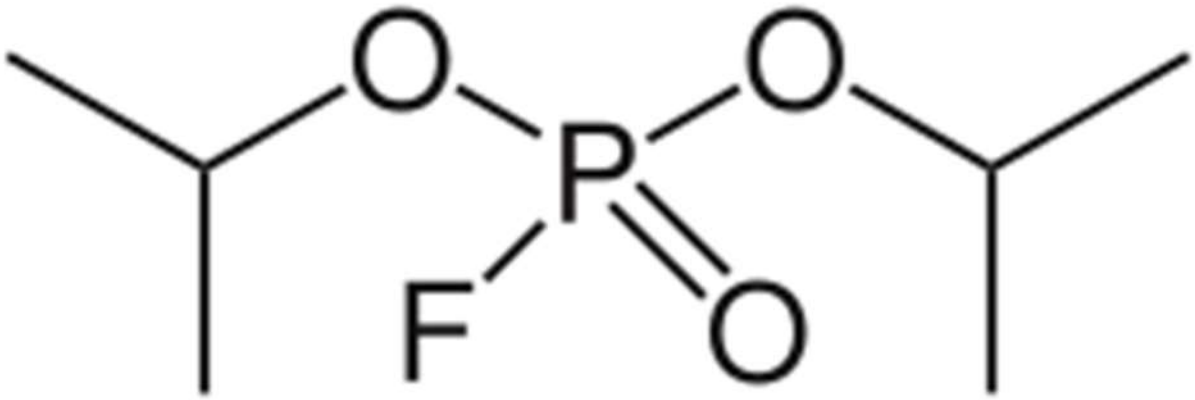
B. Irreversible Anticholinesterases

- Bind **irreversibly** (covalently) to AChE.
- Long duration: **days to weeks**.
- Mostly organophosphates.
- Examples:
  - Isofluorophate
  - Echothiophate
  - Malathion
  - Parathion

Isofluorophate (DFP – Diisopropyl fluorophosphate)

Structure

- Organophosphate compound.
- Contains a fluorophosphate ester group.
- Lipid soluble → can cross biological membranes and even blood–brain barrier (BBB).



Mechanism of Action (MOA)

- Irreversibly inhibits acetylcholinesterase (AChE) by phosphorylating its active site serine residue.
- This prevents breakdown of acetylcholine (ACh) → leads to continuous cholinergic stimulation.
- Effect is long-lasting (days to weeks) until new enzyme is synthesized.

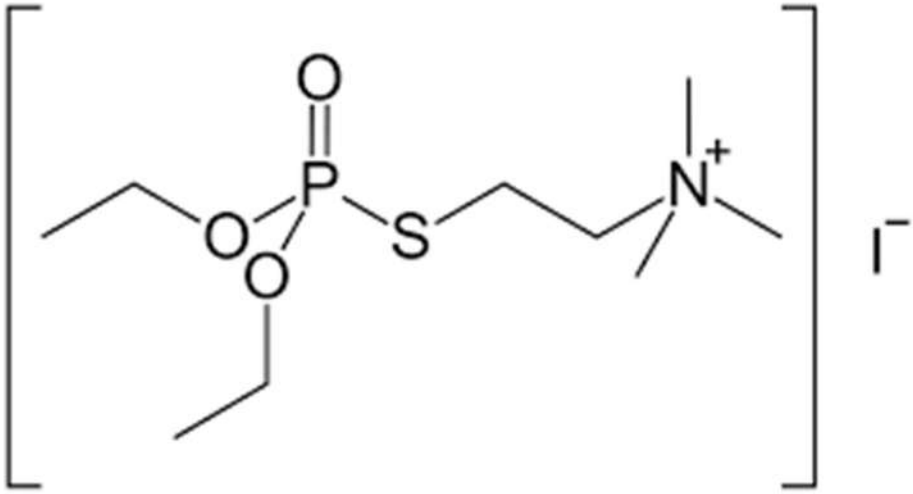
Uses

- Formerly used in chronic glaucoma (produces long-lasting miosis and ↓ intraocular pressure).
- Sometimes used in esotropia (strabismus) to induce prolonged accommodation.
- Rarely used today because of toxicity and availability of safer alternatives (like pilocarpine).

Echothiophate Iodide

Structure

- Organophosphate compound.
- Contains a phosphate ester group.
- Quaternary ammonium salt → water-soluble, does not readily cross BBB.



Mechanism of Action (MOA)

- Irreversibly inhibits acetylcholinesterase (AChE) → phosphorylates the serine hydroxyl group at the enzyme's active site.
- Prevents breakdown of acetylcholine (ACh) → leads to prolonged muscarinic stimulation.
- Mainly acts on peripheral cholinergic sites due to quaternary ammonium structure.

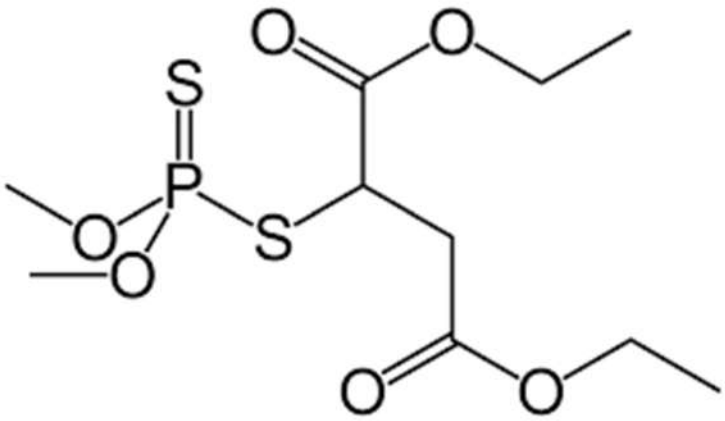
Uses

- Chronic glaucoma → reduces intraocular pressure via prolonged miosis.
- Strabismus (esotropia) → produces long-lasting contraction of the ciliary muscle.
- Rarely used systemically due to risk of cholinergic toxicity.

Malathion

Structure

- Organophosphate insecticide.
- Contains a phosphate ester group.
- Lipid-soluble → can penetrate biological membranes.
- Not used therapeutically in humans (except topical pediculicide formulations).



Mechanism of Action (MOA)

- Irreversibly inhibits acetylcholinesterase (AChE) by phosphorylating the active site serine residue.
- Prevents breakdown of acetylcholine (ACh) → accumulation at synapses.
- Continuous stimulation of muscarinic, nicotinic, and CNS receptors → cholinergic toxicity.
- Effects are long-lasting, until new enzyme is synthesized.

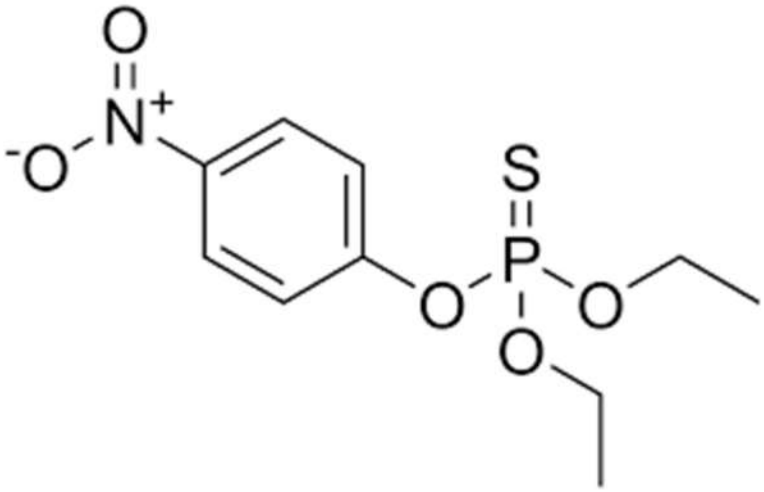
Uses

- Insecticide (agriculture and household use).
- Topical treatment of head lice (pediculicide) in humans.
- No systemic therapeutic use due to toxicity.

Parathion

Structure

- Organophosphate compound.
- Contains a phosphate ester with P=S bond (thionophosphate).
- Lipid-soluble → easily absorbed through skin, lungs, and GI tract.
- Highly toxic to humans.



Mechanism of Action (MOA)

- Irreversibly inhibits acetylcholinesterase (AChE) by phosphorylating the serine hydroxyl in the enzyme's active site.
- Accumulation of acetylcholine (ACh) at synapses → continuous stimulation of muscarinic, nicotinic, and CNS receptors.
- Long-lasting effects until new enzyme is synthesized.

Uses

- Insecticide in agriculture (widely used in past; restricted in many countries now).
- No therapeutic use in humans due to high toxicity.

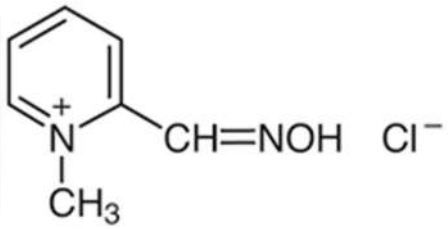
Cholinesterase Reactivators (Antidotes for Organophosphate Poisoning)

- Cholinesterase reactivators are drugs that restore the activity of acetylcholinesterase (AChE) after it has been inhibited by organophosphates or carbamates.
- Used primarily as antidotes in poisoning caused by pesticides (organophosphates) or nerve agents.

Pralidoxime Chloride (2-PAM)

Structure

- A quaternary ammonium oxime.
- Water-soluble → acts peripherally, does not cross BBB effectively.
- Contains an oxime (-C=NOH) group that reacts with phosphorylated AChE.



Mechanism of Action (MOA)

- Organophosphates phosphorylate acetylcholinesterase (AChE) → inactivation.
- Pralidoxime binds to the phosphorylated AChE → removes the phosphate group → restores enzyme activity.
- Effective only before "aging" of the enzyme occurs (irreversible bond formation after aging).
- Primarily reverses nicotinic effects (muscle weakness, paralysis).

Uses

- Antidote for organophosphate poisoning (pesticides, nerve agents).
- Used in combination with atropine:
  - Atropine → blocks muscarinic overstimulation.
  - Pralidoxime → restores AChE function at neuromuscular junction.
- Emergency treatment intravenously or intramuscularly.