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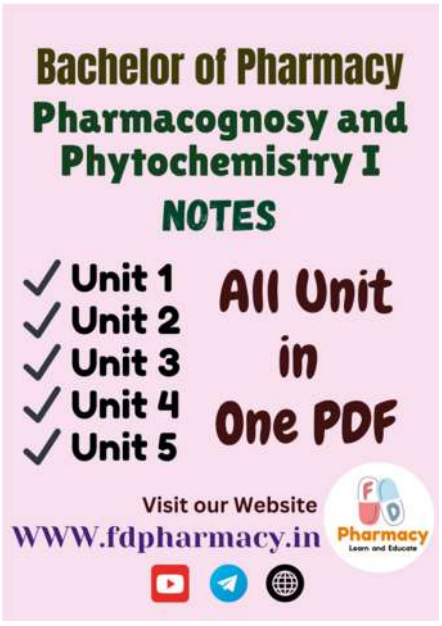
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MEDICINAL CHEMISTRY – I

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.

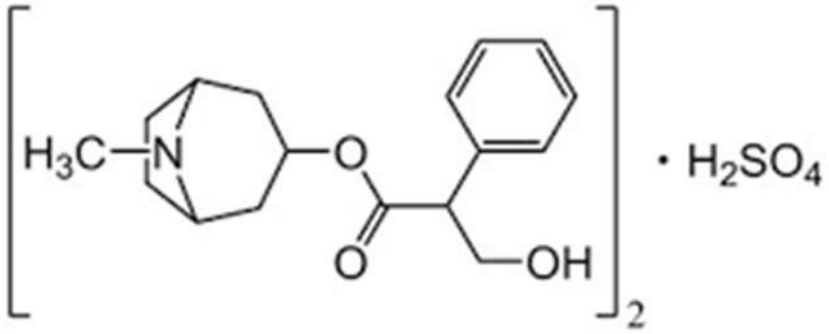
Examples

- 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.

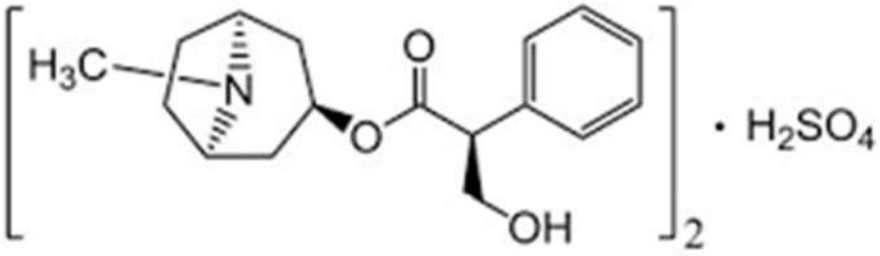
Uses

- 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).
- Cholinergic agonist toxicity.

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.

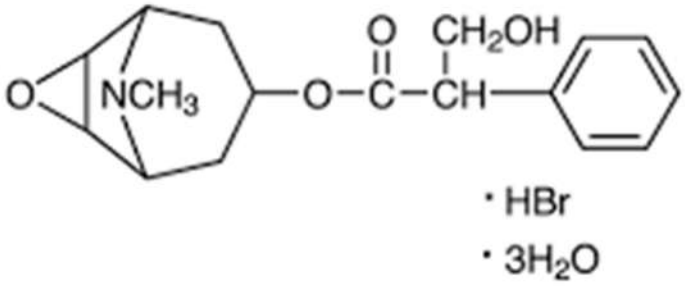
Uses

- 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.

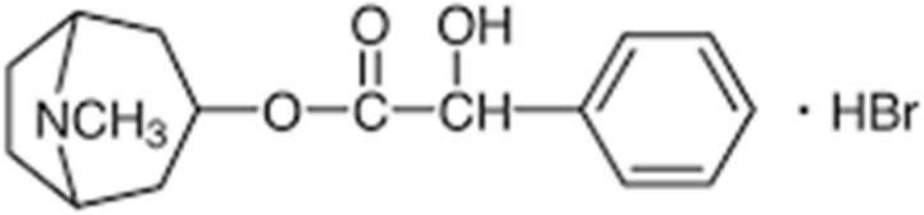
Uses

- 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.

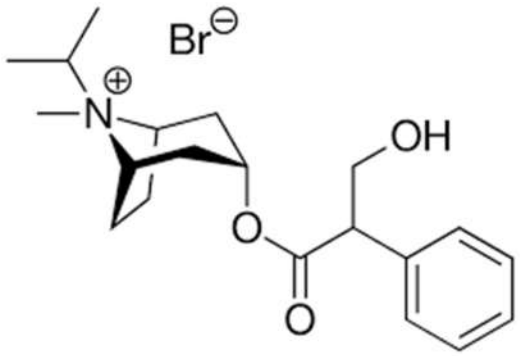
Uses

- 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.

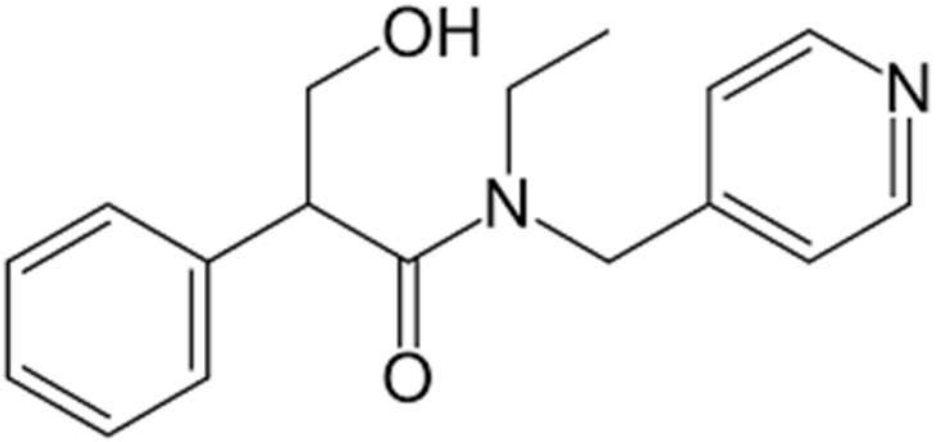
Examples

- 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 (M_3) 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.

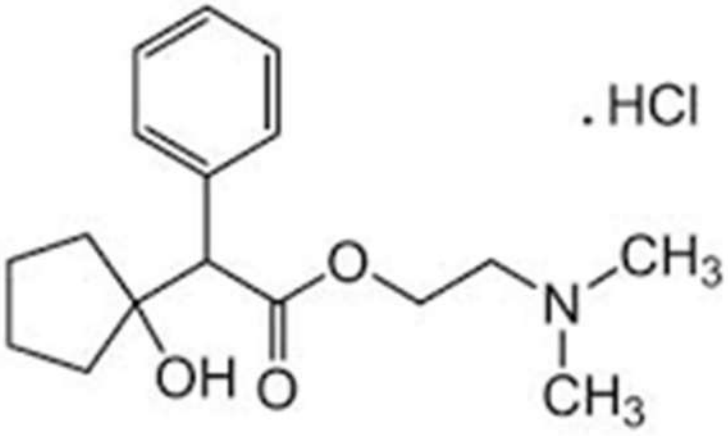
Uses

- 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.

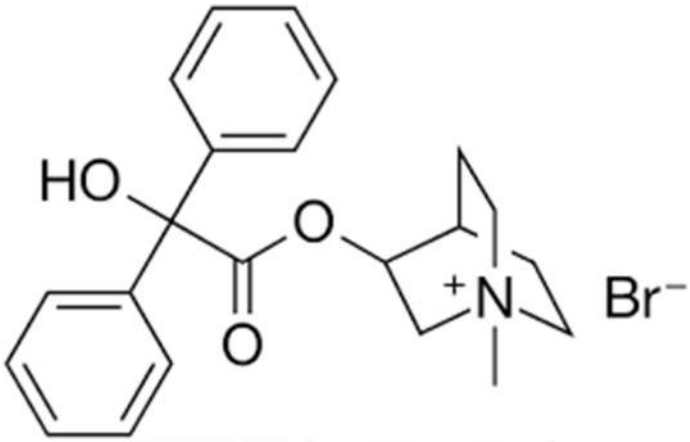
Uses

- 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.

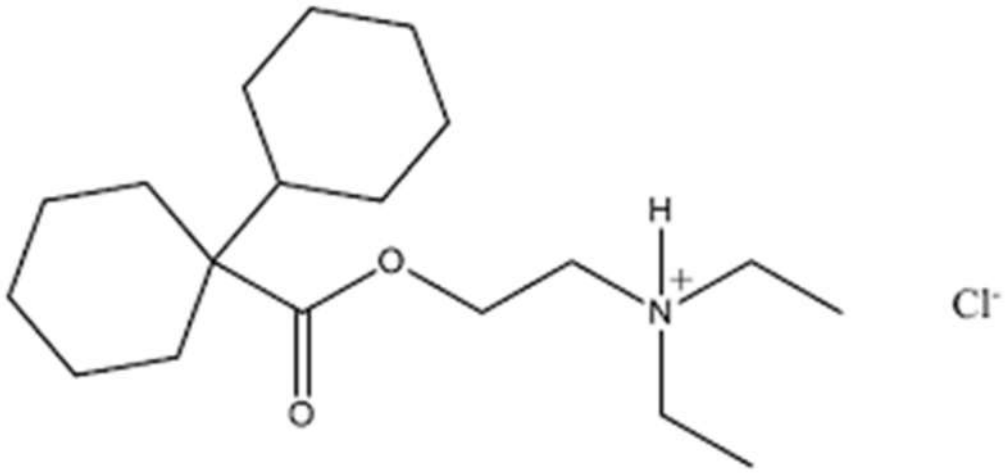
Uses

- 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.

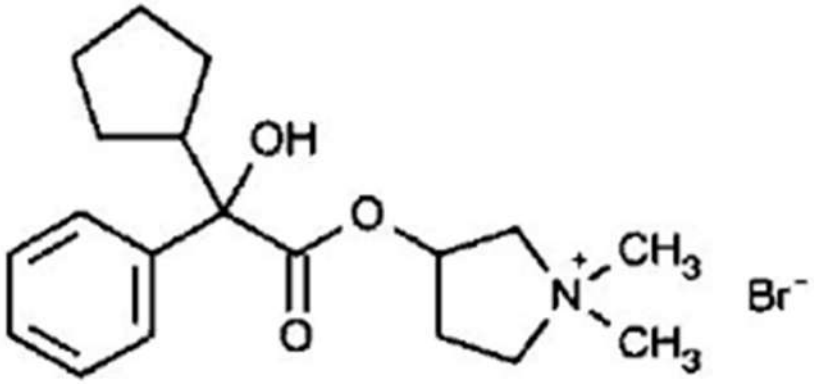
Uses

- 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.

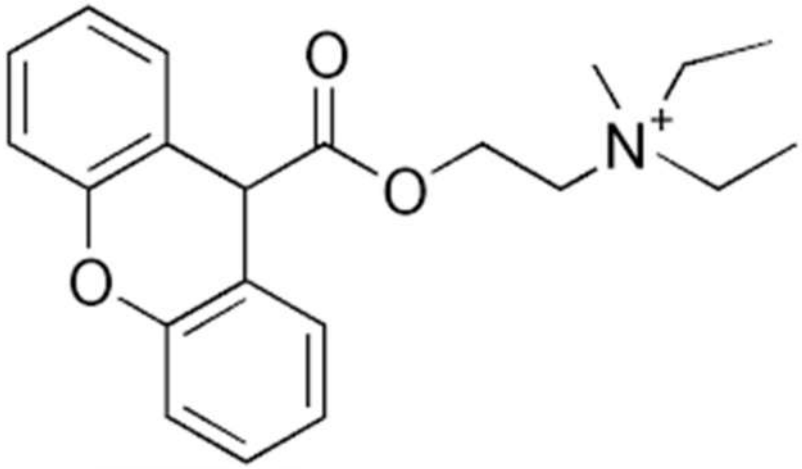
Uses

- 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.

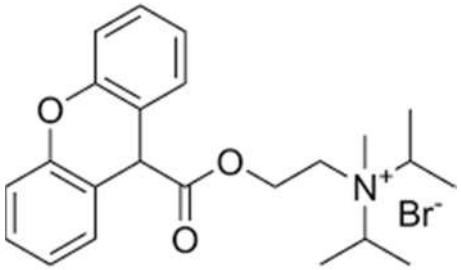
Uses

- 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.

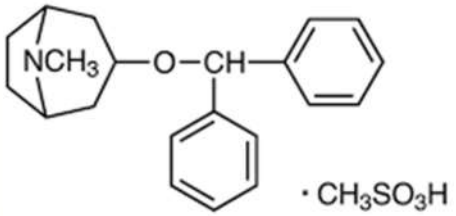
Uses

- 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.

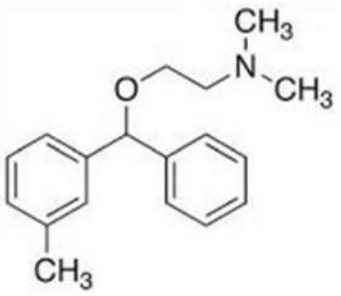
Uses

- 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.

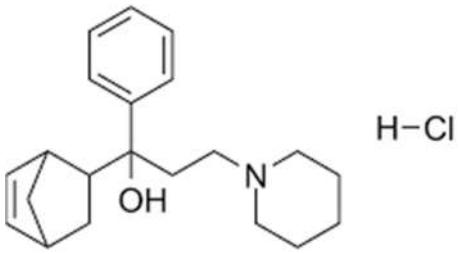
Uses

- 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.

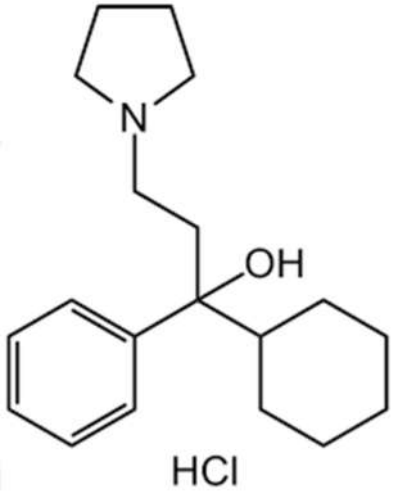
Uses

- 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.

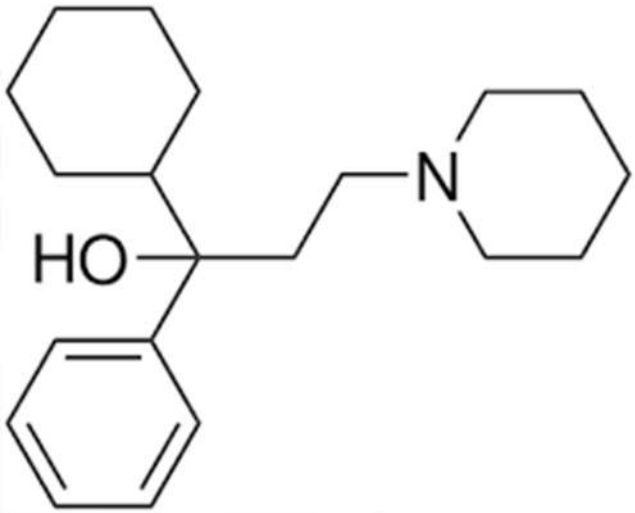
Uses

- 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 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 effects: ↓ salivation and gastric secretions.

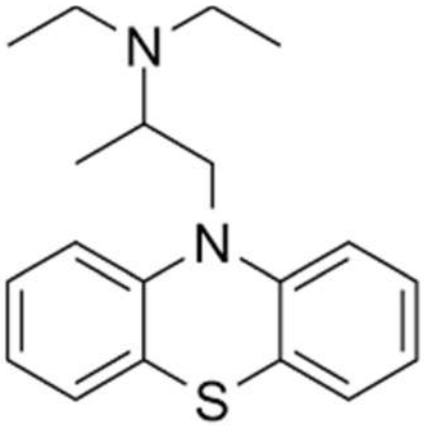
Uses

- 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).



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 to control tremors and rigidity.
- Drug-induced EPS: Caused by antipsychotic medications.
- Sometimes used in combination with levodopa therapy.