



Organic Pharmaceutical Chemistry I 3rd stage

Cholinergic Drugs and Related Agents

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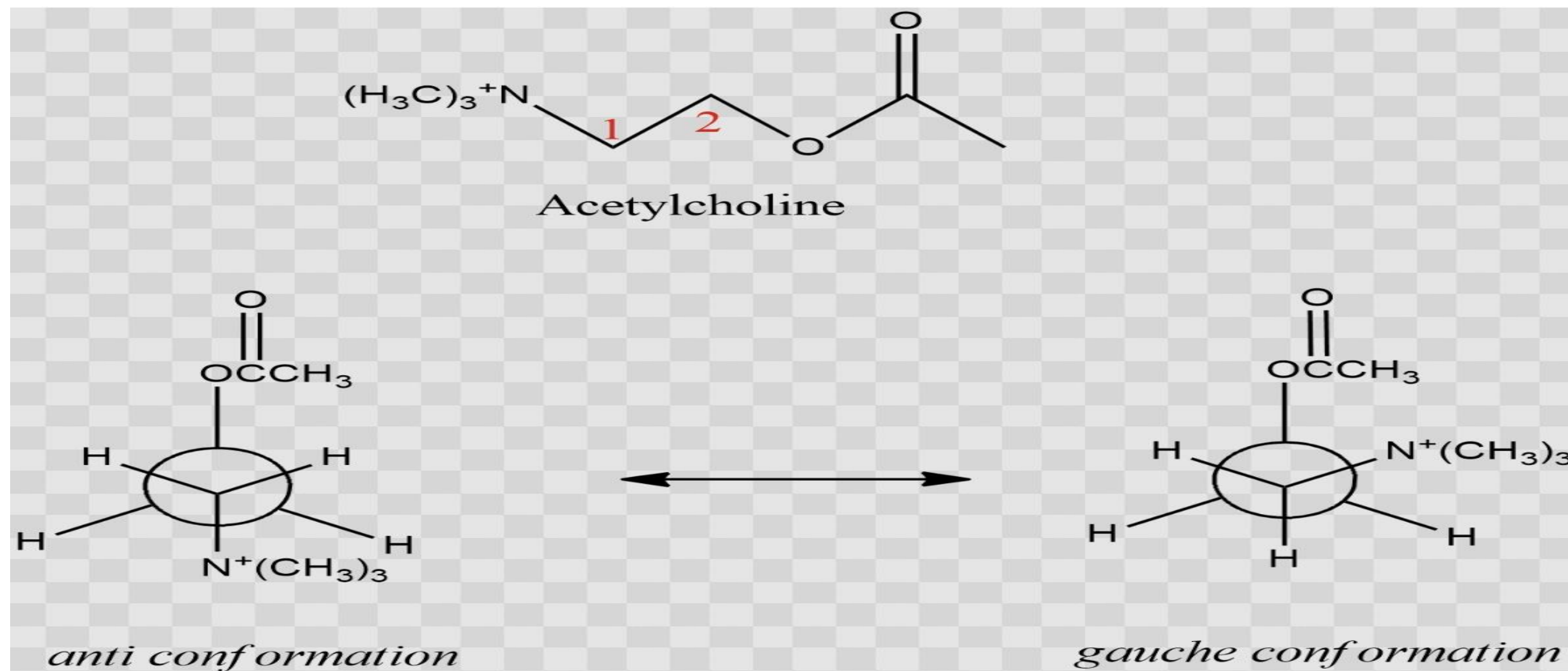
Lec 2

➤ Cholinergic Stereochemistry

The conformational properties of ACh and other cholinergic chemicals show spatial distribution of atoms in a molecule in terms of torsion angles.

A torsion angle is defined as the angle formed between two planes.

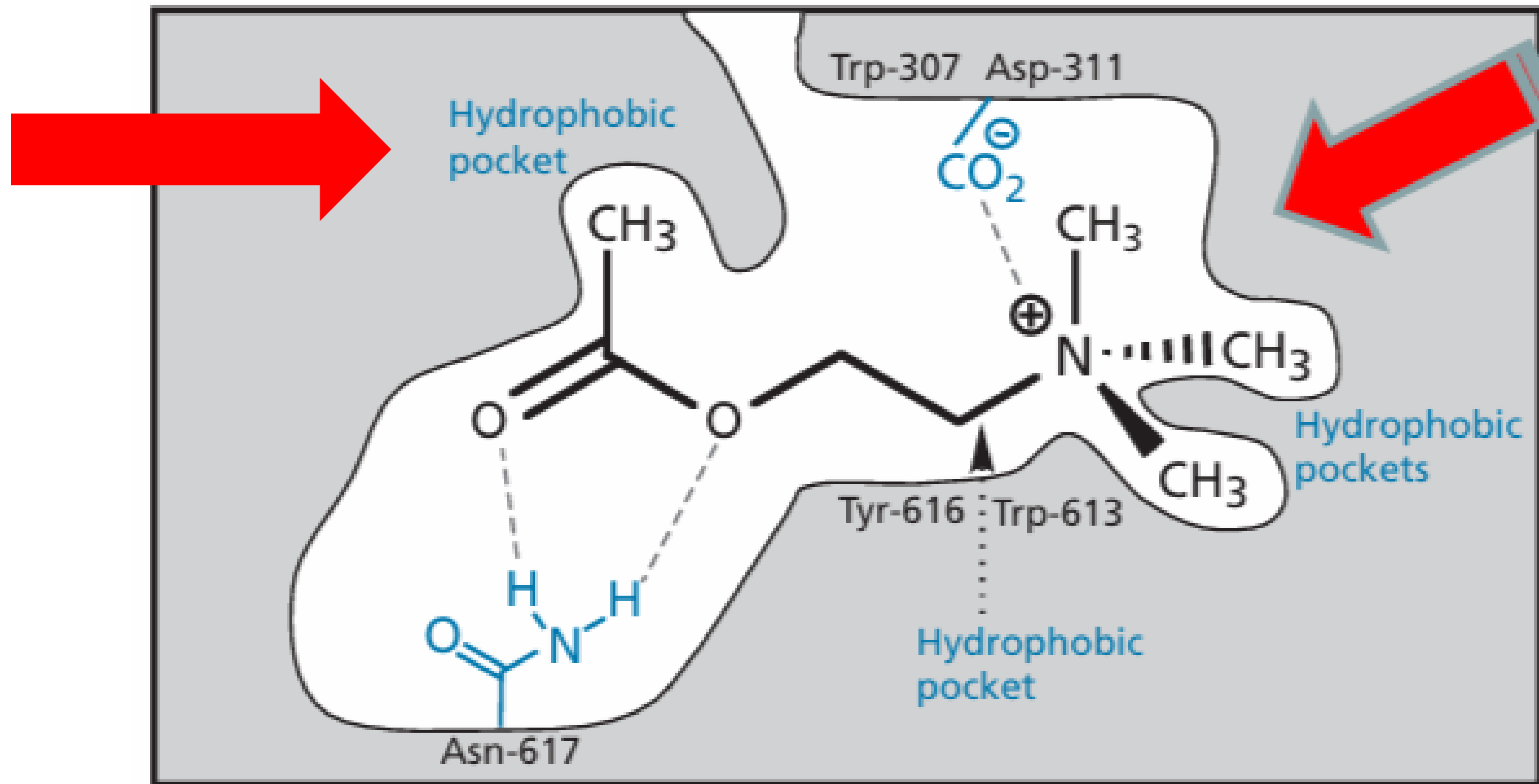
ex: ACh can form different conformations which depends on torsion angle, it determines the spatial orientation of the cationic head of ACh to the ester group.



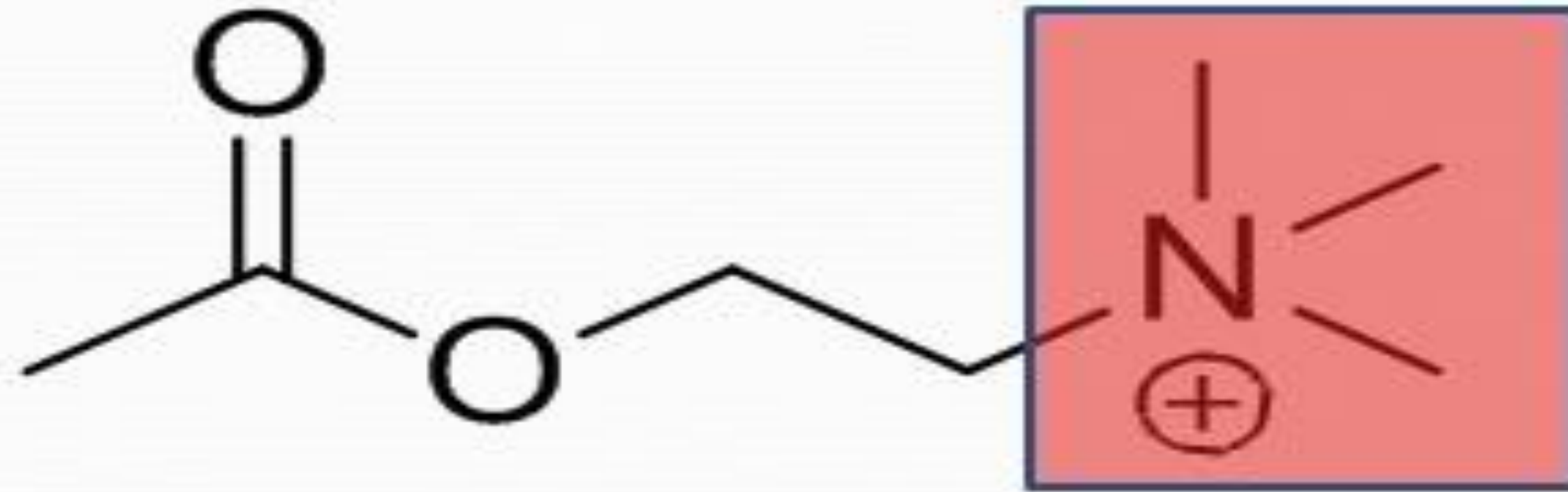
Newman
projection

Cholinergic Drugs and Related Agents

Structure–Activity Relationships of ACh



Structure–Activity Relationships of ACh



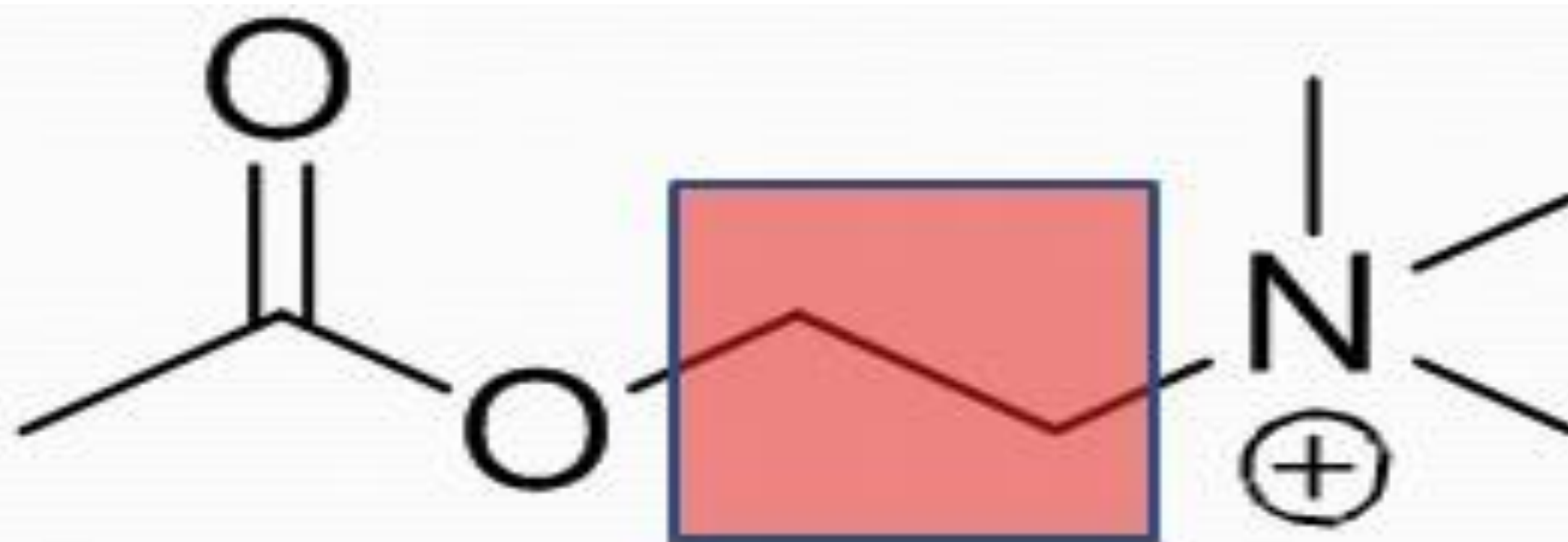
Onium gp

Quaternary nitrogen is essential



Bad for activity

Structure–Activity Relationships of ACh

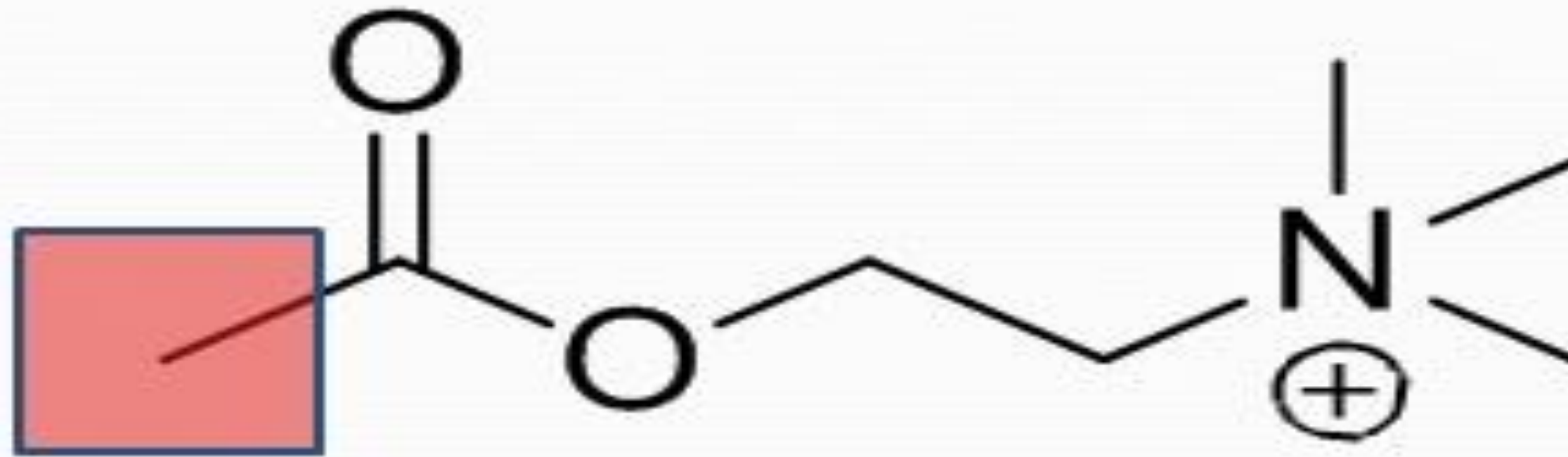


- Distance from quaternary nitrogen to ester is important
- Ethylene bridge must be retained

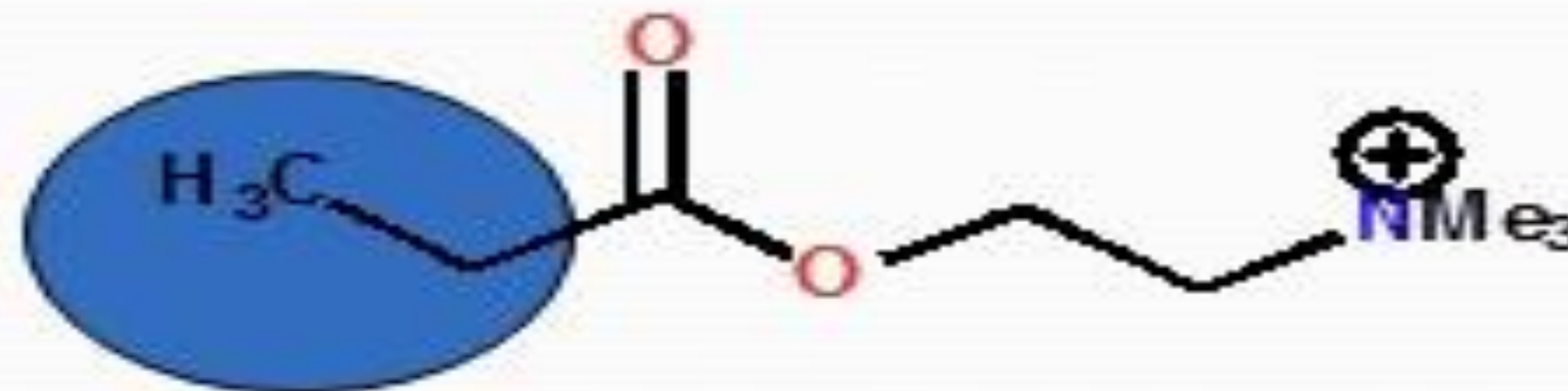


Bad for activity

Structure–Activity Relationships of Ach



Methyl group of acetoxy group cannot be extended



Much lower activity

Alterations on the molecule may be divided into three categories:

➤ **The onium group**

➤ **The ester group**

➤ **The choline moiety**

➤ **The onium group have 2 action :**

1. Is essential for intrinsic activity

2. Contributes to the affinity of the molecule for the receptors:

a. Partially through the binding energy

b. Partially because of its action as a detecting and directing group.

- **Phosphonium, sulfonium, arsenonium isosteres of onium**  **decrease the activity**
- **Substituents larger than methyl on the nitrogen:**
 - **Increase the size of the onium moiety**
 - **Produce diffusion of the positive charge**
 - **Interfere sterically with proper drug–receptor interaction, resulting in decreased activity**

The ester group in ACh contributes to the binding of the compound to the muscarinic receptor because of hydrogen bond formation at receptor site

For maximal muscarinic activity, the quaternary ammonium group should be followed by a chain of five atoms; this has been referred to as the *five-atom rule*.

Linker bridge modifications:

- Shortening  or lengthening  the chain of atoms that separates the ester group from the onium moiety **reduces muscarinic activity**.
 - An **α -substitution** on the choline moiety **decreases** both nicotinic and muscarinic activity, but muscarinic activity is decreased to a greater extent.
 - **Substitution** on the **β -carbon**, nicotinic activity is decreased to a greater degree
- *Hydrolysis by AChE is more affected by substitutions on the β - than the α -carbon.**

Ex: The hydrolysis rate of racemic acetyl β -methyl acetylcholine is about 50% of that of Ach.

Parasympathomimetics (cholinergic drugs)

Direct

Acetyl-choline
Methacholine
Carbachol
Bethanechol
Pilocarpine

Indirect

Reversible

Physostigmine
Neostigmine
Edrophonium

Irriversible

Organophosphorus
Echothiophate (used in glucoma)
War gases and Parathion

CHOLINERGIC AGONISTS

Medicinal uses :

Muscarinic agonists

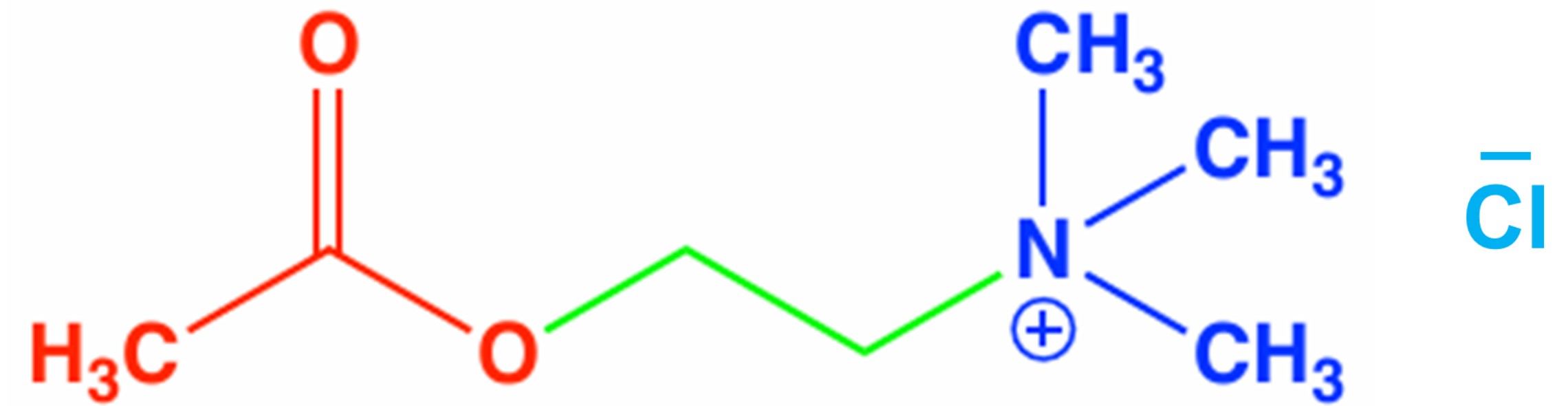
- Treatment of glaucoma .
- Treatment of certain heart defects, decreases heart muscle activity and decreases heart rate

Nicotinic agonists

- Treatment of myasthenia gravis
- lack of acetylcholine at skeletal muscle causing weakness

Cholinergic Agonists products

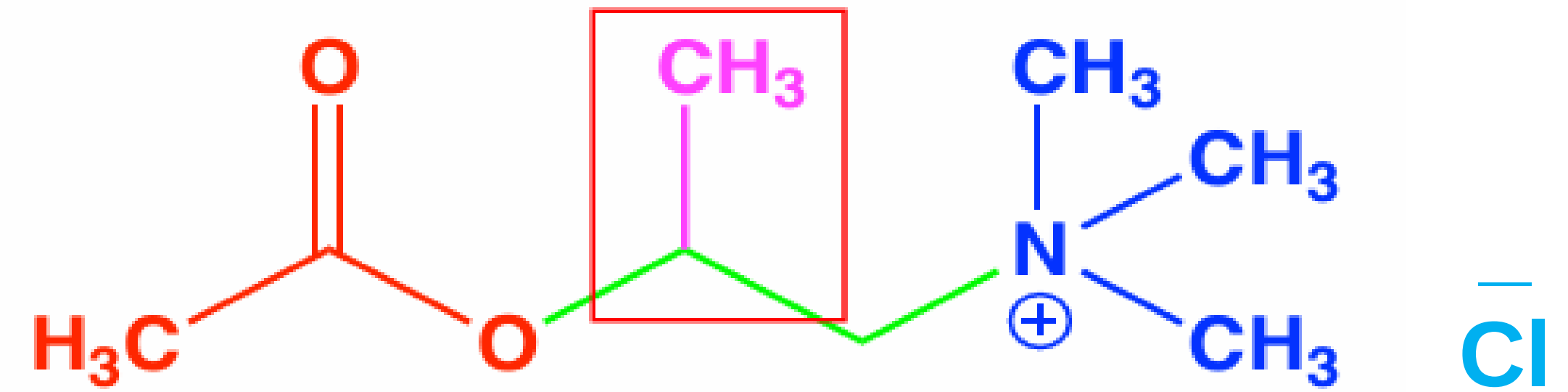
1. Acetylcholine Chloride



Acetylcholine

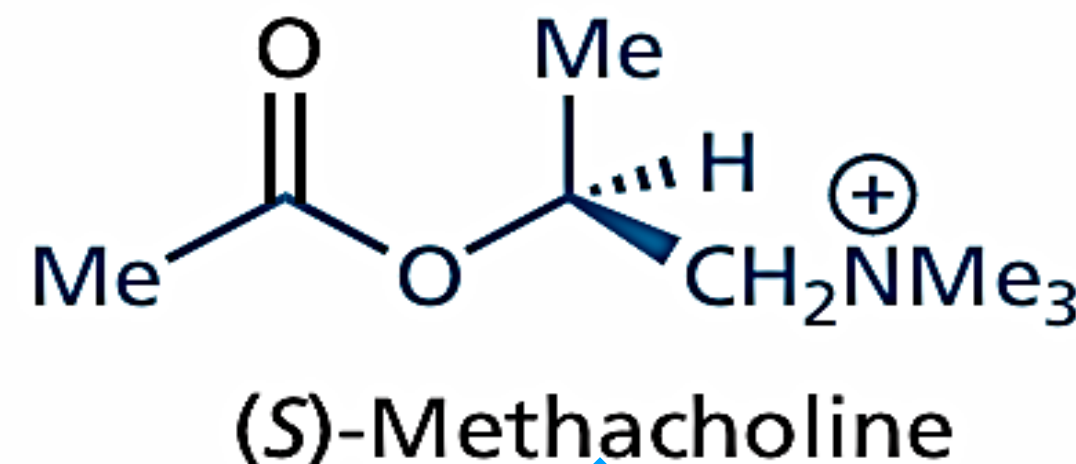
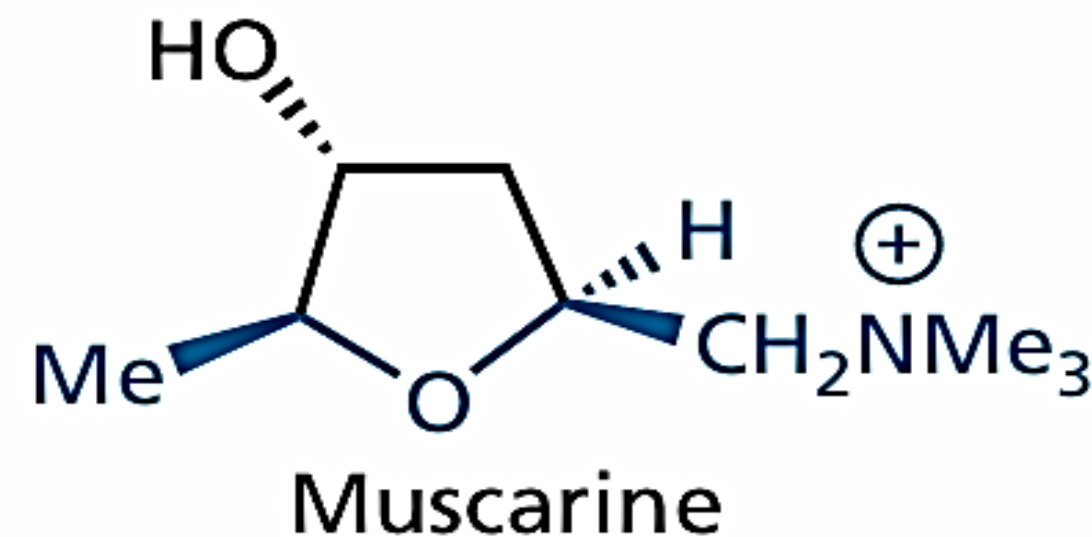
- A powerful stimulant effect on the parasympathetic nervous system.
- Its duration of action is too short for sustained effects, because of
 - Rapid hydrolysis by **esterases**
 - Lack of specificity when administered for systemic effects.

2. Methacholine Chloride (acetyl-B-methyl choline chloride)

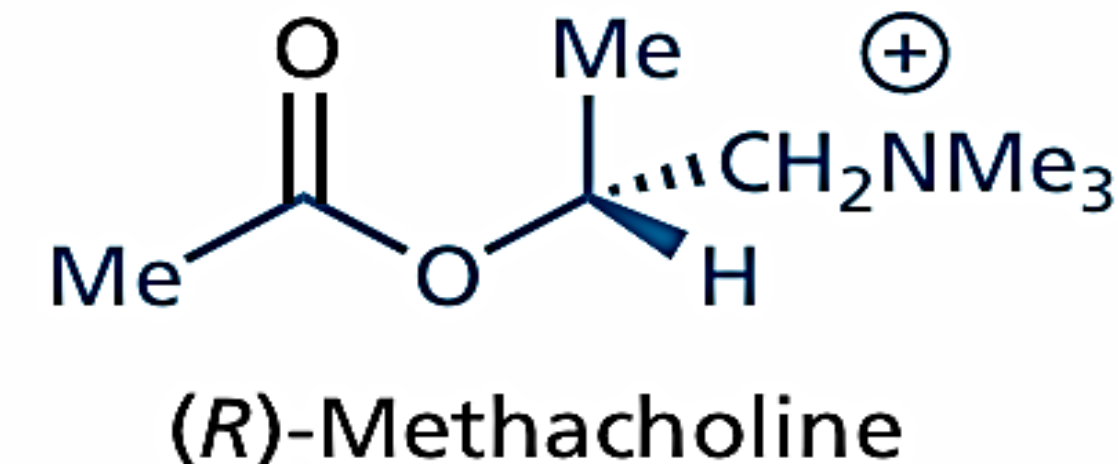


Methacholine

- It is 3 times **more stable** to hydrolysis by AChE than ACh.
- Methacholine shows **good selectivity** for the muscarinic receptor
- **No nicotinic** activity. Because the active conformation of methacholine is similar to muscarine.
- Use for treatment of glaucoma

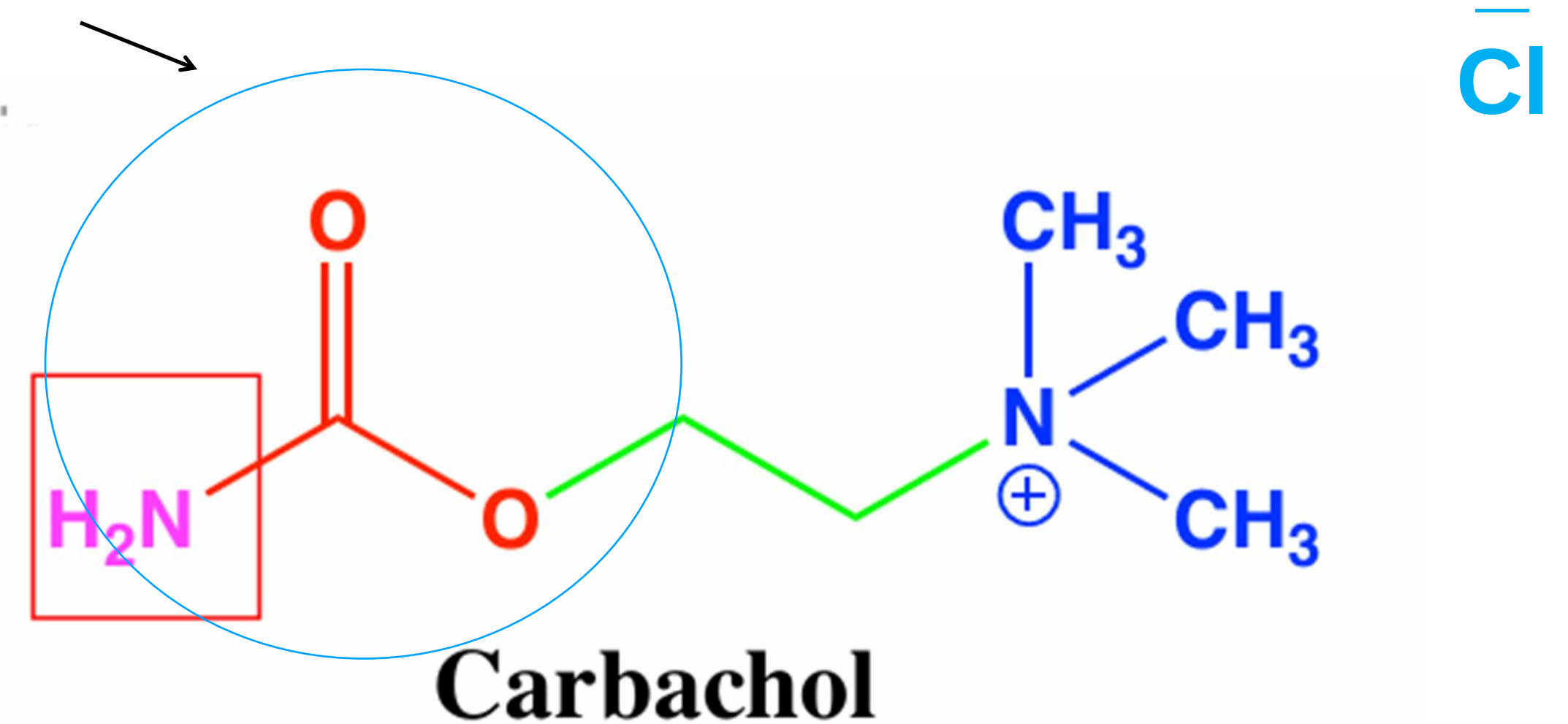


↑ Active isomer



3. Carbachol Chloride (Choline chloride carbamate)

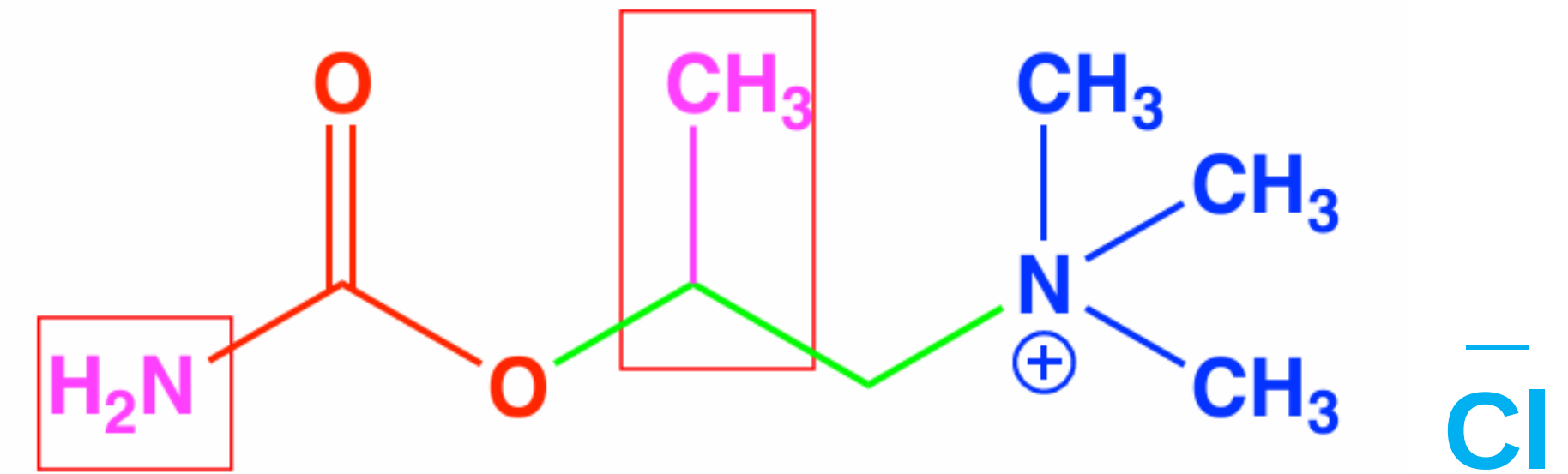
carbamate



- Act as **direct** agonist because it possesses **both muscarinic and nicotinic** properties by cholinergic receptor stimulation.
- Because its slow hydrolysis rate  prolongs the duration of Ach in the synapse.
- Carbachol is a **bioisostere** to Ach.
- Use for treatment of glaucoma.

4. Bethanechol Chloride

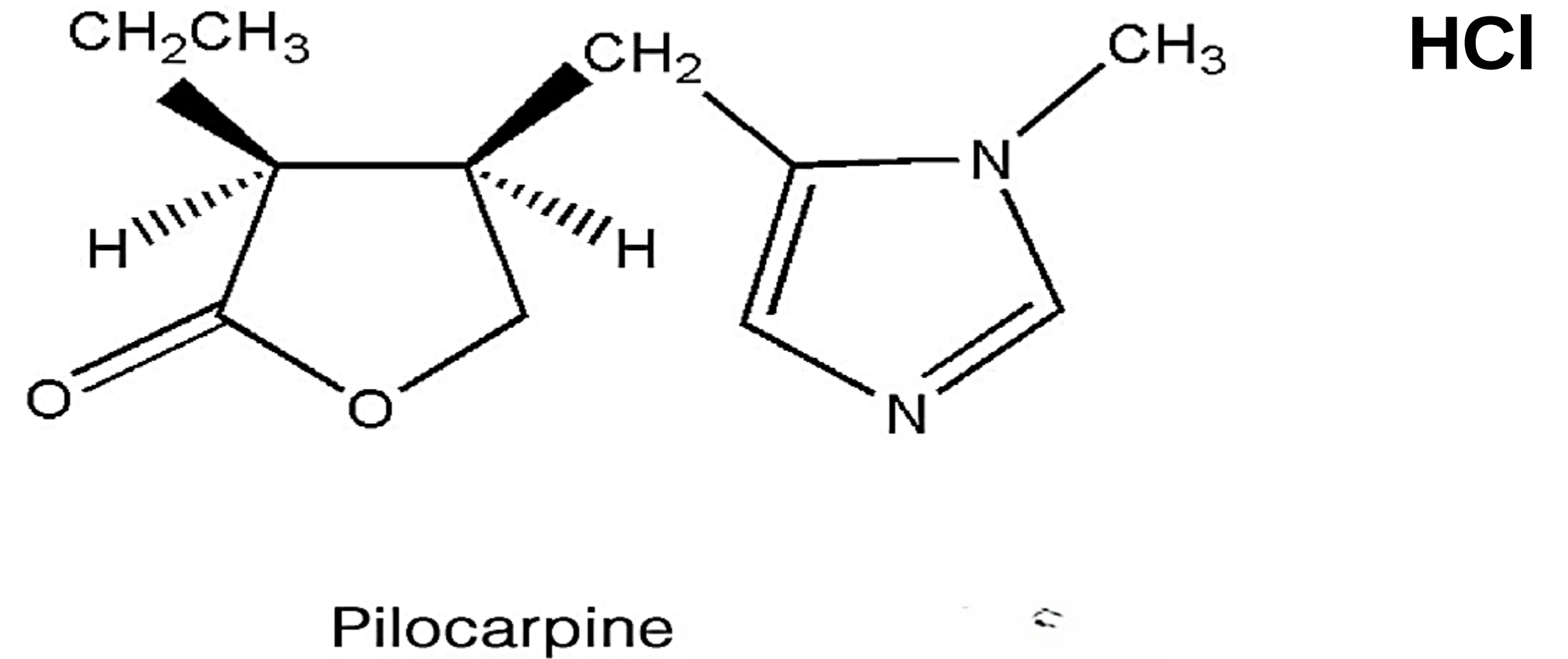
B-methyl choline chloride carbamate



Bethanechol

- **Nonspecific** in its action on muscarinic receptor subtypes but appears to be more effective at eliciting pharmacological action of **M3** receptors.
- Bethanechol is **inactivated** more **slowly** by AChE in vivo than is methacholine.
- Have stability in aqueous solutions similar to that of carbachol because of carbamyl ester
- Used to relief urinary retention and abdominal distention after surgery.

5.pilocarpine Hydrochloride



- This alkaloid is **non selective** to muscarinic Rc.
- Acts on M3 receptors in smooth muscle to cause contractions in the gut, trachea, and eye, it produces pupillary constriction (miosis). These effects are valuable in the treatment of glaucoma.



**Thank
You!!!**