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MEDICINAL CHEMISTRY – I

UNIT 3

TOPIC :

- **Cholinergic Blocking agents : SAR of cholinolytic agents**
  Solanaceous alkaloids and analogues : Atropine sulphate, Hyoscyamine sulphate, Scopolamine hydrobromide, Homatropine hydrobromide, Ipratropium bromide.
  Synthetic cholinergic blocking agents : *Tropicamide, Cyclopentolate hydrochloride, Clidinium Glycopyrrolate, bromide, Dicyclomine Methantheline bromide, hydrochloride*, Propantheline bromide, Benztropine mesylate, Orphenadrine citrate, Biperidine hydrochloride, Procyclidine hydrochloride*, Tridihexethyl chloride, Isopropamide iodide,
  Ethopropazine hydrochloride.

Cholinergic Blocking Agents (Anticholinergics / Cholinolytics / Parasympatholytics)

- Drugs or agents that **inhibit the effect of acetylcholine (ACh)** at cholinergic receptors.
- Also known as:
  - **Cholinolytic agents**
  - **Anticholinergic agents**
  - **Cholinergic antagonists**
  - **Parasympatholytic agents**
  - **Antimuscarinic agents**
- **Effect:** Block muscarinic and/or nicotinic receptors → reduce parasympathetic activity.

Classification

A. Natural / Solanaceous Alkaloids

- **Atropine sulfate**
- **Hyoscyamine sulfate**
- **Scopolamine hydrobromide**
- **Homatropine hydrobromide**
- **Ipratropium bromide** (semisynthetic derivative)

B. Synthetic Cholinergic Blockers

- **Tropicamide**
- **Cyclopentolate hydrochloride**
- **Clidinium bromide**
- **Dicyclomine hydrochloride**
- **Glycopyrrolate**
- **Methantheline bromide**
- **Propantheline bromide**
- **Benztropine mesylate**
- **Orphenadrine citrate**
- **Biperiden hydrochloride**
- **Procyclidine hydrochloride**

- **Trihexyphenidyl**
- **Ethopropazine hydrochloride**

Structure-Activity Relationship (SAR)

General Structure

- Composed of:
  - **Carbon chain** linking the functional groups
  - **Alkyl group substitutions**
  - **Quaternary or tertiary ammonium center**
  - **Heterocyclic or aromatic ring**

Substitution on Alkyl Group / Carbon Chain

- **Alkyl substitutions:**
  - Substituent **R or R'** must be **carboxylic or heterocyclic** for maximal antagonist activity.
  - Replacing heterocyclic ring with aromatic ring → **decreases activity**.
  - Different substituents on the ring → can increase potency.
- **Carbon chain length:**
  - Optimal **2 methylene units** in the chain for maximal activity.
  - Can be attached to **tertiary or quaternary amine**.
  - Nature of X group affects **physicochemical properties**, not receptor binding.

Ammonium Group

- **Quaternary ammonium compounds:** Most potent **peripheral anticholinergic activity**.
- Replacing quaternary with **tertiary or secondary amine → decreases potency**.
- Quaternary compounds → **limited CNS penetration** (useful for peripheral effects).

Solanaceous Alkaloids

- Naturally occurring **anticholinergic compounds** derived from **Solanaceae family plants** (e.g., *Atropa belladonna*, *Datura stramonium*, *Hyoscyamus niger*).
- Act as **competitive antagonists at muscarinic receptors (M1, M2, M3, etc.)** in the parasympathetic nervous system.

Mechanism of Action

- **Competitive inhibition of acetylcholine** at muscarinic receptors → blocks parasympathetic activity.
- Leads to **reduced parasympathetic tone** and unopposed sympathetic effects.

Pharmacological Effects

- **Eyes:** Pupillary dilation (**mydriasis**), relaxation of ciliary muscles → cycloplegia.
- **Heart:** Increased heart rate (**tachycardia**).
- **Glands:** Decreased salivation, sweating, lacrimation.
- **Smooth muscles:** Relaxation of bronchi, gut, bladder → decreased motility.
- **CNS (for lipophilic alkaloids like scopolamine):** Sedation, antiemetic, antispasmodic effects.

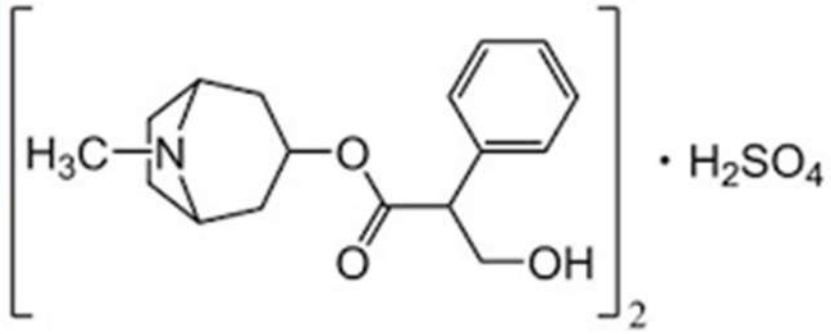
Examples

- **Atropine sulfate**
- **Hyoscyamine sulfate**
- **Scopolamine hydrobromide**
- **Homatropine hydrobromide**
- **Ipratropium bromide**

Atropine Sulfate

Source & Structure

- **Natural alkaloid** derived from *Atropa belladonna* and *Datura stramonium*.
- **Tertiary amine** → lipid-soluble → crosses **blood–brain barrier (BBB)**.
- **Sulfate salt** → water-soluble, suitable for injections and oral formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)**.
- Blocks parasympathetic effects of **acetylcholine**, leading to unopposed sympathetic activity.
- Key effects:
  - **Heart:** ↑ heart rate (tachycardia) via M2 blockade.
  - **Eyes:** Mydriasis and cycloplegia (M3 blockade).
  - **Glands:** ↓ salivation, lacrimation, sweating.
  - **Smooth muscles:** Relaxation of bronchi, gut, bladder.

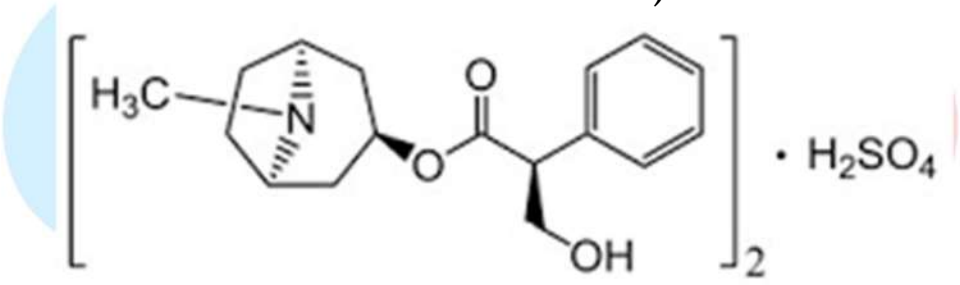
Uses

- **Bradycardia** and AV block (emergency treatment).
- **Pre-anesthetic medication** → reduces salivation and airway secretions.
- **Ophthalmology:** Mydriasis and cycloplegia.
- **Antidote for organophosphate poisoning** (used with pralidoxime).

Hyoscyamine Sulfate

Source & Structure

- **Natural alkaloid** derived from *Atropa belladonna*, *Datura stramonium*, and *Hyoscyamus niger*.
- **Tertiary amine** → lipid-soluble → crosses **blood–brain barrier (BBB)**.
- Sulfate salt → water-soluble for oral and injectable formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)**.
- Blocks **acetylcholine** at parasympathetic sites → unopposed sympathetic activity.
- Effects similar to atropine:
  - **Heart:** ↑ heart rate (M2 blockade).
  - **Eyes:** Mydriasis, cycloplegia (M3 blockade).
  - **Glands:** ↓ salivation, sweating, lacrimation.
  - **Smooth muscles:** Relaxation of bronchi, gut, bladder.

Uses

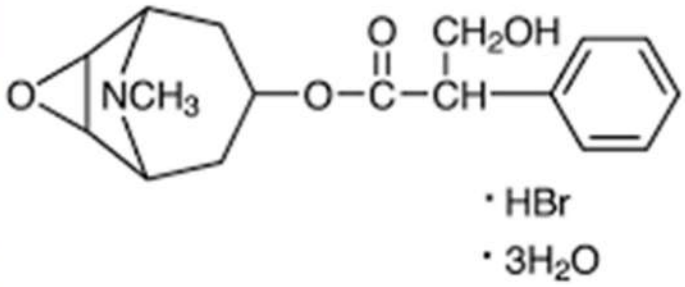
- **Gastrointestinal disorders:** Peptic ulcer, irritable bowel syndrome (reduces motility and secretions).
- **Pre-anesthetic medication:** Reduces salivary and respiratory secretions.
- **Ophthalmology:** Mydriasis and cycloplegia (less commonly used than atropine).

- **Anticholinergic therapy:** Similar to atropine; sometimes used in combination with other drugs for spasm relief.

Scopolamine Hydrobromide

Source & Structure

- **Natural alkaloid** obtained from *Hyoscyamus niger* and *Datura stramonium*.
- **Tertiary amine** → lipid-soluble → crosses **blood–brain barrier (BBB)**.
- Hydrobromide salt → water-soluble for injections, oral, and transdermal delivery.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)**.
- Blocks **acetylcholine** at parasympathetic sites → unopposed sympathetic activity.
- Strong **CNS penetration** → effective in central parasympathetic pathways.
- Effects include:
  - **CNS:** sedation, antiemetic, anti-motion sickness.
  - **Heart:** mild tachycardia (M2 blockade).
  - **Eyes:** mydriasis, cycloplegia (M3 blockade).
  - **Glands:** ↓ salivation, sweating, lacrimation.
  - **Smooth muscles:** relaxation of bronchi and gut.

Uses

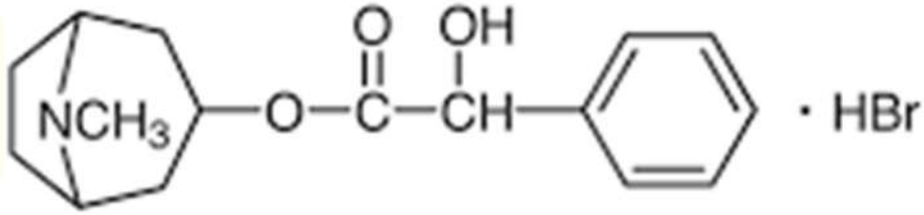
- **Motion sickness prevention and treatment** (transdermal patch or oral).
- **Postoperative nausea and vomiting**.

- **Pre-anesthetic medication:** reduces salivation and respiratory secretions.
- **Ophthalmology:** mydriasis and cycloplegia (shorter acting than atropine).
- **CNS indications:** sedation in some clinical settings.

Homatropine Hydrobromide

Source & Structure

- **Semi-synthetic derivative** of tropane alkaloids (*Atropa belladonna*).
- **Tertiary amine** → lipid-soluble → crosses **blood–brain barrier (BBB)** to a limited extent.
- Hydrobromide salt → water-soluble, used in ophthalmic and systemic formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Effects include:
  - **Eyes:** mydriasis, cycloplegia (M3 blockade).
  - **Glands:** ↓ salivation, lacrimation.
  - **Smooth muscles:** mild relaxation of bronchi and gut.
- Shorter acting than atropine → **less CNS penetration**.

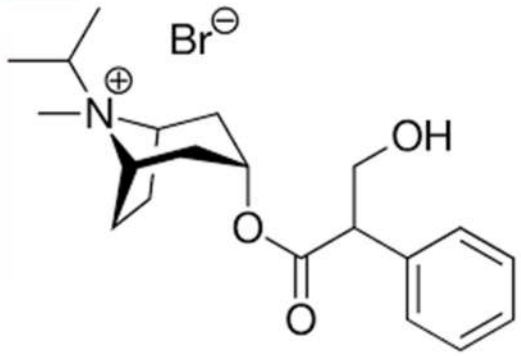
Uses

- **Ophthalmology:** Mydriasis and cycloplegia for eye examinations.
- **Diagnostic procedures:** Useful when shorter duration of action is desired compared to atropine.
- **Pre-anesthetic medication:** Less commonly used than atropine.

Ipratropium Bromide

Source & Structure

- **Synthetic quaternary ammonium derivative** of atropine.
- **Quaternary ammonium compound → poorly absorbed systemically, does not cross the blood–brain barrier (BBB)**.
- Water-soluble → suitable for inhalation and nasal formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)**.
- Blocks **acetylcholine** → inhibits parasympathetic stimulation of airway smooth muscles and glands.
- Effects are **mainly peripheral**, minimal CNS effects due to quaternary structure.
- Leads to:
  - **Bronchodilation** (relieves bronchospasm).
  - **Reduced airway secretions**.

Uses

- **Chronic obstructive pulmonary disease (COPD).**
- **Asthma** (especially in combination with β2-agonists).
- **Rhinitis** and nasal secretions control (as nasal spray).
- **Prevention of exercise-induced bronchospasm** (inhalation).

Synthetic Cholinergic Blockers (Antimuscarinic Agents)

- Laboratory-synthesized drugs that **inhibit the action of acetylcholine (ACh) at muscarinic receptors**.
- Used to **modulate parasympathetic activity** in various organs.

Mechanism of Action (MOA)

- **Competitive antagonists at muscarinic receptors (M1, M2, M3, etc.)**.
- Block parasympathetic stimulation → reduce secretions, relax smooth muscles, increase heart rate.
- Effects are generally **peripheral**, but some compounds (lipophilic tertiary amines) also act centrally.

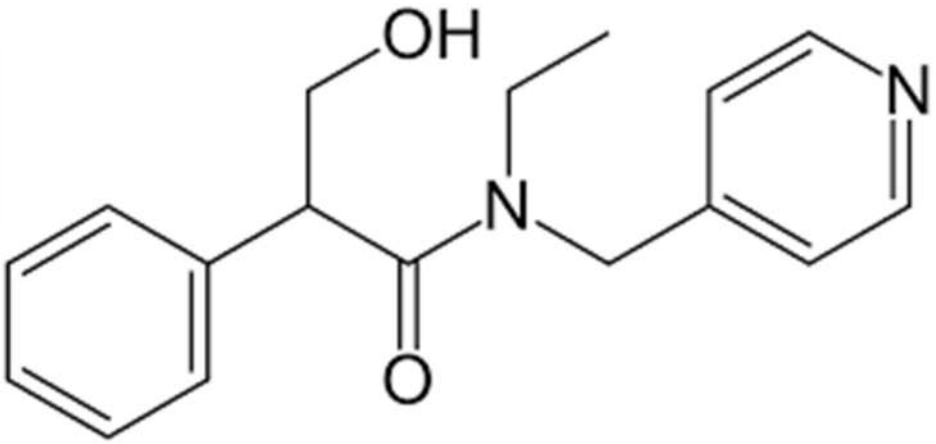
Examples

- **Tropicamide**
- **Cyclopentolate hydrochloride**
- **Clidinium bromide**
- **Dicyclomine hydrochloride**
- **Glycopyrrolate**
- **Methantheline bromide**
- **Propantheline bromide**
- **Benztropine mesylate**
- **Orphenadrine citrate**
- **Biperiden hydrochloride**
- **Procyclidine hydrochloride**
- **Trihexyphenidyl**
- **Ethopropazine hydrochloride**

Tropicamide

Source & Structure

- **Synthetic antimuscarinic (tertiary amine)**.
- **Short-acting muscarinic antagonist** → lipid-soluble, crosses **blood–eye barrier**.
- Used primarily in **ophthalmic formulations** for mydriasis.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M3) in the iris and ciliary muscles**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Effects:
  - **Mydriasis:** dilation of pupil.
  - **Cycloplegia:** relaxation of ciliary muscles.
- Short duration due to **rapid metabolism**.

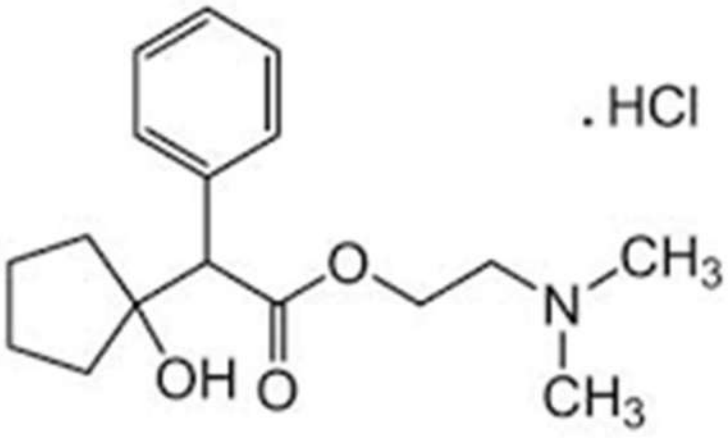
Uses

- **Ophthalmology:**
  - Pupil dilation for **fundus examination**.
  - Cycloplegic refraction in **refractive error assessment**.
  - Pre- and post-operative eye procedures requiring **temporary mydriasis**.

Cyclopentolate Hydrochloride

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Short-acting **muscarinic antagonist** → lipid-soluble, crosses **blood–eye barrier**.
- Used primarily in **ophthalmic formulations** for mydriasis and cycloplegia.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M3) in iris sphincter and ciliary muscles**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Effects:
  - **Mydriasis:** dilation of pupil.
  - **Cycloplegia:** relaxation of ciliary muscles.
- Faster onset and shorter duration than atropine, slightly longer than tropicamide.

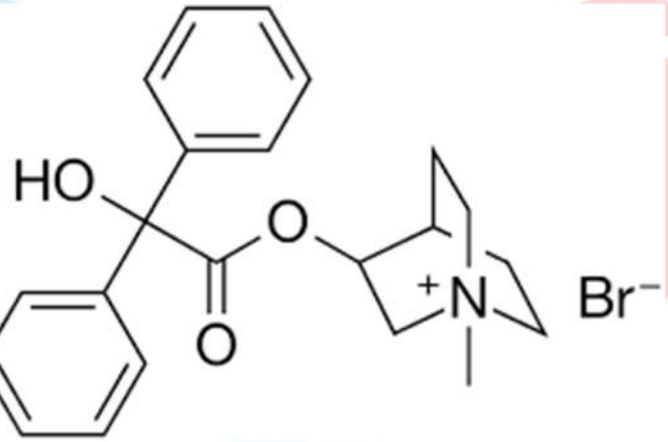
Uses

- **Ophthalmology:**
  - Cycloplegic refraction for **refractive error assessment**.
  - Pupil dilation for **fundus examination**.
  - Pre- and post-operative eye procedures requiring **temporary mydriasis**.

Clidinium Bromide

Source & Structure

- **Synthetic quaternary ammonium antimuscarinic**.
- Poorly absorbed systemically → **acts mainly peripherally**, minimal CNS penetration.
- Water-soluble → suitable for oral formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)** in the **gastrointestinal tract**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Leads to:
  - **Relaxation of smooth muscles** in GI tract → relieves spasms.
  - **Reduction of gastric and intestinal secretions**.
- Minimal systemic and CNS effects due to **quaternary ammonium structure**.

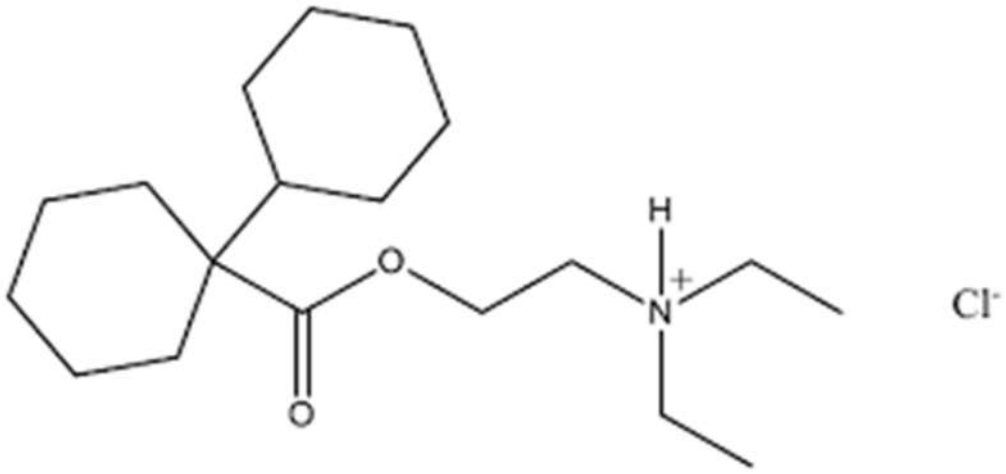
Uses

- **Irritable bowel syndrome (IBS)** → relieves abdominal cramping and pain.
- **Peptic ulcer disease** → reduces gastric acid secretion and smooth muscle spasms.
- Often combined with **other GI drugs** (e.g., chlordiazepoxide) for better symptom control.

Dicyclomine Hydrochloride

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → crosses **blood–brain barrier (BBB)** to a small extent.
- Water-soluble hydrochloride salt → suitable for oral and injectable formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)** in the **gastrointestinal tract**.
- Inhibits **acetylcholine** → reduces parasympathetic activity.
- Effects:
  - **Relaxation of smooth muscles** → relieves GI spasms.
  - **Reduction of gastric and intestinal secretions**.
- Mild CNS penetration may contribute to **antispasmodic action**.

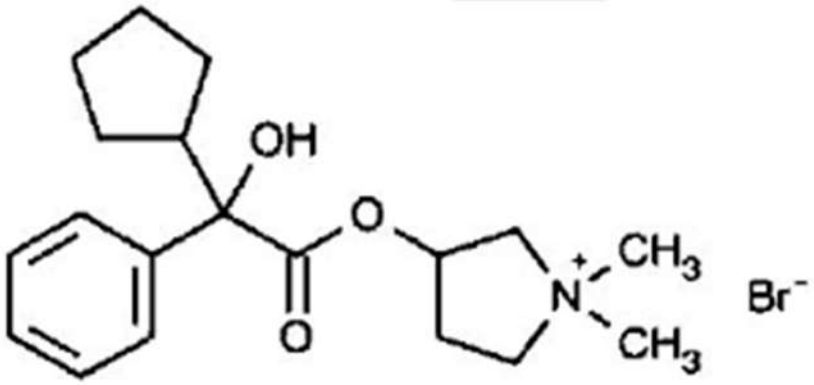
Uses

- **Irritable bowel syndrome (IBS)** → relieves abdominal pain and cramping.
- **Functional gastrointestinal disorders** with spasm and discomfort.
- Sometimes used preoperatively to reduce **GI secretions**.

Glycopyrrolate

Source & Structure

- **Synthetic quaternary ammonium antimuscarinic**.
- Poorly lipid-soluble → **does not cross the blood–brain barrier (BBB)** → minimal CNS effects.
- Water-soluble → suitable for oral, IV, IM, or subcutaneous administration.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Effects:
  - **Reduces salivary, respiratory, and gastric secretions**.
  - **Relaxes smooth muscles** of the GI tract to a small extent.
  - Minimal cardiovascular and CNS effects due to quaternary structure.

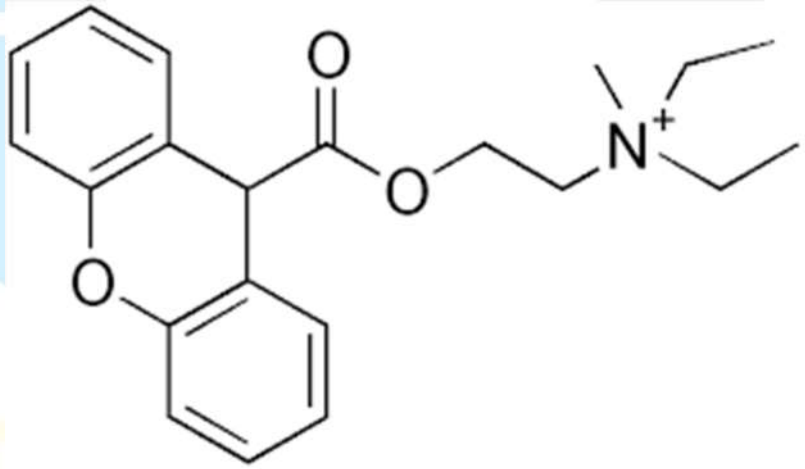
Uses

- **Pre-anesthetic medication:** Reduces salivary and respiratory secretions before surgery.
- **Peptic ulcer disease:** Adjunct therapy to reduce gastric secretions.
- **Hyperhidrosis:** Off-label use for excessive sweating.
- **Reversal of muscarinic side effects** in combination with cholinesterase inhibitors.

Methantheline Bromide

Source & Structure

- **Synthetic quaternary ammonium antimuscarinic**.
- Poorly lipid-soluble → **acts mainly peripherally**, minimal CNS penetration.
- Water-soluble → suitable for oral formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)** in the **gastrointestinal tract**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Effects:
  - **Relaxation of GI smooth muscles** → reduces spasms.
  - **Reduction of gastric acid and intestinal secretions**.
- Minimal CNS effects due to quaternary ammonium structure.

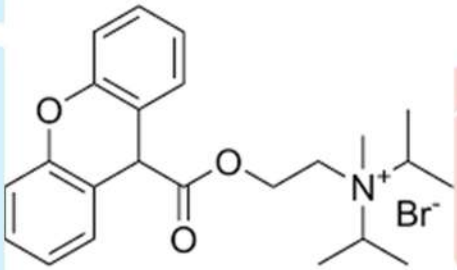
Uses

- **Peptic ulcer disease:** reduces gastric acid and smooth muscle spasms.
- **Irritable bowel syndrome (IBS):** alleviates abdominal cramps and discomfort.
- **Adjunct in GI disorders** where parasympathetic inhibition is desired.

Propantheline Bromide

Source & Structure

- **Synthetic quaternary ammonium antimuscarinic**.
- Poorly lipid-soluble → **peripheral action only**, minimal CNS penetration.
- Water-soluble → suitable for oral formulations.



Mechanism of Action (MOA)

- **Competitive antagonist at muscarinic receptors (M1, M2, M3)** in the **gastrointestinal tract and glands**.
- Blocks **acetylcholine** → parasympathetic inhibition.
- Effects:
  - **Relaxation of GI smooth muscles** → reduces abdominal cramps and spasms.
  - **Reduction of gastric and intestinal secretions**.
  - **Decrease in salivary secretions**.
- Minimal CNS effects due to quaternary ammonium structure.

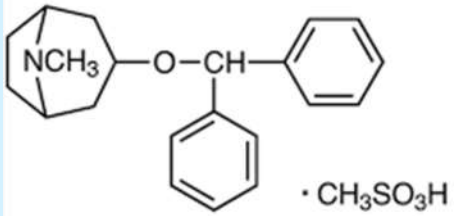
Uses

- **Peptic ulcer disease:** decreases gastric acid secretion and relieves spasms.
- **Irritable bowel syndrome (IBS):** alleviates abdominal cramps.
- **Hyperhidrosis:** off-label use to reduce excessive sweating.
- **Adjunct therapy** in GI disorders requiring parasympathetic inhibition.

Benztropine Mesylate

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → **crosses the blood–brain barrier (BBB)** → central effects.
- Used mainly for **CNS disorders**.



Mechanism of Action (MOA)

- **Competitive antagonist at central muscarinic receptors (M1, M2, M3)** in the **basal ganglia**.
- Blocks **acetylcholine** → restores **dopamine–acetylcholine balance** in the CNS.
- Effects:
  - Reduces **excess cholinergic activity** associated with Parkinsonism and drug-induced extrapyramidal symptoms.
  - Mild peripheral antimuscarinic effects: ↓ salivation, mild GI effects.

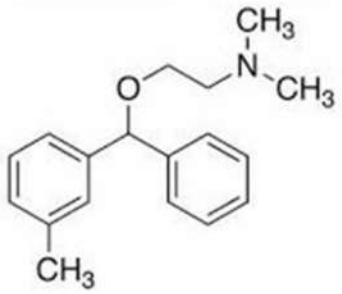
Uses

- **Parkinson's disease:** adjunct therapy for tremors and rigidity.
- **Extrapyramidal symptoms (EPS):** caused by antipsychotic drugs (e.g., haloperidol).
- Sometimes used in combination with **levodopa** therapy.

Orphenadrine Citrate

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → **crosses the blood–brain barrier (BBB)** → central effects.
- Structurally related to diphenhydramine; combines **anticholinergic and mild antihistaminic properties**.



Mechanism of Action (MOA)

- **Competitive antagonist at central and peripheral muscarinic receptors (M1, M2, M3)**.
- Blocks **acetylcholine** → reduces parasympathetic activity.
- Effects:
  - **CNS:** Relieves muscle rigidity and tremors by acting on central cholinergic pathways.
  - **Peripheral:** mild reduction in salivation and smooth muscle activity.
- Also exhibits **mild NMDA receptor antagonism**, contributing to analgesic and muscle relaxant effects.

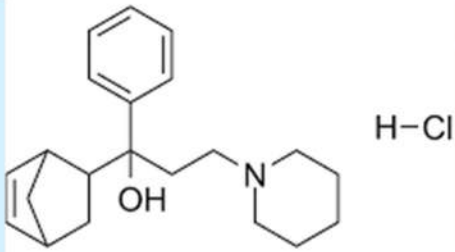
Uses

- **Musculoskeletal disorders:** Relief of muscle spasms and rigidity.
- **Adjunct in Parkinson's disease:** Controls tremors and extrapyramidal symptoms.
- **Pain management:** Sometimes used for acute musculoskeletal pain due to central anticholinergic and mild analgesic action.

Biperiden Hydrochloride

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → **crosses the blood–brain barrier (BBB)** → central effects.
- Used primarily in **Parkinson's disease and drug-induced extrapyramidal symptoms (EPS)**.



Mechanism of Action (MOA)

- **Competitive antagonist at central muscarinic receptors (M1, M2, M3)** in the **basal ganglia**.
- Blocks **acetylcholine** → restores **dopamine–acetylcholine balance** in the CNS.
- Effects:
  - **CNS:** Reduces tremors, rigidity, and bradykinesia in Parkinsonism.
  - Mild peripheral antimuscarinic effects: ↓ salivation, ↓ GI secretions.

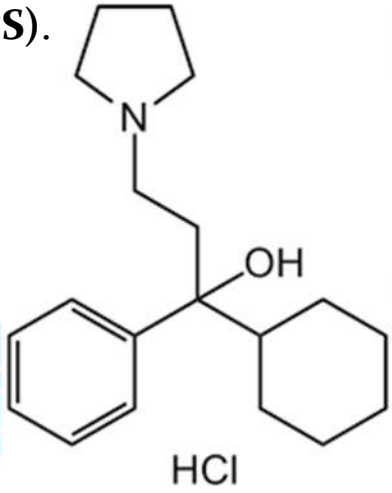
Uses

- **Parkinson's disease:** Adjunct therapy for tremors and rigidity.
- **Drug-induced EPS:** Caused by antipsychotic medications (e.g., haloperidol, chlorpromazine).
- Sometimes combined with **levodopa** therapy to improve motor control.

Procyclidine Hydrochloride

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → **crosses the blood–brain barrier (BBB)** → central effects.
- Used primarily for **Parkinson's disease and drug-induced extrapyramidal symptoms (EPS)**.



Mechanism of Action (MOA)

- **Competitive antagonist at central muscarinic receptors (M1, M2, M3)** in the **basal ganglia**.
- Blocks **acetylcholine** → restores **dopamine–acetylcholine balance** in the CNS.
- Effects:
  - **CNS:** Reduces tremors, rigidity, and bradykinesia in Parkinsonism.
  - Mild peripheral antimuscarinic effects: ↓ salivation, ↓ gastric secretions.

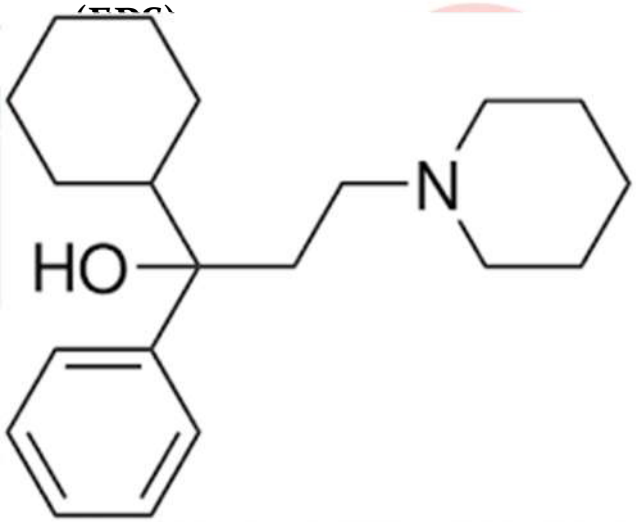
Uses

- **Parkinson's disease:** Adjunct therapy for tremors and rigidity.
- **Drug-induced EPS:** Caused by antipsychotic medications (e.g., haloperidol, chlorpromazine).
- Sometimes used in combination with **levodopa** therapy.

Trihexyphenidyl Hydrochloride

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → **crosses the blood–brain barrier (BBB)** → central effects.
- Primarily used in **Parkinson's disease and drug-induced extrapyramidal sympto**



Mechanism of Action (MOA)

- **Competitive antagonist at central muscarinic receptors (M1, M2, M3)** in the **basal ganglia**.
- Blocks **acetylcholine** → restores **dopamine–acetylcholine balance** in the CNS.
- Effects:
  - **CNS:** Reduces tremors, rigidity, and bradykinesia in Parkinsonism.
  - Mild peripheral effects: ↓ salivation and gastric secretions.

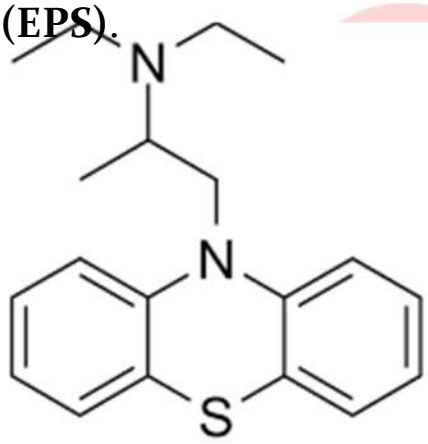
Uses

- **Parkinson's disease:** Adjunct therapy to control tremor and rigidity.
- **Drug-induced EPS:** Caused by antipsychotic medications.
- Sometimes combined with **levodopa** for enhanced effect.

Ethopropazine Hydrochloride

Source & Structure

- **Synthetic tertiary amine antimuscarinic**.
- Lipid-soluble → **crosses the blood–brain barrier (BBB)** → central effects.
- Primarily used in **Parkinson's disease and drug-induced extrapyramidal symptoms (EPS)**.



H−Cl

Mechanism of Action (MOA)

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- Blocks **acetylcholine** → restores **dopamine–acetylcholine balance** in the CNS.
- Effects:
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  - Mild peripheral antimuscarinic effects: ↓ salivation, ↓ GI secretions.

Uses

- **Parkinson's disease:** Adjunct therapy to control tremors and rigidity.
- **Drug-induced EPS:** Caused by antipsychotic medications.
- Sometimes used in combination with **levodopa** therapy.