CHAPTER -7

CHOLINERGIC BLOCKING AGENTS

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INTRODUCTION

Excitation of the parasympathetic division causes release of acetylcholine at neuroeffector junctions in different target organs. Chemical substances acting antagonistically at the M-cholinoreceptor (mainly muscarinic cholinergic receptors) are designated parasympatholytics or Anticholinegic agents are chemical substances that blocks the acetylcholine neurotransmitter in the nervous system. These agents inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Anticholinergic drugs reduce the effects of ACh by competitively inhibiting its binding to muscarinic cholinergic receptors. The nerve fibers of the parasympathetic system are responsible for the involuntary movement of smooth muscles present in the gastrointestinal tract, urinary tract, lungs, and many other parts of the body. In general, muscarinic antagonists cause little blockade at nicotinic receptors; however, the quaternary ammonium derivatives of atropine are generally more potent at muscarinic receptors and exhibit a greater degree of nicotinic blocking activity, and consequently are more likely to interfere with ganglionic or neuromuscular transmission. At high or toxic doses, central effects of atropine and related drugs are observed, generally CNS stimulation followed by depression; since quaternary compounds penetrate the blood-brain barrier poorly, they have little or no effect on the CNS.

Anticholinergic Drugs Classification

Parasympatholytics Drugs/Anticholinergic Drugs

Solanaceous alkaloids
- Atropine Sulphate
- Scopolamine Hyoscyamine Sulphate

Semi synthetic amino-alcohol ester
- Scopolamine hydrobromide
- Methscopolamine hydrobromide
- Homatropine, Tiotropium
- Ipratropium

Amino alcohol drugs
- Procyclidine hydrochloride
- Tridihexethyl chloride
- Tolteridine

Synthetic amino-alcohol ester
- Cyclopentolate HCl
- Dicyclomine HCl
- Eucartropine HCl
- Glycoprrolate
- Mepenzolate Bromide
- Methantheline bromide
- Oxyphencyclimine HCl
- Propentheline bromide
- Trospium
- Oxybutymin

New Muscarinic antagonists
- Telenzepine, Quinuclidinyl
- Benzilate

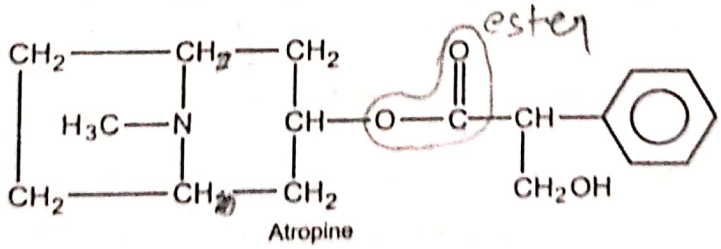
Miscellaneous
- Solifenacin
- Darifenacin
- Propenthaline

Amino amide drugs
- Tropicamide

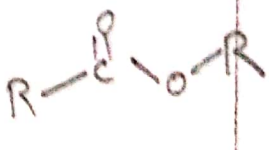
Amino ether drugs
- Orphenadrine citrate
- Benztropine

SAR OF CHOLINOLYTIC AGENTS

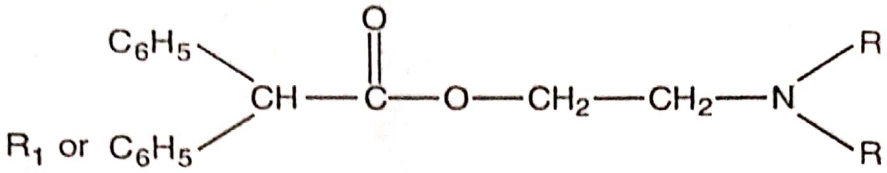
1) The first drug or the prototype drug in this category is Atropine.



Atropine



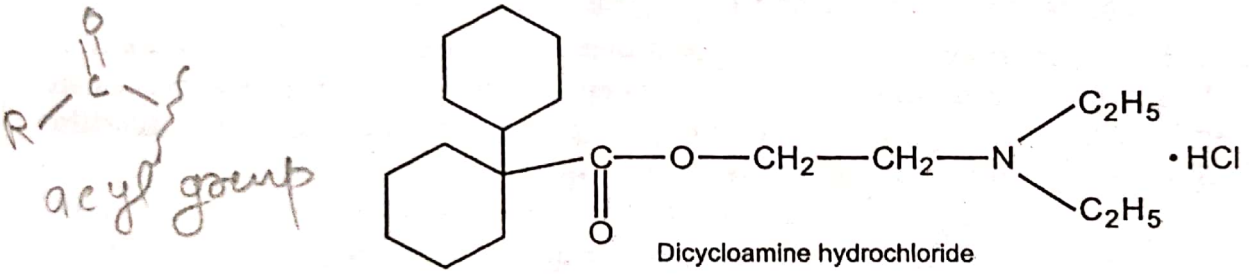
1. As acetylcholine and atropine are acetic acid ester of aminoalcohol, so many substituted acetic acid esters of amino alcohols were prepared. Unlike, acetyl choline the terminal ester carbon in atropine had a bulky substituent.
2. Esters of phenylacetic acid was prepared but it had very little activity. So, esters of diphenyl acetic acid are prepred.



R_1 and R groups must be carbocyclic or heterocyclic but if both are cyclic in nature it will give maximum antagonist potency i.e. R = alkyl

R_1 = hydroxylalkyl, cycloalkyl or heterocyclic

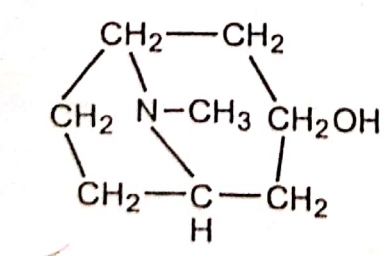
3. In antagonist, the nitrogen atom need not be always quaternary in nature. The presence of an N-methyl groups on atropine or scopolamine changes the activity of the ligand by preventing a close interaction between the ligand and the membrane or lipophillic sites on the receptor. This methyl group also prevents the penetration into the brain.
4. The acyl group in an antagonist is always larger than the acyl group in acetylcholine. Larger the acyl group the compound will be full antagonist.
5. N-substitution should be 2 or 3 ethyl groups for optimal potency. For example, Dicyclomine hydrochloride.



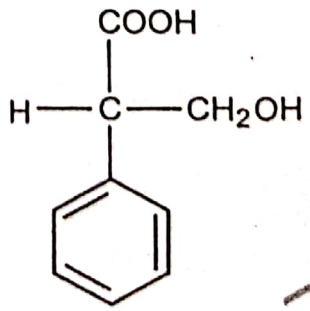
Dicycloamine hydrochloride

SOLANACEOUS ALKALOIDS AND ANALOGUES

Solanaceous alkaloids are the esters of the tropine (bicyclic amino alcohol 3-tropanol) and tropic acid Atropa belladona, Hyoscyamus niger and Datura Stramonium plants give alkaloids like hyoscyamine, atropine and hyoscine. These all alkaloids are called as solanaceous alkaloids as these plants beongs to the family Solanaceae. These alkaloids causes inhibition of the parasympathetic nervous system and stimulation of higher centres of nervous system.



Tropine

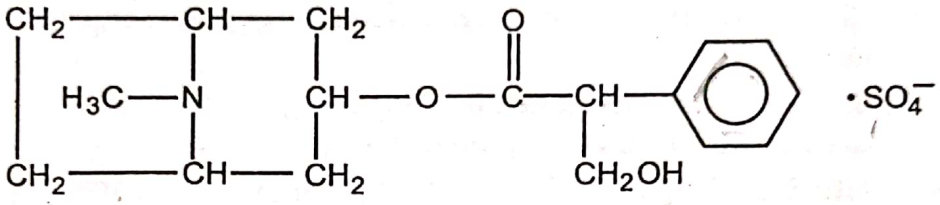


Tropic acid

Atropine is a racemic mixture and its levorotatory isomer is hyoscyamine. Hyoscine is

an ester of tropic acid and scopine which is quite different from tropine. Solanaceous alkaloids have a basic piperidine ring system and can exists in both chair and boat conformations. The anticholinergic effect of solanaceous alkaloids is due to the presence of intact ester of tropine and tropic acid and also free –OH group is essential for the activity. These alkaloids have antispasmodic actions on the smooth muscles i.e. reduces the tone of smooth muscles and decreases the gastric and intestinal motility. Various modifications in the structure of solanaceous alkaloids have been made while retaining the tropine portion as such to obtained drug with increased potency. Various solanaceous alkaloids and their analogues are as follows :

1) Atropine Sulfate



IUPAC Name : (1R, 3r, 5S)- Tropan-3-yl (±) tropate sulphate

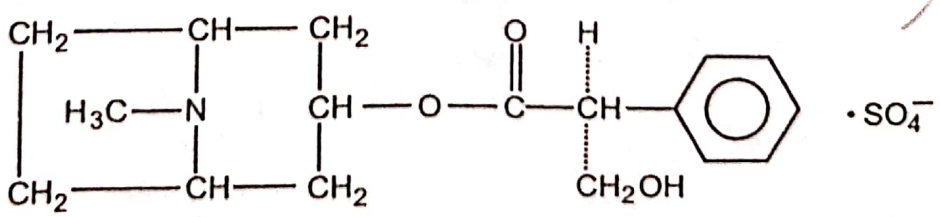
Properties : It is a racemic mixture of hyoscyamine obtained from roots of belladona. It occurs as colourless, white crystalline powder. It is very soluble in water. It effloresces in dry air. It should be kept in well-closed container and protected from light. It is readily absorbed by G.I.T. It is excreted in urine, partly as a metabolite.

Mechanism of Action : Atropine has both central and peripheral action. It first stimulates and then depresses the C.N.S. It has antispasmodic actions on smooth muscles. It reduces the tone of smooth muscle and diminishes the gastric and intestinal motility.

Uses :

1. It is used in the treatment of gastric and duodenal ulcers.
2. In renal and billiary colic, it is used in the treatment of smooth muscles spasm.
3. In the symptomatic treatment of parkinsonism it is used to depress the C.N.S.
4. Atropine is also used to reduce bronchial and salivary secretion before the induction of general anaesthesia.
5. Atropine also have cycloplegic and mydriatic action.

2) Hyoscyamine sulphate



IUPAC Name : (1R, 3r, 5S) Tropan-3-yl(s)-tropate sulphate dehydrate.

Properties : It occurs as a white crystalline powder or colourless needles which is very

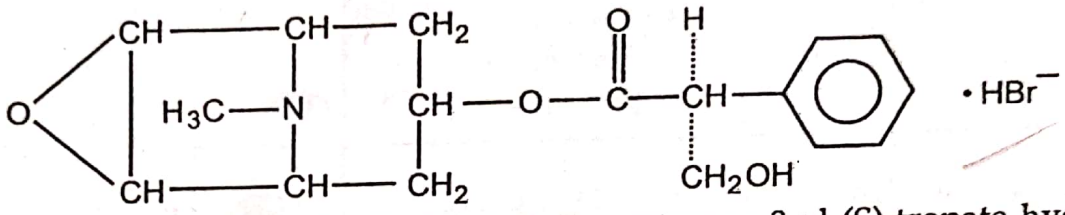
soluble in water, practically insoluble in ether. It should be stored in an airtight container protected from light.

Mechanism of Action : It's action is similar to atropine as it is more potent than atropine in its central and peripheral effects.

Uses :

1. It is used to prevent motion sickness.
2. It is used as an adjunct in treatment of gastric and duodenal ulcers.
3. It is also used in treatment of parkinsonism.

3) Scopolamine hydrobromide



IUPAC Name : (1S, 3S, 5R, 6R, 7S)-6, 7- Epoxytropan-3-yl (S)-tropate hydrobromide trihydrate.

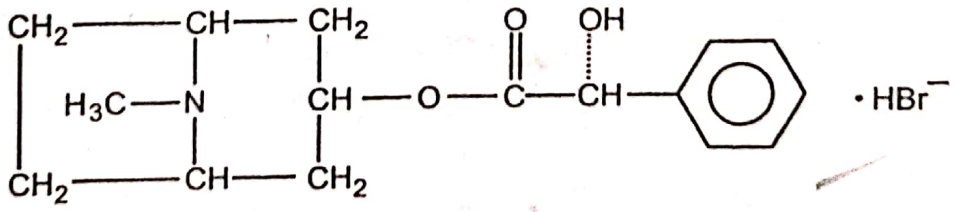
Properties : It occurs as a colourless or white crystalline powder, efflorescent in nature. It is freely soluble in water. It should be kept in a well-fitted airtight container and protected from light.

Mechanism of Action : It is more potent than atropine. It has more rapid onset and shorter duration of action than atropine but is more toxic.

Uses :

1. It has mydriatic and cycloplegic actions.
2. With morphine, scopolamine is used in acute mania and delirium.
3. It is also used in the treatment of motion sickness.

4) Homatropine Hydrobromide



IUPAC Name : (1R, 3r, 5S)-3-(RS)-Mandeloyloxy-tropanium bromide.

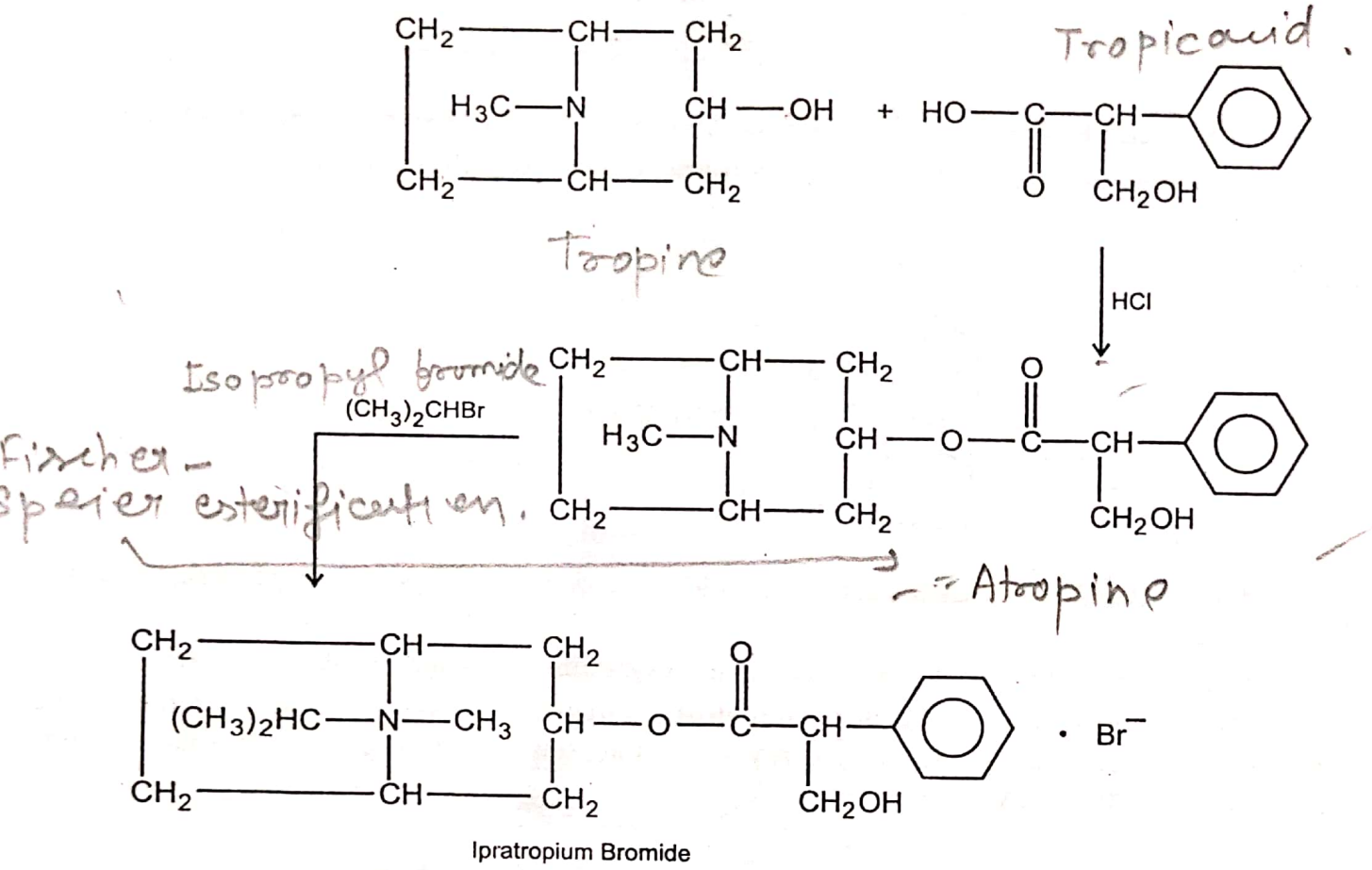
Properties : It occurs as colourless or a white crystalline powder which is freely soluble in water. It should be kept in well-closed container and protected from light.

Mechanism of Action : It is an ester of (±) mandelic acid with tropine having one tenth the potency of atropine.

Uses : It is used topically as mydriatic and cycloplegic due to its rapid onset of action.

Cycloplegia is paralysis of ciliary muscle of the eye.

5) Ipratropium bromide



Ipratropium Bromide

IUPAC Name : 8-methyl-8-(1-methylethyl)-8-azonia-bicyclo [3,2,1] oct-3-yl]-3-hydroxy-2-phenyl propanoate.

Properties : It is white or almost white crystalline powder, soluble in water.

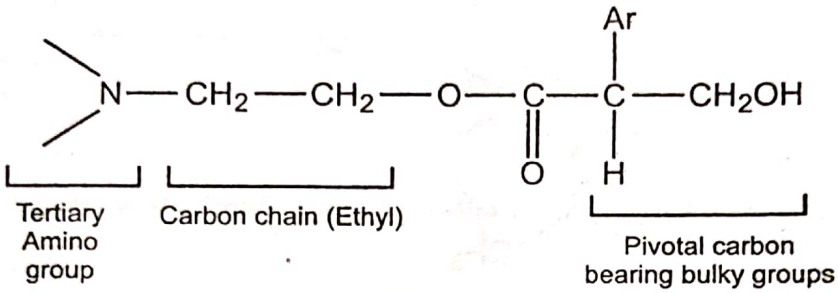
Mechanism of action : It is quaternary ammonium compound which blocks muscarinic acetylcholine receptors. It is non-selective muscarinic antagonist.

Uses :

1. It is used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma in form of inhalation.
2. It's nasal solution can reduce rhinorrhea (nasal cavity filled with mucous fluid) but not use in nasal congestion.
3. In combination with β-adrenergic agonists it increases the dilating effect on bronchi.

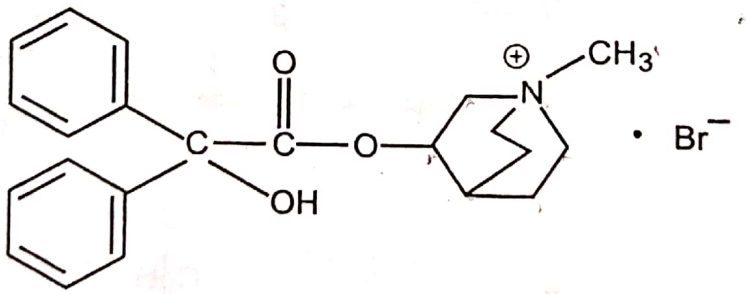
SAR OF SYNTHETIC CHOLINERGIC BLOCKING AGENTS

Solanaceous alkaloids lack selectivity and has various serious side effects. This led to the development of synthetic anticholinergic agents. Atropine was the prototype drug which is an ester of an amino alcohol with a branched and bulky carboxylic acid. Various modifications have been made in the structure of Atropine to give drugs which act mainly by competitive antagonism to acetylcholine. Most of the anticholinergic drugs have the basic structure as

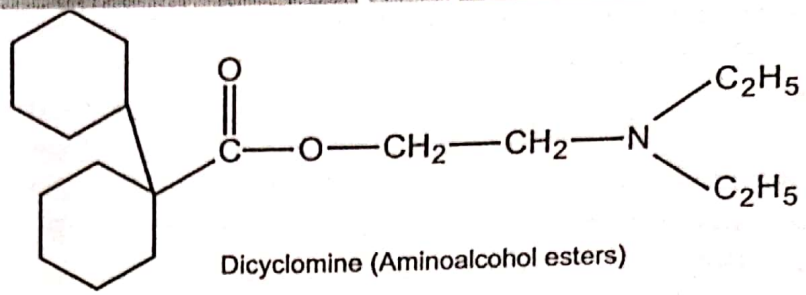


1. The tertiary amino group can be protonated to form a cationic head which is of great importance as its positive charge is attracted to negative charge present on the anionic centre of muscarinic receptor. N-methyl substitution is optimal but N-ethyl and n-propyl/n-butyl substitution decreases the potency.
2. The pivotal carbon must have atleast one aromatic group to have Vander Waals interactions with the receptor and one cycloaliphatic group like cyclohexyl for hydrophobic bonding with the receptor.

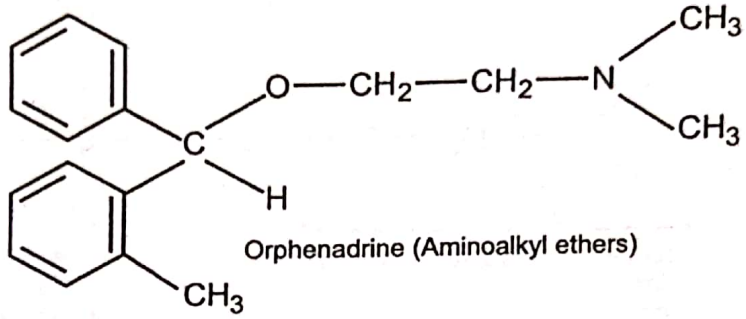
   If two phenyl groups are present, they are more potent as compared to one phenyl and one cyclohexyl group for example, Clidinium Bromide.



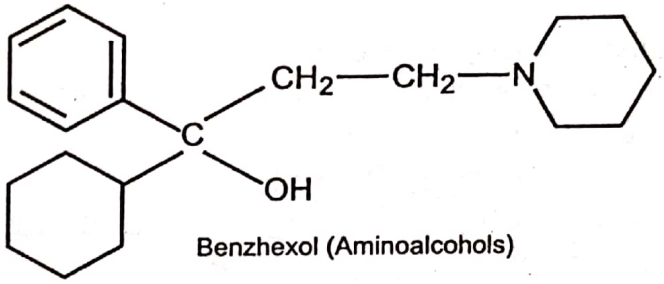
3. Increase in the length of the carbon chain decreases the activity. Branching at the carbon [β] to the nitrogen atom decreases the activity.
4. The main chain of carbon atoms may include other atoms like oxygen, sulphur, nitrogen etc. to give highly potent compounds. Depending upon these functional groups the synthetic anticholinergics are classified as aminoalcohol esters, aminoalkyl ethers, aminoamides etc. For example,



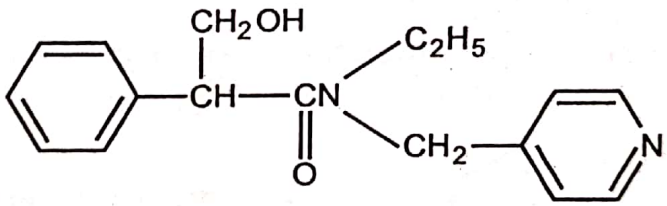
Dicyclomine (Aminoalcohol esters)



Orphenadrine (Aminoalkyl ethers)

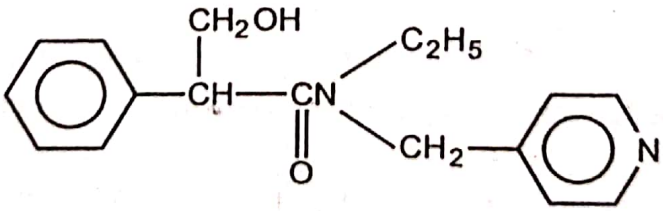


Benzhexol (Aminoalcohols)



Tropicamide (Aminoamides)

1) Tropicamide



IUPAC Name : N-Ethyl-N-(4-Pyridylmethyl) tropamide

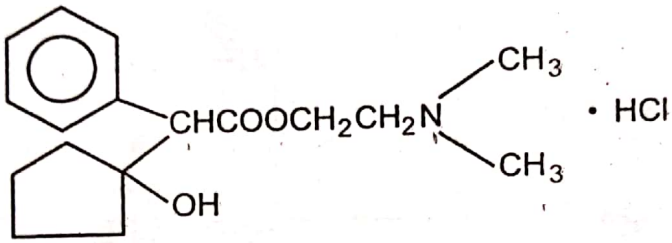
Properties : Tropicamide is a white or almost white crystalline powder which is slightly soluble in water.

Mechanism of Action : It act mainly by competitive antagonism to acetylcholine.

Uses :

1. It is an antimuscarinic drug that produces short acting mydriasis (dilation of pupil) and cycloplegia (paralysis of cilliary muscle of eye).
2. Due to its short duration of action it is used for dilated fundus examinations and before or after eye surgery.
3. Tropicamide eye drops are often used to treat anterior uveitis (inflammation of uvea).
4. It is also used with other sympathomimetic agent to dilate the iris muscle.

2) Cyclopentolate Hydrochloride



IUPAC Name : 2-Dimethylamino ethyl-2-(1-hydroxy cyclopentyl)-2 phenylacetate hydrochloride.

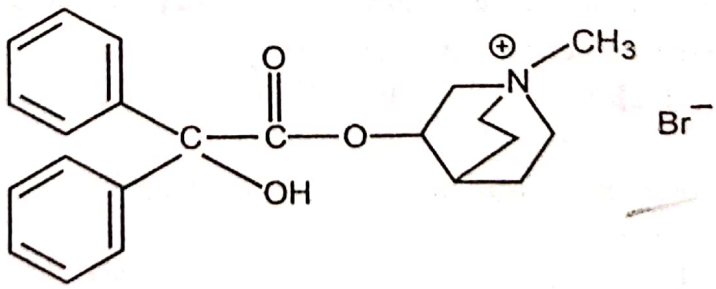
Properties : It is a white or almost white crystalline powder, soluble in water.

Mechanism of Action : It is a competitive antagonist of acetylcholine. It binds to the receptor in place of acetylcholine and reverses its actions. It acts more quickly than atropine and has a shorter duration of action.

Uses :

1. It is used as an eye drop to produce cycloplegia and mydriasis.

3) Clidinium Bromide



IUPAC Name : 3-[(2-hydroxy-2, 2-diphenylacetyl)oxy]-1-methyl-1-azabicyclo [2.2.2] octan-1-ium bromide

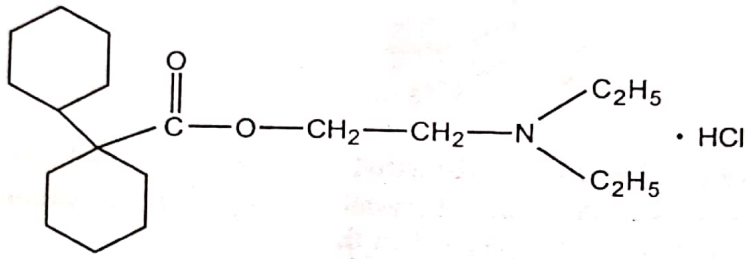
Properties : It is white crystalline powder.

Mechanism of action : It binds to muscarinic acetylcholine receptors present on the smooth muscles and secretory glands and finally inhibits the receptors. It relaxes smooth muscles and decreases biliary tract secretions.

Uses :

1. It is used as an antispasmodic and as an antiulcer. It is generally given in combination with chlordiazepoxide.
2. It decreases biliary tract secretions and is used in the treatment of irritable bowel syndrome.
3. It is also used in the treatment of acute enterocolitis.

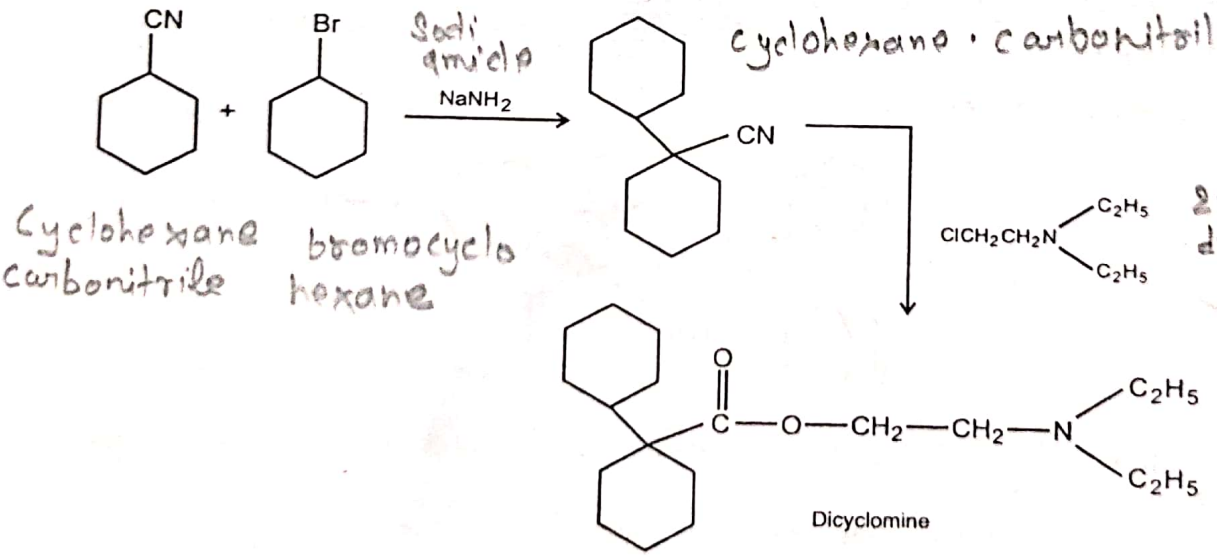
4) Dicyclomine Hydrochloride



IUPAC Name : 2-Diethylaminoethyl bicyclohexyl-1-Carboxylate Hydrochloride

Properties : It is a white or almost white crystalline powder, soluble in water

Synthesis



Sodi amide

cyclohexane · carbonitrile

Cyclohexane carbonitrile

bromocyclo hexane

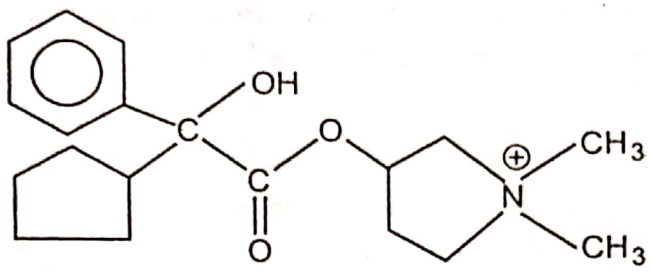
2-chloro-N,N-diethylethanamine

Mechanism of Action : It acts as non selective smooth muscle relaxant. It has specific anticholinergic effect at muscarinic receptors and has direct effect on smooth muscles.

Uses :

1. It relieves muscles spasms in g.i.t., so,used in the treatment of irritable bowel syndrome.
2. It is also used as an adjunct in the treatment of gastric and duodenal ulcer.

5) Glycopyrrolate



IUPAC Name : 3-[2-cyclopentyl (hydroxy) phenyl acetoxy]-1, 1-dimethyl pyrrolidine.

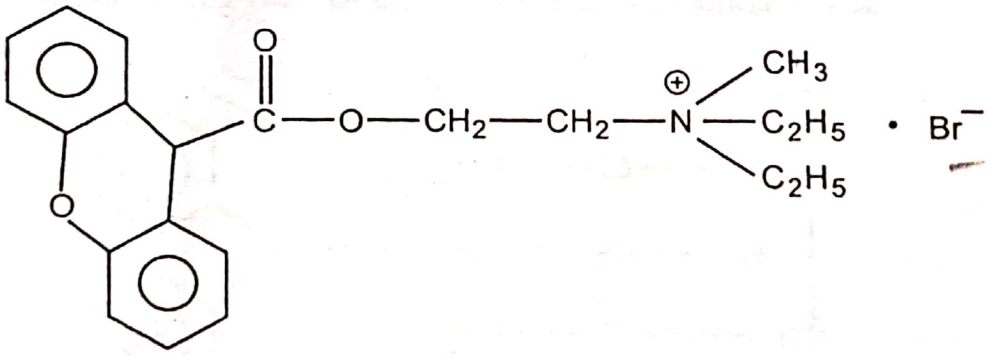
Properties : It is a synthetic quaternary amine. It is white solid crystalline powder, odorless, soluble in cold water having m.pt. 193°C. It is reactive with oxidizing agent.

Mechanism of action : Glycopyrronium blocks muscarinic receptors thus inhibiting cholinergic transmission.

Uses :

1. It is used before surgery to reduce salivary, bronchial and gastric secretions.
2. It is also used with neostigmine to reduce its muscarinic effect like bradycardia.
3. It is used to treat gastric ulcer by reducing acidic secretion.
4. Glycopyrrolate inhalation used to treat chronic obstructive pulmonary disease (COPD)

6) **Methantheline bromide**



IUPAC Name : N,N-diethyl-N-methyl-2-[(9H-Xanthen-9-ylcarbonyl)oxy]-ethanamium bromide.

Properties : It is white or yellowish white powder, slightly hygroscopic in nature, very soluble in water and stored in air tight containers. It decompose in small intestine and excreted in urine.

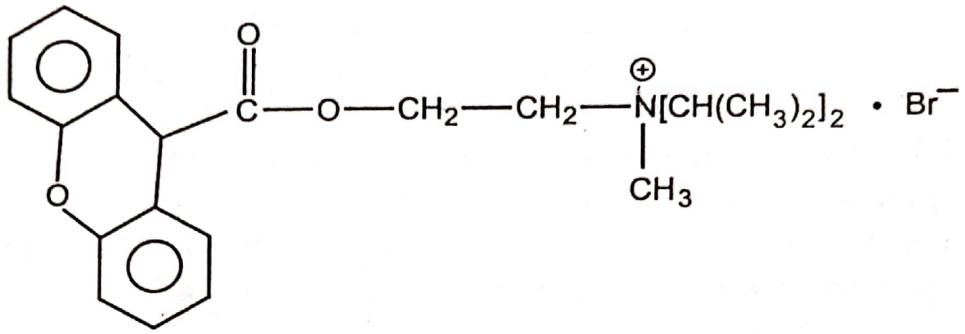
Mechanism of Action : It binds to the muscarinic receptors but do not activate it, hence it blocks the actions of endogeneous acetylcholine.

Uses :

1. It is used to relief cramps or spasms of stomach intestine and bladder.

2. It is given in combination with antacid in the treatment of peptic ulcer.
3. It is also used to control, prevention and improvement of pancreatitis, gastritis, pylorospasm, reflex neurogenic bladder.

7) Propantheline Bromide



IUPAC Name : (2-Hydroxy ethyl) diisopropyl methyl ammonium bromide xanthene-9-carboxylate

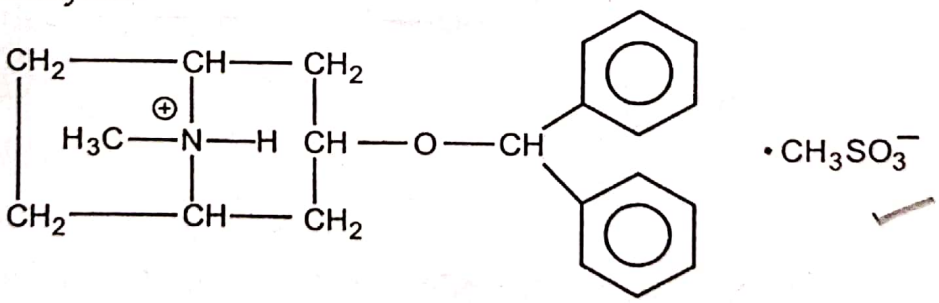
Properties : It is white or almost white crystalline powder, slightly hygroscopic in nature. It is very soluble in nature. It is stored in air tight container.

Mechanism of Action : It blocks the action of Acetylcholine by binding to muscarinic receptors present in various smooth muscles like gut bladder and eye.

Uses :

1. It is used in the treatment of spasm of the stomach, intestine and bladder.
2. It is also used in the treatment of excessive sweating.
3. It is used in combination with antacid to treat gastric ulcers.

8) Benztropine mesylate



IUPAC Name : (1R, 3r, 5S)-3-Benzhydryloxy tropane methane sulphonate.

Properties : It is a white crystalline powder, very soluble in water. It should be kept in well-closed container. It is absorbed from G.I.T.

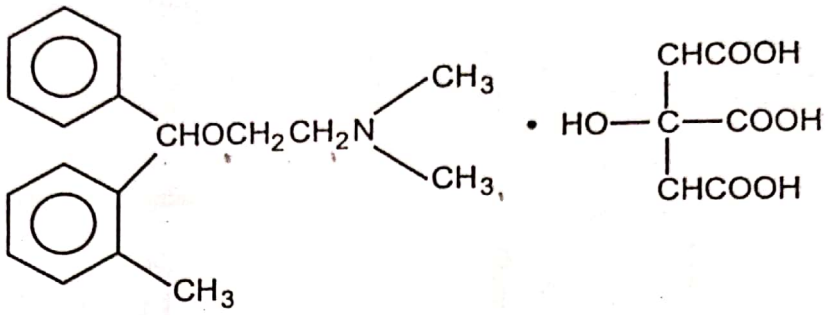
Mechanism of Action : It is centrally acting anticholinergic or antihistamine agent. It is selective M_1 muscarinic antagonist.

Uses :

1. It is used in treatment of parkinsonism.
2. It also have antihistaminic and local anaesthetic activity.
3. Sometimes it is also used for the treatment of dystonia (a rare disorder that causes abnormal muscle contraction)

4. In veterinary it is used to treat priapism (in which a penis remains erect for hours in absence of stimulation)

9) Orphenadrine citrate



IUPAC Name : Dimethyl [2-(2-methyl benzhydryloxy ethyl] amine citrate.

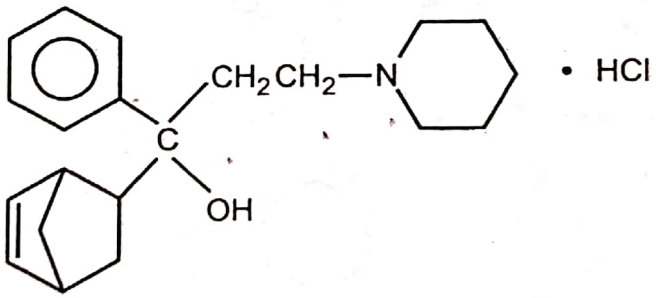
Properties : It is white or almost crystalline powder, freely soluble in water. It is readily absorbed from the G.I.T. and excreted in the urine.

Mechanism of Action : It is well known non selective acetylcholine receptor antagonist and also H_1 receptor antagonist (antihistamine).

Uses :

1. Orphenadrine is used to relieve pain due to spasms of voluntary muscle.
2. It is also used in the treatment of Parkinson's disease.
3. Orphendrine is sometimes used to treat pain arising from rheumatoid arthritis.

10) Biperidine Hydrochloride



IUPAC Name : (1RS, 2SR, 4RS)-1-(Bicyclo [2,2,1] hept-5-en-2-yl)-1-phenyl-3-(Piperidin-1-yl) propan-1-ol.

Properties : It is a white, crystalline powder, slightly soluble in water. It should be stored in air tight container protected from light. It is readily absorbed by G.I.T.

Mechanism of Action : It acts as a centrally blocking agent and blocks M_1 muscarinic receptors. It blocks all the peripheral structures which are innervated by parasympathetic system.

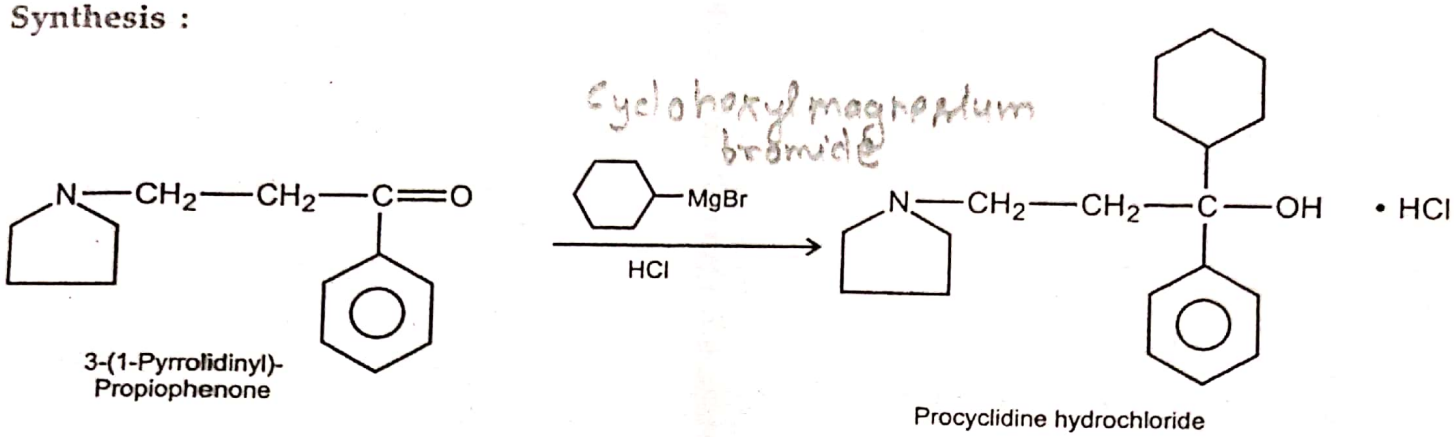
Uses :

1. It is used in treatment of parkinson's disease.
2. It is used to relieve the side effects related to antipsychotic drugs.
3. It also relieve muscle rigidity and reduce abnormal sweating and salivation.

4. Biperidine is also given in the treatment of organophosphorous toxicity.
5. By intravenous route Biperiden is used for neuroleptic malignant syndrome.

11) Procyclidine Hydrochloride

Synthesis :



3-(1-Pyrrolidinyl)-Propiophenone

Procyclidine hydrochloride

IUPAC Name : α-cyclohexyl-α-phenyl-1-pyrrolidine-propanol hydrochloride.

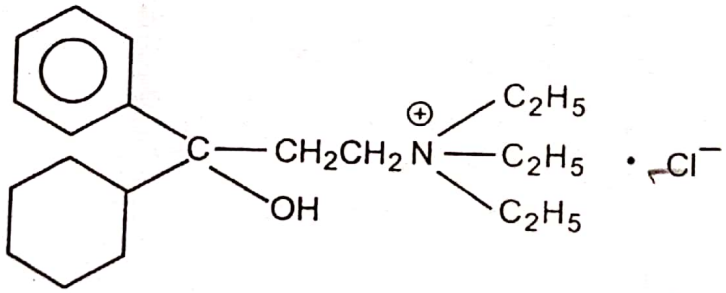
Properties : It is a white crystalline powder which is sparingly soluble in water.

Mechanism of Action : It is an anticholinergic which blocks muscarinic receptor.

Uses :

1. It is used for the treatment of drug induced parkinsonism.
2. It is also used in treatment of Akathisia (movement disorder) and acute dystonia (Neurological movement disorder).

12) Tridihexethyl chloride



IUPAC Name : 3-cyclohexyl-N, N, N-triethyl-3-hydroxy-3-phenyl propan-1-aminium chloride.

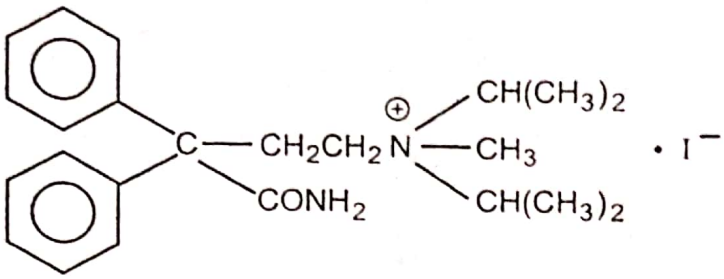
Properties : It is a white crystalline powder soluble in water.

Mechanism of action : It binds the muscarinic acetyl-choline receptor and block all three muscarinic receptor.

Uses :

1. It is used as an antispasmodic and antiulcer.
2. It may be used in combination with other drugs to treat acquired nystagmus (condition of involuntary eye movement). This drug is discontinue due to its unwanted side effects.

13) Isopropamide iodide



IUPAC Name: (3-Carbamoyl-3, 3-diphenyl propyl) diisopropyl methyl ammonium iodide.

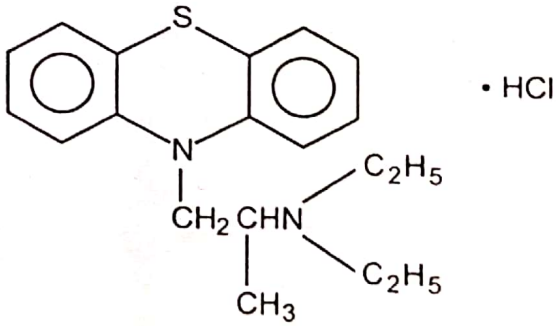
Properties : It is white crystal or powder form. It is sensitive to light so, it stored in air tight container. It is freely soluble in water, ethanol, chloroform but insoluble in ether.

Mechanism of Action : It has similar action like other anti cholinergic drugs that blocks the muscarinic receptors.

Uses :

1. It is long acting quaternary compound used in treatment of peptic ulcer and various other states of gastrointestinal hyperactivity.
2. It is also used for treatment of muscular contraction that cause pain, cold, gastritis and hyperchlorhydria.

14) Ethopropazine Hydrochloride



IUPAC Name : 10-[2-(Diethylamino) propyl] phenothiazine hydrochloride.

Properties : It is a white or slightly creamy white crystalline powder which is slightly soluble in water. It is stored in well closed container and protected from light.

Mechanism of Action : It partly block central cholinergic receptor and helps to balance cholinergic and dopaminergic activity in the ganglia.

Uses :

1. It is used in the treatment of parkinsonism.
2. It also have anaesthetic, ganglionic blocking, antihistaminic or slightly antihistaminic properties.