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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.

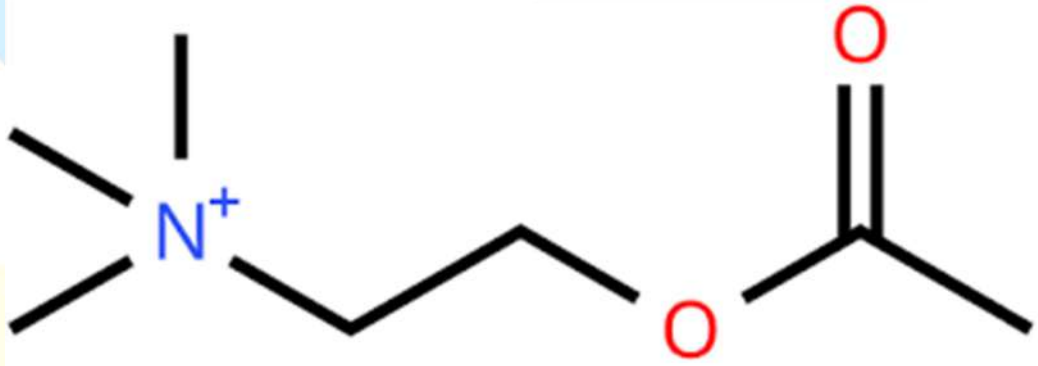
Examples

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).

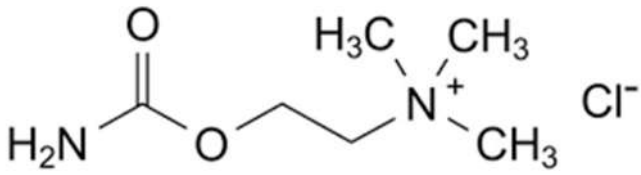
- **Occasionally used in ophthalmology** for short-term reduction of intraocular pressure.

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**:

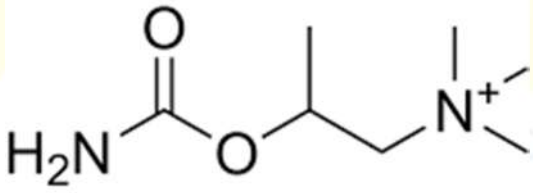
- Treatment of **glaucoma** (reduces intraocular pressure).
- Produces **miosis** during intraocular surgery.

- 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).

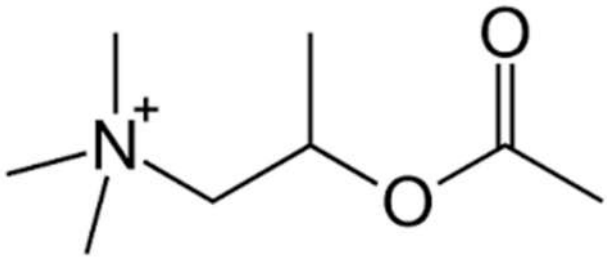
Uses

- **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.

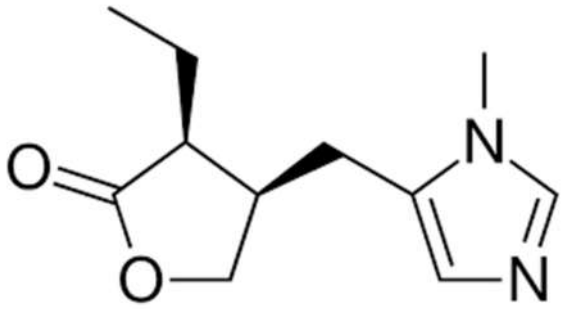
Uses

- **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 (M1–M3)**.
- 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

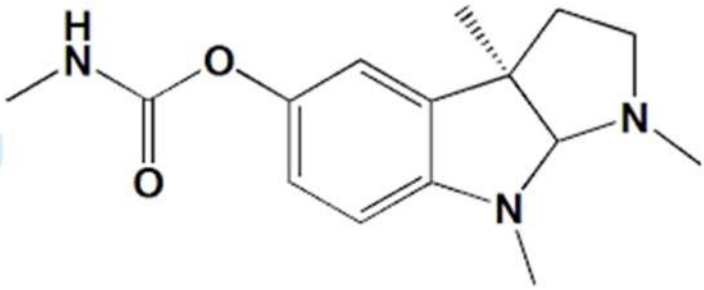
A. Reversible Anticholinesterases

- 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

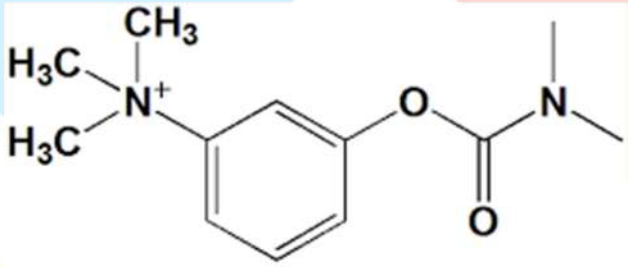
- **Ophthalmic**:
  - Treatment of **glaucoma** (reduces intraocular pressure by causing miosis and ↑ aqueous humor drainage).
- **Neurological**:
  - Treatment of **anticholinergic drug poisoning** (e.g., atropine, scopolamine overdose) because it crosses BBB.
- **Alzheimer's disease**:

- 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

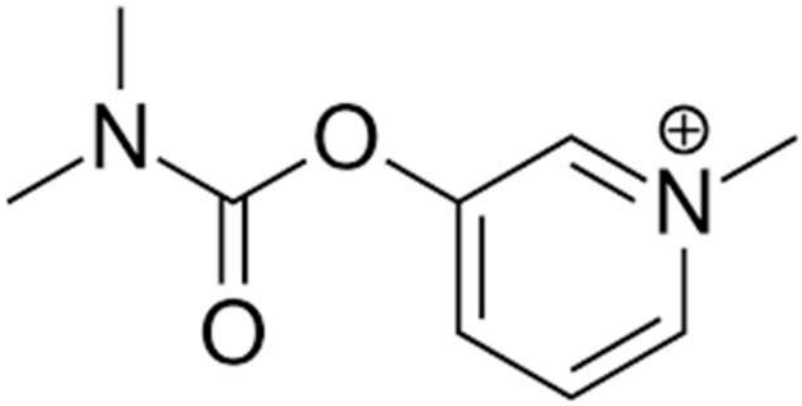
- **Myasthenia gravis** → improves muscle strength by enhancing neuromuscular transmission.
- **Postoperative paralytic ileus & urinary retention** → stimulates smooth muscle contraction.

- **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

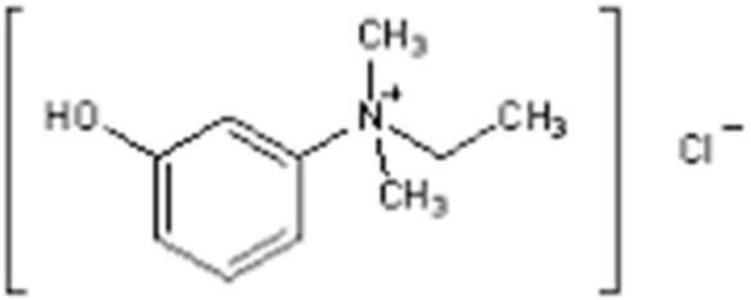
- **Myasthenia gravis (drug of choice for long-term management)** → improves muscle strength.

- **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**.

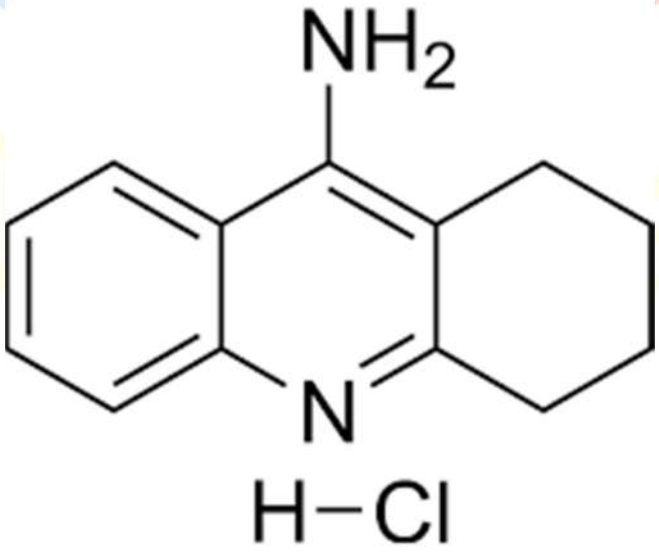
- Improvement after injection → myasthenic crisis.
- Worsening of symptoms → cholinergic crisis.

- **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**.

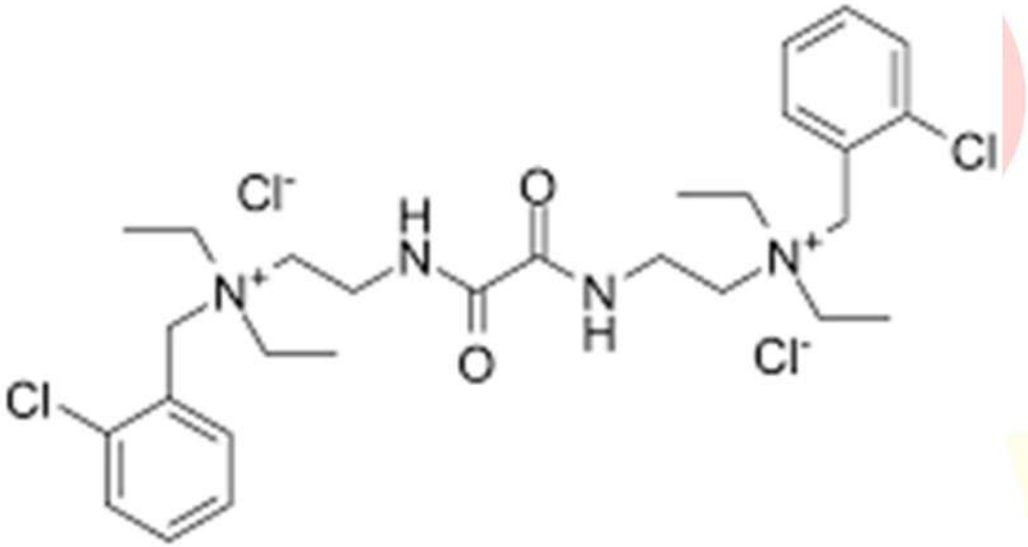
Uses

- **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.

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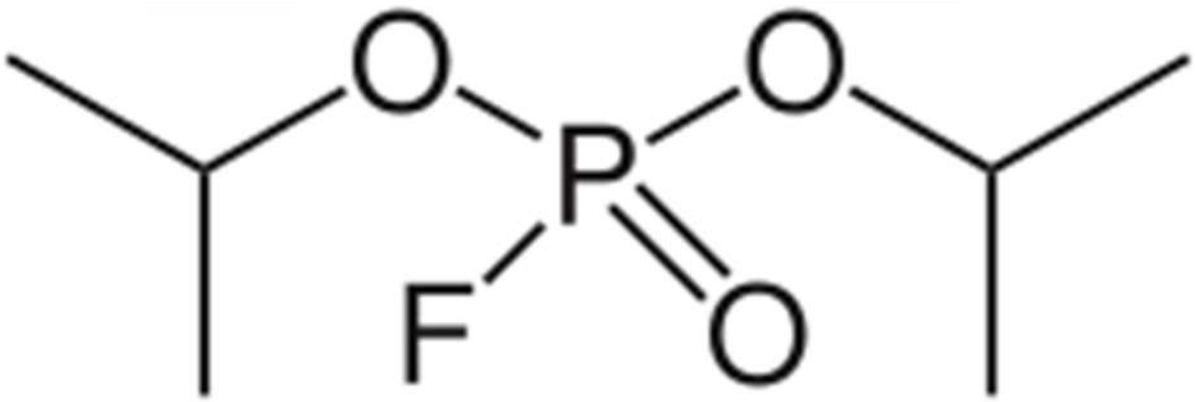
B. Irreversible Anticholinesterases

- 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

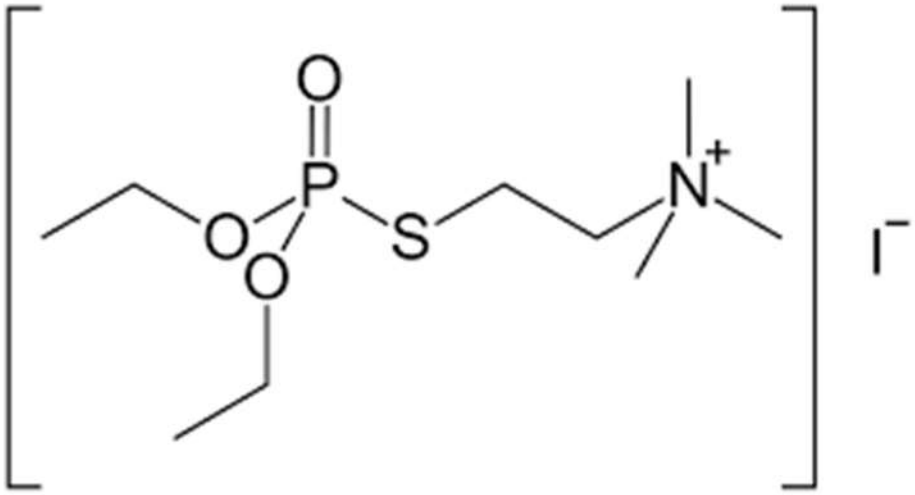
- Formerly used in **chronic glaucoma** (produces long-lasting miosis and ↓ intraocular pressure).
- Sometimes used in **esotropia (strabismus)** to induce prolonged accommodation.

- 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

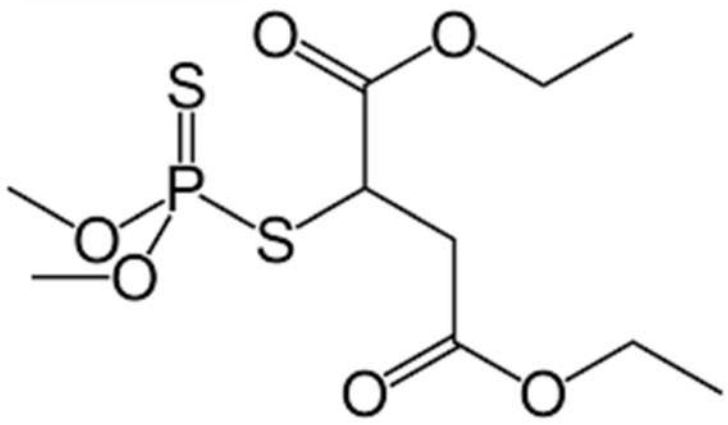
- **Chronic glaucoma** → reduces intraocular pressure via **prolonged miosis**.

- **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.

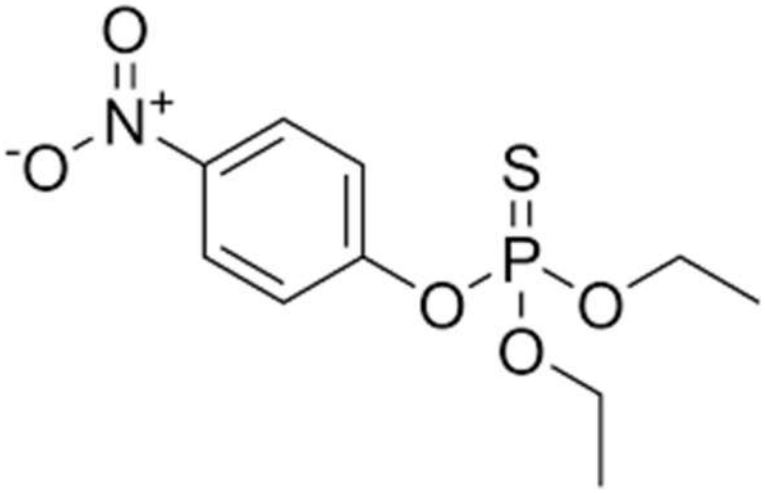
Uses

- **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.

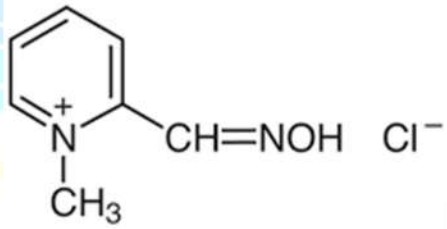
Cholinesterase Reactivators (Antidotes for Organophosphate Poisoning)

- **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**.