Parasympathomimetic agents

Presented By;-

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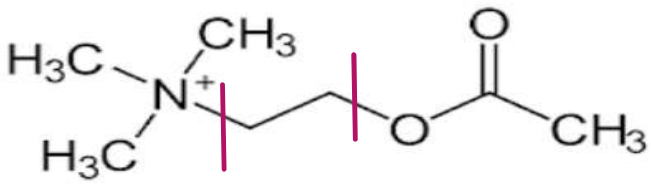
Specialization:- Pharmaceutical Chemistry

Parasympathomimetic agents

- Parasympathomimetic agents are drugs that **mimic the actions** of the *parasympathetic nervous system* by *stimulating cholinergic receptors.*
- It used in glaucoma, myasthenia gravis, urinary retention, and Alzheimer's disease.

Cholinergic drug + Cholinergic receptors ⟶ **parasympathetic Action**

SAR of Parasympathomimetic agents

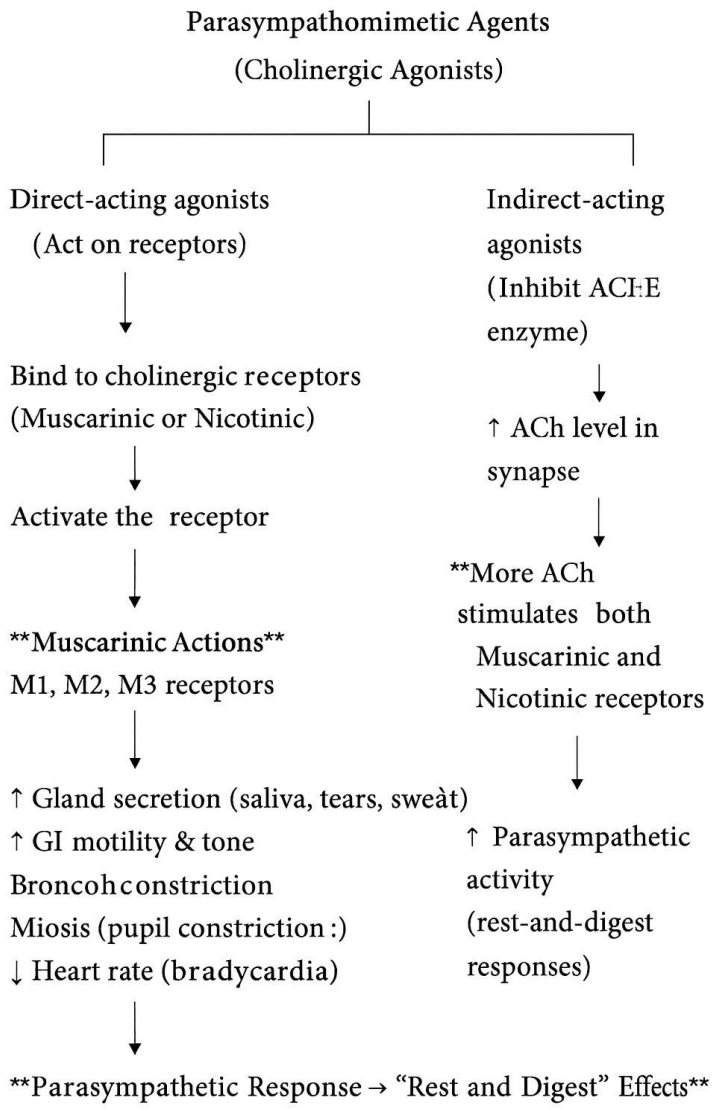


Structural Feature	Required for Activity	SAR Modifications and Effects
Quaternary Ammonium Group (N+(CH3)3)	Essential for ionic binding to the anionic site (aspartate residue) of the receptor.	**Nitrogen Substitution:-** Replacing nitrogen with arsenic, phosphorus, sulfur, or selenium significantly decreases activity.
Nitrogen Charge	The atom in the nitrogen position must be positively charged for muscarinic activity.	**Alkyl Group Size:-** Replacing the three methyl groups with larger alkyl groups reduces or abolishes agonist potency.
Ethylene Bridge (-CH2CH2-)	The two-carbon chain is optimal for maintaining the correct distance between the quaternary nitrogen and the ester group for receptor binding.	**Chain Length:-** Lengthening or shortening the chain from two carbons generally reduces activity.
Ester Group (CH3COO-)	Important for hydrogen bonding and hydrophobic interactions with the receptor's esteratic site.	**Ester Replacement:-** Replacing the ester group with a ketone or ether group can increase the compound's stability and potency by resisting hydrolysis by AChE.
β-Methyl Group	The presence and stereochemistry of a methyl group on the beta carbon (relative to the nitrogen) influences activity and stability.	**Stereochemistry:-** (S)-enantiomers (like methacholine) are generally more active at muscarinic receptors than their (R)-counterparts. It also hinders enzymatic hydrolysis.

Classification of Parasympathomimetic agents

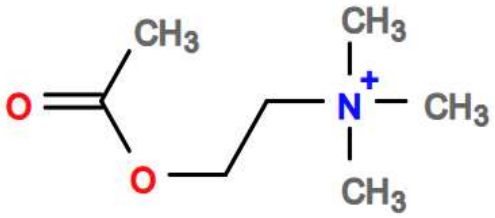
1. **Direct acting agents:-** Acetylcholine, Carbachol*, Bethanechol, Methacholine, Pilocarpine.
2. **Indirect acting/ Cholinesterase inhibitors (Reversible & Irreversible):-** Physostigmine, Neostigmine*, Pyridostigmine, Edrophonium chloride, Tacrine hydrochloride, Ambenonium chloride, Isofluorphate,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

MOA of Parasympathomimetic agents

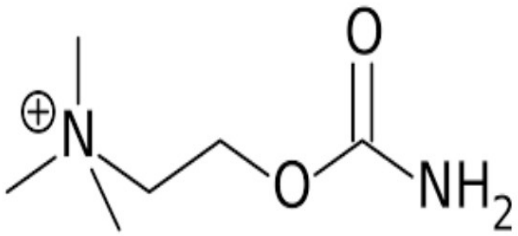


A. Direct-Acting Cholinergic Agents

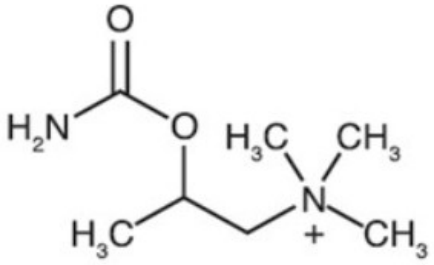
Drug	Introduction	Mechanism of Action (MOA)	Uses
Acetylcholine (ACh)	Natural neurotransmitter; very short-acting; rapidly destroyed by AChE.	Direct agonist at muscarinic & nicotinic receptors → ↑ parasympathetic activity.	Induction of miosis during eye surgery (rarely used therapeutically).
Carbachol*	Synthetic carbamate analog of ACh; not broken by AChE; long acting.	Direct agonist at muscarinic + nicotinic receptors. Resistant to hydrolysis.	Glaucoma (reduces IOP), miosis induction during eye surgery.
Bethanechol	Carbamate derivative with β-methyl (pure muscarinic action).	Selective muscarinic agonist → ↑ GI motility, ↑ bladder contraction.	Urinary retention, atonic bladder, GI atony.
Methacholine	β-methyl substituted ACh analog; selective for muscarinic receptors.	Direct muscarinic agonist; mildly resistant to AChE.	Diagnosis of bronchial hyperreactivity (methacholine challenge test).
Pilocarpine	Natural alkaloid; tertiary amine; well absorbed.	Direct muscarinic agonist (M1, M2, M3). ↑ secretions, causes miosis.	Glaucoma, xerostomia (dry mouth), Sjögren's syndrome.



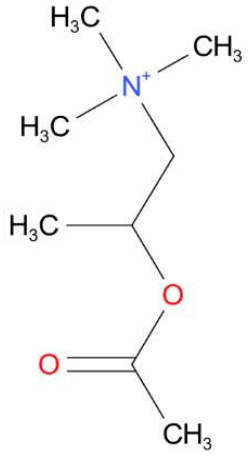
Acetylcholine



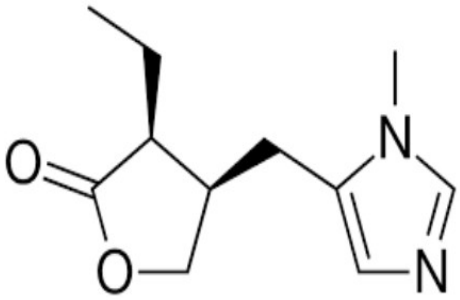
Carbachol



Bethanechol

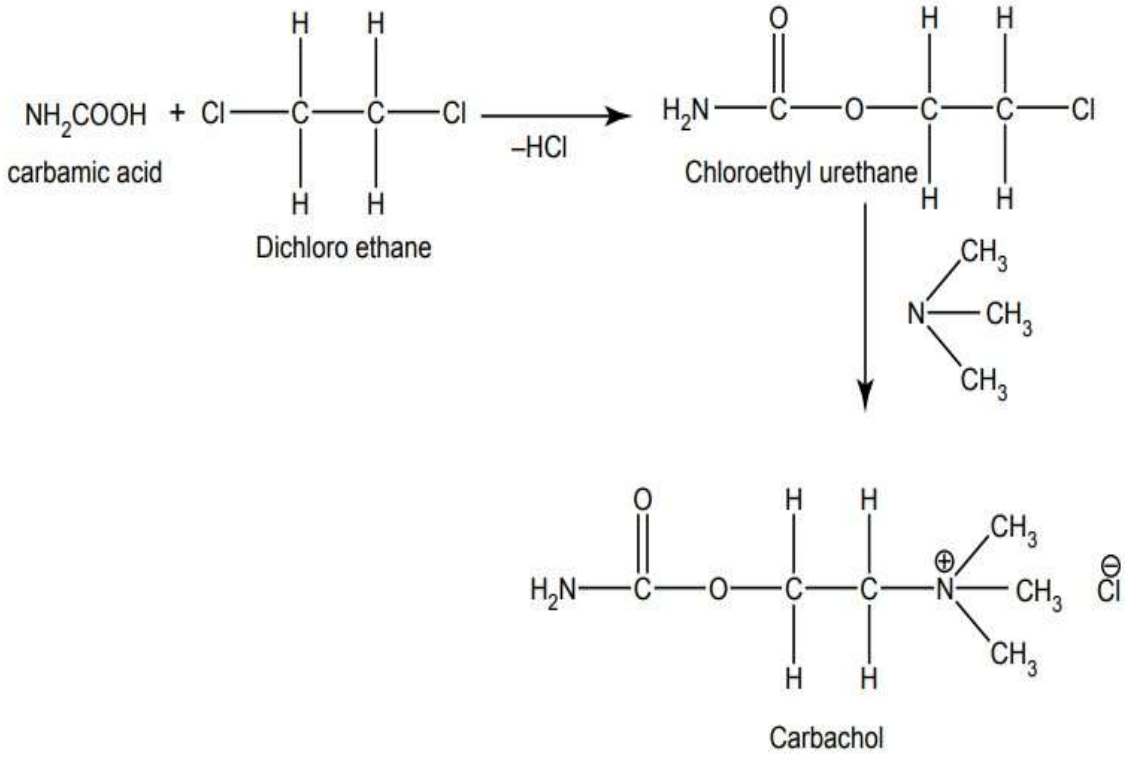


Methacholine



Pilocarpine

Synthesis of Carbachol



B. Reversible Cholinesterase Inhibitors

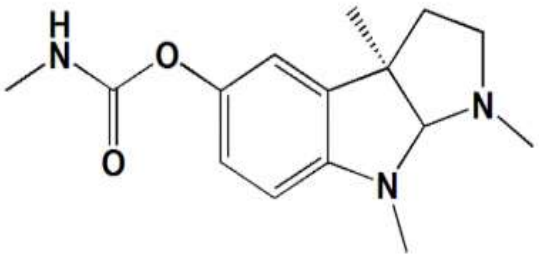
Drug	Introduction	MOA	Uses
Physostigmine	Natural alkaloid; tertiary amine (crosses BBB).	Reversible AChE inhibitor → ↑ ACh at M & N receptors.	Glaucoma, atropine poisoning, anticholinergic toxicity.
Neostigmine*	Synthetic quaternary amine; peripheral action.	Reversible AChE inhibition + direct nicotinic agonist action at NMJ.	Myasthenia gravis, reversal of non-depolarizing muscle relaxants, urinary retention.
Pyridostigmine	Longer-acting analog of neostigmine.	Reversible AChE inhibitor → ↑ ACh at NMJ.	Long-term management of myasthenia gravis.
Edrophonium chloride	Short-acting quaternary alcohol.	Reversible competitive AChE inhibitor (very short duration).	Diagnosis of myasthenia gravis (Tensilon test).
Tacrine hydrochloride	First AChE inhibitor for Alzheimer's (rarely used now).	Reversible AChE inhibition in CNS.	Alzheimer’s disease (rare now due to hepatotoxicity).
Ambenonium chloride	Potent quaternary AChE inhibitor.	Reversible AChE inhibition (long duration).	Myasthenia gravis (second-line).

C. Irreversible Cholinesterase Inhibitors (Organophosphates)

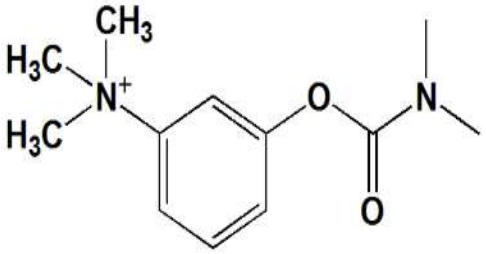
Drug	Introduction	MOA	Uses
Isofluorphate (DFP)	Highly lipid-soluble organophosphate.	Irreversible phosphorylation of AChE → enzyme inactivated.	Glaucoma (rare due to toxicity).
Echothiophate iodide	Organophosphate with long duration; less lipid soluble.	Irreversible inhibition of AChE → prolonged ↑ ACh.	Glaucoma (chronic use).
Parathion	Insecticide; prodrug converted to paraoxon.	Irreversible phosphorylation of AChE → cholinergic crisis.	Agricultural insecticide (toxic to humans).
Malathion	Safer insecticide; prodrug activated to malaoxon.	Irreversible AChE inhibition (in insects > humans).	Pediculosis (lice), agricultural insecticide.

D. Cholinesterase Reactivator

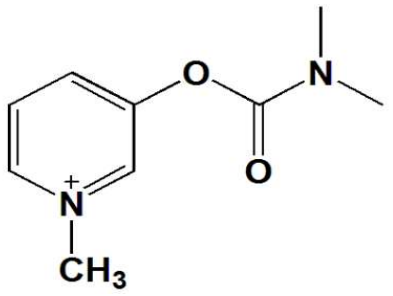
Drug	Introduction	MOA	Uses
Pralidoxime chloride (2-PAM)	Oxime antidote for organophosphate poisoning.	Reactivates AChE by cleaving phosphate–enzyme bond; reverses nicotinic effects.	Treatment of organophosphate poisoning (with atropine).



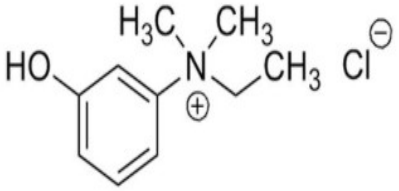
Physostigmine



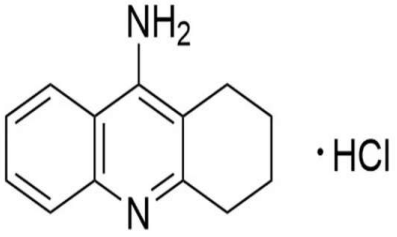
Neostigmine



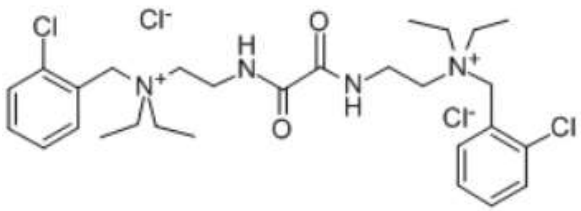
Pyridostigmine



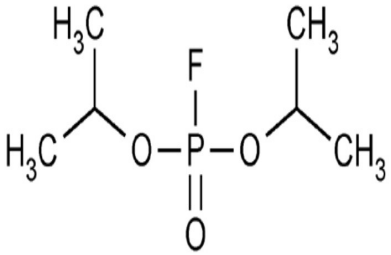
Edrophonium chloride



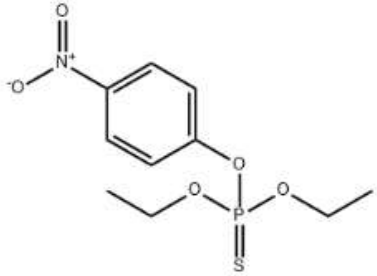
Tacrine hydrochloride



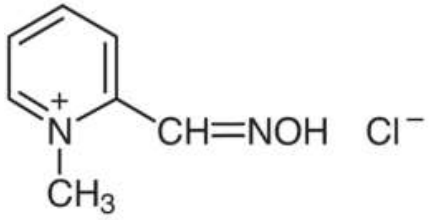
Ambenonium chloride



Isofluorphate

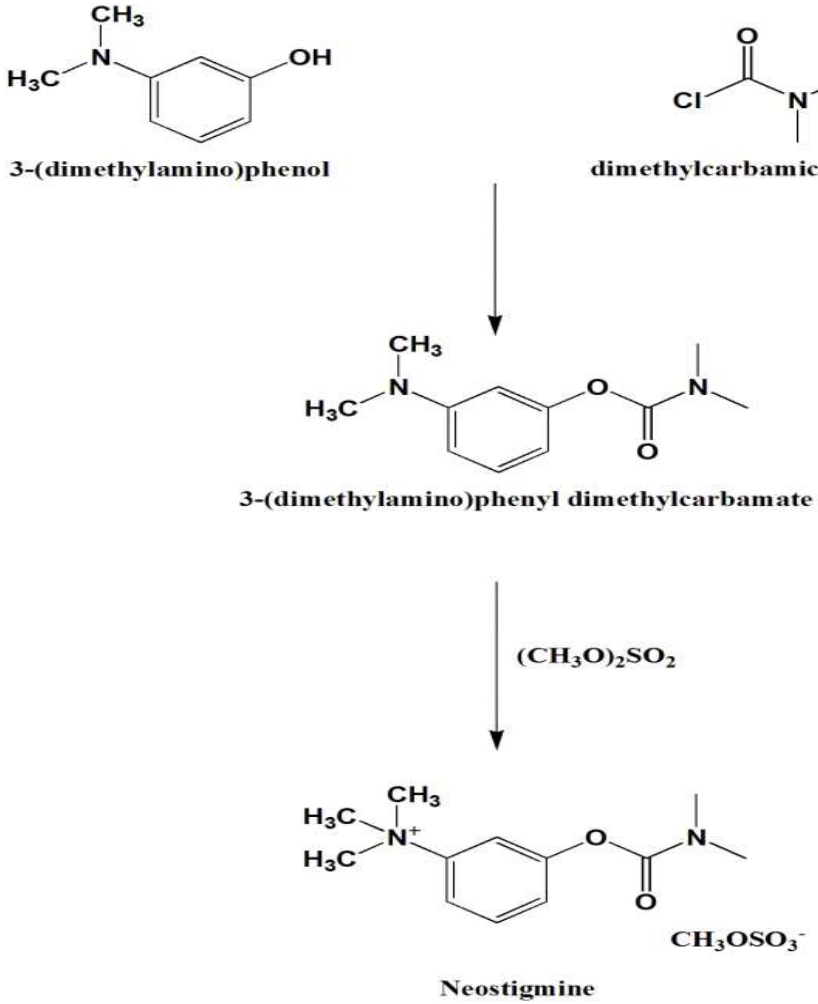


Parathione



Pralidoxime chloride

Synthesis of Neostigmine



i. Reaction of 3-dimethylaminophenol and N-dimethylcarbonyl chloride to form dimethylcarbamate.
ii. Alkylation of the above formed compound using dimethylsulfate to get neostigmine

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Thank you

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