PARASYMPATHETIC SYSTEM EFFECTIVE DRUGS

(CHOLINERGIC AND ANTICHOLINERGIC DRUGS)

(PARASYMPATHOMIMETICS and PARASYMPATHOLYTICS)

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Pharmaceutical Chemistry III

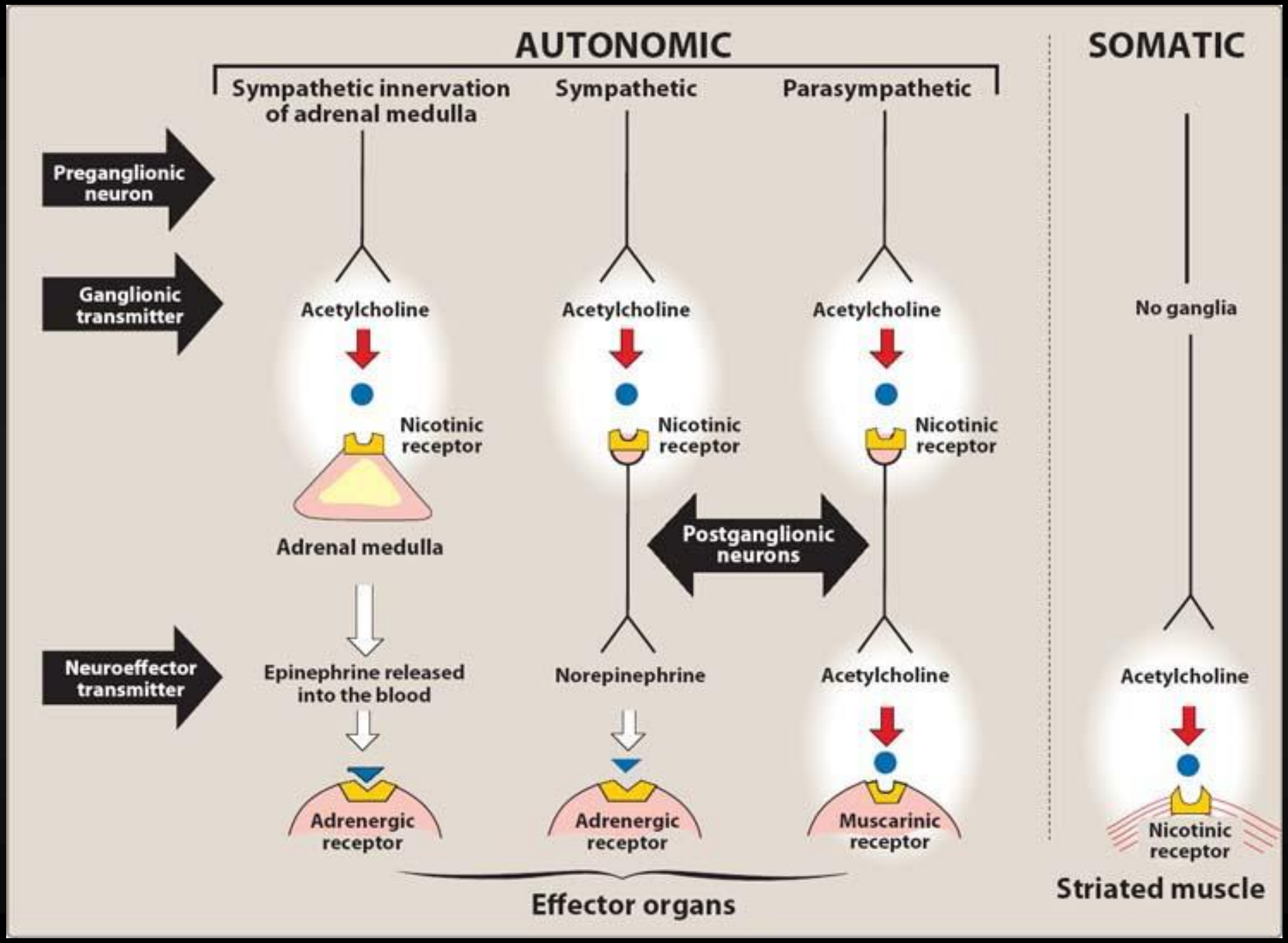
Types of Receptors ;

Acetylcholine receptors have been subdivided into two major pharmacological types (muscarinic and nicotinic), based on their selective response to two alkoloids; muscarine and nicotine. Both receptors have subtypes.

Ganglia ; Nicotinic,

Effector organs; Muscarinic

The type of receptor of sympathetic system is adrenergic


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Neuroeffector transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Striated muscle

Classification of the Cholinergic Drugs

I. Drug enhancing cholinergic activity

(Parasympathomimetics=Acetylcholine-like activity)

A. Cholinergic receptor agonists

A1. Acetylcholine-like (ACh) agonists

B. Antiacetylcholine esterase agents

B1. Competitive antagonists

B2. Short-acting inhibitors (Carbamates)

B3. Long-acting inhibitors (Organophosphorus)

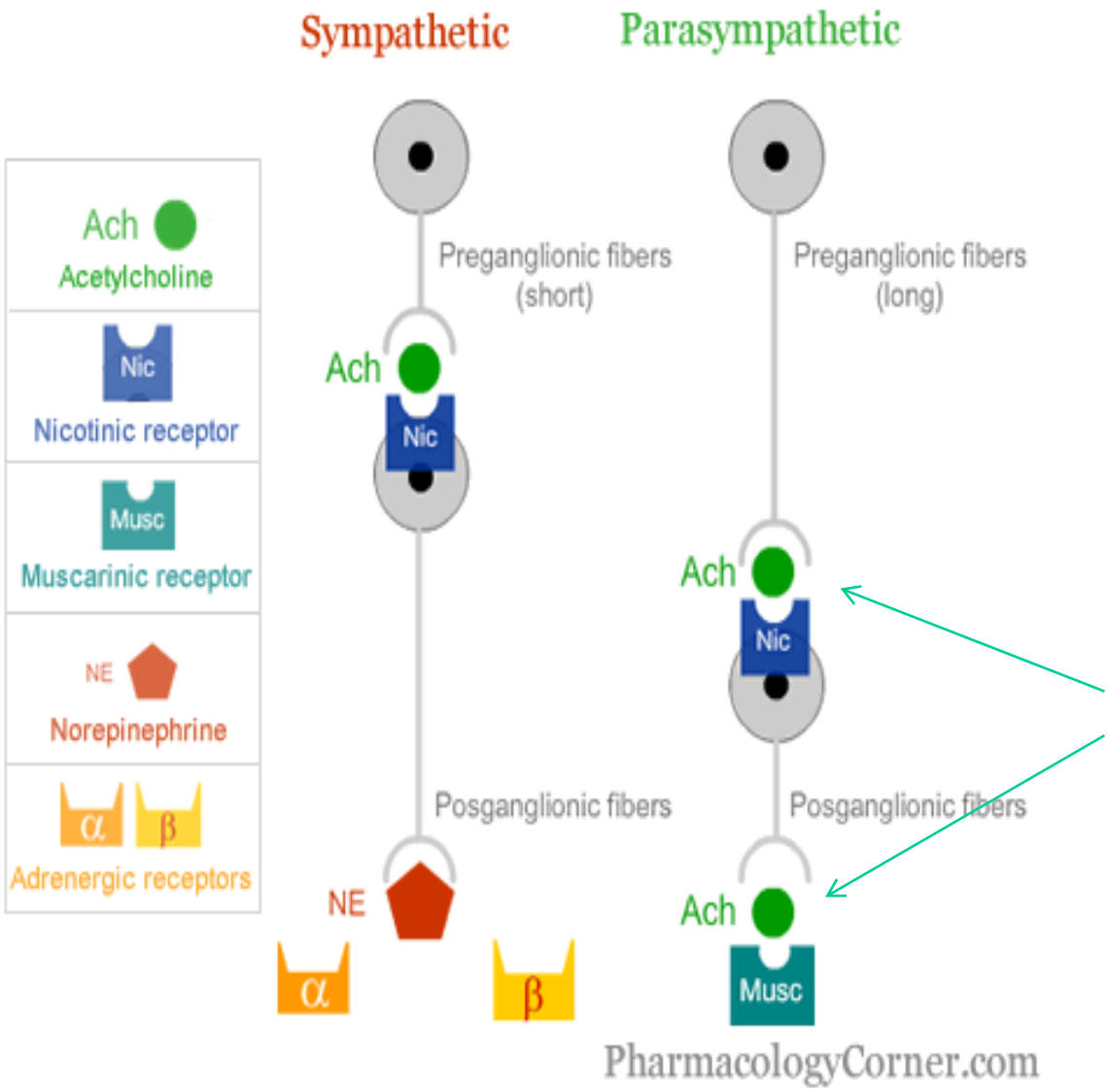
II. Drug suppressing the cholinergic activity

(Anticholinergics = Parasympatholytics)

A. Muscarinic antagonists

B. Nicotinic antagonists

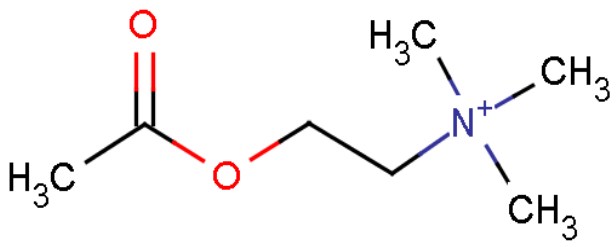
Reference: *Pharmaceutical Chemistry Edited by: David G Watson, Churchill Livingston. Elseiver, 2011.*



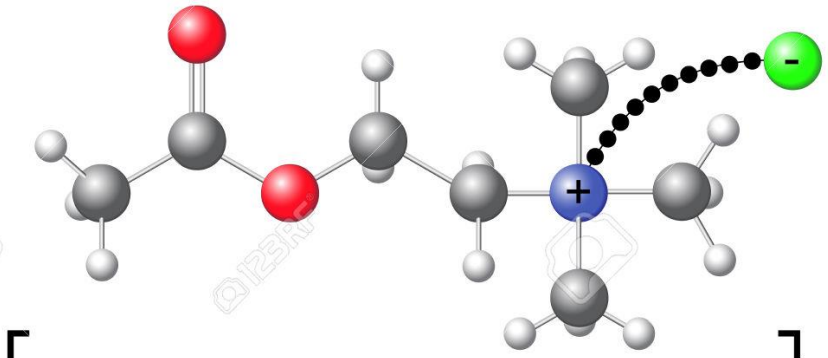
In the **Cholinergic system**, the neurotransmitter responsible for message transfer is **ACETYLCHOLINE (ACh)**

Acetylcholine (ACh)

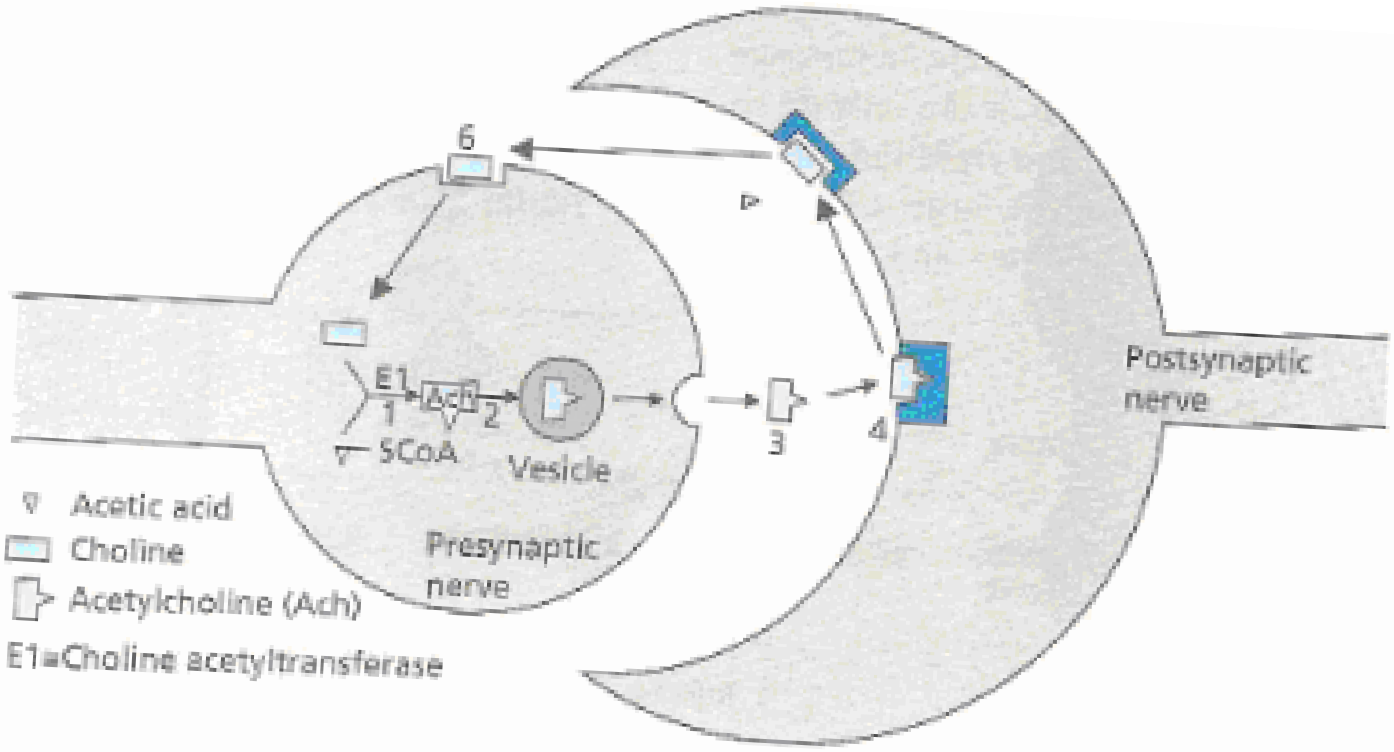
Acetylcholine is a "symbol" of this group as a neuromediator. **However, there is no therapeutic value. Because the effect of it is not selective and the period of action is too short.**



Acetylcholine



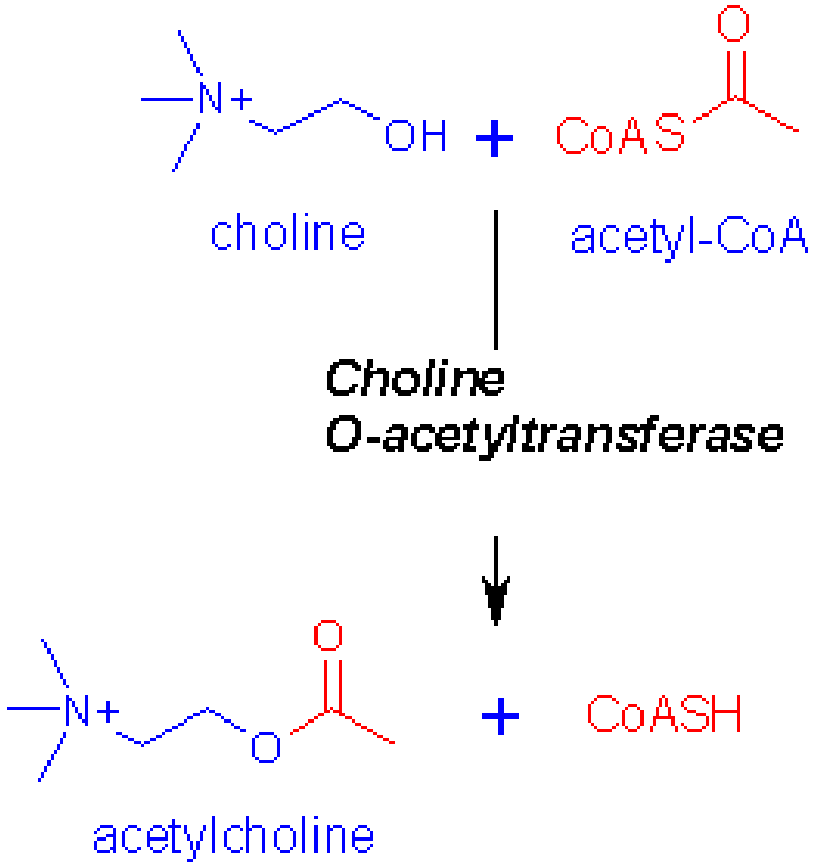
Cholinergic System

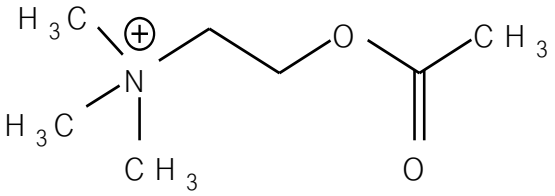


Synapse with acetylcholine acting as the neurotransmitter.

Biosynthesis of acetylcholine

ACh is biosynthesized in cholinergic neurons by the enzyme choline acetyltransferase utilizing acetyl coenyzme A (acetyl-S-CoA) and choline.





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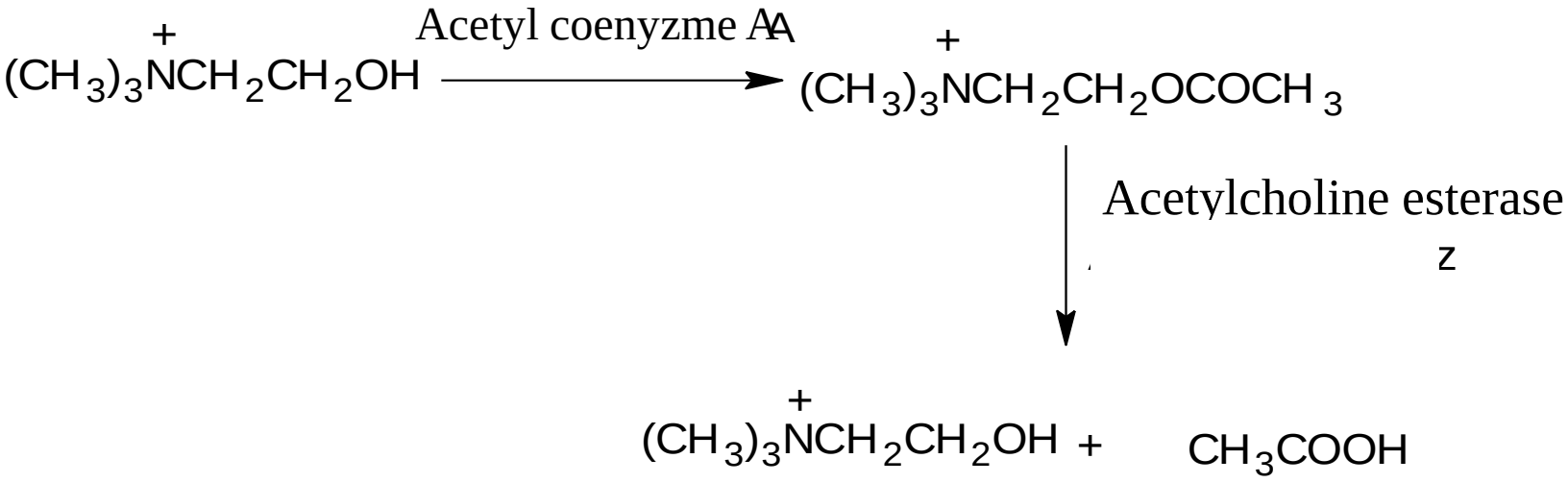
Synthesis and Storage of Acetylcholine (ACh)

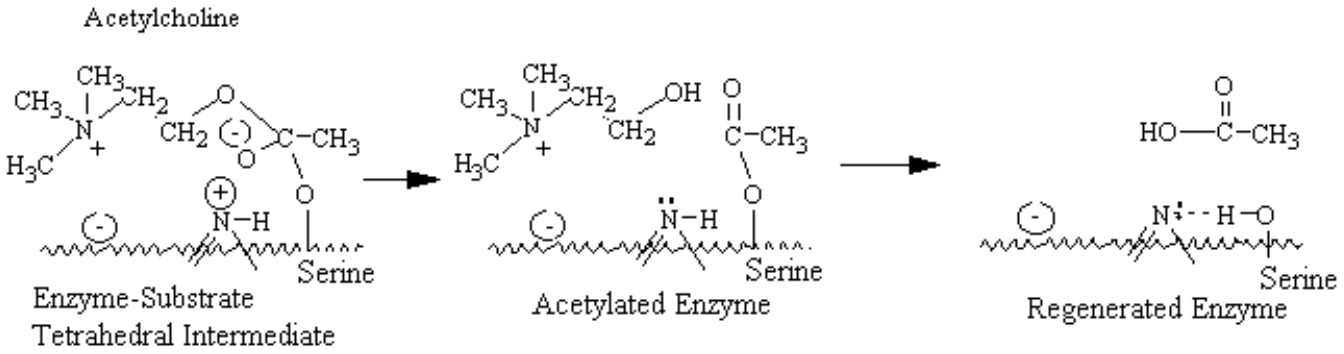


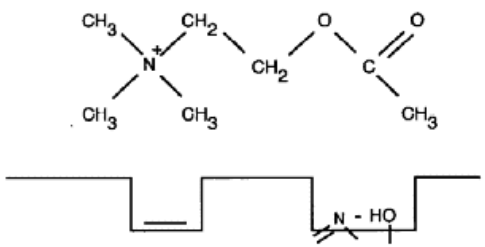
Specific choline esterases have been localized in pre- and postsynaptic membranes. As a result of hydrolysis, choline is taken into the axon with active transport to form ACh. Acetic acid is removed by blood.

It is also present in non-specific cholinesterases such as pseudocholinesterase and butyrylcholinesterase.

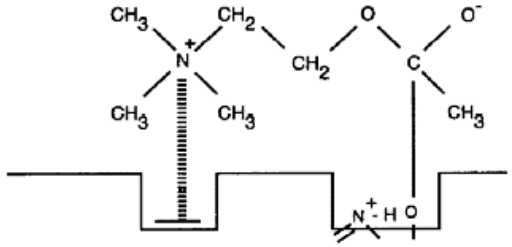
Acetylcholine, which is stored in the nerve vesicles after the synthesis, is released by pouring into the synapse cavity when the warning is received.

After completing its function, (acetyl) is hydrolyzed to Choline and Acetic acid by cholinesterases (in the presence of water).

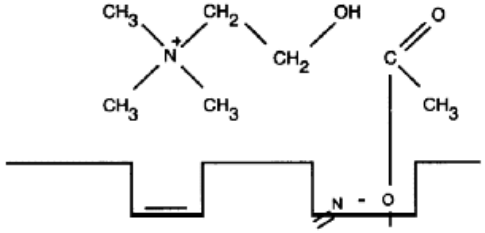




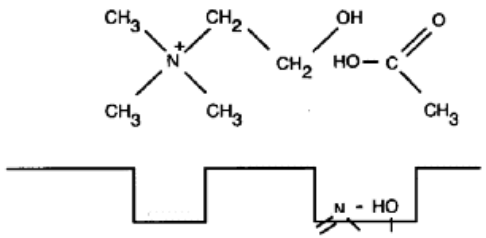
1. Acetylcholine molecule and active site of enzyme shown together but not having undergone any interaction.



2. Acetylcholine combined with enzyme to form a substrate-enzyme intermediate (short lived).



3. The ester link in the acetylcholine has been broken and free choline has been formed.



4. The acyl group has become detached from the enzyme leaving: choline, acetic acid, and the enzyme returned to its original state.

I. Drug enhancing cholinergic activity

A. Cholinergic receptor agonists

A1. Acetylcholine-like (ACh) agonists

I. Drug enhancing cholinergic activity

ACh is the prototypical muscarinic and nicotinic agonist; however, **it is a poor therapeutic agent** due to **its lack of receptor specifity and the chemical instability** (i.e. ease of hydrolysis) **in aqueous media, the gastrointestinal tract, and serum.**

ACh is also poorly absorbed across lipid membranes due to the quaternary ammonium functional group.

I. Drug enhancing cholinergic activity

Cholinergic drugs have similar effects on the cholinergic nerves and on the inner organs of cholinergic stimulation, and they used for this purpose in treatment.

However, they are limited because they do not have the selective effects of drugs in this group.

Treatment values are increasing at the rate of development of selective effects

The stimulation of the acetylcholine receptor is in two ways:

- Attachment of cholinergic agonists to the direct acetylcholine receptor, triggering nicotinic or muscarinic effects, or both.

- Binding of indirect agonists (inhibition of ACh hydrolysis by AChE, thus prolonging the effect of the existing ACh.

***Kaynak**: Medicinal Chemistry : A Molecular and Biochemical Approach, Third Edition, Deited by: Thomas Nogrady, Donald F. Weaver, Oxford University Press, 2005.*

I. Drug enhancing cholinergic activity

A. Cholinergic receptor agonists

A1. Acetylcholine-like (Ach) agonists (Direct effect)

-Acetylcholine
-Metacholine
-Bethanechol
-Carbachol
-Cevimeline
-Pilocarpine

Synthesis of Acetylcholine:

1) $CH_2 - CH_2$ (O) + $:N(CH_3)_3$ $\xrightarrow{H_2O}$ $HO\text{-}CH_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3 \cdot OH^-$

ethylene oxide — Choline

2) $HO\text{-}CH_2\text{-}CH_2\text{-}Cl + :N(CH_3)_3 \longrightarrow HO\text{-}CH_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3 \cdot Cl^-$

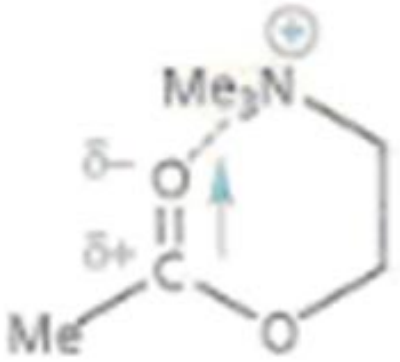
Glycolmonochlorohidrin — **Choline chloride**

$HO\text{-}CH_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3 \cdot Cl^- + (CH_3CO)_2O \longrightarrow$ **Acetylcholine**

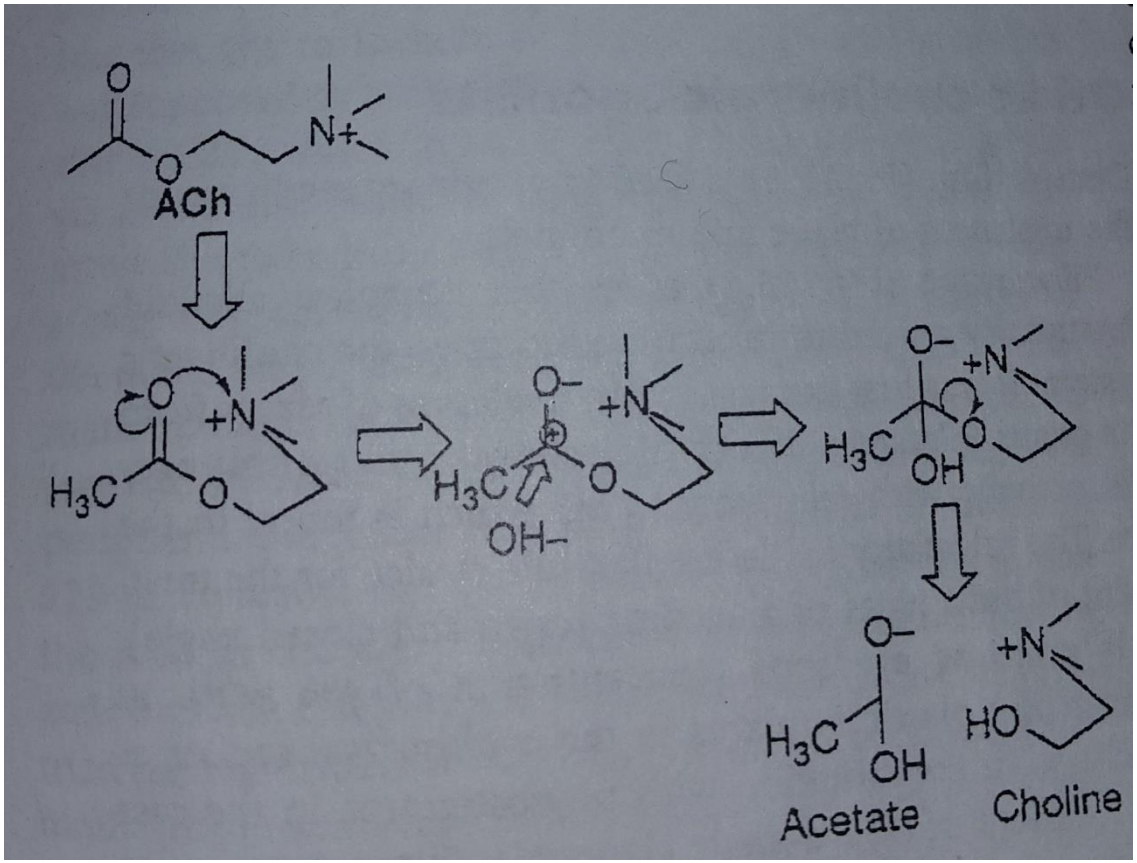
Choline chloride

Instability of Acetylcholine

Acetylcholine has both nicotinic and muscarinic activity. However, hydrolysis occurs rapidly with AChE and aqueous solutions. The ester function of ACh is not stable due to hydrolysis with either chemical and enzymatic activity. Chemical hydrolysis makes acetylcholine inactive by oral administration.

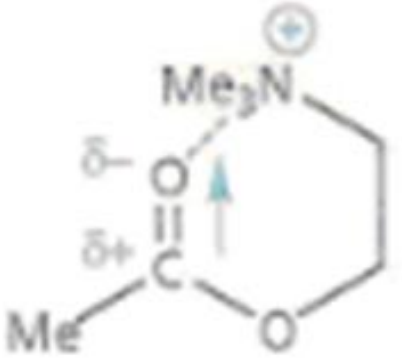


Effect of the proximity of quaternary ammonium group on the hydrolysis of ACh



Instability of Acetylcholine

This instability arises from the proximity of a quaternary ammonium function to an ester group, as it attracts the electron pairs on the oxygen to move towards its positive charge, thus withdrawing the electrons from the carbon-oxygen bond on the ester function towards the oxygen. This will make the dipole C-O greater, hence more prone to attack by a nucleophile (even weak nucleophile such as water)



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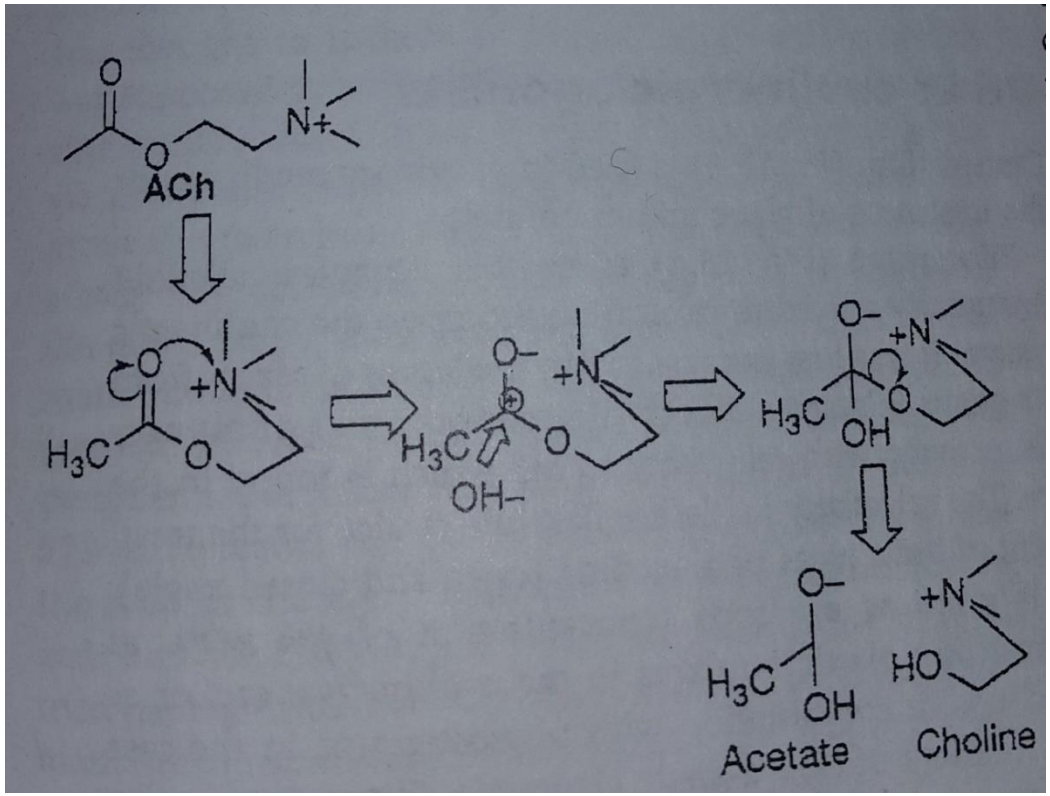
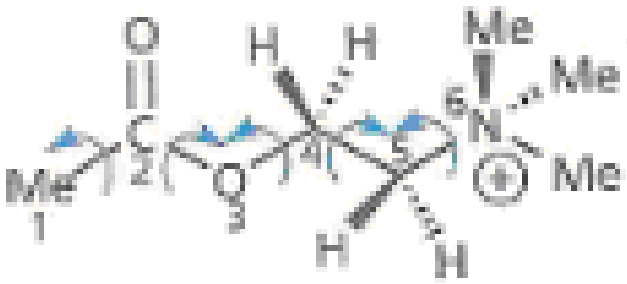
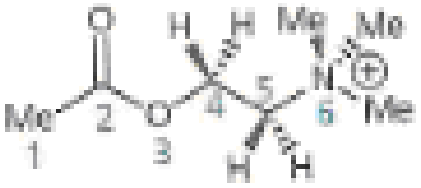
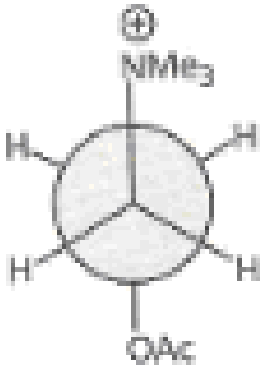


Conformational isomerism of ACh:

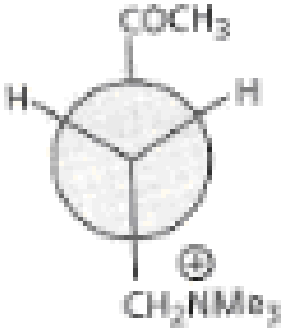


Bond rotations in acetylcholine leading to different conformations.





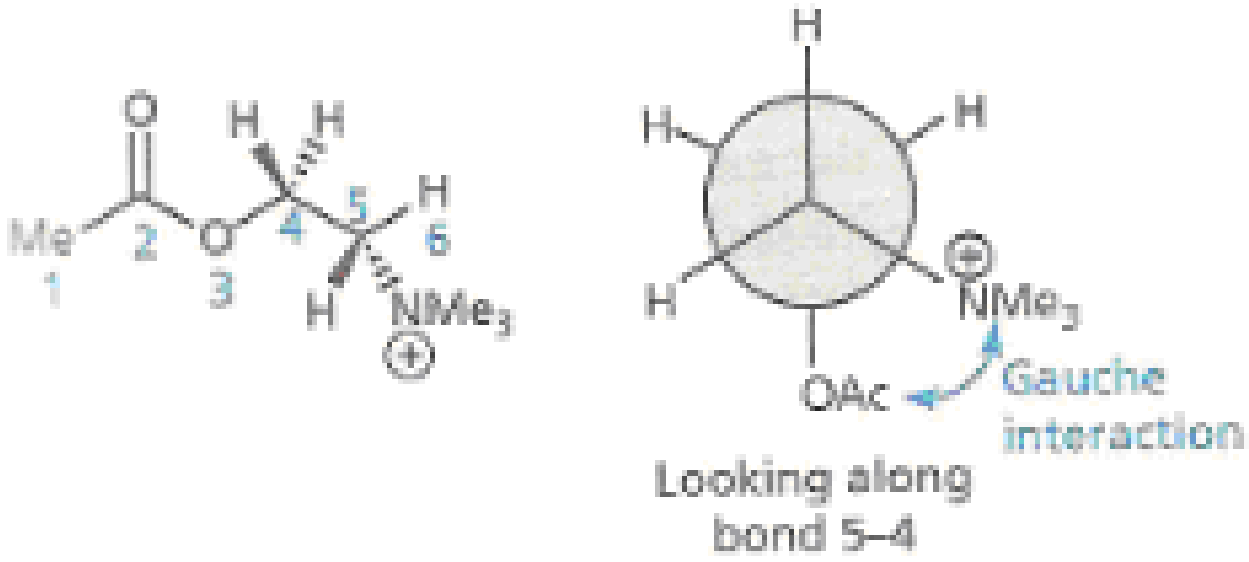
Looking along bond 5–4



Looking along bond 4–3

ACh Sawhorse ve Newman projection

Stereochemical Properties of ACh and the ACh Receptors:

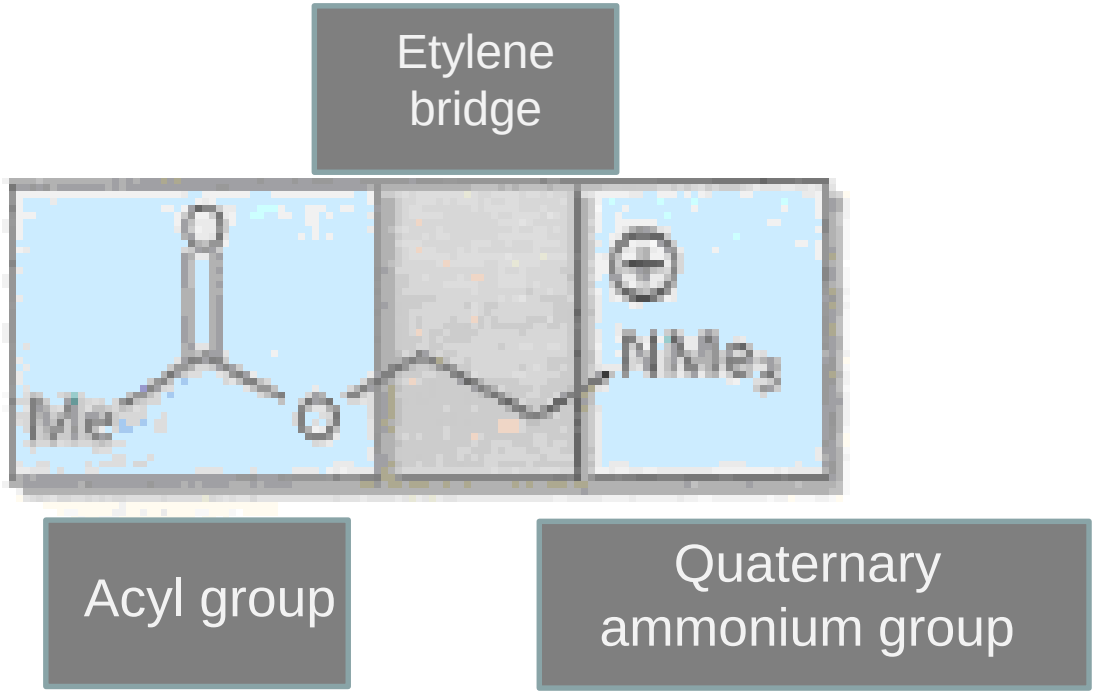


Gauche conformers of ACh

Although ACh is achiral, the ACh receptor exhibits chirality with respect to the binding of cholinergic agonists and antagonists.

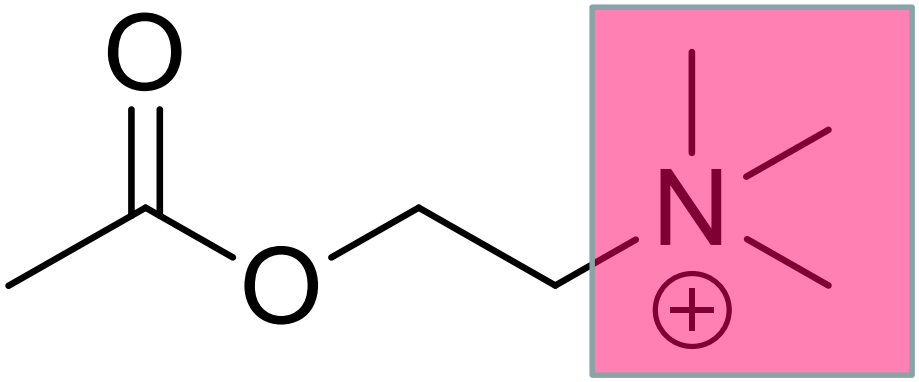
• The stereochemistry of ACh resides in the rotation about ∫ bonds (i.e., conformational isomerism) and ACh can exist in an infinite number of conformations as illustrated by Newman projections .

Acetylcholine: Structure, SAR (Structure-Activity Relationship) and Binding to Receptore

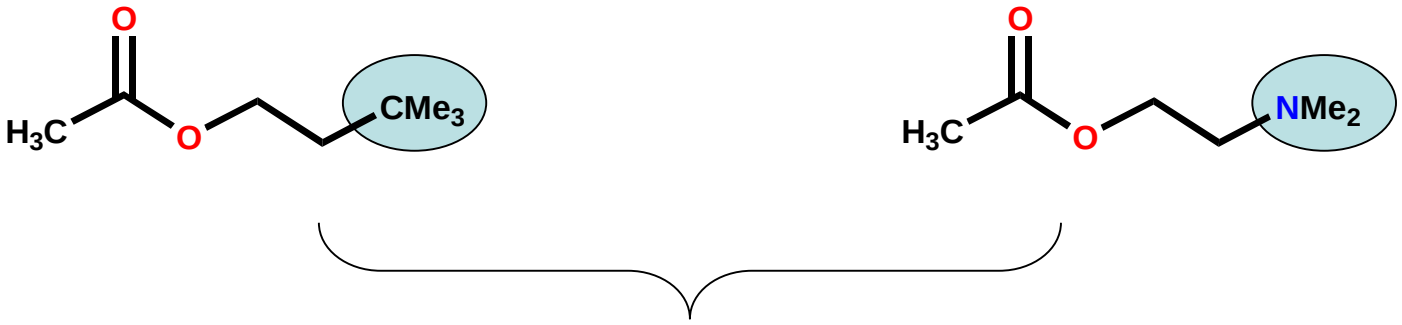


Acetylcholine

SAR for acetylcholine

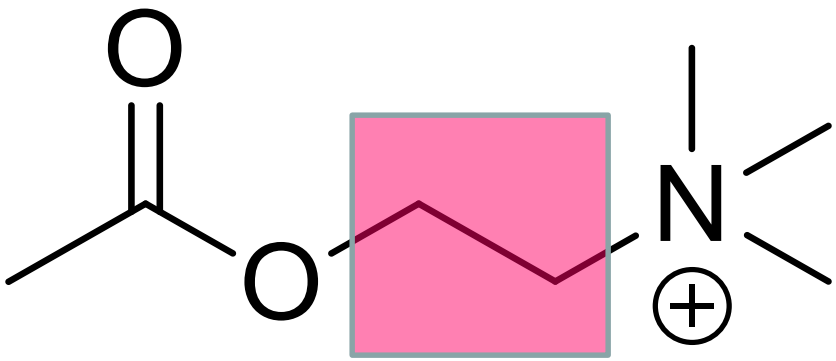


Quaternary nitrogen is essential

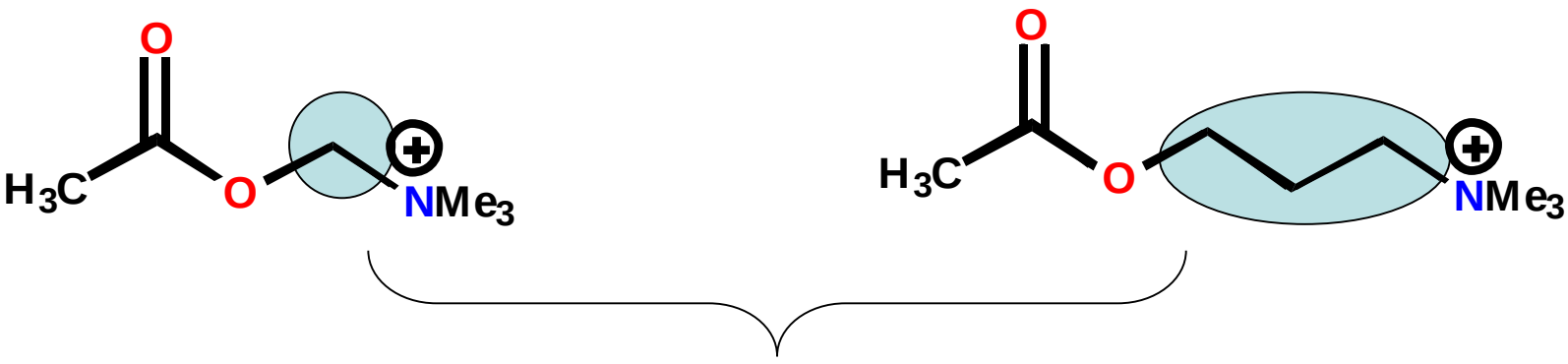


Bad activity

SAR for acetylcholine

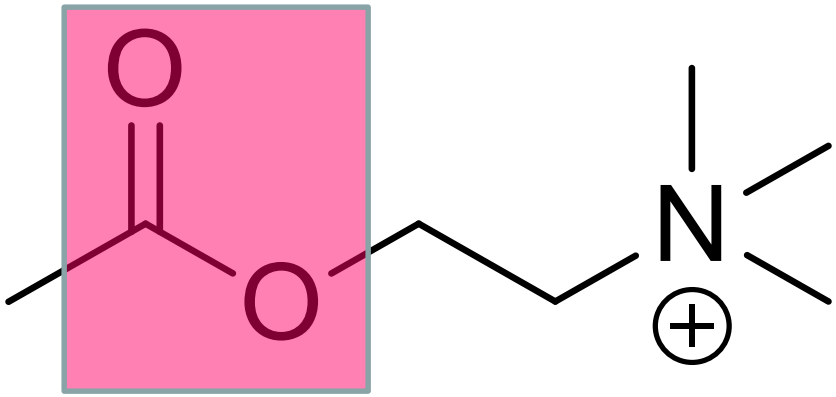


- **Distance from quaternary nitrogen to ester is important**
- **Ethylene bridge must be retained**

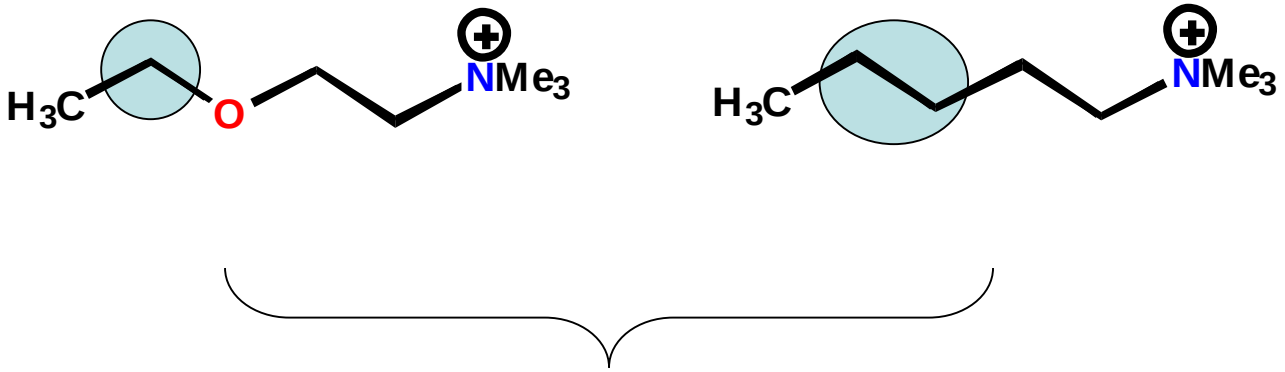


Bad activity

SAR for acetylcholine

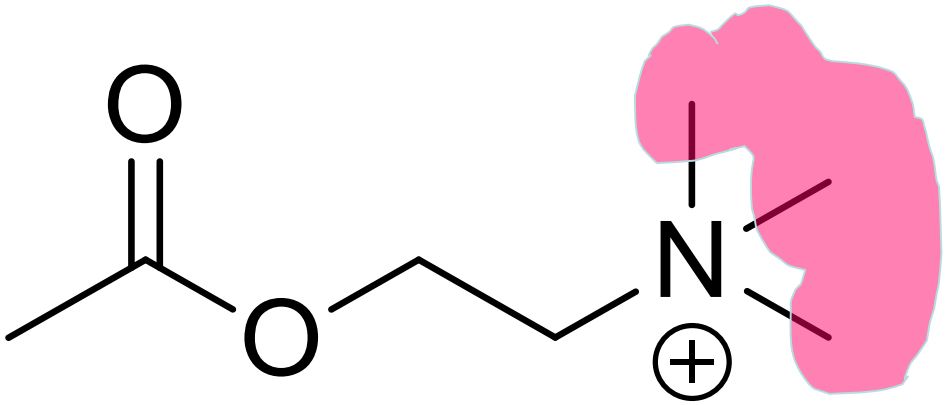


Ester is important

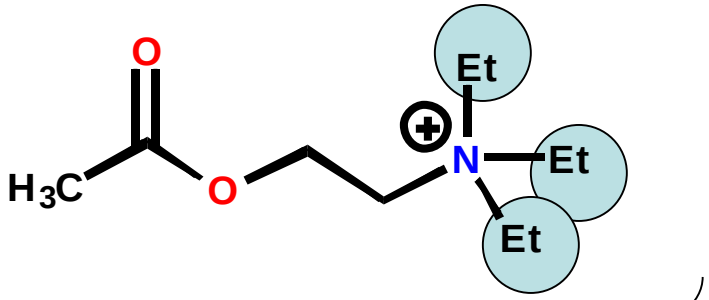


Bad activity

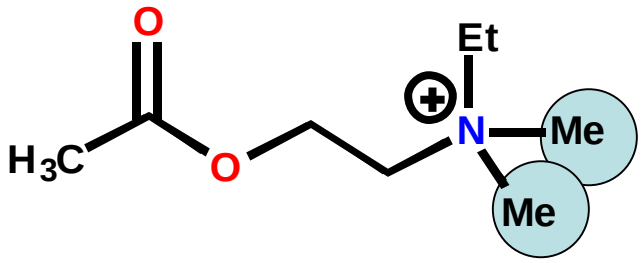
SAR for acetylcholine



Minimum of two methyl groups on quaternary nitrogen

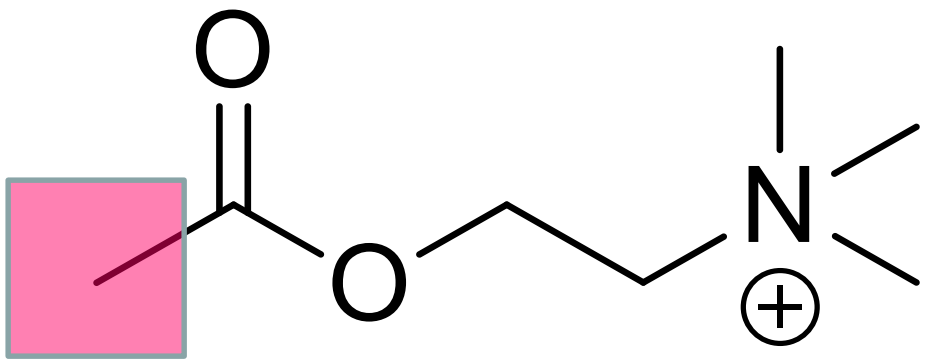


Lower activity

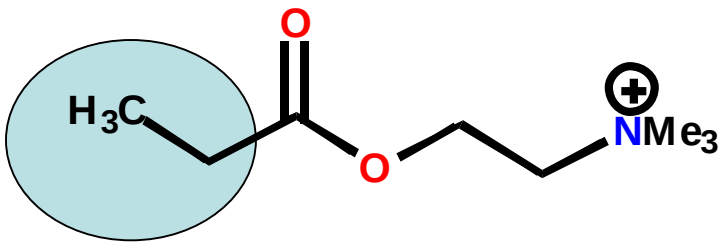


Active

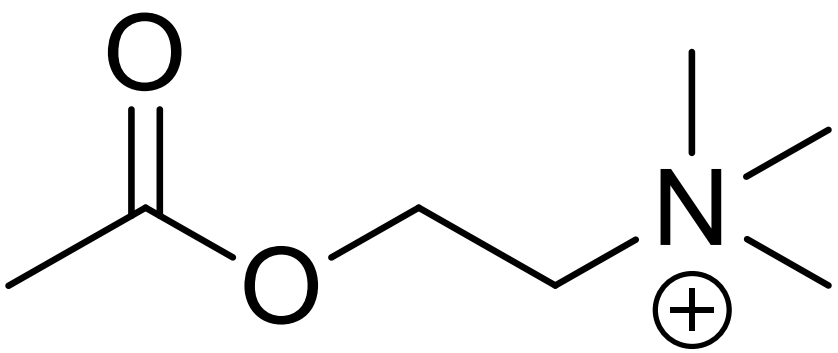
SAR for acetylcholine



Methyl group of acetoxy group cannot be extended



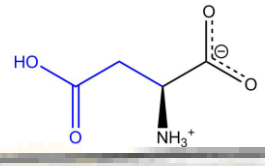
SAR for acetylcholine

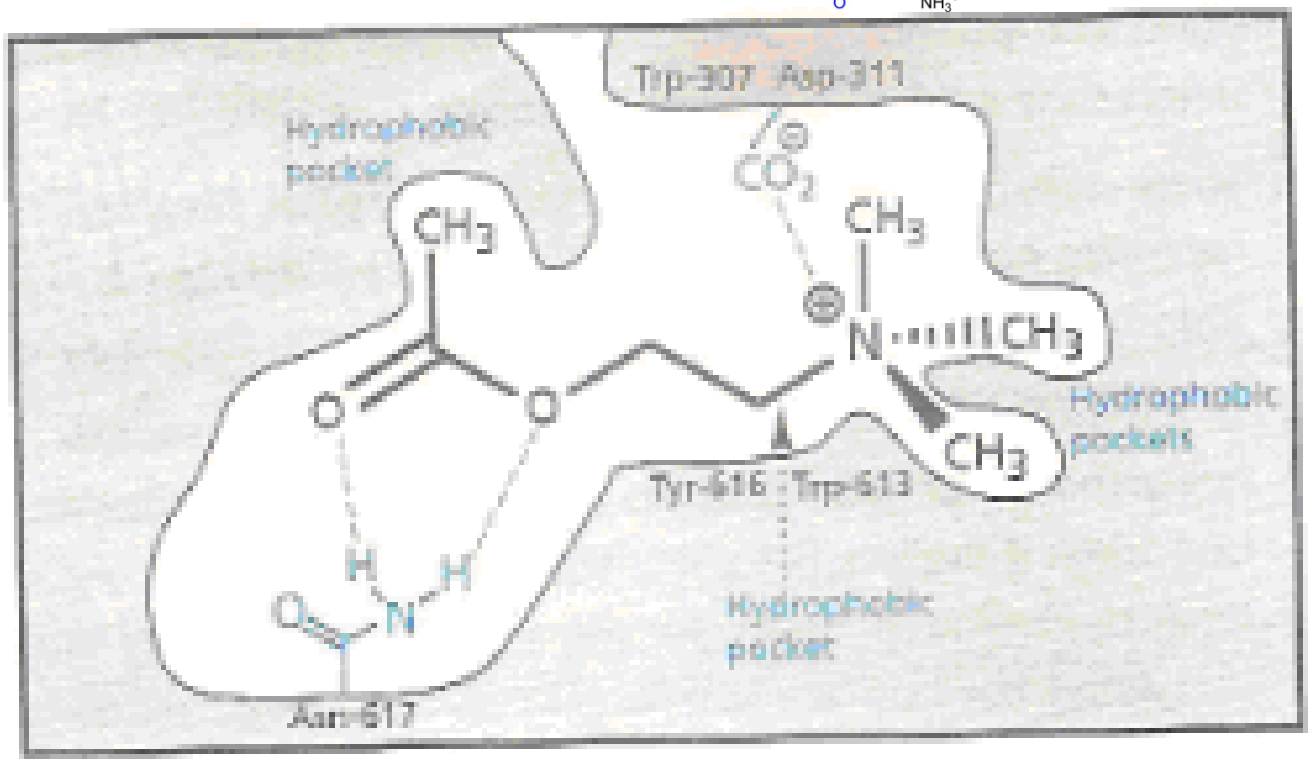


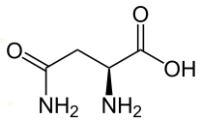
Conclusions:

- **Tight fit between ACh and binding site**
- **Methyl groups fit into small hydrophobic pockets**
- **Ester interacting by H-bonding**
- **Quaternary nitrogen interacting by ionic bonding**

Acetylcholine: Structure, SAR and Binding site of to Muscarinic Receptor

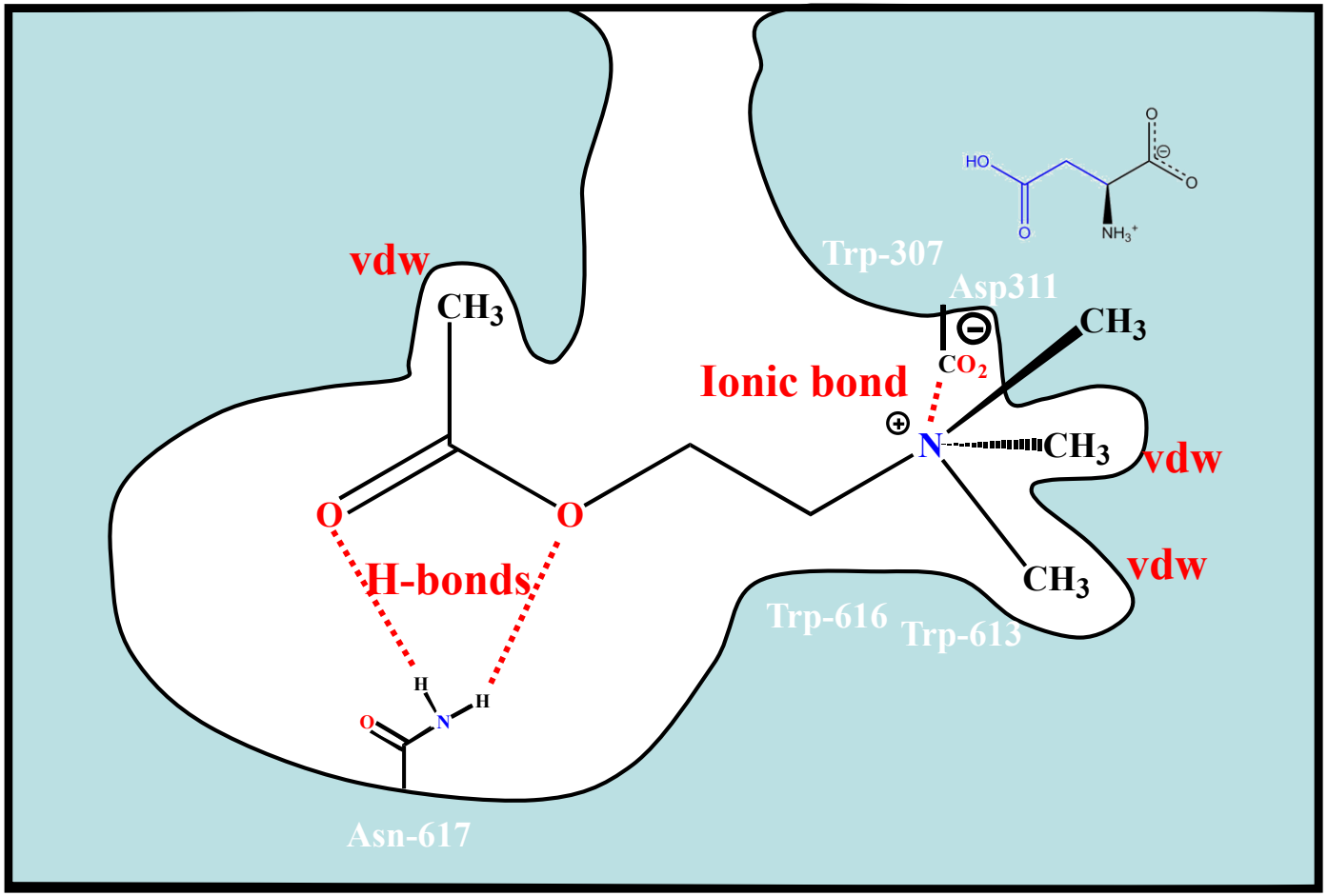


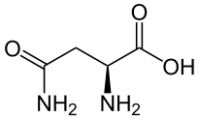




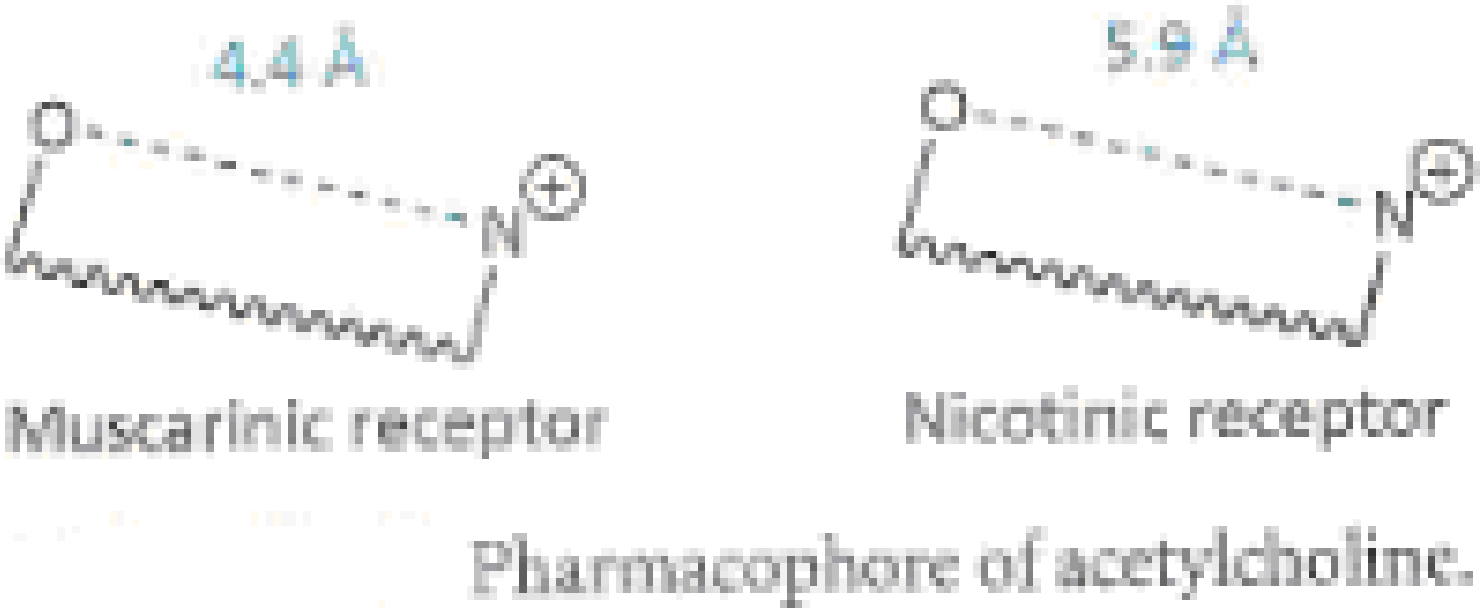
Muscarinic receptor binding site.

Binding site (muscarinic)





Acetylcholine: Structure, SAR and Binding site of Muscarinic Receptor



Pharmacophore of acetylcholine.

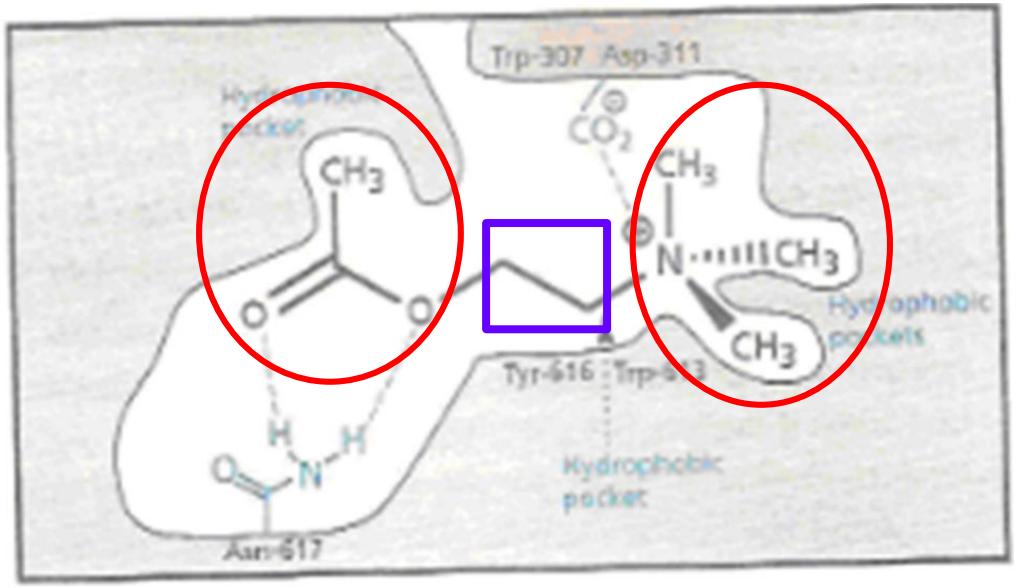
Acetylcholine: Structure, SAR and Binding site of to Muscarinic Receptor

ACh has a very short plasma half-life. Because it hydrolysis by esterases (AChE, pseudocholinesterase, butyrylcholinesterase) in the circulation. For this reason, ACh as a therapeutic agent is not convenient, and modifications are needed to ensure;

- Stability against acid hydrolysis (oral drugs)
- Stability against chemical hydrolysis in the blood (longer lasting)
- Stability against enzymatic hydrolysis (longer lasting)
- Organ selectivity (Pharmacokinetic)
- Receptor type (Pharmacodynamic)

For this purpose, new derivatives were prepared in the cationic head on the molecule, in the chain between the oxygen-nitrogen atoms and in the ester structure.

Acetylcholine: Structure, SAR and Binding site of Muscarinic Receptor



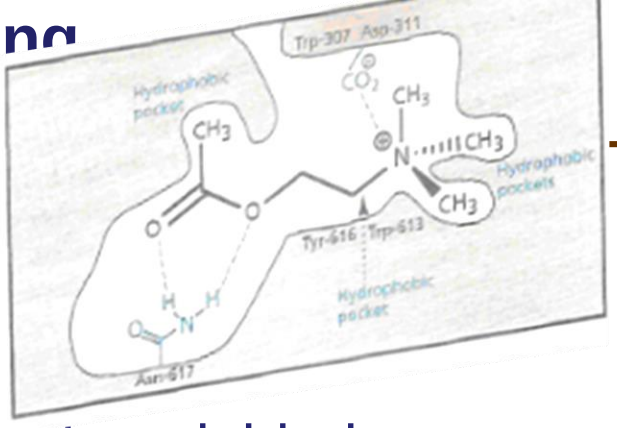
The rules of SAR;

- **Ammonium group**

- **Ester group** (The size of the ester functional group should not be increased. Because the receptor is located in a very small hydrophobic region.

- **Ethylene bridge** (There must be 2 carbons on the bridge connecting the two regions, and this chain should be neither extended nor shortened)

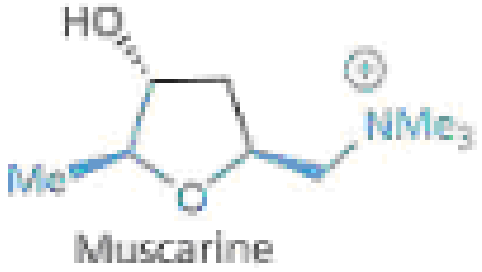
Acetylcholine: Structure, SAR and Binding site of Muscarinic Receptor



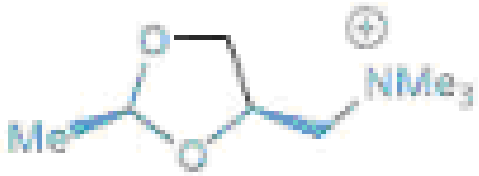
The rules of SAR;

- Ring analogs of acetylcholine

(ACh is quite flexible. Muscarine is quite rigid and binds more specifically to the receptor. Muscarine is a ring analog that will limit flexibility of ACh in its conformation. The dioxolane compound developed with this idea is more effective than the muscarinic analogues. **Rigid derivatives of acetylcholine have also been important in determining active conformation.**



Muscarine



dioxolane

Rigid molecules incorporating the acetylcholine skeleton (C–C–O–C–C–N).

EFFECTS OF ACETYLCOLINE AND SIMILARS

-There are both nicotinic and muscarinic effects,

- Subcutaneous and IM can be administered,
- Acetylcholine stimulates cholinergic receptors in the gut to promote normal secretory and motor activity
- Cholinergic activity in the gut will increase peristalsis and facilitates movement of flatus and feces
- The secretory functions of the salivary and gastric glands also stimulated
- Acetylcholine stimulates cholinergic receptors in the urinary system to promote urination
- Results in contraction of the detrusor muscle and relaxation of the urinary sphincter to facilitate emptying of the urinary blad

EFFECTS OF ACETYLCOLINE AND SIMILARS

- Decreased heart rate, vasodilation, variable BP effects

- Increased tone and contractility in GI smooth muscle, relaxation of sphincters, increased salivary gland and GI secretions

- Increased tone and contractility of smooth muscle in urinary bladder and relaxation of the sphincter

- Increased tone and contractility of bronchial smooth muscle

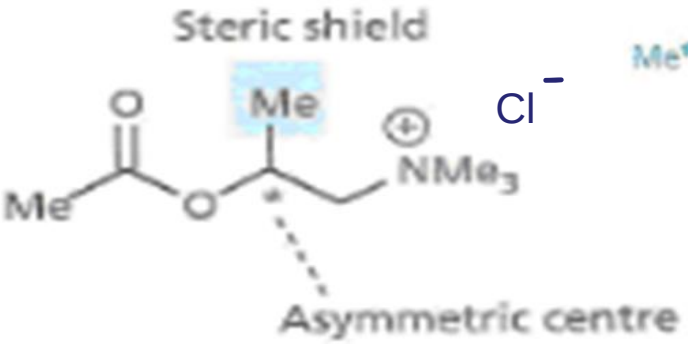
- Increased respiratory secretions

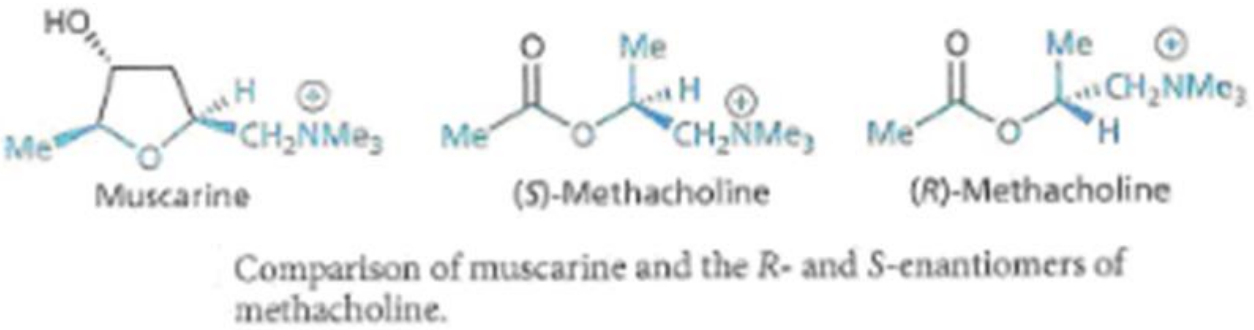
- Constriction of pupils (miosis) and contraction of ciliary muscle

- Sweat, tears, nose, etc. increase in secretions.

A1. Acetylcholine-like (ACh) agonists
Modification of the acetylcholine

Methacholine





Comparison of muscarine and the *R*- and *S*-enantiomers of methacholine.

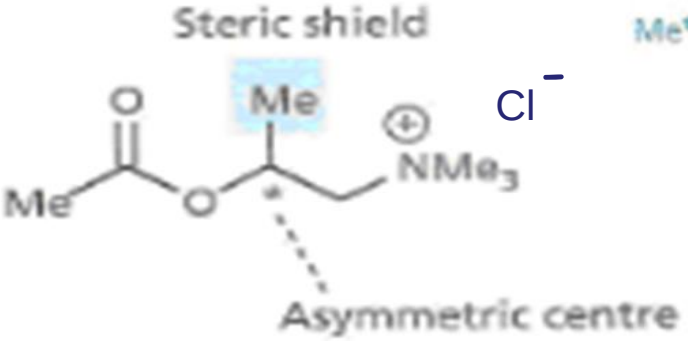
Steric effect

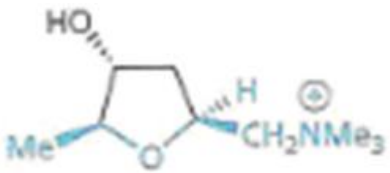
2-(Acetoxy(propyl-trimethylamonium)chloride

- Adding an alkyl group on the beta position relative to the quaternary ammonium group will provide a shield which will inhibit nucleophilic attacks and also provide an electroinductive group which will decrase the dipole activity of the ester function.
- This alkyl group should be only a small one; in fact, anything larger than a methyl group yields better stability but a poorer activity.

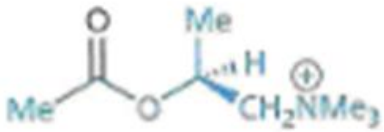
A1. Acetylcholine-like (ACh) agonists
Modification of the acetylcholine

Methacholine

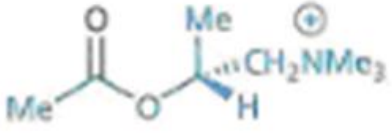




Muscarine



(*S*)-Methacholine



(*R*)-Methacholine

Comparison of muscarine and the *R*- and *S*-enantiomers of methacholine.

Steric effects

- **Methacholine** is mainly used via inhalation for the diagnosis of asthma. It is water-soluble drug and it is not active via oral absorption and does not cross the blood-brain barrier (BBB). The addition of an extra methyl group creates a chiral centre.
- Extra methyl group led to enhanced selectivity at the muscarinic receptor and diminshed activity at the nicotinic receptor.
- Methacholine was designed to ensure stability against chemical hydrolysis, but the additional group appeared to provide hindrance to access of cholinesterase as well, and methacholine is three times more resistant to esterase hydrolysis than ACh.

A1. Acetylcholine-like (Ach) agonists
Modification of the acetylcholine

Carbachol (Carbamylcholine) **Miostat^{R}**

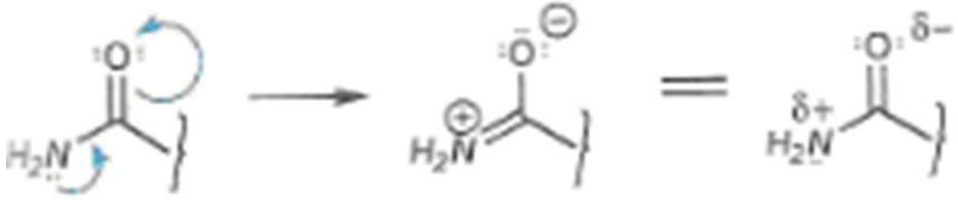
2-[((aminocarbonyl)oxy)ethyl]trimethylammonium chlorid

2-[((carbamoyl)oxy)ethyl]trimethylammonium chloride

Ester of carbamic acide

Electronic effects

- **Another approach to reduce the attacks of nucleophiles is to decrase the dipole activity by countering the positive dipole charge on the carbonyl carbon. This could be achieved by replacing the alkyl function with an amine group to create a carbamate. The lone pair of electrons on the nitrogen delocalises, countering the partial positive charge formed on the carbonyl carbon, hence making it less vulnerable to nucleophilic attack.**



Resonance structures of carbachol.

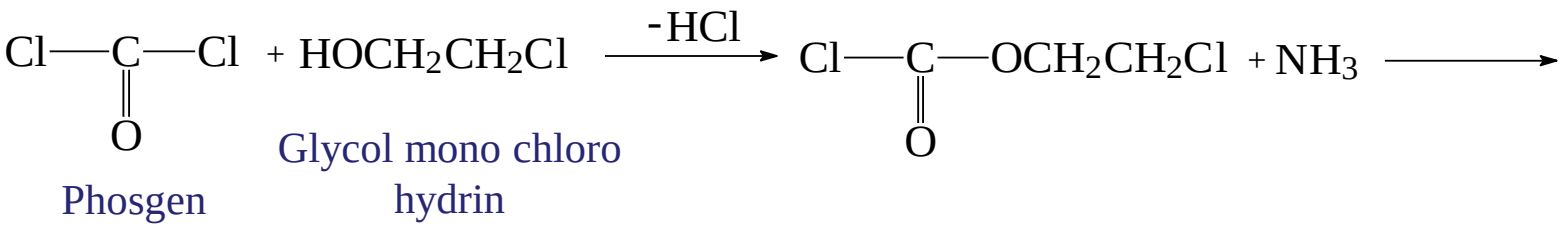
A1. Acetylcholine-like (ACh) agonists
Modification of the acetylcholine

Carbachol (Carbamylcholine)

- The «Carbachol» compound obtained by evaluating electronic effects is a non-selective cholinergic compound resistant to cholinesterases.

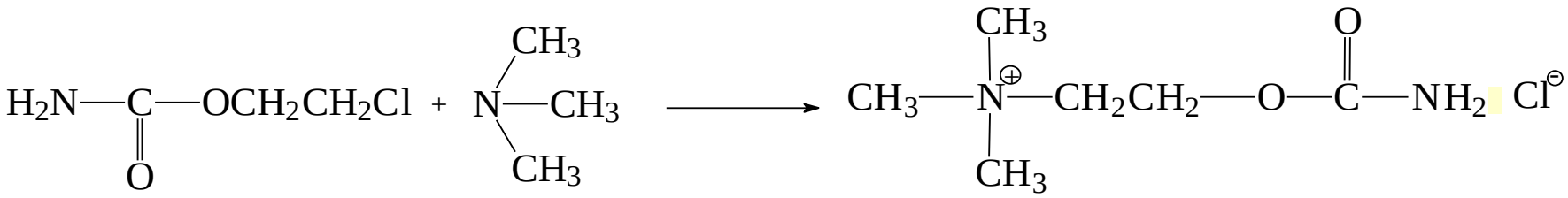
- Thus, there are both nicotinic and muscarinic effects. (Oral) tablet, subcutaneous administration, and also ophthalmic solutions.

Synthesis of Carbachol:



Phosgen

Glycol mono chloro hydrin

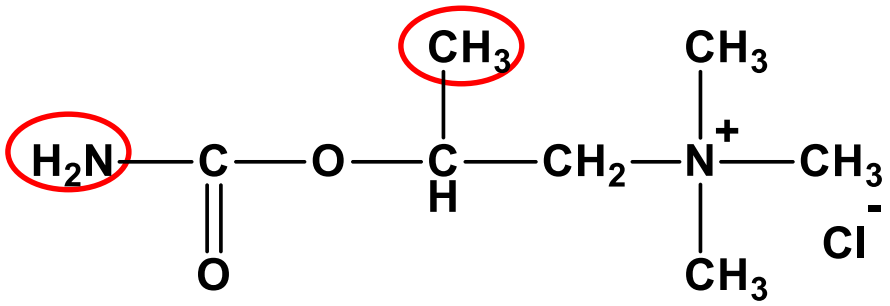


A1. Acetylcholine-like (ACh) agonists
Modification of the acetylcholine

- «**Bethanechol**» combines the two modifications

Combination of both Steric ve Electronic effects

Bethanecol Cl^- Myocholine tablet Myotonine tablet



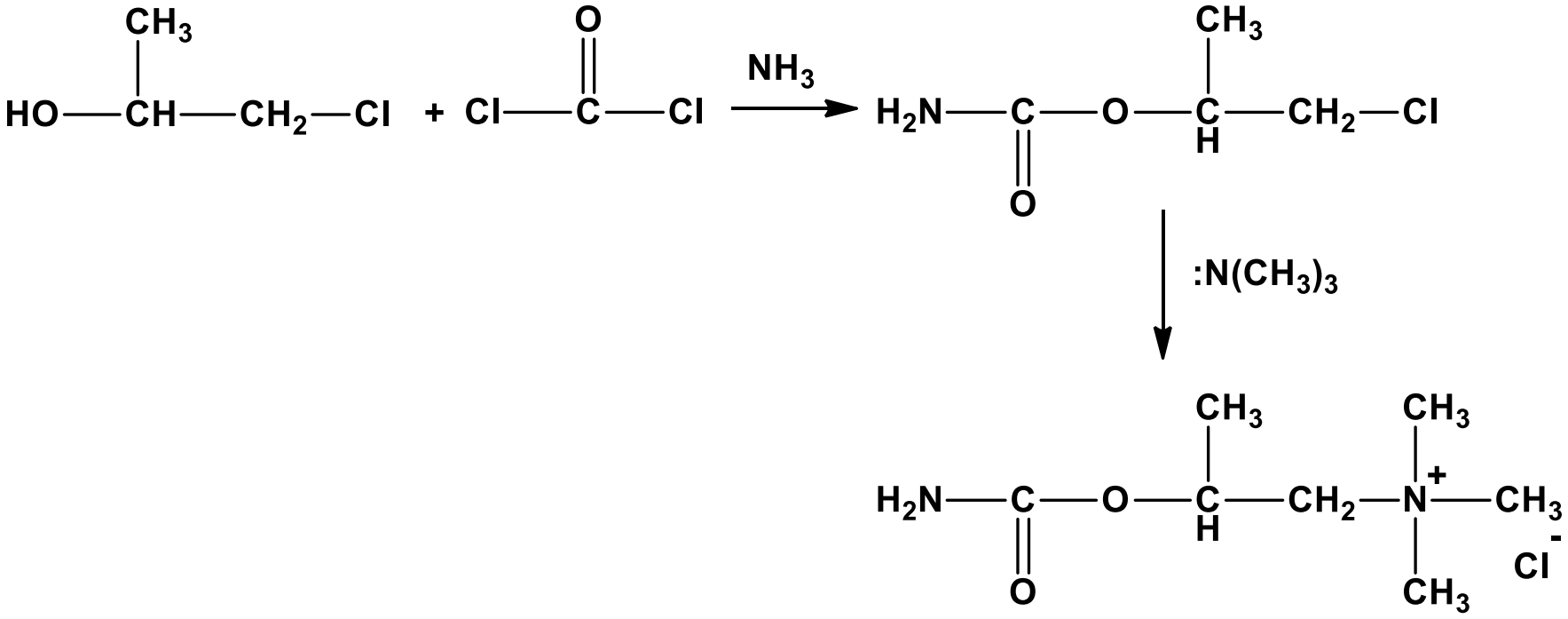
2-((carbamoyl)oxy)propyl)trimethylammonium chloride

The methyl derivative of Carbamylcholine. The CH_3 group on the molecule increases the stability against hydrolysis.

It does not show nicotinic action. Oral and subcutaneous administration is performed in the gastrointestinal tract, in the bladder atresia and postoperative dystonias.

- **It is resistant to both chemical and enzymatic hydrolysis and consequently has a relatively long half-life of 60-90 minutes.**
- It is a chiral drug due to the methyl addition at the beta-position relative to the quaternary ammonium.
- The muscarinic receptor is strongly stereoselective and (S)-bethanechol is 1000 times more potent than (R)-bethanechol.
- But this drug is still produced as racemates

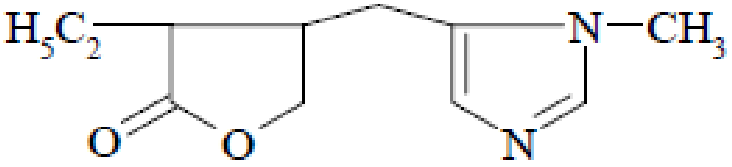
Synthesis of Bethanecol chloride



A1. Acetylcholine-like (ACh) agonists

(Parasympathomimetic Alkaloids ve Synthetic Similars)

PILOCARPINE Pilosed Pilokarsol Pilogel Pilomin göz dam **Salagen** tb



3-Ethyl-4-(1-methyl-5-imidazolylmethyl)-2-oxo-tetrahydrofuran

It is isolated from *Pilocarpus Jaborandi* plant. It is used in the form of nitrate or HCl salt.

Ophthalmology (to reduce intraocular pressure in Glaucom) due to miotic effect is used in 1-6% solutions.

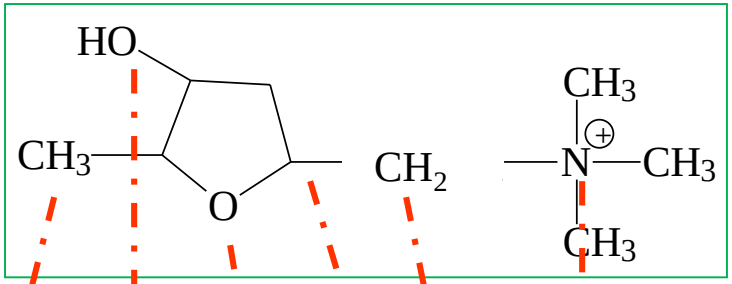
Pilocarpine is also used as an antidote for toxicity caused by scopolamine or atropine.

A1. Acetylcholine-like (ACh) agonists

(Parasympathomimetic Alkaloids ve Synthetic Similars)

MUSCARINE

It is obtained from Amanita Muscaria. The most common of mushroom poisons. It is a type of organic poison that mimics the cholinergic system compounds and causes excessive cholinergic activity. Pharmacologically, for experimental purposes, affects muscarinic receptors in small doses, producing known parasympathomimetic effects (muscarinic effects).



CH_3- CO – O – CH_2CH_2 - $N(CH_3)_3$

Tetrahidro-4-hidroksi-N,N,N,5-tetrametil-2-furanmetanamonyum

Effects of Muscarinic (Parasympathomimetic) Causes :

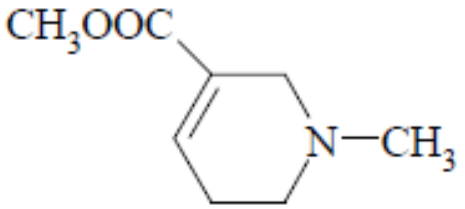
-Lacrimation (tear secretion),
-Increased saliva /
-Sweating,
-Miosis,
-Nausea and vomiting, } appear **in mushroom poisoning**
-Significant hypotension, }
-bradycardia,
-Circulation collapse.

A1. Asetilkolin benzeri diğer agonistler

(Parasempatomimetik Alkaloidler ve Sentetik Benzerleri)

Arecholine

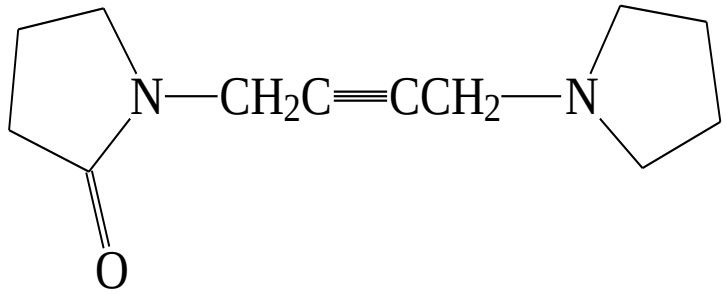
In addition to muscarinic effects, it also shows nicotinic effects. It is not used as a medicine in human health.



Oxotremorine

It causes tremors similar to Parkinson's disease.

For this reason, it is used in the testing of antiparkinson drugs in experimental animals.

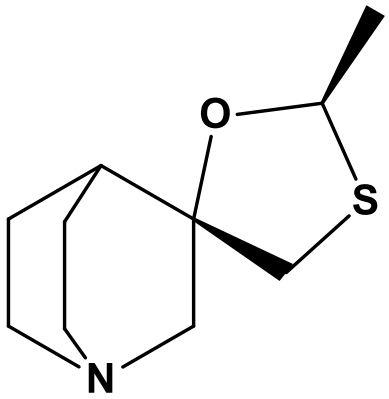


1-(2-oxo-1-pyrolidinyl)-4-(1-pyrolidinyl)-2-butyn

A1. Asetilkolin benzeri diğer agonistler

(Parasempatomimetik Alkaloidler ve Sentetik Benzerleri)

Cevimeline **Evoxac®**



***cis*-2-Methylspiro(1,3-oxathiolane-5,3)quinuclidine**

(*cis*-Quinuclidine-3-spiro-5'-2-methyl-1,3-oxathiolane)

Cevimeline is a new direct-acting muscarinic highly selective for the M3 receptor. It is used for the treatment of dry mouth associated with Sjögren's syndrome, an autoimmune disease where atypical antibodies destroy the glands which produce tears and saliva.

Sjögren's sendromu: Tükrük bezinin çalışmaması ile ilgili

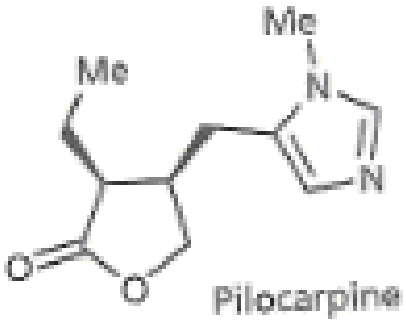
Clinical uses of cholinergic agonists

Clinical uses of muscarinic agonists:

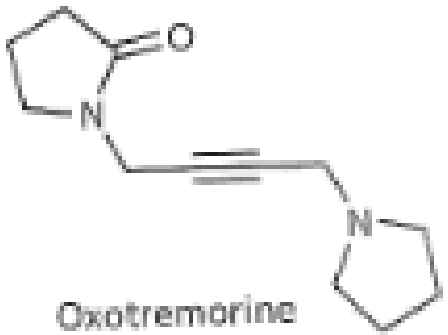
glaucoma treatment

GIS and urinary tract activation after surgery

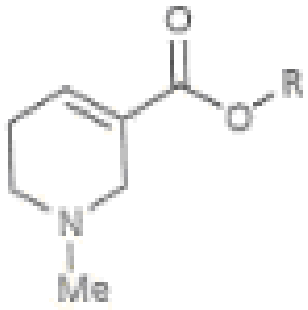
Treatment of certain heart defects by reducing the activity of heart muscle and heart rate



Pilocarpine



Oxotremorine



Arecoline (R=Me) and analogues

Examples of muscarinic agonists.