Medicinal Chemistry-I

Unit-III: Cholinergic Agents

- Direct acting agents
- Indirect acting
- Cholinesterase reactivator
- Cholinergic Blocking agents
- Solanaceous alkaloids and analogues
- Synthetic cholinergic blocking agents

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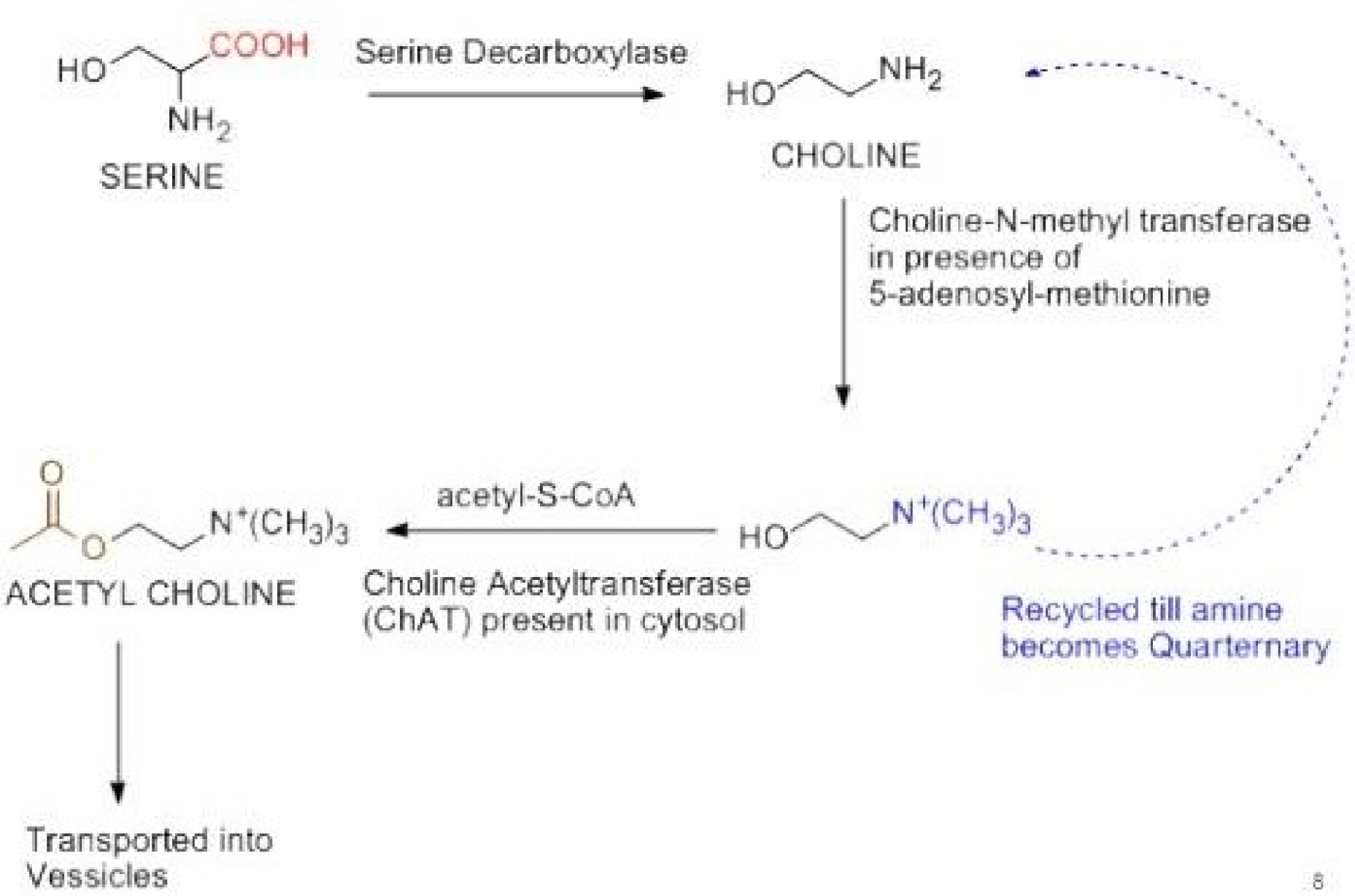
BIO-SYNTHESIS OF Acetylcholine



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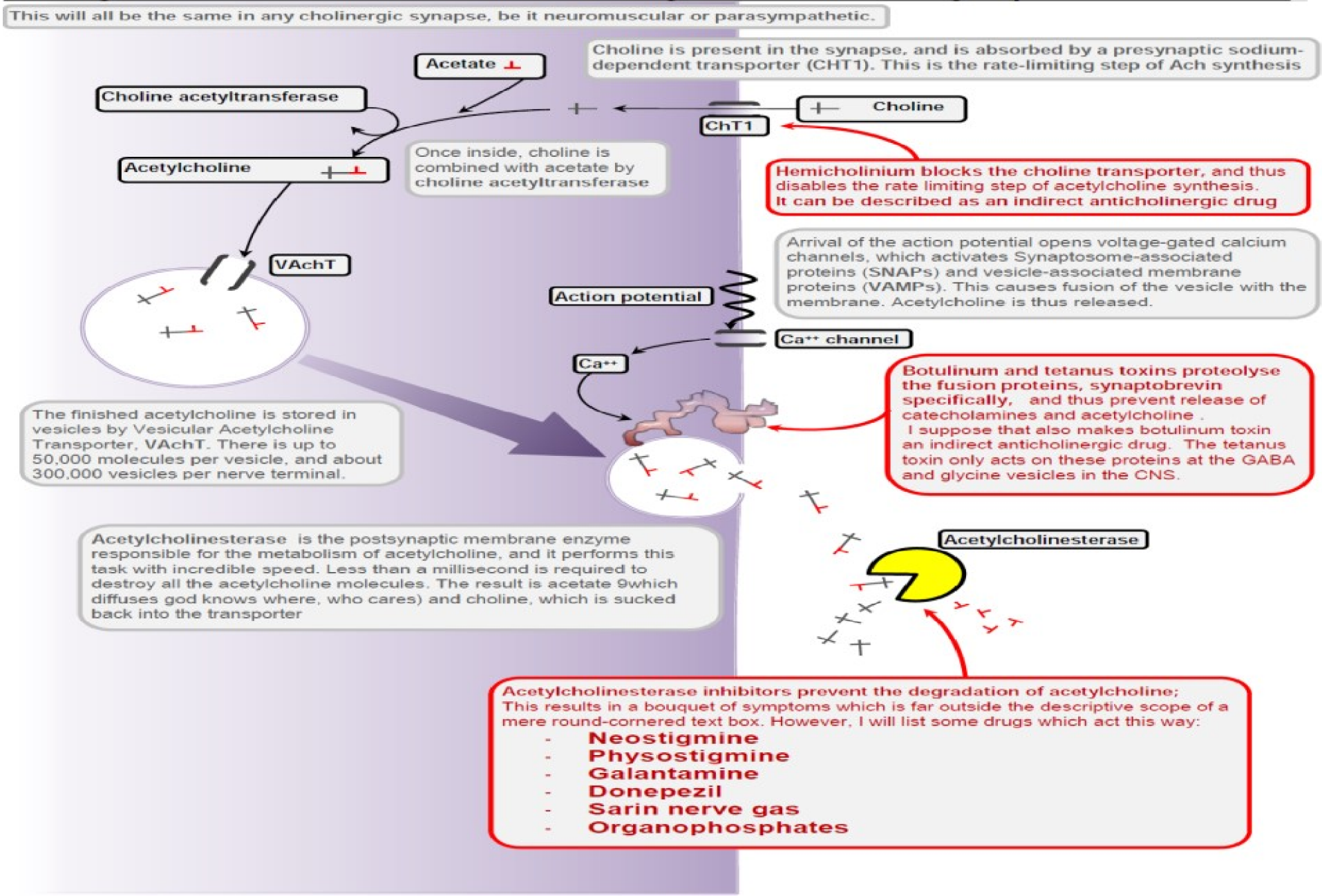
Storage release and metabolism of acetylcholine at the synapse



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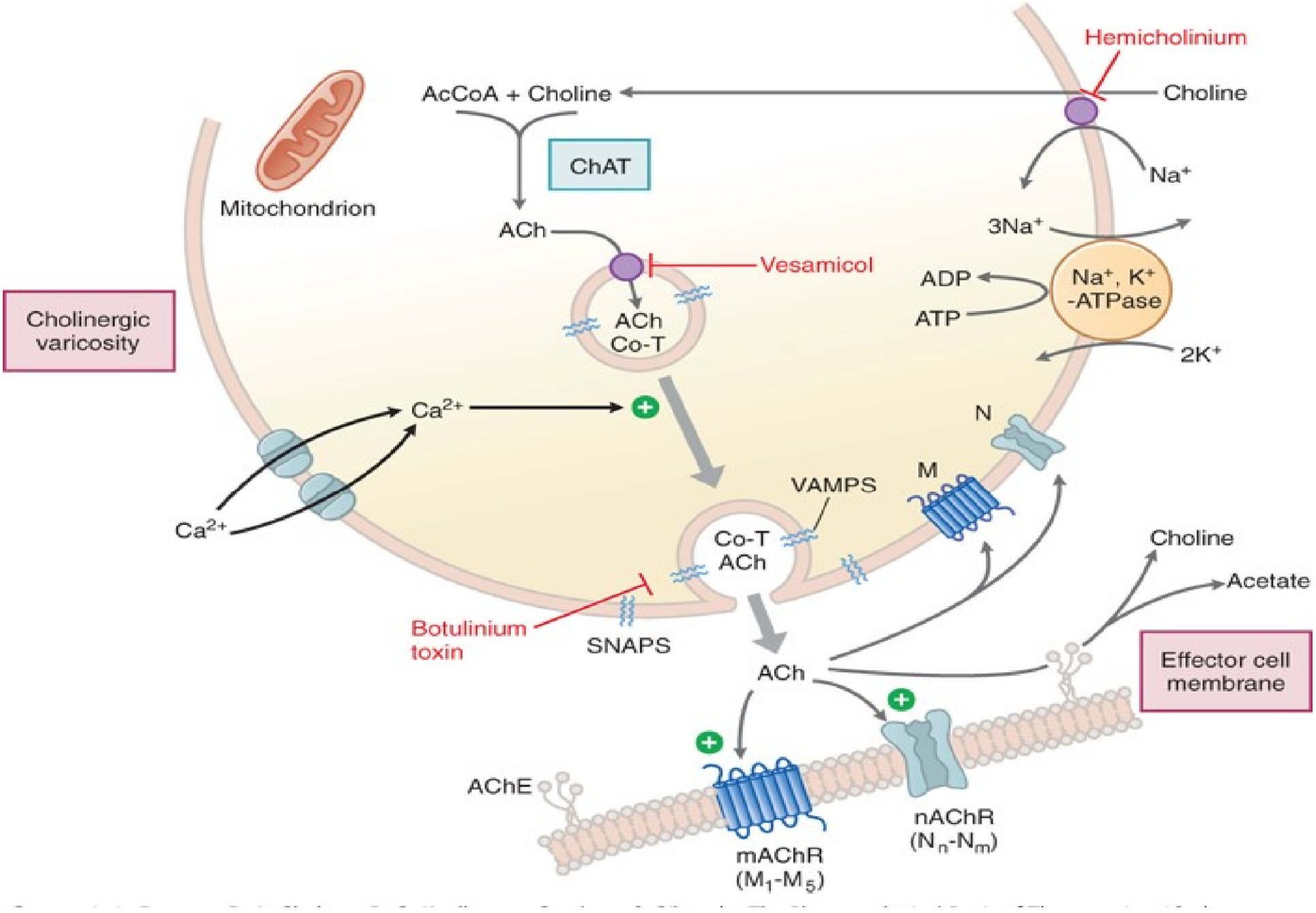
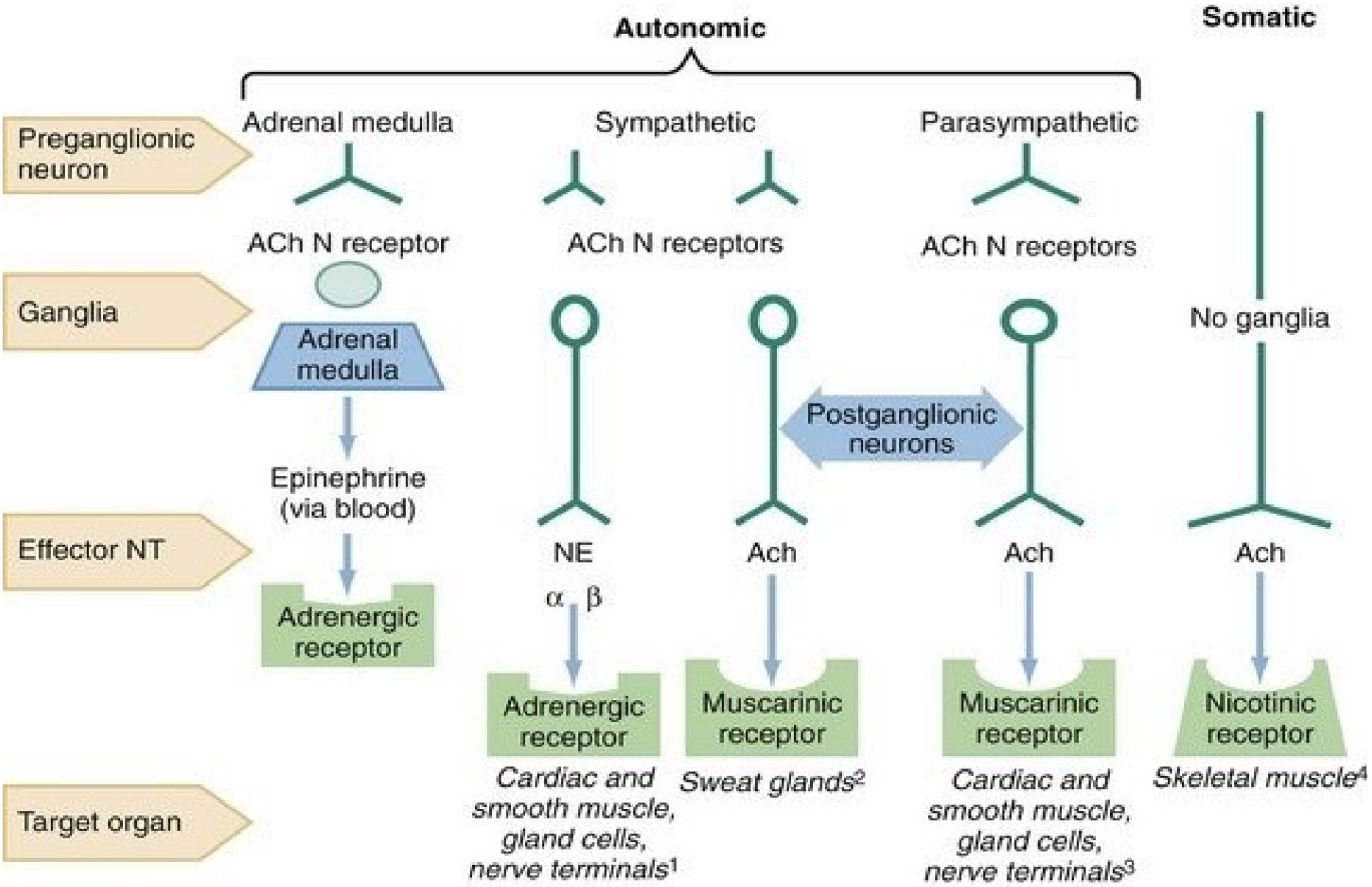

Hemicholinium
Choline
AcCoA + Choline
ChAT
Mitochondrion
Na+
ACh
3Na+
Vesamicol
ADP
Na+, K+
-ATPase
ATP
Cholinergic
varicosity
ACh
Co-T
2K+
Ca2+
N
M
VAMPS
Ca2+
Co-T
ACh
Choline
Acetate
Botulinium
toxin
SNAPS
ACh
Effector cell
membrane
AChE
nAChR
(Nn-Nm)
mAChR
(M1-M5)

Distribution of Cholinergic receptors



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Nicotinic receptors

- The nicotine is never observed in to normal (nonsmoker) person still the receptors known as nicotinic, this is because this type of receptors are known as nicotinic, because these types of receptors stimulated by nicotine which mimics the action of Ach but having more affinity than Ach.
- They are ligand gated ion channel having pentameric structure. Activation of this causes opening of ion channel which causes influx of cation & leads to depolarization and generate action potential (AP).
- Depending on the location they are classified as N_M & N_N.

N_M: They are presence on the neuromuscular junction mainly on the skeletal muscles. They cause depolarization at the muscle end plate which leads to contraction of muscle. They are pentameric having 2α, β, δ and γ or ε subunits and agonist by nicotine and PTMA and antagonist by tubocurarine.

N_N: These are present on autonomic ganglia, adrenal mdulla and CNS. At autonomic ganglia it causes depolarization of postsynaptic neurons and propogate impulses through it. In the adrenal medulla releases adr & NA by same mechanism. And at the CNS causes excitation & inhibition depending up on the neuronal chemical. Nicotine and di methyl phenyl piprizinium are agonist and hexamethonium is antagonist to them.

Muscarinic receptors

- The substance known as muscarine from mushroom (amatina muscaria) is activating these type of receptors, so named as muscarinic receptors. They are G-protein coupled receptors (GPCRs). When Ach binds with them, they activated by Gi , containing 7-helical segments of amino acids where the amino end of chain is extracellular and carboxyl end of chain is intracellular & inhibit action of AC.
- By molecular cloning they are subdivided in to M_1, M_2, M_3, M_4, and M_5.

- M_1 : It is presence on the autonomic ganglia, on the gastric gland and at the certain part of the brain like hippocampus from limbic system and at the corpous straitum. It has role in gastric secretion. And histamine release. It acts through Gq protein and activates phospholipase C (PLc) which generate DAG & IP3 as 2 messenger. Some time they also activate PL-A2.

- M_2: they are act through Gi protein hich inhibits all the functional activities. Located on the heart (SA node, AV node, atria, ventricle), on the cholinergic nerve ending and visceral smooth muscle. They inhibit AC resulting in hyperpolarisation of the neurons and decrease activity of SA node & conduction through AV node leads to bradycardia.

- M_3: it is located on the visceral smooth muscle, iris, ciliary muscle and exocrine glands. They are also GPCRs acts by Gq protein. Their activity is dominated in smooth muscle the\an M2.

- M_4: not abundant in body. They transmit neurotransmitter in certain areas of brain and acts through Gi protein.

- **M_5:** it acts by Gq protein. Derifinacin is selective antagonist & related to dopamine release.

Cholinergic Receptor Subtype, Distribution and Function

	M_1		M_2	M_3
1. Location and function subserved	*Autonomic ganglia:* *Gastric glands:* *CNS:*	Depolarization (late EPSP) Hist. release, acid secretion Learning, memory, motor functions	*SA node:* Hyperpolarization, ↓ rate of impulse generation *AV node:* ↓ velocity of conduction *Atrium:* shortening of APD, ↓ contractility *Ventricle:* ↓ contractility (slight) (receptors sparse) *Cholinergic nerve endings:* ↓ ACh release *CNS:* tremor, analgesia *Visceral smooth muscle:* contraction	*Visceral smooth muscle:* contraction *Iris:* constriction of pupil *Ciliary muscle:* contraction *Exocrine glands:* secretion *Vascular endothelium:* release of NO→ vasodilatation
2. Nature	Gq-protein coupled		Gi/Go-protein coupled	Gq-protein coupled
3. Transducer mechanism	IP_3/DAG—↑ cytosolic Ca^{2+}, PLA_2↑—PG synthesis		K^+ channel opening, ↓ cAMP	IP_3/DAG—↑ cytosolic Ca^{2+} PLA_2↑—PG synthesis
4. Agonists*	MCN-343A, Oxotremorine		Methacholine	Bethanechol
5. Antagonists*	Pirenzepine, Telenzepine		Methoctramine, Tripitramine	Solifenacin, Darifenacin

M1: The M1 is primarily a neuronal receptor located on ganglion cells and central neurones, especially in cortex, hippocampus and corpus striatum. It plays a major role in mediating gastric secretion, relaxation of lower esophageal sphincter (LES) caused by vagal stimulation, and in learning, memory, motor functions, etc.

M2: Cardiac muscarinic receptors are predominantly M2 and mediate vagal bradycardia. Autoreceptors on cholinergic nerve endings are also of M2 subtype. Smooth muscles express some M2 receptors as well which, like M3, mediate contraction.

M3: Visceral smooth muscle contraction and glandular secretions are elicited through M3 receptors, which also mediate vasodilatation through EDRF release. Together the M2 and M3 receptors mediate most of the well-recognized muscarinic actions including contraction of LES.

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Cholinergic Receptor Subtype, Distribution and Function

	N_M	N_N
1. Location and function subserved	*Neuromuscular junction:* depolarization of muscle end plate —contraction of skeletal muscle	*Autonomic ganglia:* depolarization —postganglionic impulse *Adrenal medulla:* catecholamine release *CNS:* site specific excitation or inhibition
2. Nature	Has intrinsic ion channel, pentamer of $\alpha 2\ \beta\ \varepsilon$ or γ and δ subunits, each subunit has 4 TM segments	Has intrinsic ion channel, pentamer of only α or α,β subunits, each subunit has 4 TM segments
3. Transducer mechanism	Opening of cation (Na^+, K^+) channels	Opening of cation (Na^+, K^+, Ca^{2+}) channels
4. Agonists	PTMA, Nicotine	DMPP, Nicotine
5. Antagonists	Tubocurarine, α-Bungarotoxin	Hexamethonium, Trimethaphan

NM: These are present at skeletal muscle endplate: are selectively stimulated by phenyl trimethyl ammonium (PTMA) and blocked by tubocurarine. They mediate skeletal muscle contraction.

NN: These are present on ganglionic cells (sympathetic as well as parasympathetic), adrenal medullary cells (embryologically derived from the same site as ganglionic cells) and in spinal cord and certain areas of brain. They are selectively stimulated by dimethyl phenyl piperazinium (DMPP), blocked by hexamethonium, and constitute the primary pathway of transmission in ganglia.

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Comparison of Cholinergic effects with Adrenergic Effects

Sympathetic System	**Parasympathetic System**
1 .Dilates Pupil, Allowing More light To Pass into Eyes.	1) Constrict Pupil
2) Heart Beat Acclerated.	2) Heartbeat Retarded
3) Stimulates Lacrymal Gland Secreation	3)Prevant Lacrymal Gland Secreation.
4) Prevent Gut Peristalsis.	4) Stimulate Gut Peristalisis
5) Inhibit Secreation of Salivery Gland and Digestive Gland	5) Stimulate Secreation of Salivery Gland and Digestive Gland
6) Stimulate Adrenal Secretion	6) Inhibit
7) Stimulate Secretion of Sweat	7) Inhibit
8) Stimulate Ejaculation of Semen	8) Stimulate External Genital and Increase Sex Urges
9) Closes Anus By Contracting Anal Spincter.	9) Relax Anal Spincter.
10) Relax Urinary Bladder But Contract Its Sphincter.	10) Contract Urinary Bladder But Relax Its Sphincter

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Classification of Cholinergic Drugs

Depending upon type of Action

Cholinergic Agonists: Acetylcholine, Methacholine, Bethanicol,Carbachol, etc.
Cholinergic Antagonists: Atropine, Homoatropine, Propantheline, etc.
Acetylcholine-esterase Inhibitors: Physostigmine, Neo-stigmine, Pyridostigmine, etc.

Depending upon type of Receptors

Muscarinic Receptor

→Agonists: Acetylcholine, Carbachol, Methacholine, Bethanicol, Pilocarpine, Muscarine, etc.

→ Antagonists: Atropine, Pirenzapine, Galamine, tec.

Nicotinic Receptor

→Agonist: Nicotine, Lobeline, Decamethonium, etc.

→ Antagonist: Galamine, Pancuronium, Atracurarium, etc.

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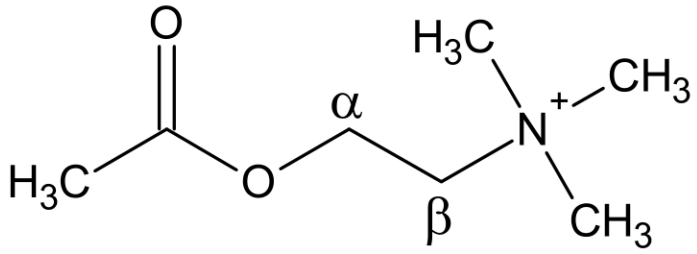
SAR of Acetylcholine



The structure of Acetylcholine can be divided into 3 parts.

#1 Acyloxy group

→ Increase in methyl groups decreases activity.

→ Increases in molecular mass or aromatic substitution has antagonistic activity.

→ replacement of ester with ketones produces chemically stable & potentially active compounds.

→ Replacement of methyl with amino (carbamate) resists the metabolic hydrolysis but retains the activity of acetylcholine.

#2 Ethylene Bridge

→ Increase in chain length reduces activity.

→ Replacement of hydrogen with methyl group increases activity but groups larger than methyl decreases activity.

→ α and β – methyl substitution affect selectivity to receptors. α – methyl substitution has nicotinic selectivity & β – methyl substitution has muscarinic selectivity .

#3 Quaternary ammonium

→ Quaternary ammonium is essential for cholinergic activity. Replacement of Nitrogen with Sulphur, Arseic, Selenium, etc. decreases activity.

→ Replacement of methyl of ammonium decreases activity.

→ Primary, Secondary, Tertiary, are less active than quaternary ammonium.

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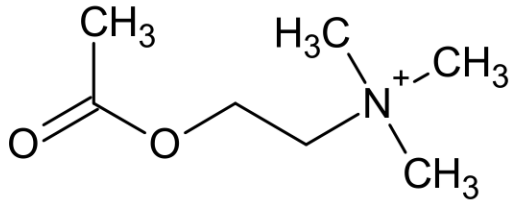
Direct acting Parasympathomimetic agents

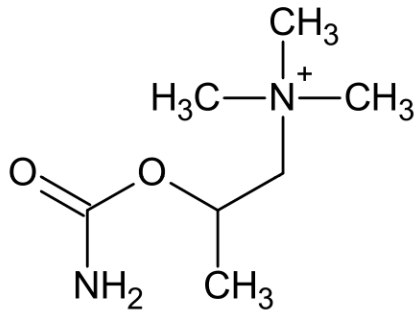
Acetylcholine



2-(acetyloxy)-*N*,*N*,*N*-trimethylethanaminium

Uses: Drugs that bind to and activate cholinergic receptors and non-selectively elicit all cholinergic effects. Drugs used to cause dilation of the blood vessels

Bethanechol



2-(carbamoyloxy)-*N*,*N*,*N*-trimethylpropan-1-aminium

Bethanechol is a parasympathomimetic (cholinergic) used for the treatment of acute postoperative and postpartum nonobstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention. Bethanechol, a cholinergic agent, is a synthetic ester which is structurally and pharmacologically related to acetylcholine. It increases the tone of the detrusor urinae muscle, usually producing a contraction sufficiently strong to initiate micturition and empty the bladder. It stimulates gastric motility, increases gastric tone, and often restores impaired rhythmic peristalsis.

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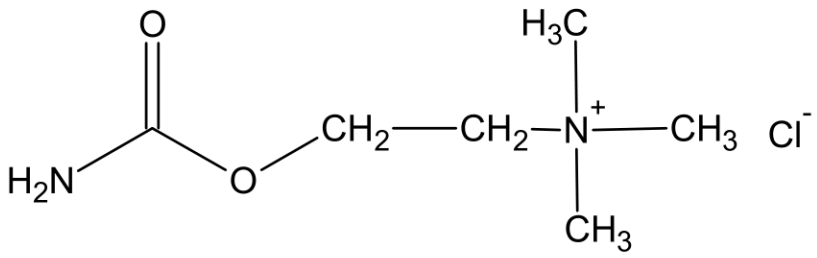
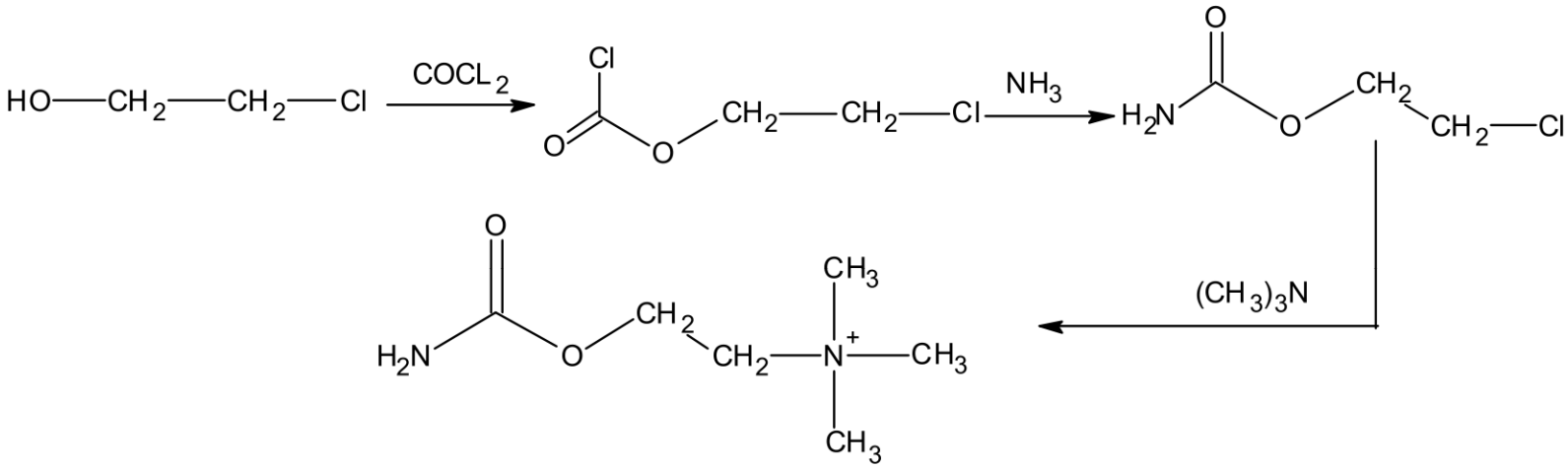
Carbachol



2-[(Aminocarbonyl)oxy]-*N*,*N*,*N*-trimethylethanaminium chloride

Synthesis:



Uses: Carbachol is a potent cholinergic (parasympathomimetic) agent which produces constriction of the iris and ciliary body resulting in reduction in intraocular pressure. The exact mechanism by which carbachol lowers intraocular pressure is not precisely known. In the cat and rat, carbachol is well-known for its ability to induce rapid eye movement (REM) sleep when microinjected into the pontine reticular formation. Carbachol elicits this REM sleep-like state via activation of postsynaptic muscarinic cholinergic receptors .

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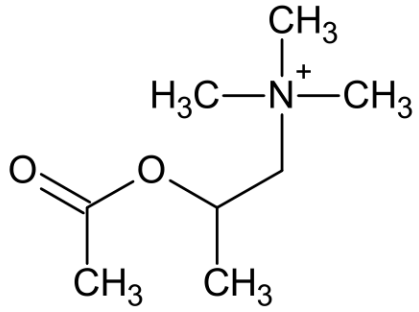
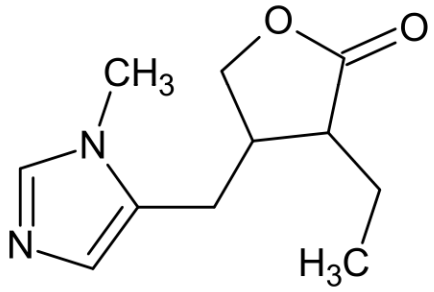
Methacholine



2-(acetyloxy)-*N*,*N*,*N*-trimethylpropan-1-aminium

Uses: Methacholine acts as a non-selective muscarinic receptor agonist to stimulate the parasympathetic nervous system. It is highly active at all of the muscarinic receptors. Causes Bronchoconstrictor by narrowing of the lumen of a bronchus or bronchiole.

Pilocarpine

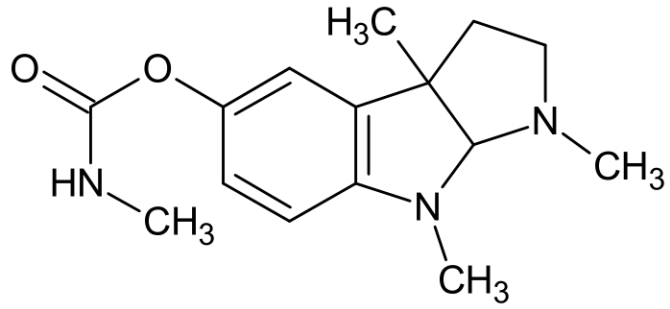


3-ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)-one

Uses: Pilocarpine is a choline ester miotic and a positively charged quaternary ammonium compound. Pilocarpine, in appropriate dosage, can increase secretion by the exocrine glands. The sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucous cells of the respiratory tract may be stimulated. When applied topically to the eye as a single dose it causes miosis, spasm of accommodation, and may cause a transitory rise in intraocular pressure followed by a more persistent fall.

Indirect acting Parasympathomimetics/ Cholinesterase inhibitors

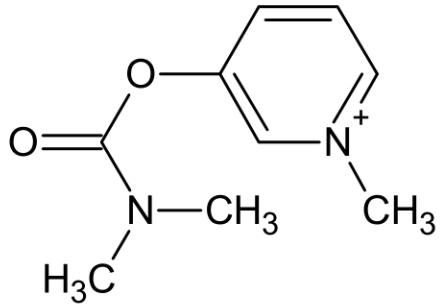
Physostigmine



1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl methylcarbamate

Uses: Physostigmine is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor which effectively increases the concentration of acetylcholine at the sites of cholinergic transmission. Physostigmine is used to treat glaucoma. Because it crosses the blood-brain barrier, it is also used to treat the central nervous system effects of atropine overdose.

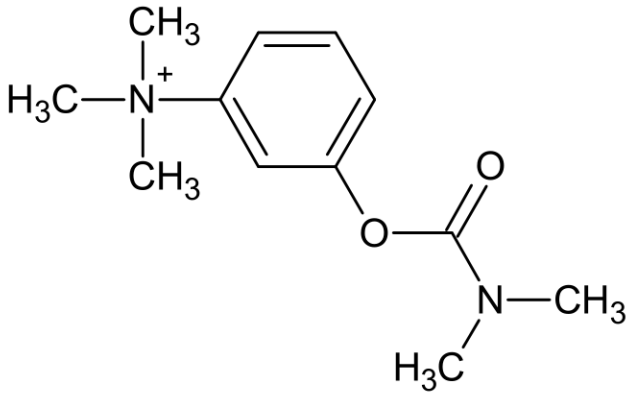
Pyridostigmine



3-[(dimethylcarbamoyl)oxy]-1-methylpyridinium

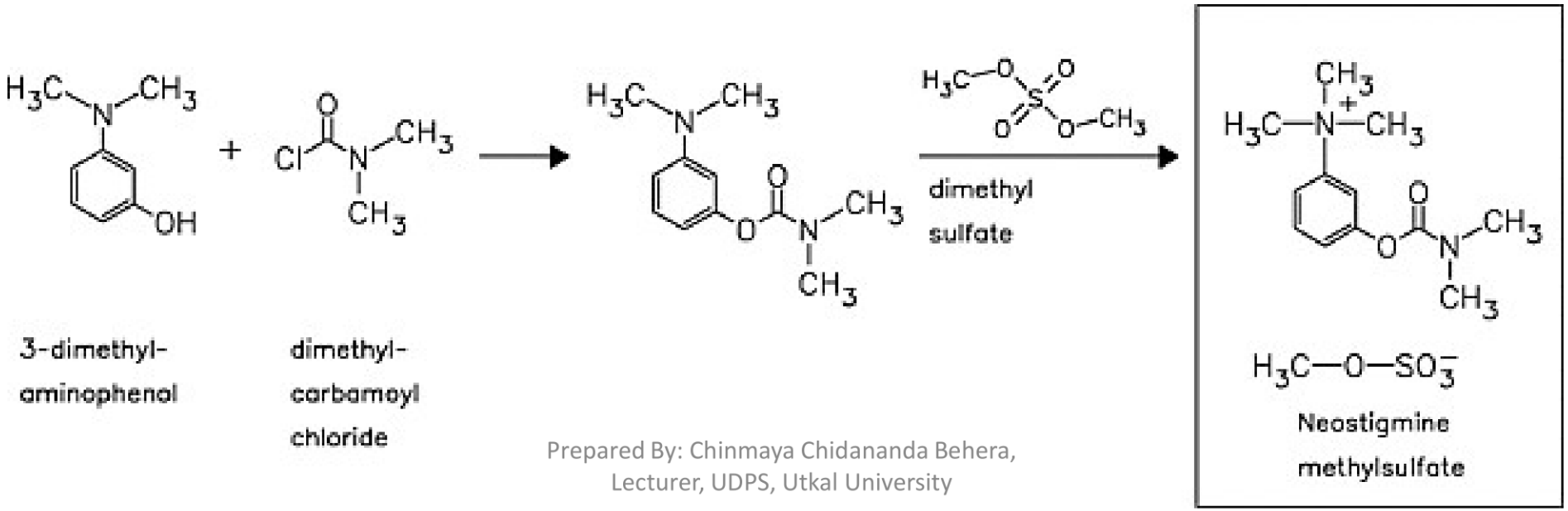
Uses: Pyridostigmine is a parasympathomimetic and a reversible cholinesterase inhibitor. Since it is a quaternary amine, it is poorly absorbed in the gut and doesn't cross the blood-brain barrier. Pyridostigmine has a slightly longer duration of action than NEOSTIGMINE. It is used in the treatment of myasthenia gravis and to reverse the actions of muscle relaxants.

Neostigmine



3-[(dimethylcarbamoyl)oxy]-*N*,*N*,*N*-trimethylanilinium

Uses: Neostigmine is a cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the effects of muscle relaxants such as gallamine and tubocurarine. Neostigmine, unlike physostigmine, does not cross the blood-brain barrier. By inhibiting acetylcholinesterase, more acetylcholine is available in the synapse, therefore, more of it can bind to the fewer receptors present in myasthenia gravis and can better trigger muscular contraction.



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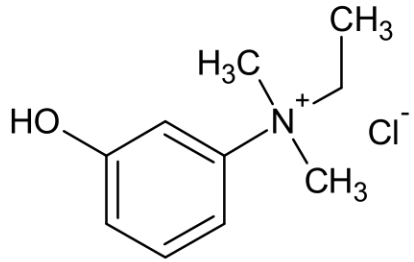
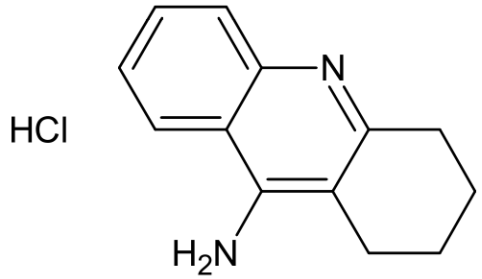
Edrophonium chloride



N-ethyl-3-hydroxy-*N*,*N*-dimethylanilinium chloride

Uses: Edrophonium Chloride is the chloride salt form of edrophonium, a short and rapid-acting cholinesterase inhibitor with parasympathomimetic activity. Echothiophate chloride potentiates the action of endogenous acetylcholine by inhibiting acetylcholinesterase that hydrolyzes acetylcholine. When applied topically to the eye, this agent prolongs stimulation of the parasympathetic receptors at the neuromuscular junctions of the longitudinal muscle of the ciliary body, thereby increases aqueous humor outflow from the eye and reduces intraocular pressure.

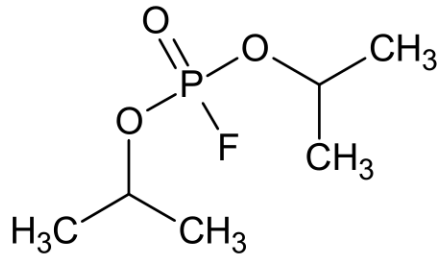
Tacrine hydrochloride



1,2,3,4-tetrahydroacridin-9-amine hydrochloride

Uses: Tacrine Hydrochloride is the hydrochloride salt form of tacrine, an aminoacridine derivative with cognitive stimulating property. Although the mechanism of action has not been fully elucidated, tacrine hydrochloride may bind reversibly to cholinesterase, acetylcholinesterase as well as butyrylcholinesterase, thereby decreasing the breakdown of acetylcholine, and prolonging synaptic actions as well as increased release of acetylcholine. In addition, this agent inhibits monoamine oxidase (MAO) and may inhibit the reuptake of catecholamines and serotonin.

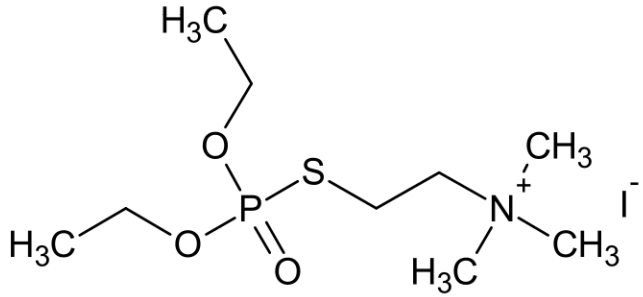
Isofluorphate



dipropan-2-yl phosphorofluoridate

Uses: Isoflurophate is used as ocular drops in the treatment of chronic glaucoma. Isoflurophate is an organophosphorus compound that acts as an irreversible cholinesterase inhibitor. As such, it displays parasympathomimetic effects. Isoflurophate is used in the eye to treat certain types of glaucoma and other eye conditions, such as accommodative esotropia. They may also be used in the diagnosis of certain eye conditions, such as accommodative esotropia. Isoflurophate damages the acetylcholinesterase enzyme and is therefore irreversible, however, pralidoxime can displace organophosphates such as isoflurophate from acetylcholinesterase, but only if administered before isoflurophate damages (alkylates) the enzyme.

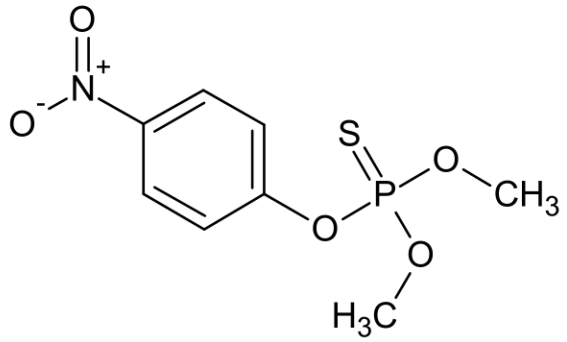
Echothiophate iodide



2-[(diethoxyphosphoryl)sulfanyl]-*N*,*N*,*N*-trimethylethanaminium iodide

Uses: Echothiophate Iodide is the iodide salt form of echothiophate, a long-acting cholinesterase inhibitor with parasympathomimetic activity. Echothiophate iodide potentiates the action of endogenous acetylcholine by inhibiting acetylcholinesterase that hydrolyzes acetylcholine. When applied topically to the eye, this agent prolongs stimulation of the parasympathetic receptors at the neuromuscular junctions of the longitudinal muscle of the ciliary body, thereby increases aqueous humor outflow from the eye and reduces intraocular pressure.

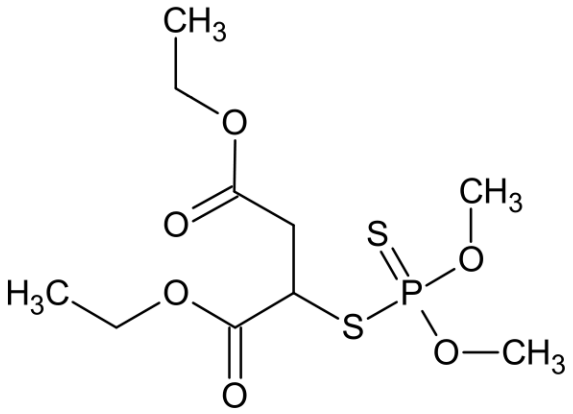
Parathione



O,*O*-dimethyl *O*-(4-nitrophenyl) phosphorothioate

Uses: It is a Cholinestrage inhibitor. The neurotransmitter ACETYLCHOLINE is rapidly hydrolyzed, and thereby inactivated, by cholinesterases. When cholinesterases are inhibited, the action of endogenously released acetylcholine at cholinergic synapses is potentiated. Pesticides designed to control insects that are harmful to man.

Malathion



diethyl 2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioate

Uses: Malathion is a cholinesterase inhibitor organophosphate insecticide commonly used to control mosquitos and other flying insects. Pharmaceutically, malathion is used to eliminate head lice. The principal toxicological effect of malathion is cholinesterase inhibition, due primarily to malaoxon and to phosphorus thionate impurities.

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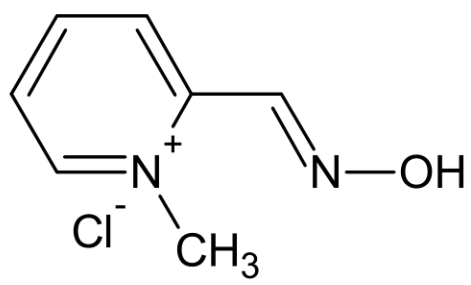
Cholinesterase reactivator:
Pralidoxime chloride



2-[(*E*)-(hydroxyimino)methyl]-1-methylpyridinium chloride

Uses: It is and Cholinesterase Reactivator and used to reverse the inactivation of cholinesterase caused by organophosphates or sulfonates. They are an important component of therapy in agricultural, industrial, and military poisonings by organophosphates and sulfonates.

Cholinergic Blocking Agents-antagonist (Anticholinergic Agent)

An anticholinergic drug is a drug or an agent that competes with the neurotransmitter "acetylcholine" for its binding sites at synaptic junctions thereby suppressing or inhibiting its activity and thus preventing the transmission of parasympathetic nerve impulses.

Depending on the type of receptor to act on, anticholinergic drugs are either classified as muscarinic antagonists or nicotinic antagonists.

Mechanism of Action of Cholinergic Blocking Agents: Competitive antagonists for Ach.

Effects of Cholinergic Blocking Agents:

Cardiovascular

–Small doses: decrease heart rate
–Large doses: increase heart rate

CNS

–Small doses: decrease muscle rigidity and tremors
–Large doses: drowsiness, disorientation, hallucinations

Eye

–Dilated pupils (mydriasis)
–Decreased accommodation due to paralysis of ciliary muscles (cycloplegia)

Gastrointestinal

–Decrease intestinal and gastric secretions
–Decrease motility and peristalsis

Genitourinary

–Relaxed detrusor muscle
–Increased constriction of internal sphincter
–Result: urinary retention

Glandular

–Decreased bronchial secretions, salivation, sweating

Respiratory

–Decreased bronchial secretions
–Dilated bronchial airways

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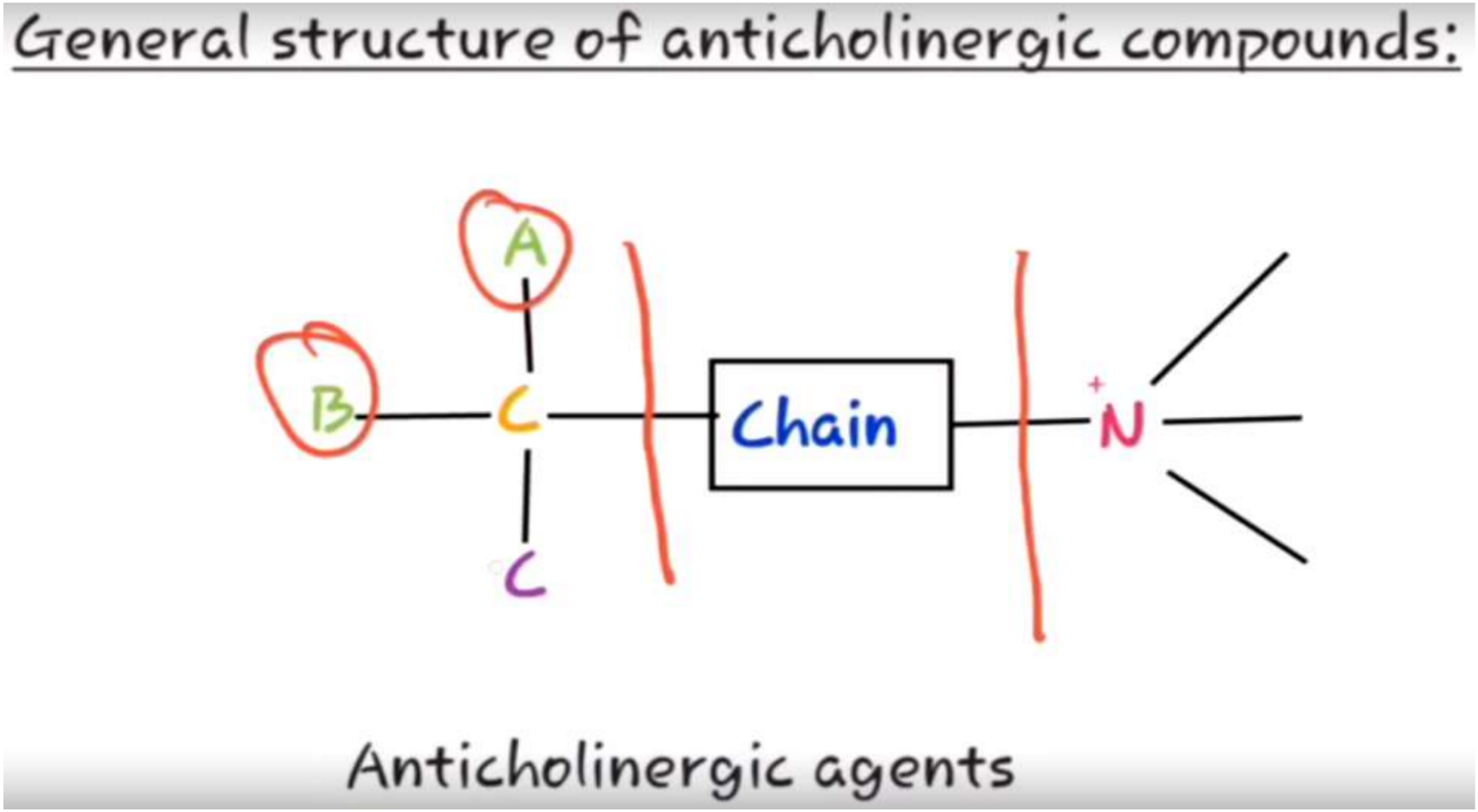
Chemical class of Cholinergic Blocking Agents :

Natural : Atropine, Hyoscyamine, Scopolamine, Belladonna, etc.

Synthetic/Semisynthetic: Tropicamide, Cyclopentolate hydrochloride, Clidinium bromide, Dicyclomine hydrochloride, etc.

SAR of Anti-Cholinergic Drugs



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Modifications in cationic head:

- Quaternary ammonium compounds possess most potent anticholinergic activity.
- Tertiary amines also possess the antagonist activity but they bind to the receptor in the protonated form.
- Methyl, ethyl, propyl or isopropyl groups are tolerated.

Modifications in chain:

- Ester group provides the most potent anticholinergic activity.
- The substituent may also be ether or amino alcohol.
- Substituent may sometimes be completely absent too.

Cyclic substitution/ A and B substitution:

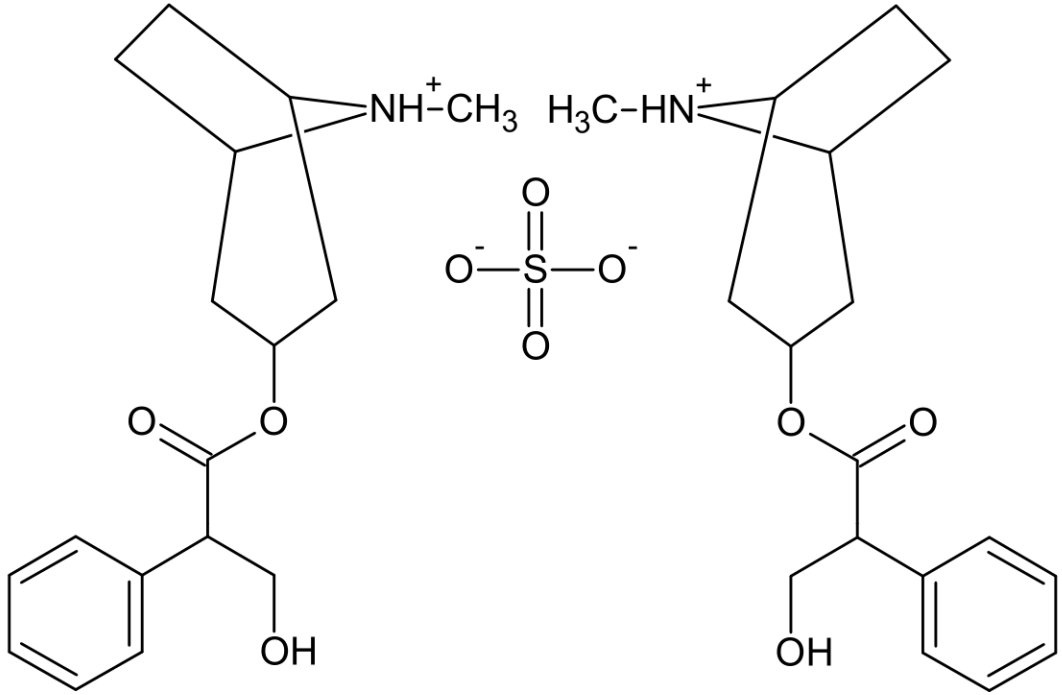
- Substituent could be cycloalkyl, aromatic rings, or hetrocyclic rings.
- Substituent of carbocyclic or hetrocyclic ring gives maximal antagonist potency.
- One ring is aromatic and the other is saturated or possessing only one olefenic bond.
- The rings could be identical but the more potent compounds are found to have different ring substitution.

Substitution at C or Hydroxyl group substitution:

- The substituent can be hydrogen atom or hydroxyl group or hydroxymethyl group.
- Antagonist with hydroxyl group or hydroxymethyl group are more potent.

Solanaceous alkaloids and analogues

Atropine sulphate



(8-methyl-8-azoniabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenylpropanoate;sulfat

Uses:

Atropine Sulfate is the sulfate salt of atropine, a naturally-occurring alkaloid isolated from the plant Atropa belladonna. Atropine functions as a sympathetic, competitive antagonist of muscarinic cholinergic receptors, thereby abolishing the effects of parasympathetic stimulation. This agent may induce tachycardia, inhibit secretions, and relax smooth muscles.

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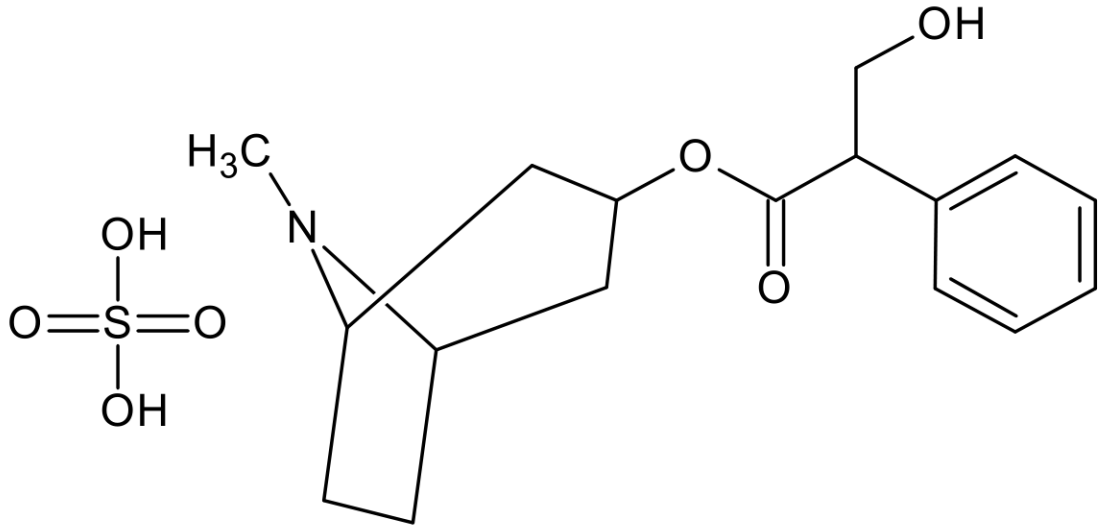
Hyoscyamine sulphate



8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-3-hydroxy-2-phenylpropanoate;sulfuric acid

Uses: Hyoscyamine Sulfate is the sulfate salt of a belladonna alkaloid derivative and the levorotatory form of racemic atropine isolated from the plants Hyoscyamus niger or Atropa belladonna. Hyoscyamine functions as a non-selective, competitive antagonist of muscarinic receptors, thereby inhibiting the parasympathetic activities of acetylcholine on the salivary, bronchial, and sweat glands, as well as the eye, heart, bladder, and gastrointestinal tract. These inhibitory effects cause a decrease in saliva, bronchial mucus, gastric juices, and sweat. Furthermore, its inhibitory action on smooth muscle prevents bladder contraction and decreases gastrointestinal motility.

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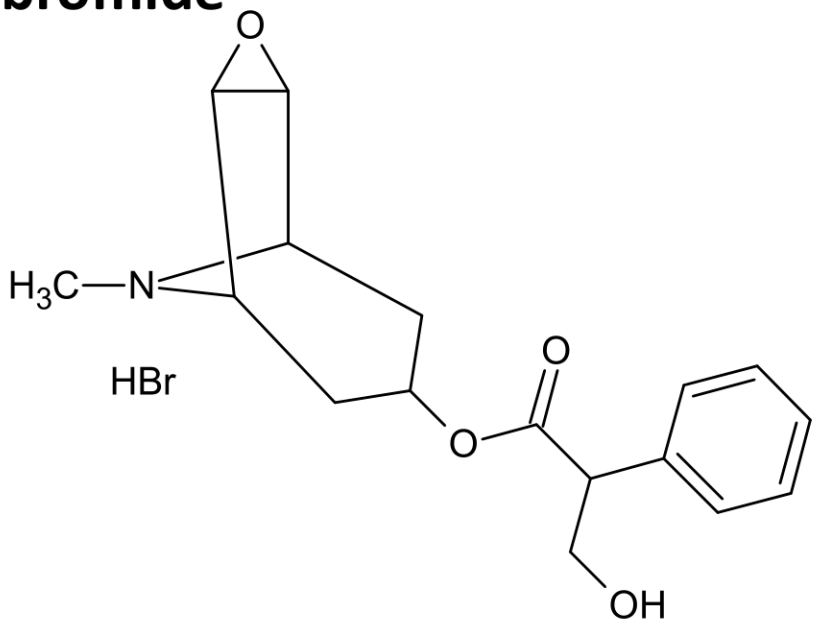
Scopolamine hydrobromide



(9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl) 3-hydroxy-2-phenylpropanoate; hydrobromide

Uses: Scopolamine Hydrobromide is the hydrobromide salt form of scopolamine, a tropane alkaloid derived from plants of the nightshade family (Solanaceae), specifically Hyoscyamus niger and Atropa belladonna, with anticholinergic, antiemetic and antivertigo properties. Structurally similar to acetylcholine, scopolamine antagonizes acetylcholine activity mediated by muscarinic receptors located on structures innervated by postganglionic cholinergic nerves as well as on smooth muscles that respond to acetylcholine but lack cholinergic innervation. The agent is used to cause mydriasis, cycloplegia, to control the secretion of saliva and gastric acid, to slow gut motility, and prevent vomiting.

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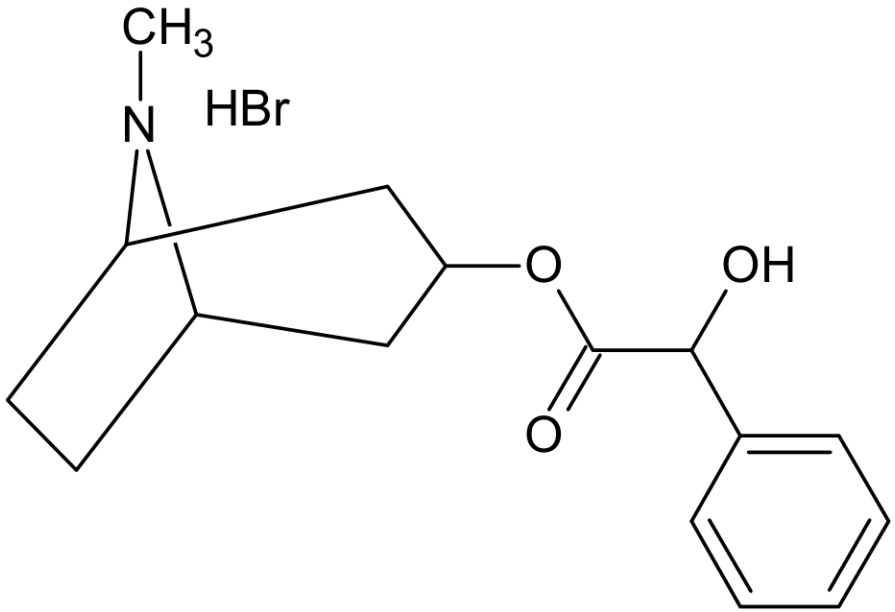
Homatropine hydrobromide



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

Uses: Homatropine Hydrobromide is the hydrobromide salt form of homatropine, a synthetic tertiary amine alkaloid with antimuscarinic properties. Homatropine, a competitive inhibitor of acetylcholine at the muscarinic receptor, blocks parasympathetic nerve stimulation. When applied topically to the eye, dilation of the pupil (mydriasis) and paralysis of accommodation (cycloplegia) result from the local anticholinergic effects on the ciliary muscle and iris.

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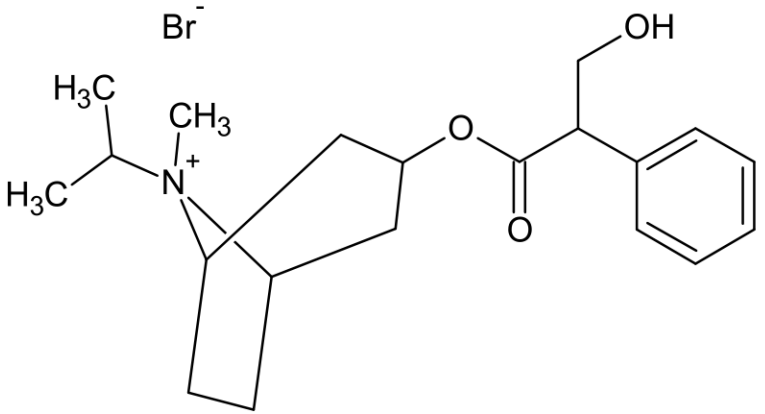
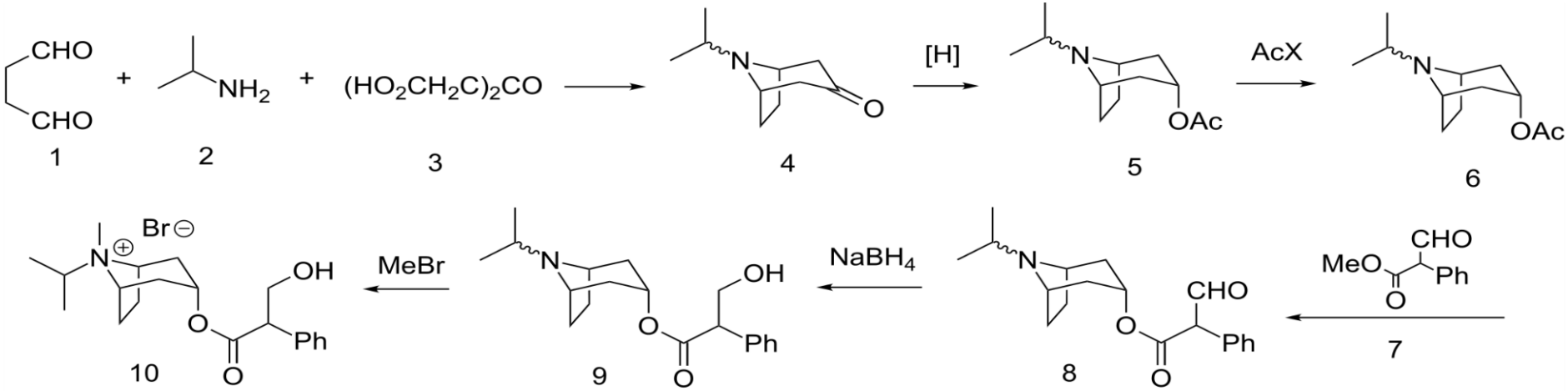
Ipratropium bromide



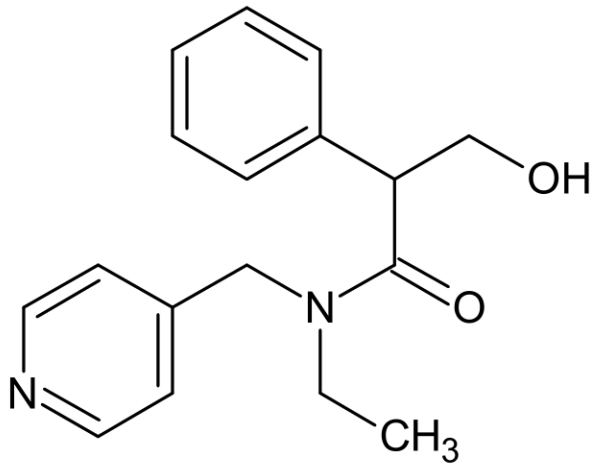
(8-methyl-8-propan-2-yl-8-azoniabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenylpropanoate;bromide

Uses: Ipratropium Bromide is the bromide salt form of ipratropium, a synthetic derivative of the alkaloid atropine with anticholinergic properties. Ipratropium antagonizes the actions of acetylcholine at parasympathetic, postganglionic, effector-cell junctions. When inhaled, ipratropium binds competitively to cholinergic receptors in the bronchial smooth muscle thereby blocking the bronchoconstrictor actions of the acetylcholine mediated vagal impulses. Inhibition of the vagal tone leads to dilation of the large central airways resulting in bronchodilation.



Synthetic cholinergic blocking agents:

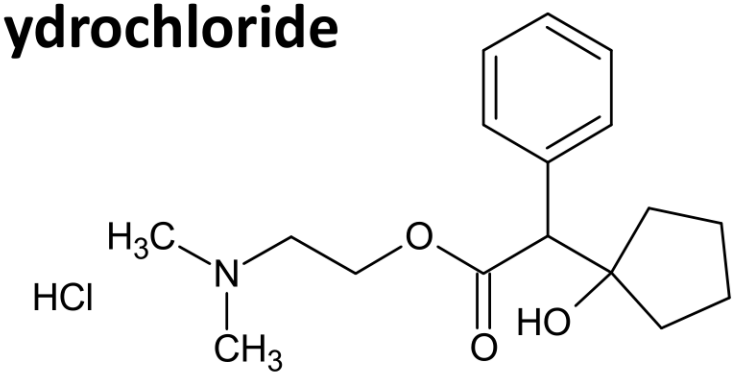
Tropicamide



N-ethyl-3-hydroxy-2-phenyl-N-(pyridin-4-ylmethyl)propanamide

Uses: Tropicamide belongs to the group of medicines called anti-muscarinics. Tropicamide blocks the receptors in the muscles of the eye (muscarinic receptors). These receptors are involved controlling the pupil size and the shape of the lens. By blocking these receptors, tropicamide produces dilatation of the pupil (mydriasis) and prevents the eye from accommodating for near vision (cycloplegia). Tropicamide is given as eye drops to dilate the pupil and relax the lens so that eye examinations can be carried out thoroughly.

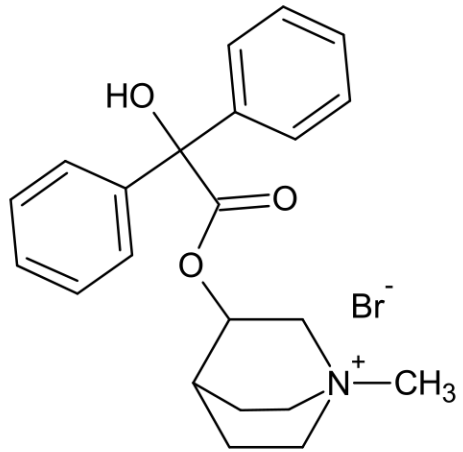
Cyclopentolate Hydrochloride



2-(dimethylamino)ethyl 2-(1-hydroxycyclopentyl)-2-phenylacetate;hydrochloride

Uses: Cyclopentolate Hydrochloride is the hydrochloride salt form of cyclopentolate, an anticholinergic drug. Administered in the eye, cyclopentolate hydrochloride blocks the acetylcholine receptor in the sphincter muscle of the iris and the ciliary muscle, thereby preventing contraction. This dilates the pupil, producing mydriasis, and prevents the eye from accommodating.

Clidinium bromide



(1-methyl-1-azoniabicyclo[2.2.2]octan-3-yl) 2-hydroxy-2,2-diphenylacetate;bromide

Uses: It inhibit the actions of the parasympathetic nervous system and is used therapeutically as MUSCARINIC ANTAGONISTS.

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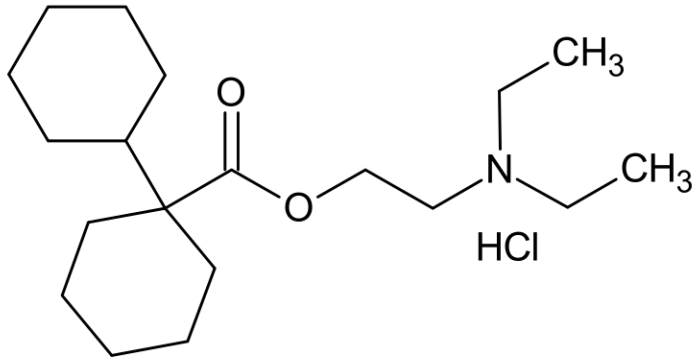
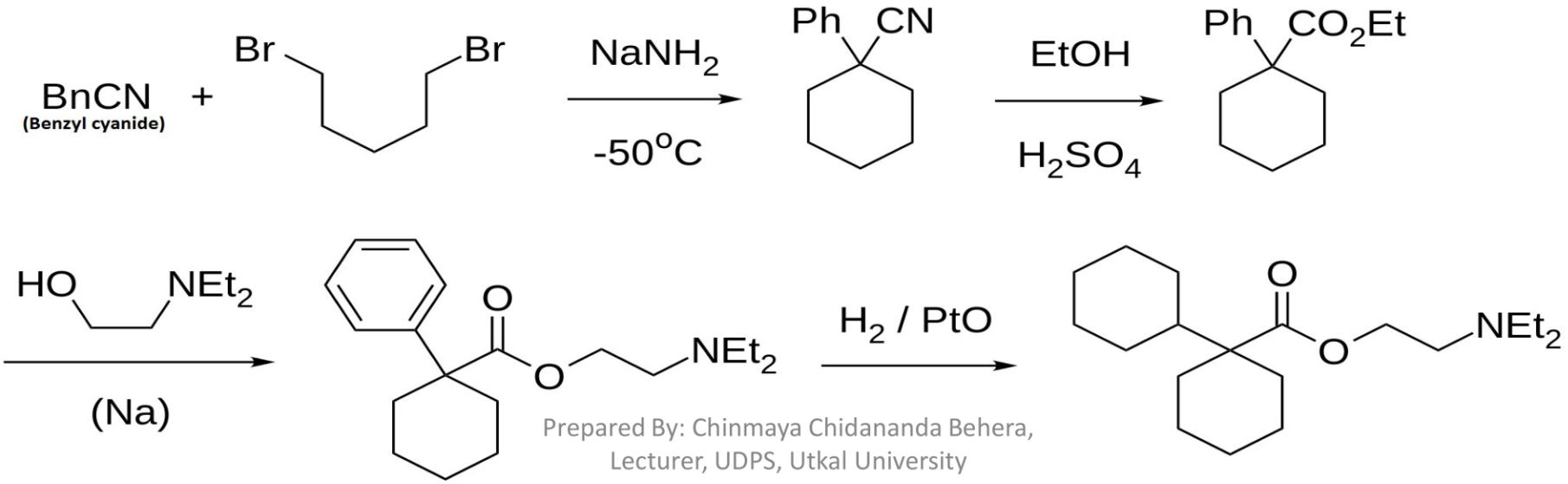
Dicyclomine hydrochloride



2-(diethylamino)ethyl 1-cyclohexylcyclohexane-1-carboxylate;hydrochloride

Uses: Dicyclomine Hydrochloride is the hydrochloride salt form of dicyclomine, a synthetic analog of acetylcholine with antimuscarinic activity. Dicyclomine hydrochloride antagonizes muscarinic receptors on smooth muscle in the gastrointestinal (GI) tract, thereby preventing the actions of acetylcholine and reducing GI smooth muscle spasms.

Synthesis:



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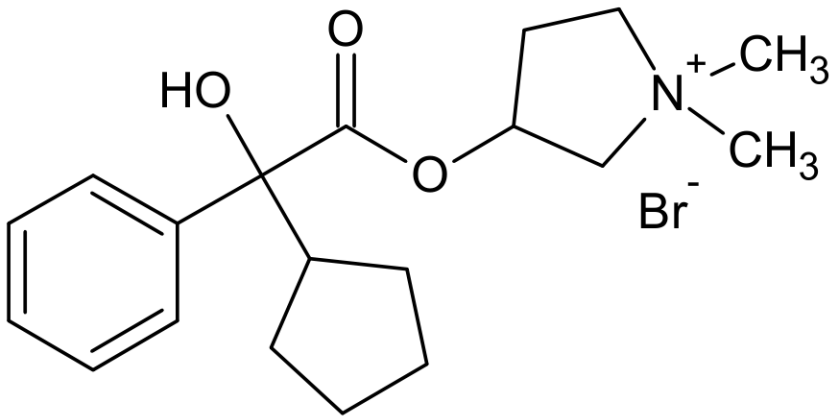
Glycopyrrolate



(1,1-dimethylpyrrolidin-1-ium-3-yl) 2-cyclopentyl-2-hydroxy-2-phenylacetate;bromide

Uses: Glycopyrrolate is a synthetic quaternary ammonium that is an anticholinergic agent with antispasmodic activity. Glycopyrrolate competitively binds to peripheral muscarinic receptors in the autonomic effector cells of, and inhibits cholinergic transmission in smooth muscle, cardiac muscle, the sinoatrial (SA) node, the atrioventricular (AV) node, exocrine glands and in the autonomic ganglia. Blockage of cholinergic transmission, in smooth muscle cells located in the gastrointestinal tract and the bladder, causes smooth muscle relaxation and prevents the occurrence of painful spasms. In addition, glycopyrrolate inhibits the release of gastric, pharyngeal, tracheal, and bronchial secretions.

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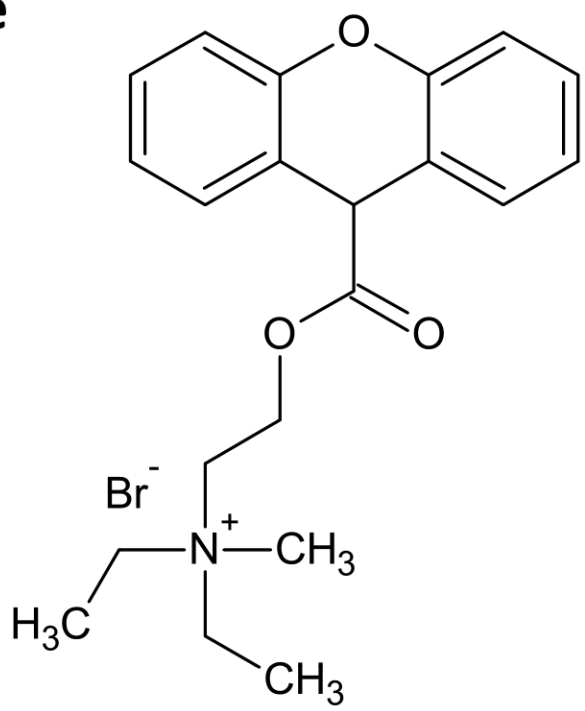
Methantheline bromide



diethyl-methyl-[2-(9H-xanthene-9-carbonyloxy)ethyl]azanium;bromide

Uses: It binds to but do not activate MUSCARINIC RECEPTORS, thereby blocking the actions of endogenous ACETYLCHOLINE or exogenous agonists and have widespread effects including actions on the iris and ciliary muscle of the eye, the heart and blood vessels, secretions of the respiratory tract, GI system, and salivary glands, GI motility, urinary bladder tone, and the central nervous system.

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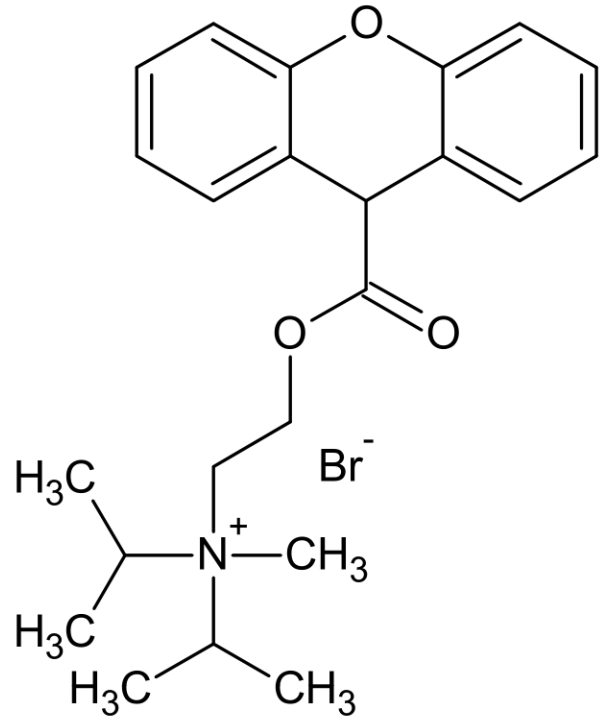
Propantheline bromide



methyl-di(propan-2-yl)-[2-(9H-xanthene-9-carbonyloxy)ethyl]azanium;bromide

Uses: Propantheline Bromide is the bromide salt form of propantheline, a quaternary ammonium compound structurally related to belladonna alkaloids. Propantheline bromide competitively antagonizes acetylcholine activity mediated by muscarinic receptors at neuroeffector sites on smooth muscle and exocrine gland cells. An aspartic acid residue present in the N-terminal portion of the third trans-membrane helix of the muscarinic receptor is believed to form an ionic bond with the tertiary or quaternary nitrogen of the antagonist. Antagonism leads to a reduction of exocrine glands secretions and to relax bronchial muscle and reduce tone and motility of intestinal smooth muscle.

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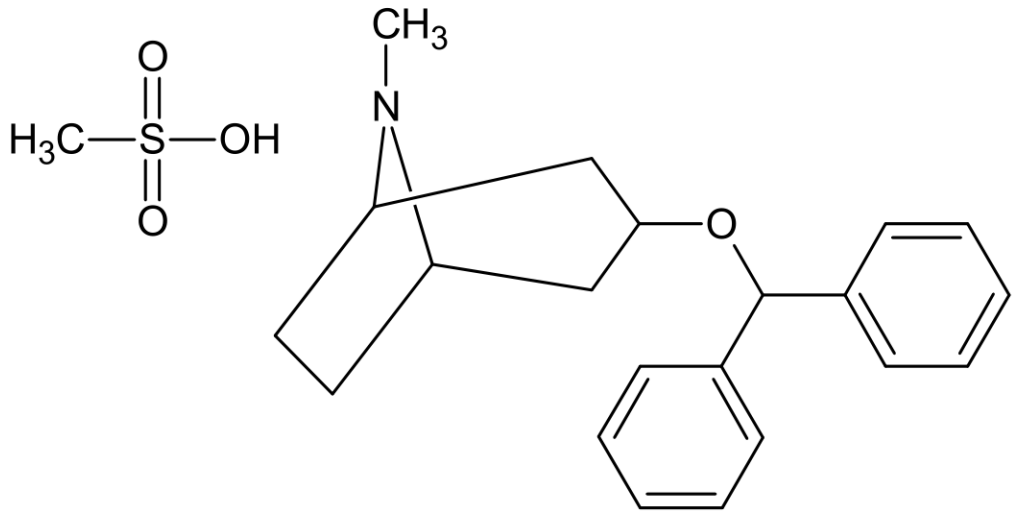
Benztropine mesylate



3-benzhydryloxy-8-methyl-8-azabicyclo[3.2.1]octane;methanesulfonic acid

Uses: Benztropine Mesylate is a synthetic antiparkinson tertiary amine structurally related to atropine, Benztropine Mesylate acts as a central muscarinic antagonist and inhibits dopamine uptake. With antihistaminic and local anesthetic properties as well, it is indicated for symptomatic relief of parkinsonism and drug-induced extrapyramidal reactions.

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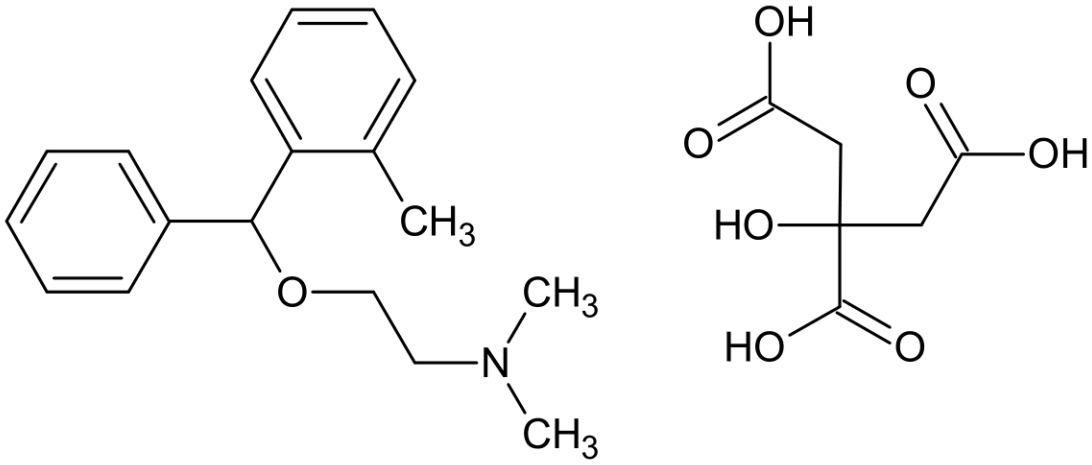
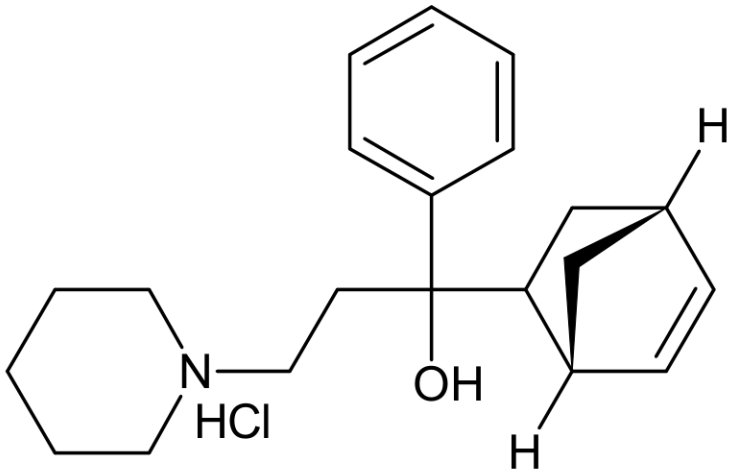
Orphenadrine citrate



N,N-dimethyl-2-[(2-methylphenyl)-phenylmethoxy]ethanamine;citrate

Uses: Orphenadrine Citrate is the citrate salt form of orphenadrine with a muscle relaxant property. Although the mechanism of action has not been fully elucidated, orphenadrine citrate appears to block cholinergic receptors, thereby interfering with the transmission of nerve impulses from the spinal cord to the muscles. It does not produce myoneural block, nor does it affect crossed extensor reflexes.

Biperidine hydrochloride



1-[2-bicyclo[2.2.1]hept-5-enyl]-1-phenyl-3-piperidin-1-ylpropan-1-ol;hydrochloride

Uses: It is used to treat the stiffness, tremors, spasms, and poor muscle control of Parkinson's disease. It is also used to treat and prevent these same muscular conditions when they are caused by drugs such as chlorpromazine (Thorazine), fluphenazine (Prolixin), perphenazine (Trilafon), and others.

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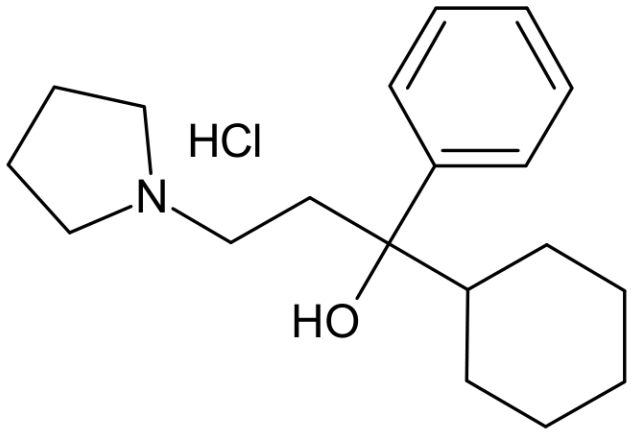
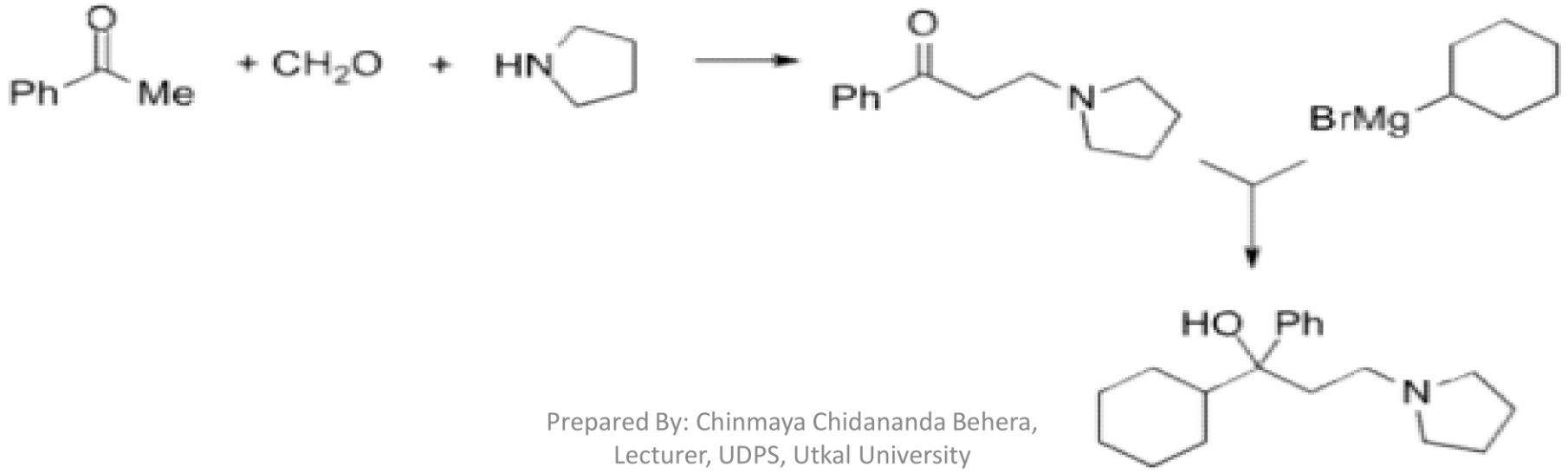
Procyclidine hydrochloride



1-cyclohexyl-1-phenyl-3-pyrrolidin-1-ylpropan-1-ol;hydron;chloride

Uses: It is an anticholinergic/**antispasmodic** drug used to treat symptoms of Parkinson's disease or involuntary movements due to the**side effects** of certain psychiatric drugs (antipsychotics such as chlorpromazine/haloperidol).

Synthesis:



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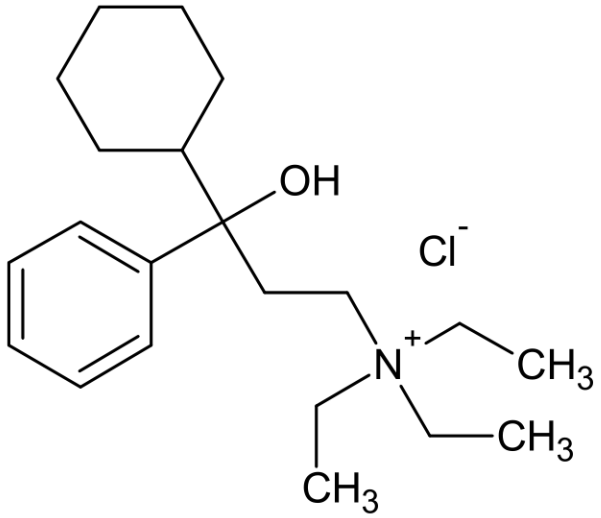
Tridihexethyl chloride



(3-cyclohexyl-3-hydroxy-3-phenylpropyl)-triethylazanium;chloride

Uses: It is an anticholinergic, antimuscarinic and **antispasmodic** drug. It may be used, usually in combination with other drugs, to treat acquired nystagmus or peptic ulcer disease.
Tridihexethyl binds the muscarinic acetylcholine receptor. It may block all three types of muscarinic receptors including M-1 receptors in the CNS and ganglia, M-2 receptors in the heart (vagus) and M-3 receptors at the parasympathetic NEJ system. The muscarinic acetylcholine receptors mediate various cellular responses, including inhibition of adenylate cyclase, breakdown of phosphoinositides and modulation of potassium channels through the action of G proteins. Tridihexethyl inhibits vagally mediated reflexes by antagonizing the action of acetylcholine. This in turn reduces the secretion of gastric acids in the stomach.

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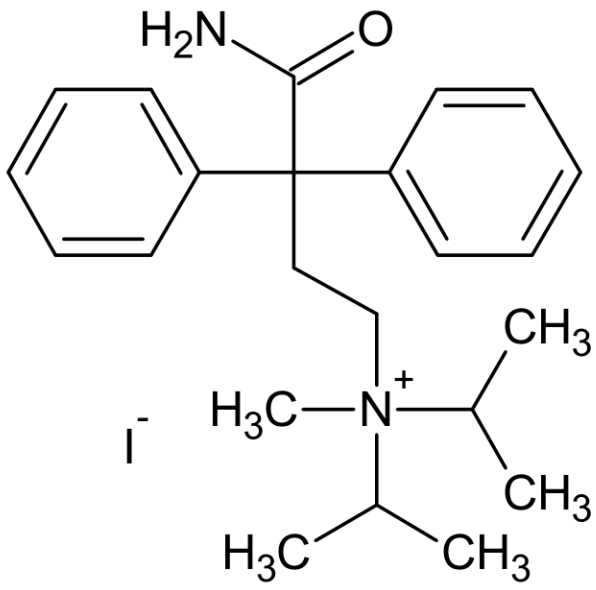
Isopropamide iodide



(4-amino-4-oxo-3,3-diphenylbutyl)-methyl-di(propan-2-yl)azanium;iodide

Uses: Isopropamide is a long-acting quaternary anticholinergic drug. It is used in the treatment of peptic ulcer and other gastrointestinal disorders marked by hyperacidity and hypermotility.

Inhibition here decreases acidity and motility, aiding in the treatment of gastrointestinal disorders.

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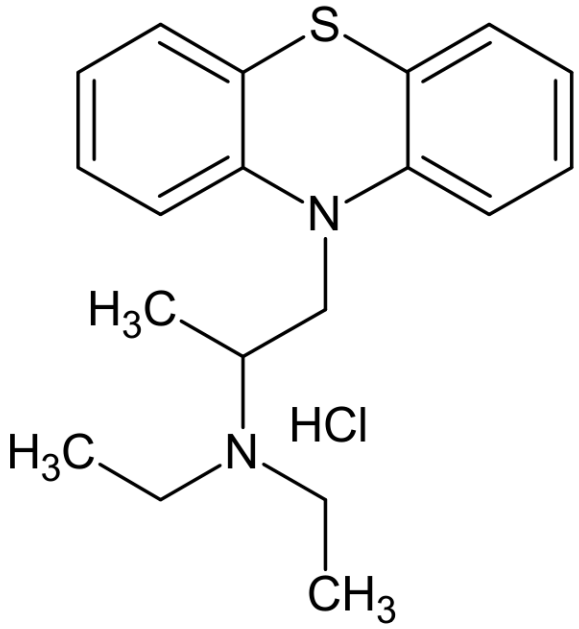
Ethopropazine hydrochloride



N,N-diethyl-1-phenothiazin-10-ylpropan-2-amine;hydrochloride

Uses: Ethopropazine, a phenothiazine and antidyskinetic, is used in the treatment of Parkinson's disease. By improving muscle control and reducing stiffness, this drug permits more normal movements of the body as the disease symptoms are reduced. It is also used to control severe reactions to certain medicines such as reserpine, phenothiazines, chlorprothixene, thiothixene, loxapine, and haloperidol. Unlike other NMDA antagonists, ethopropazine — because of its anticholinergic action — is largely devoid of neurotoxic side effects. Ethopropazine also has a slight antihistaminic and local anesthetic effect.

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