

## Semester-IV

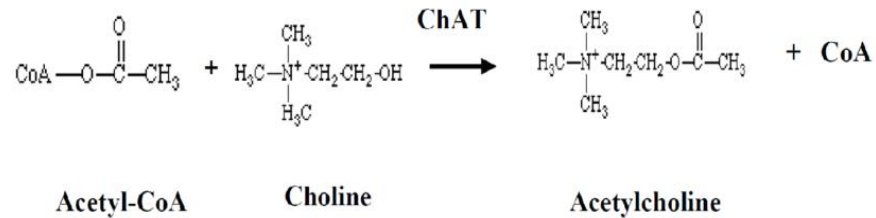
### Sub Name-medicinal chemistry-I (sub code-BP-402T)

#### Cholinergic Neurotransmitters

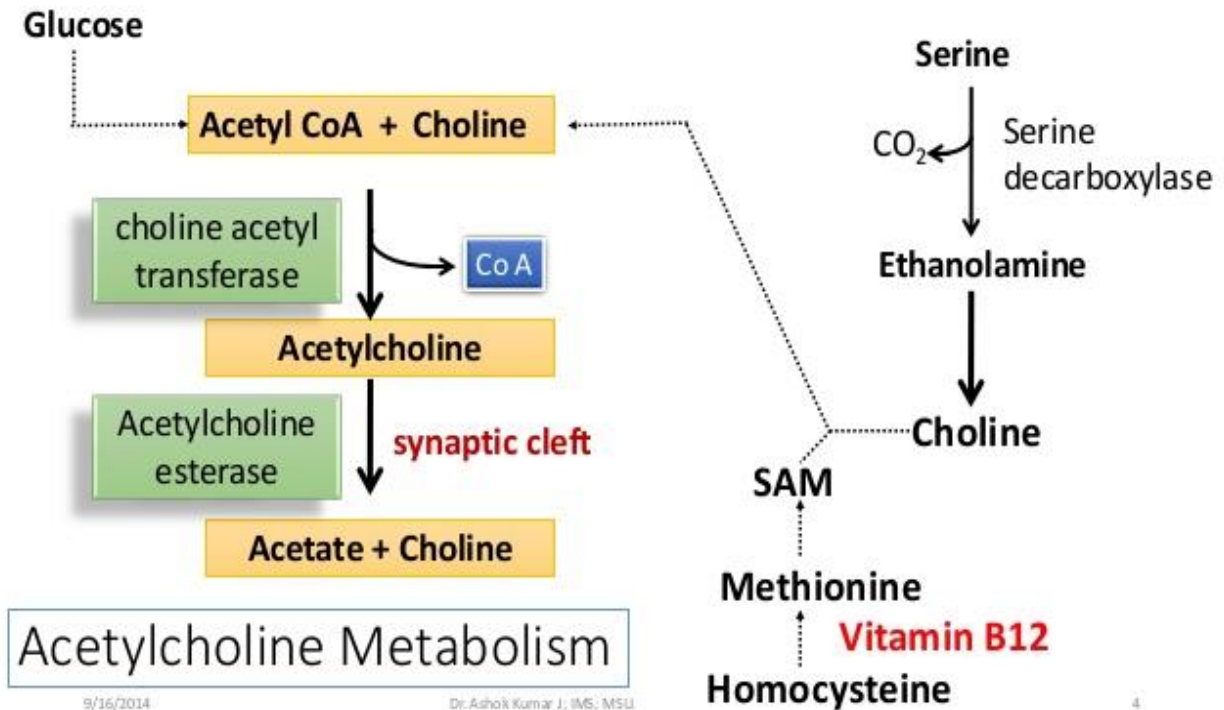
##### Objective

Biosynthesis and catabolism of acetylcholine.

Cholinergic receptors (Muscarinic and Nicotinic) and their distribution.



#### Metabolism of acetylcholine



## Cholinergic receptors & their distribution

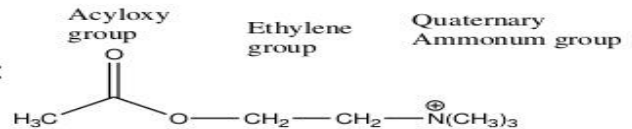
**Table 7-1.** Subtypes and characteristics of cholinceptors.

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M <sub>1</sub>		Nerves	Seven transmembrane segments, G <sub>q/11</sub> protein-linked	IP <sub>3</sub> , DAG cascade
M <sub>2</sub>	Cardiac M <sub>2</sub>	Heart, nerves, smooth muscle	Seven transmembrane segments, G <sub>i/o</sub> protein-linked	Inhibition of cAMP production, activation of K <sup>+</sup> channels
M <sub>3</sub>		Glands, smooth muscle, endothelium	Seven transmembrane segments, G <sub>q/11</sub> protein-linked	IP <sub>3</sub> , DAG cascade
M <sub>4</sub>		CNS	Seven transmembrane segments, G <sub>i/o</sub> protein-linked	Inhibition of cAMP production
M <sub>5</sub>		CNS	Seven transmembrane segments, G <sub>q/11</sub> protein-linked	IP <sub>3</sub> , DAG cascade
N <sub>M</sub>	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer ( $\alpha_2\beta\gamma$ ) <sup>1</sup>	Na <sup>+</sup> , K <sup>+</sup> depolarizing ion channel
N <sub>N</sub>	Neuronal type, ganglion receptor	Postganglionic cell body, dendrites	$\alpha$ and $\beta$ subunits only as $\alpha_2\beta_2$ or $\alpha_3\beta_3$	Na <sup>+</sup> , K <sup>+</sup> depolarizing ion channel

## Parasympathomimetic Agents

A Parasympathomimetic drug, sometimes called a cholinomimetic drug or cholinergic receptor stimulating agent is a substance that stimulates the parasympathetic nervous system (PSNS). These chemicals are also called cholinergic drugs because acetylcholine (ACh) is the neurotransmitter used by the PSNS. Chemicals in this family can act either directly by stimulating the nicotinic or muscarinic receptors (thus mimicking acetylcholine), or indirectly by inhibiting cholinesterase, promoting acetylcholine release, or other mechanisms.

## SAR of cholinergics/Muscarinic agonist



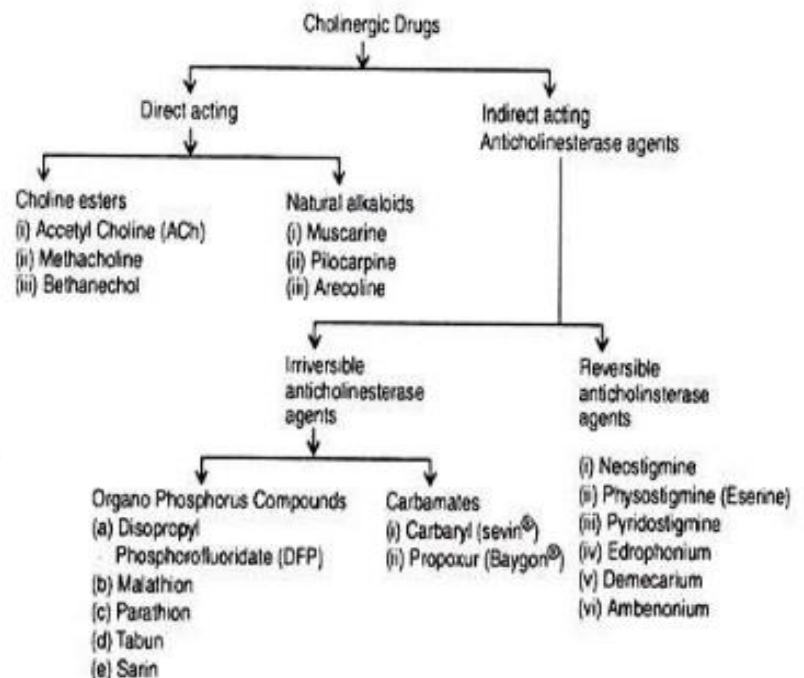
1. Presence of nitrogen in quaternary ionic form is important for agonist activity
2. Presence of three methyl group in Nitrogen is needed for agonist activity
3. A "rule of five" idea states that there should be no more than 5 atoms between the Nitrogen and the terminal Hydrogen
4. Inclusion of methyl group in beta carbon to N makes muscarinic selective in alpha carbon to N makes nicotinic selective
5. The ester group isn't mandatory as quaternary amine group but an oxygen atom is required in this region
6. Replacing the ester with carbamate, ether or ketone function resists hydrolysis while maintaining activity

## CLASSIFICATION OF DRUGS

The parasympathomimetic agents are classified into the following:

• **Directly acting cholinergic drugs**-These drugs mimic the actions of ACh at muscarinic and nicotinic receptors by binding directly to these receptors.

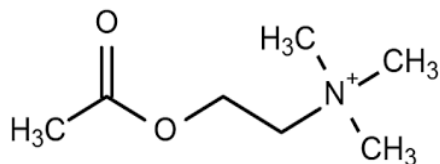
• **Indirectly acting cholinergic drugs**-These drugs act by inhibiting the activity of acetylcholinesterase (AChE) enzyme which degrades ACh to inactive products: choline and acetic acid.



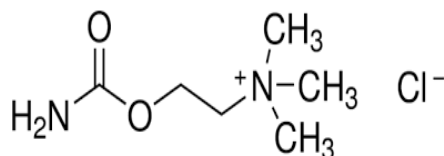
## Mechanism of Action

Acholinergic, Parasympathomimetic, synthetic analog of acetylcholine that stimulates muscarinic, postganglionic parasympathetic receptors. Therapeutic Effect: Results in smooth muscle contraction of the airways and increased tracheobronchial secretions.

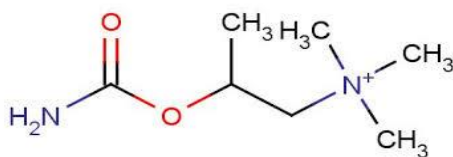
1. Acetylcholine  
trimethylammonium carbamate



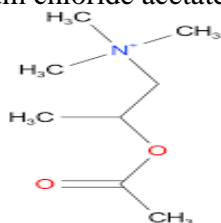
2. Carbachol  
(2-hydroxyethyl) trimethylammonium chloride carbamate.



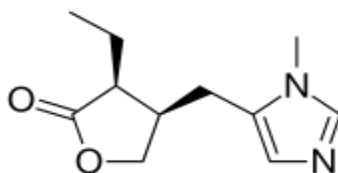
3. Bethanechol  
(2-hydroxypropyl) trimethylammonium chloride carbamate  $\beta$ -methylcholine chloride carbamate



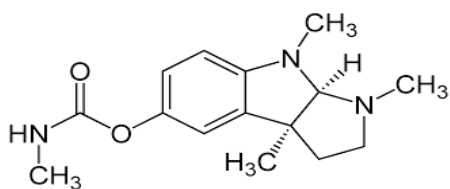
4. Methacholine  
(2-hydroxypropyl) trimethylammonium chloride acetate



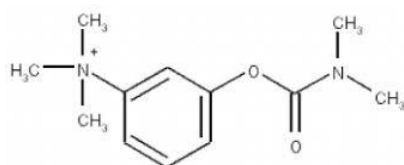
5. Pilocarpine  
3-Ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)-methyl] furan-2 (3H)-one



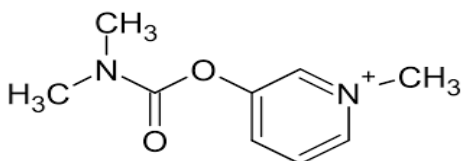
6. Physostigmine  
(3as,8ar)-1,3a,8-trimethyl-1H,2H,3H,3ah,8H,8ah-pyrrolo[2,3-b] indole-5-yl N-methylcarbamate



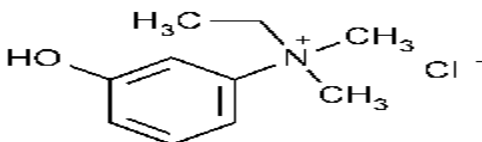
7. Neostigmine  
(m-hydroxyphenyl) trimethylammonium bromide dimethylcarbamate



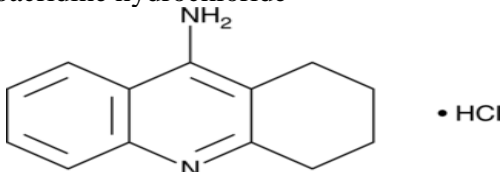
8. Pyridostigmine  
3-hydroxy-1-methylpyridinium bromide dimethylcarbamate



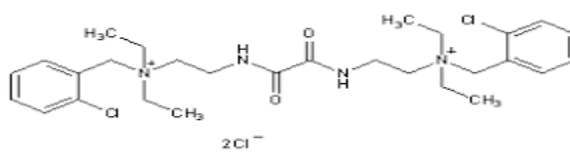
9. Edrophonium chloride  
Ethyl (m-hydroxyphenyl) trimethylammonium chloride



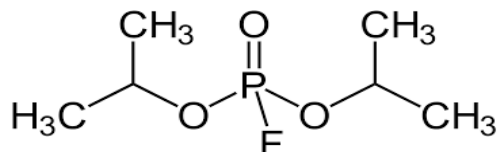
10. Tacrine hydrochloride  
1,2,3,4-tetrahydro-9-aminoacridine hydrochloride



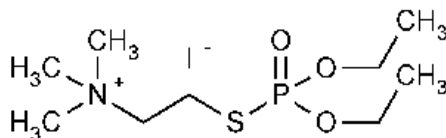
11. Ambenonium chloride  
[oxalylbis (iminoethylene) ]bis [o-chlorobenzyl) diethyl ammonium] dichloride



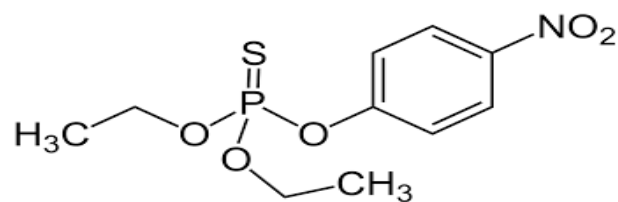
12. Isofluorphate  
Bis(propan-2-yl) fluorophosphates



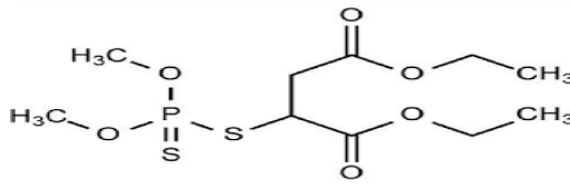
13. Echothiophate iodide  
(2-mercaptoethyl) trimethylammonium iodide



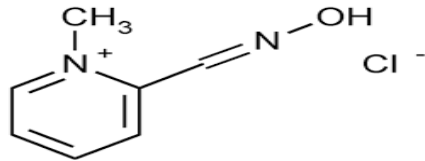
14. Parathion  
O,O-diethyl-O-p-nitro phenyl phosphorothioate



15. Malathion  
2-[(dimethoxyphosphinothioyl) thio] butanedioic acid diethyl ester



16. Pralidoxime chloride  
2-formyl-1-methylpyridinium chloride oxime



### Uses of Parasympathomimetic Agents

- Pilocarpine can be used to treat some disorders of the eye, such as glaucoma, which is characterized by elevated intraocular pressure.
- Pilocarpine is an effective treatment for glaucoma because one effect is to contract the ciliary muscle, which allows for fluid drainage of the eye.

### Adverse effects of Parasympathomimetic Agents

- Cardiovascular symptoms: bradycardia, hypotension.
- Gastrointestinal symptoms: ↑ salivation, diarrhea, abdominal pain, uncontrolled urination.
- Increased sweating, salivation, and gastric secretion.
- Nausea.
- Ocular symptoms: miosis, lacrimation.

### Cholinergic Blocking Agents:

Cholinergic Blocking Agents Drugs that block or inhibit the actions of acetylcholine (ACh) in the parasympathetic nervous system (PSNS).

## Cholinergic Blocking Agents: Chemical Class

### Natural

atropine  
belladonna  
hyoscyamine  
scopolamine

### Synthetic/Semisynthetic

anisotropine	clidinium
dicyclomine	glycopyrrolate
hexocyclium	homatropine
ipratropium	isopropamide
oxybutynin	propantheline
tolterodine	tridihexethyl

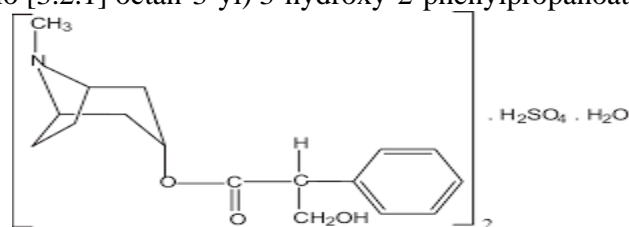
## Cholinergic-Blocking Drugs Mechanism of Action

Drugs that block or inhibit the actions of acetylcholine (ACh) in the parasympathetic nervous system (PSNS)

- **anticholinergics**
- Compete with ACh & block ACh at the muscarinic receptors in the PSNS
  - ACh is unable to bind to the receptor site and cause a cholinergic effect

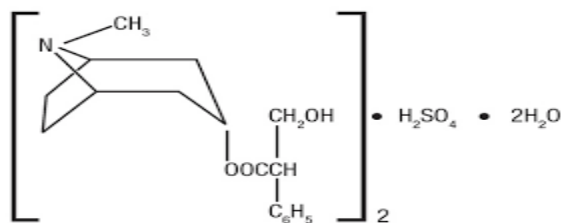
**Once these drugs bind to receptors, they inhibit nerve transmission at these receptors**

1. Atropine sulphate  
(8-methyl-8-azabicyclo [3.2.1] octan-3-yl) 3-hydroxy-2-phenylpropanoate

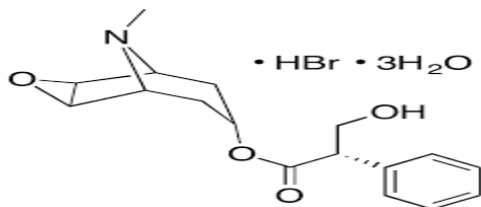


2. Hyoscyamine sulphate  
[1R,5S]-8-methyl-8-azabicyclo [3.2.1] octan-3-yl] (2S)-3-hydroxy-2-phenylpropanoate  
sulfuric acid

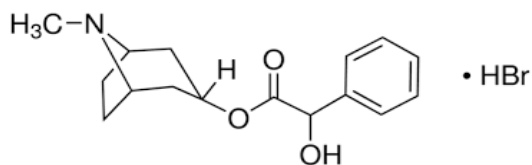




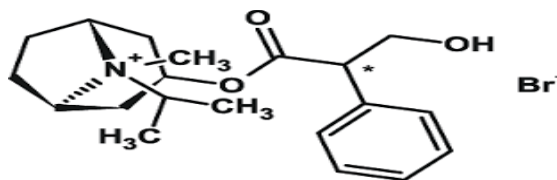
3. Scopolamine hydrobromide  
(1S, 3S, 5R, 6R,7S)-6,7-Epoxytropan-3-yl (2S)-3-hydroxy-2-phenylpropanoate



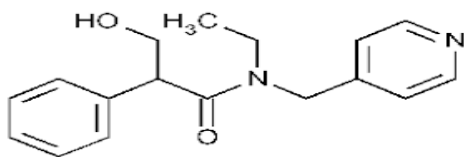
4. Homatropine hydrobromide  
(8-methyl-8-azabicyclo [3.2.1] octan-3yl) 2-hydroxy-2-phenylacetate hydrobromide



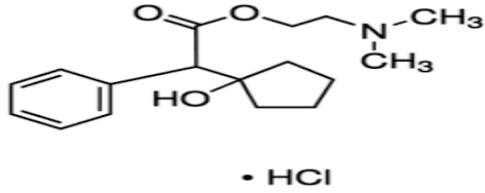
5. Ipratropium bromide  
(8-methyl-8-propan-2-yl-8-azoniabicyclo [3.2.1] octan-3yl) 2-hydroxy-2-phenylpropanoate bromide



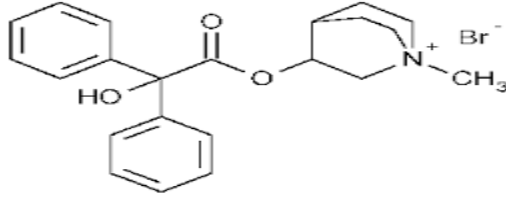
6. Tropicamide



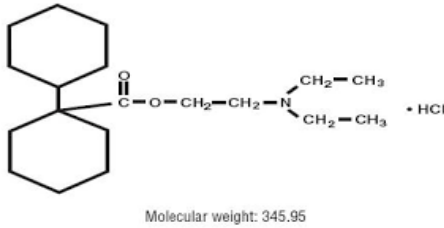
7. Cyclopentolate hydrochloride  
2-dimethylaminoethyl 1-hydroxy- $\alpha$ -phenylcyclopentaneacetate hydrochloride



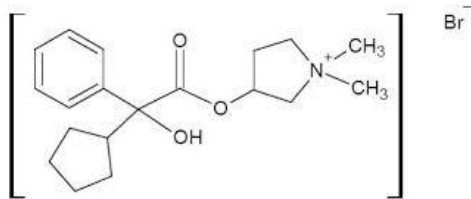
8. Clidinium bromide  
3-hydroxy-1-methylquinuclidinium bromide



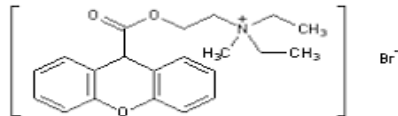
9. Dicyclomine hydrochloride  
2-(diethyl amino) ethyl bicyclohexyl-1-carboxylate hydrochloride



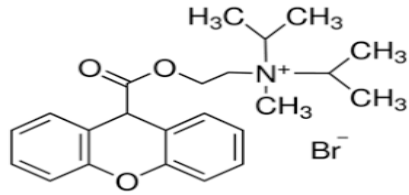
10. Glycopyrrolate  
3-hydroxy-1,1-dimethylpyrrolidinium bromide  $\alpha$ -cyclopentylmandelate



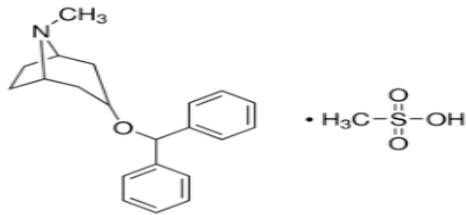
11. Methantheline bromide  
Diethyl(2-hydroxyethyl) methyl ammonium bromide xanthenes-9-carboxylate



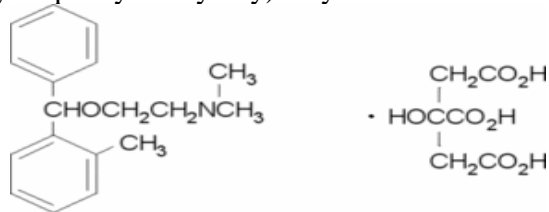
12. Propantheline bromide  
(2-hydroxy-ethyl) diisopropylmethylammonium bromide xanthenes-9-carboxylate



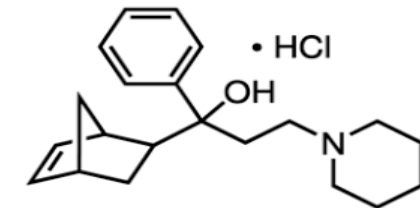
13. Benztropine mesylate  
3 $\alpha$ -(diphenylmethoxy)-1 $\alpha$ H, 5 $\alpha$  H-tropane methanesulfonate



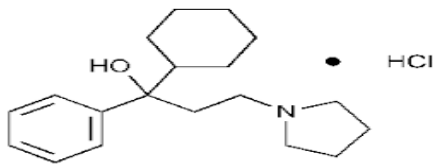
14. Orphenadrine citrate  
N,Ndimethyl-2-(o-methyl- $\alpha$ -phenylbenzyloxy) ethylamine citrate



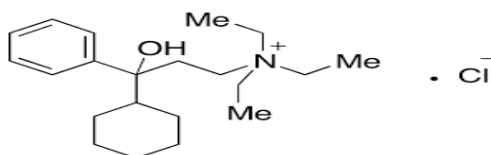
15. Biperidine hydrochloride  
1-bicyclo [2.2.1] hept-5-en-2yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol hydrochloride



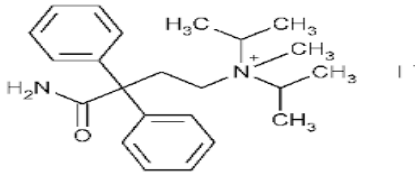
16. Procyclidine hydrochloride  
1-cyclohexyl-1phenyl-3-pyrrolidin-1-ol-ylpropan-1-ol hydrochloride



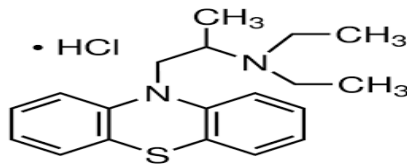
17. Tridihexethyl chloride  
(3-cyclohexyl-3-hydroxy-3-phenylpropyl) trimethylammonium chloride



18. Isopropamide iodide  
(3-carbamoyl-3,3-diphenylpropyl) diisopropylmethylammonium iodide



19. Ethopropazine hydrochloride  
10-[2-(diethyl amino) propyl]phenothiazine monohydrochloride



**Uses of Cholinergic Blocking Agents:**

- Dizziness (including vertigo and motion sickness-related symptoms)
- Extrapyramidal symptoms, a potential side-effect of antipsychotic medications.
- Gastrointestinal disorders (e.g., peptic ulcers, diarrhea, pylorospasm, diverticulitis, ulcerative colitis, nausea, and vomiting)
- Genitourinary disorders (e.g., cystitis, urethritis, and prostatitis)
- Insomnia, although usually only on a short-term basis
- Respiratory disorders (e.g., asthma, chronic bronchitis, and chronic obstructive pulmonary disease [COPD]).

**Adverse effects of Cholinergic Blocking Agents**

- excess including seizures,
- muscle weakness, bradycardia, bronchoconstriction,
- Lacrimation, salivation, bronchorrhea, vomiting, and diarrhea.

**Learning outcomes**

- Students know about the chemical synthesis of some drugs