ANTICOLINERGICI & ANTICOLINESTERASICI

Parte II

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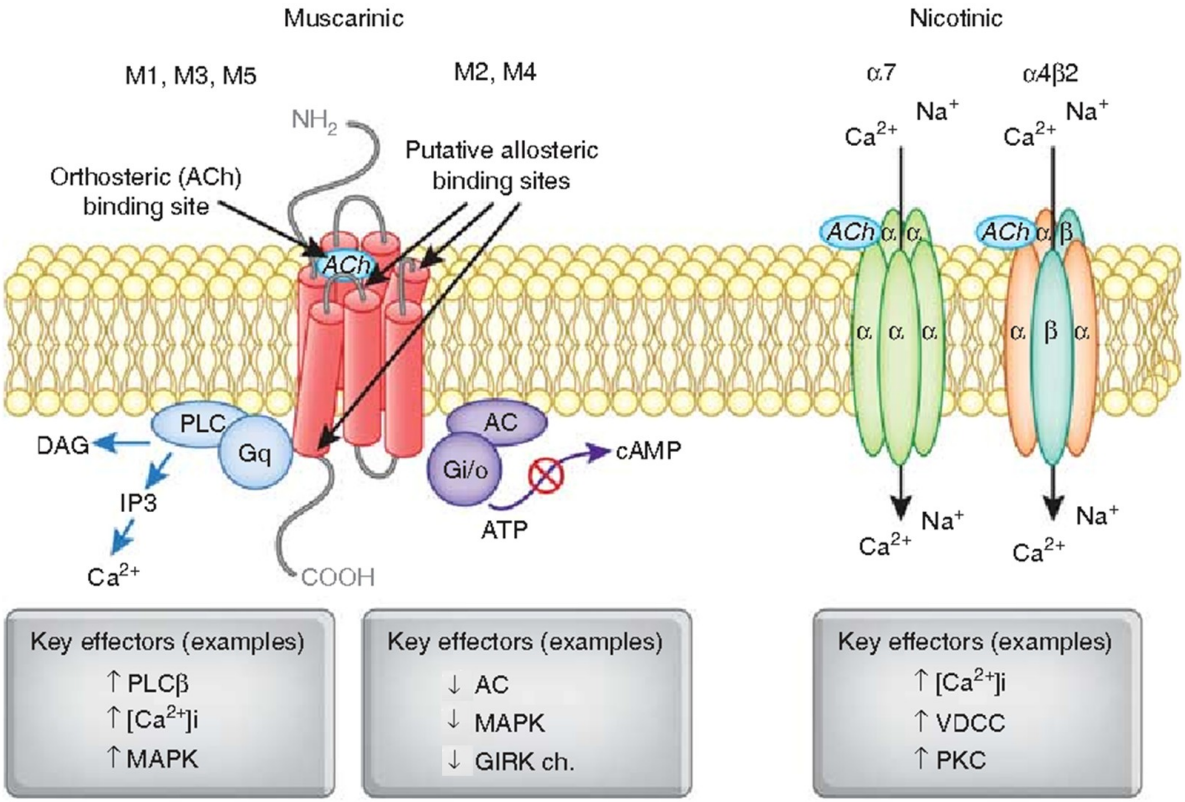
12. Cholinergic Antagonists



- **Drugs which bind to cholinergic receptor but do not activate it**
- **Prevent acetylcholine from binding**
- **Opposite clinical effect to agonists - lower activity of acetylcholine**

credits: https://egpat.com/tutorials/cholinergic-agonists/introduction

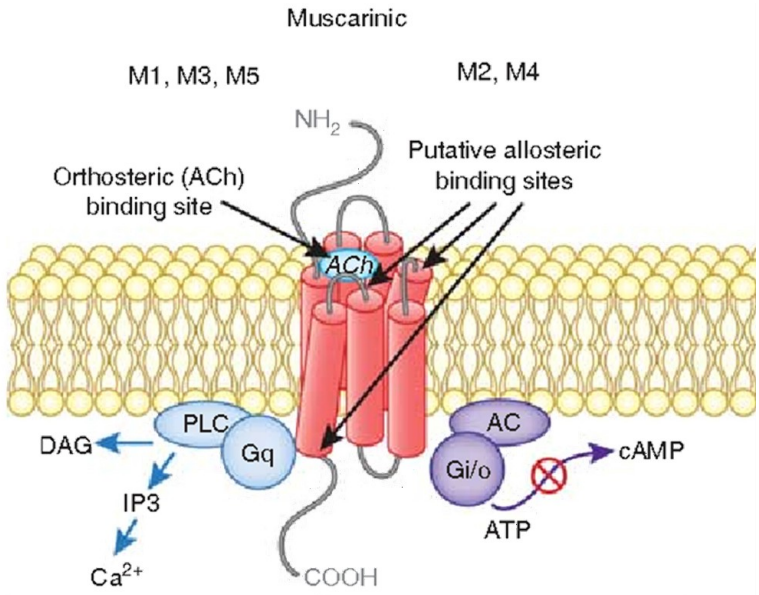
12. Cholinergic Antagonists (Muscarinic receptor)

Clinical Effects

- Decrease of saliva and gastric secretions
- Relaxation of smooth muscle
- Decrease in motility of GIT and urinary tract
- Dilation of pupils

Uses

- Shutting down digestion for surger
- Ophthalmic examinations
- Relief of peptic ulcers
- Treatment of Parkinson's Disease
- Anticholinesterase poisoning
- Motion sickness



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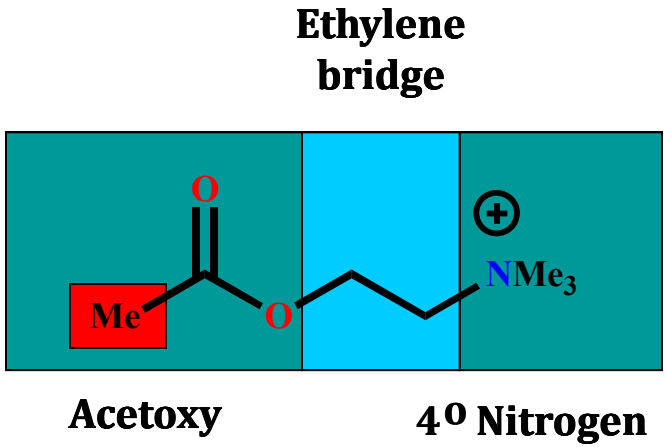
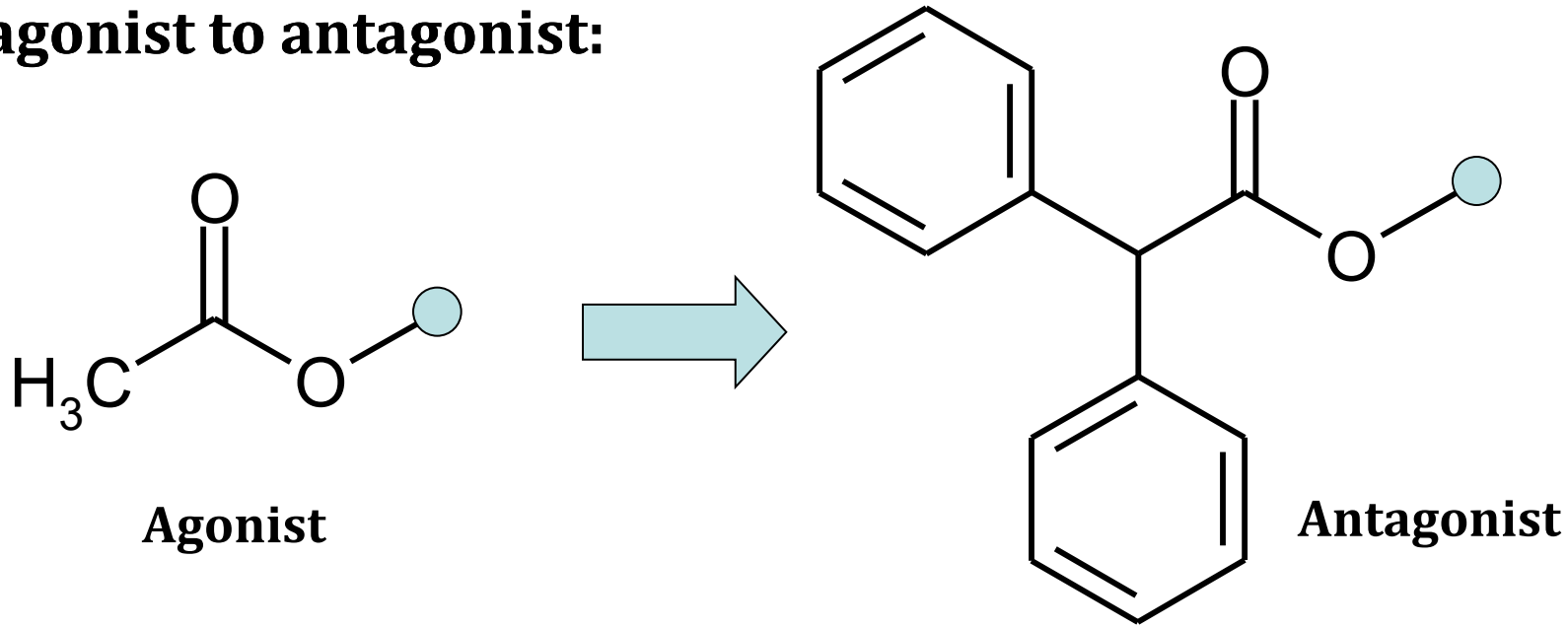
6. SAR for acetylcholine



From agonist to antagonist:



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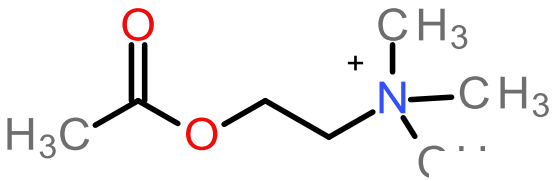
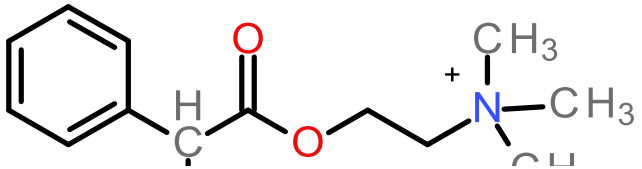
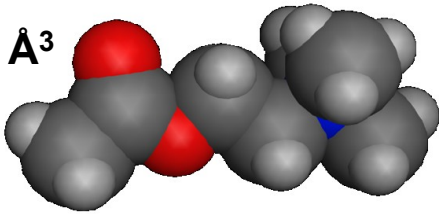
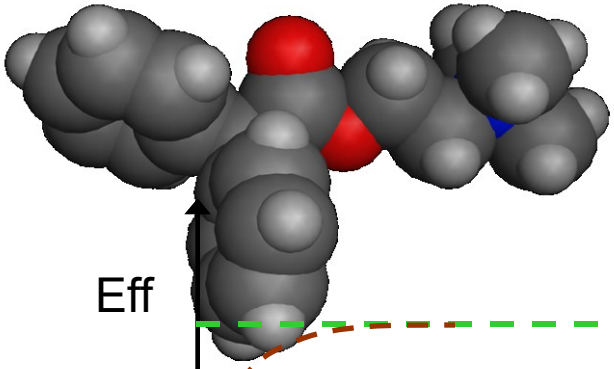
From agonist to antagonist…



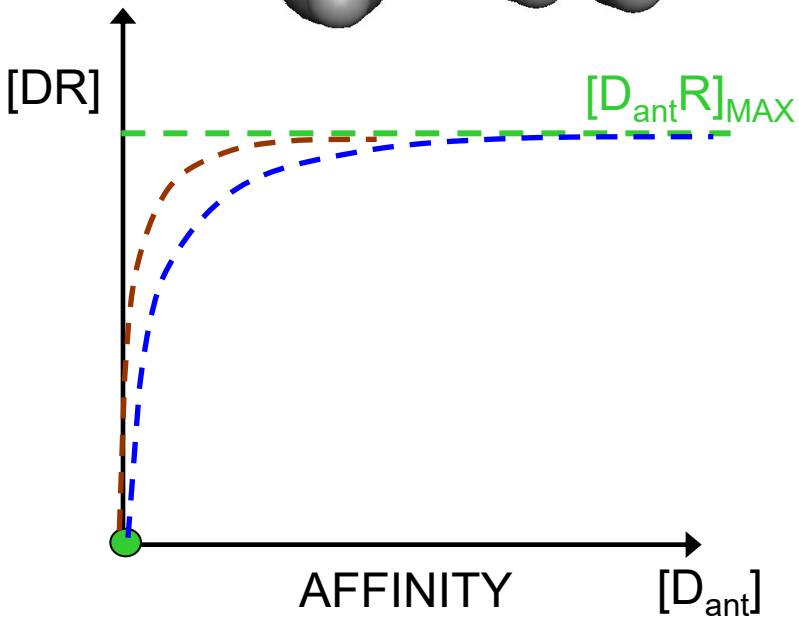


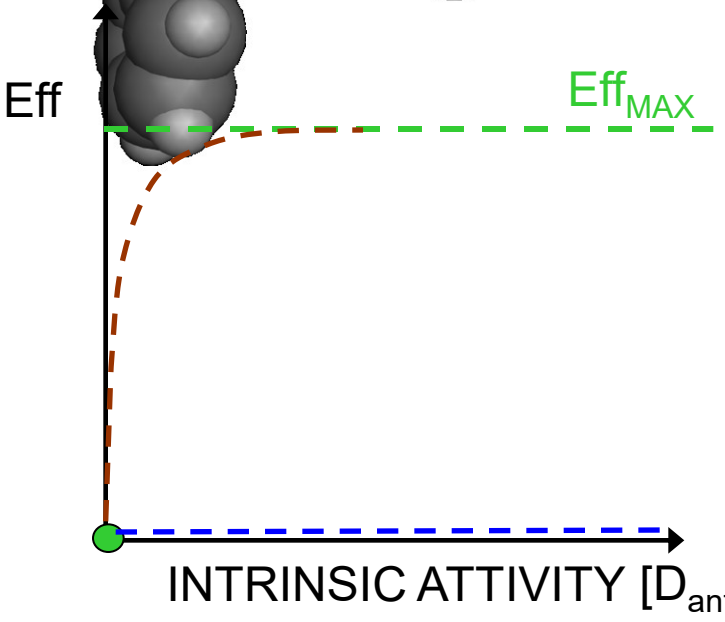
L ≅ 12 Å
Volume ≅ 163 Å^3





≅ 324 Å^3





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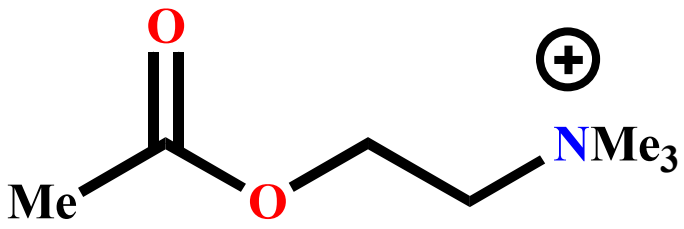
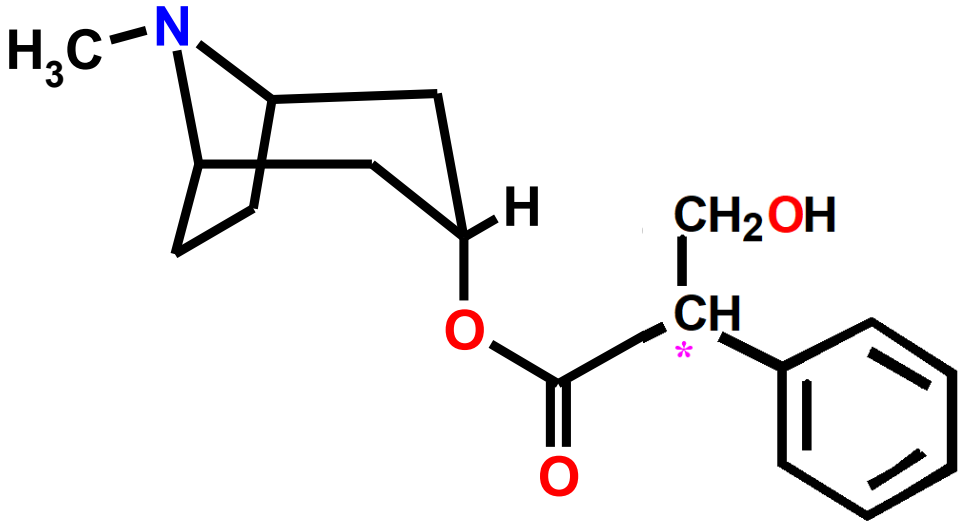
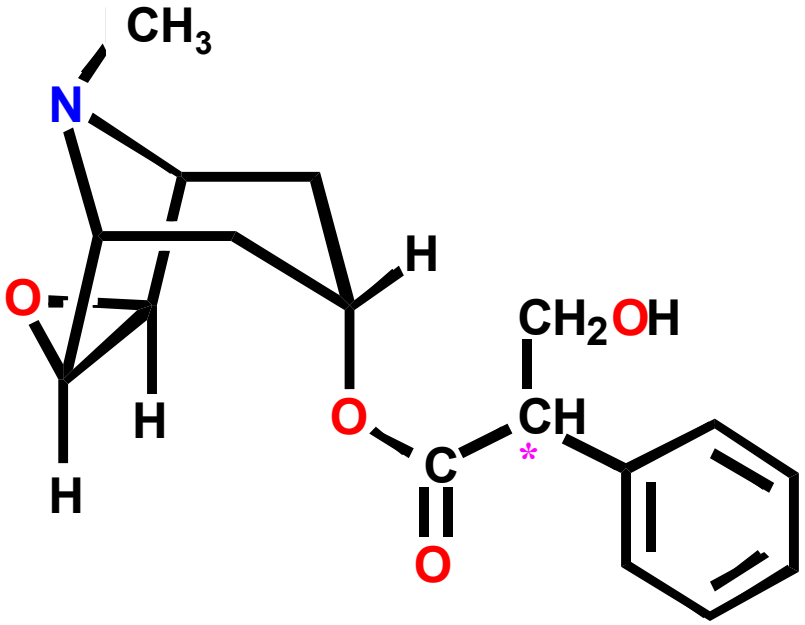
Let's start by learning from mother nature …



Ach



Atropine



Scopolamine

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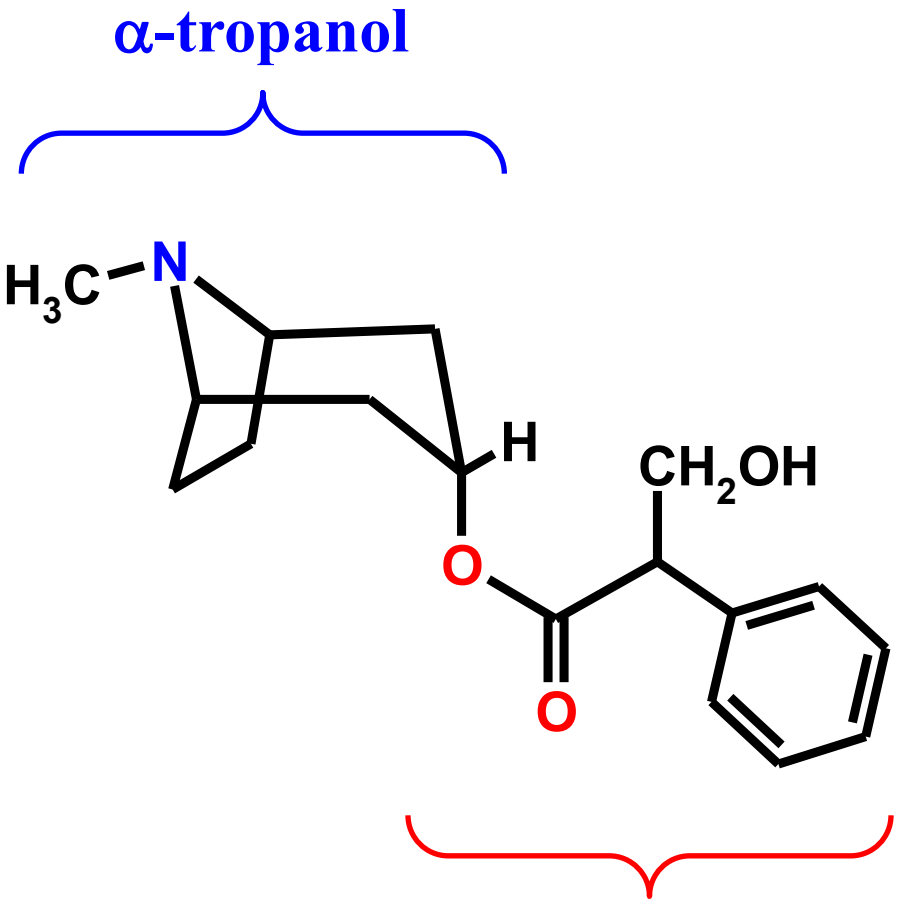
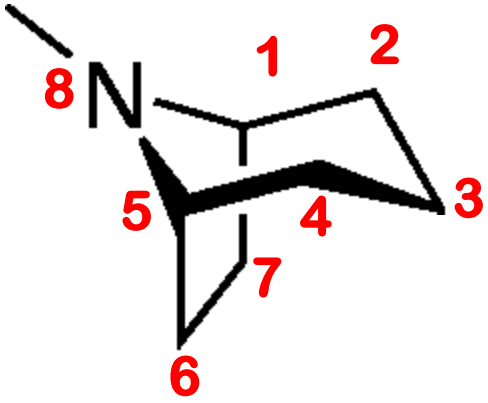
12. Cholinergic Antagonists (Muscarinic receptor)

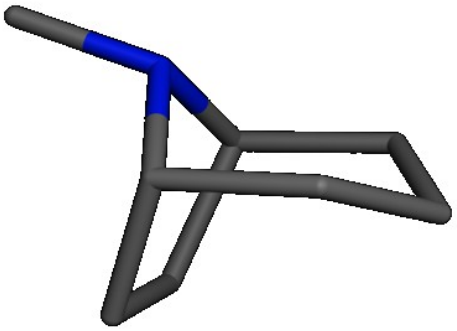
12.1 Atropine

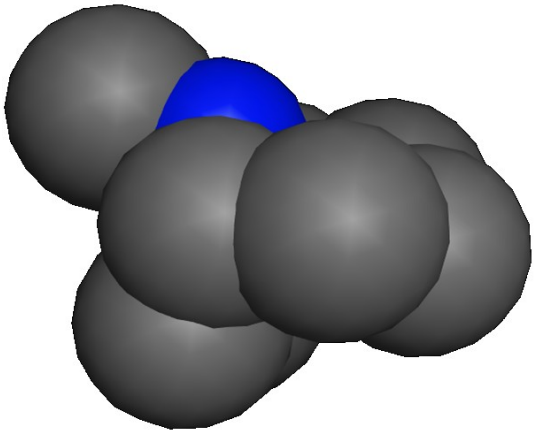


Atropa Belladonna (Solanaceae)

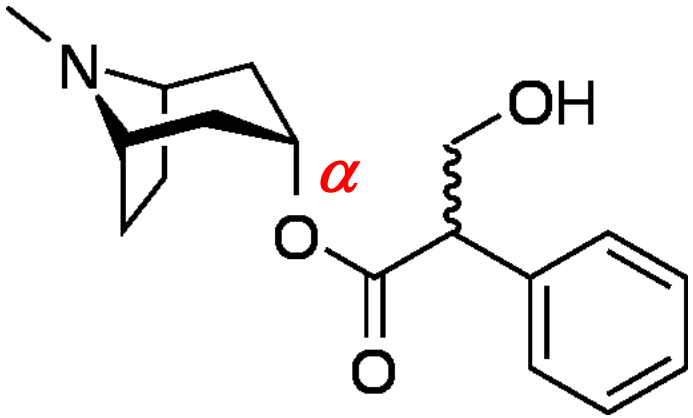
Tropane derivatives





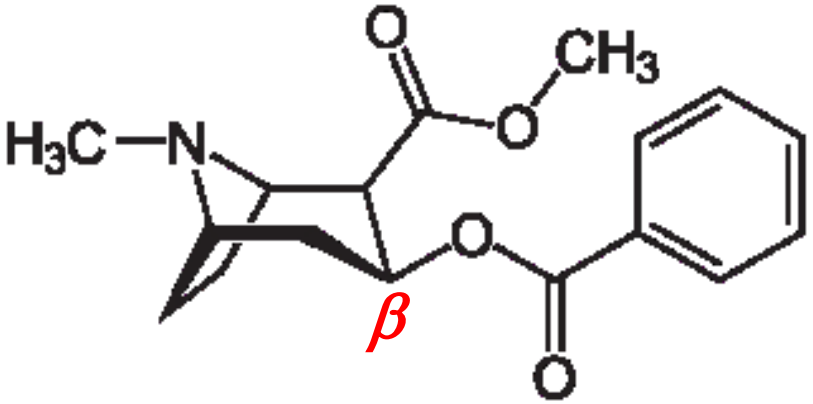


8-methyl-8-azabicyclo[3.2.1]octane



Atropine

(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) 3-hydroxy-2-phenylpropanoate



Cocaine

methyl (*1R,2R,3S,5S)-3- (benzoyloxy)-8-methyl-8-azabicyclo[3.2.1] octane-2-carboxylate*

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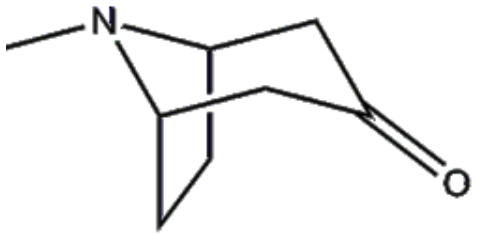
Tropane derivatives

Mother nature…



$Al(isoBut)_2H$ / THF → **95 : 5**

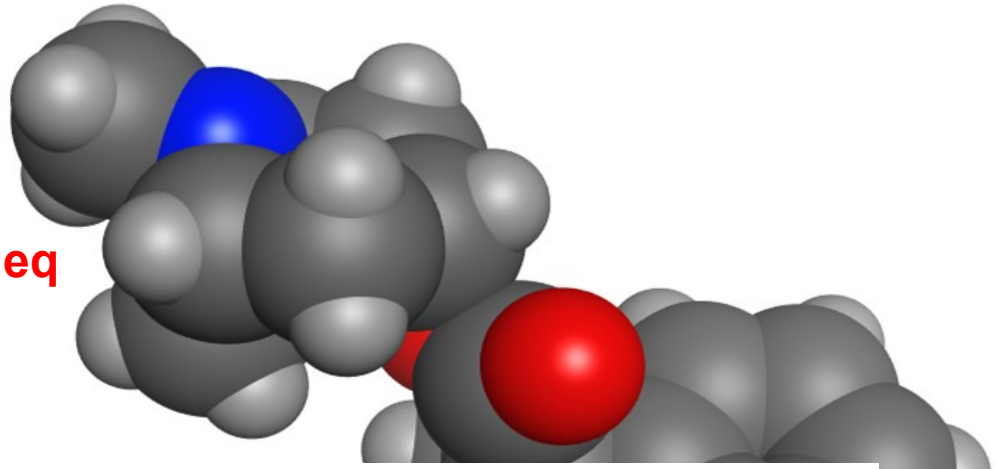
Na/Hg (2%) / H_2O (H_2SO_4, pH = 3.4) → **25 : 75**

versus **the human chemistry!**

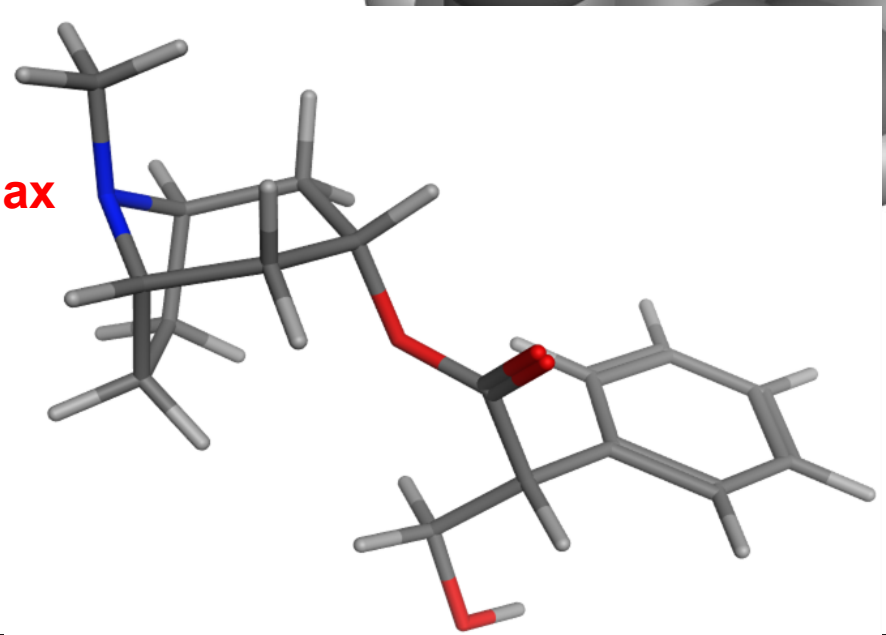
12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine

eq



ax



L = 15.6 Å

Vol ≅ 290 Å^3

log P = 1.8

MW = 289.4

PSA ≅ 50Å^2

O + N = 4

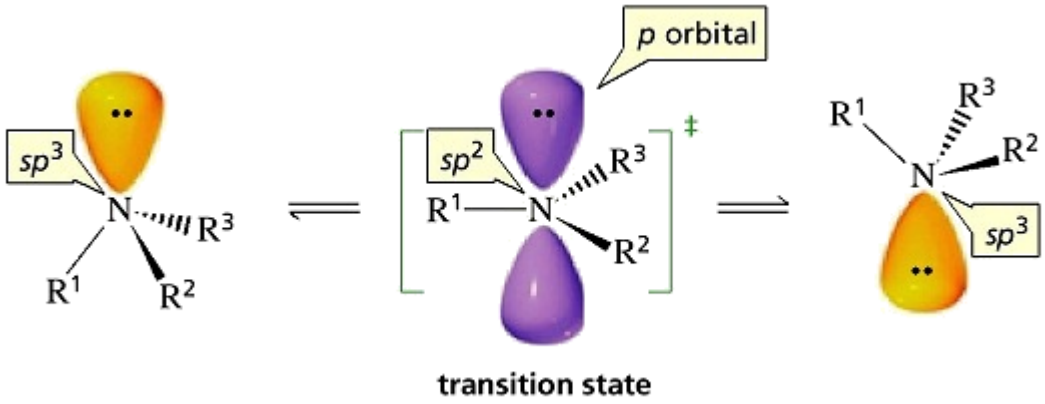
pKa = 9.4

Ep (eq) = 47.9 kcal/mol

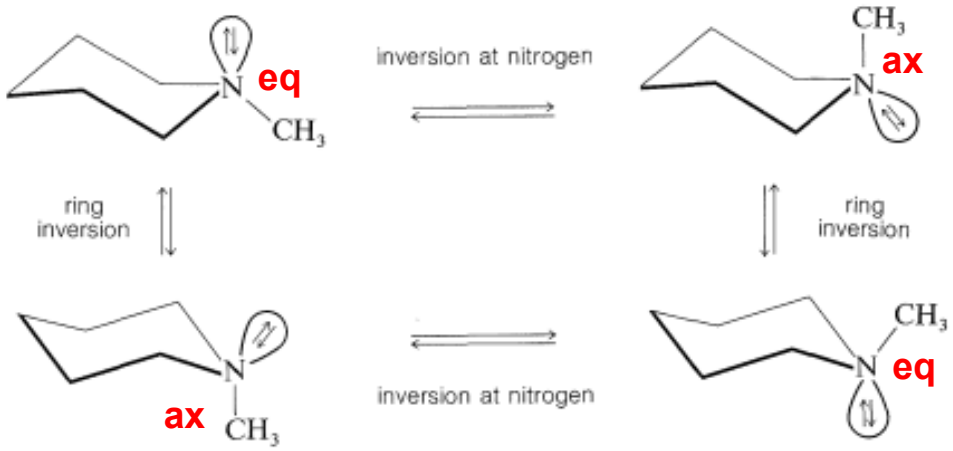
Ep (ax) = 49.6 kcal/mol

12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Nitrogen inversion...



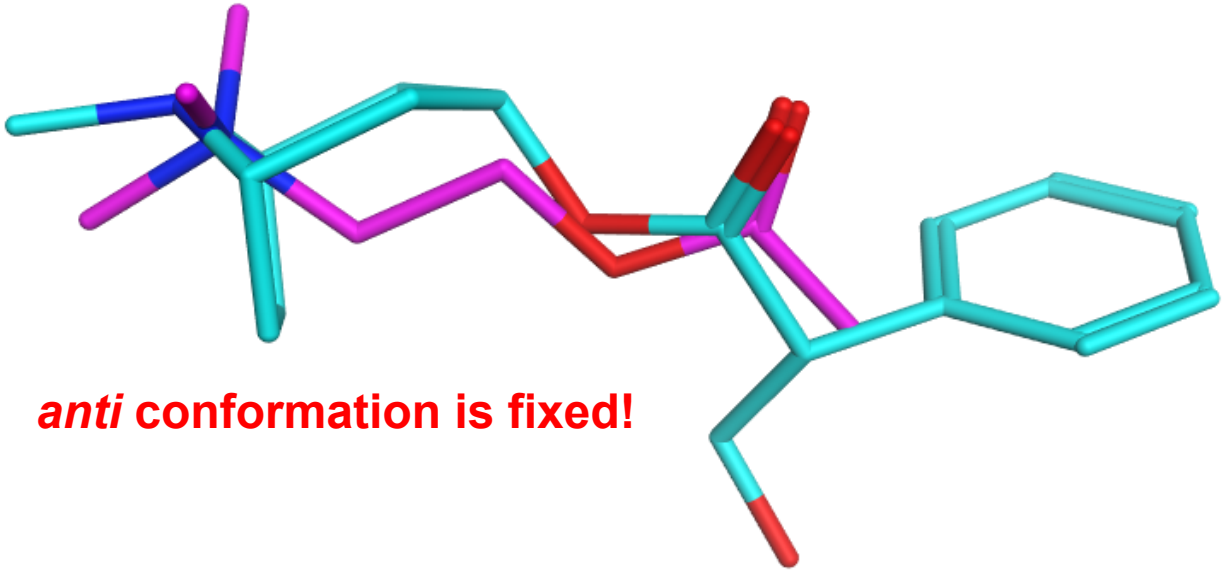
Piperidine



Thanks, Zorro96!!

12. Cholinergic Antagonists (Muscarinic receptor)

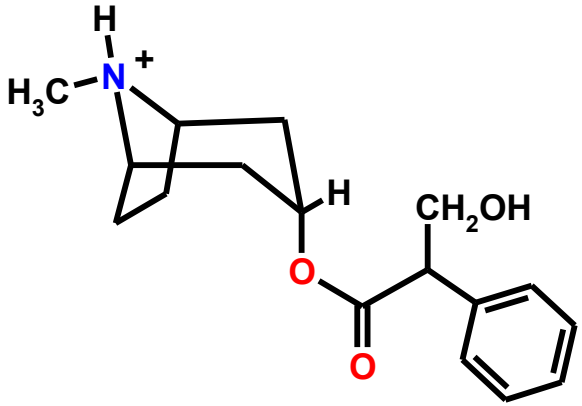
12.3 Comparison of atropine with acetylcholine

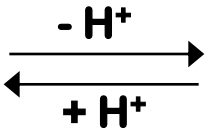


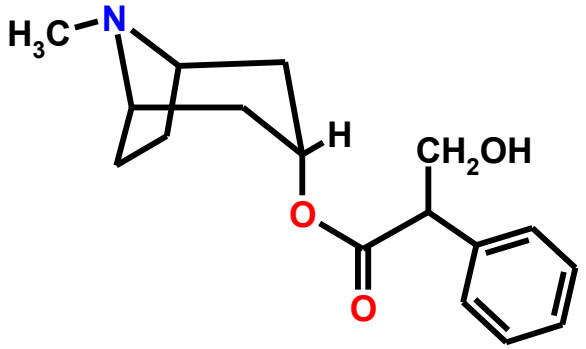
anti conformation is fixed!

- Relative positions of ester and nitrogen similar in both molecules
- Nitrogen in atropine is ionised
- Amine and ester are important binding groups (ionic + H-bonds)
- Aromatic ring of atropine is an extra binding group (vdW)
- Atropine binds with a different induced fit - no activation
- Atropine binds more strongly than acetylcholine

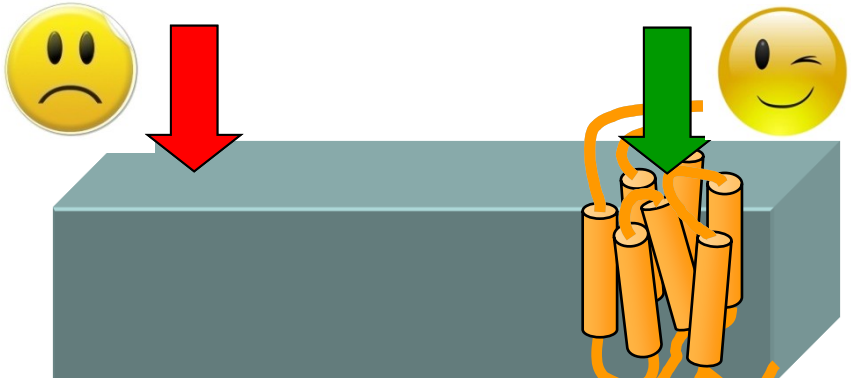
Pharmacodynamics versus Pharmacokinetics:

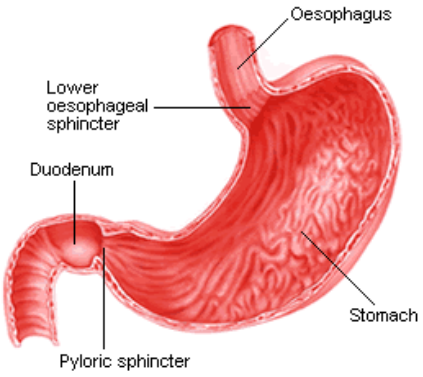


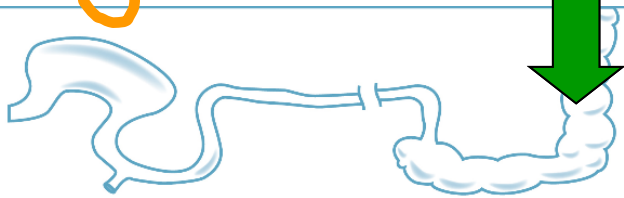




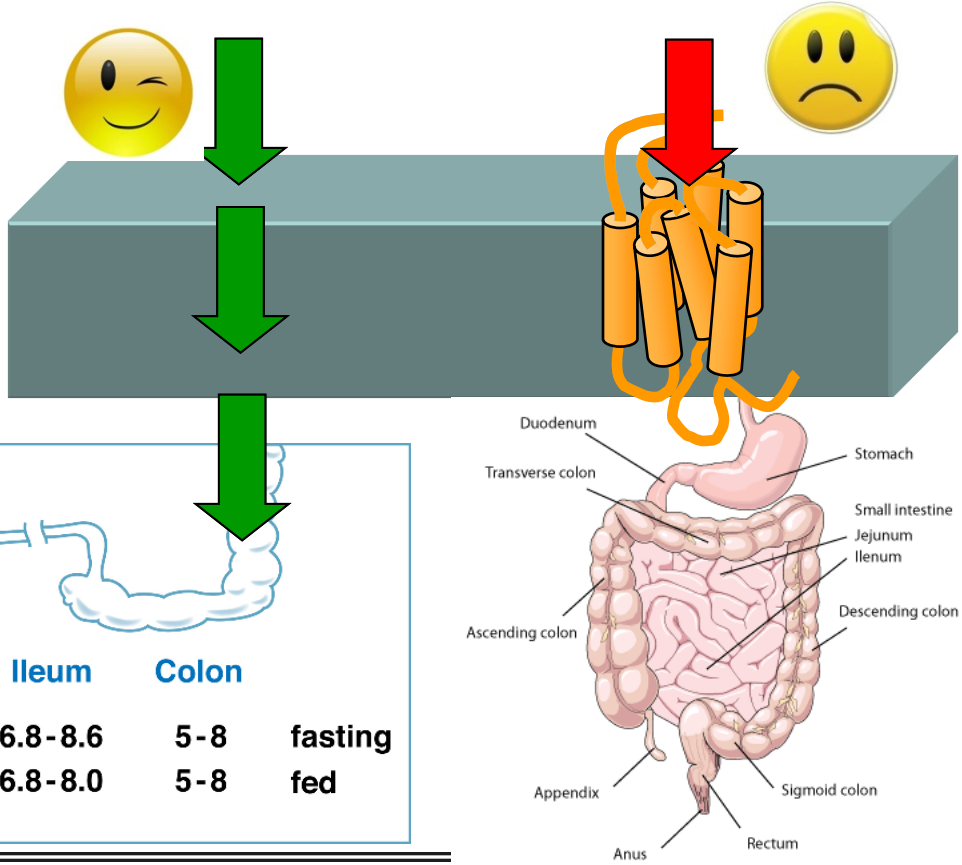
logP = 1.8







	Stomach	Jejunum	Ileum	Colon	
pH	1.4-2.1	4.4-6.6	6.8-8.6	5-8	fasting
	3-7	5.2-6.2	6.8-8.0	5-8	fed



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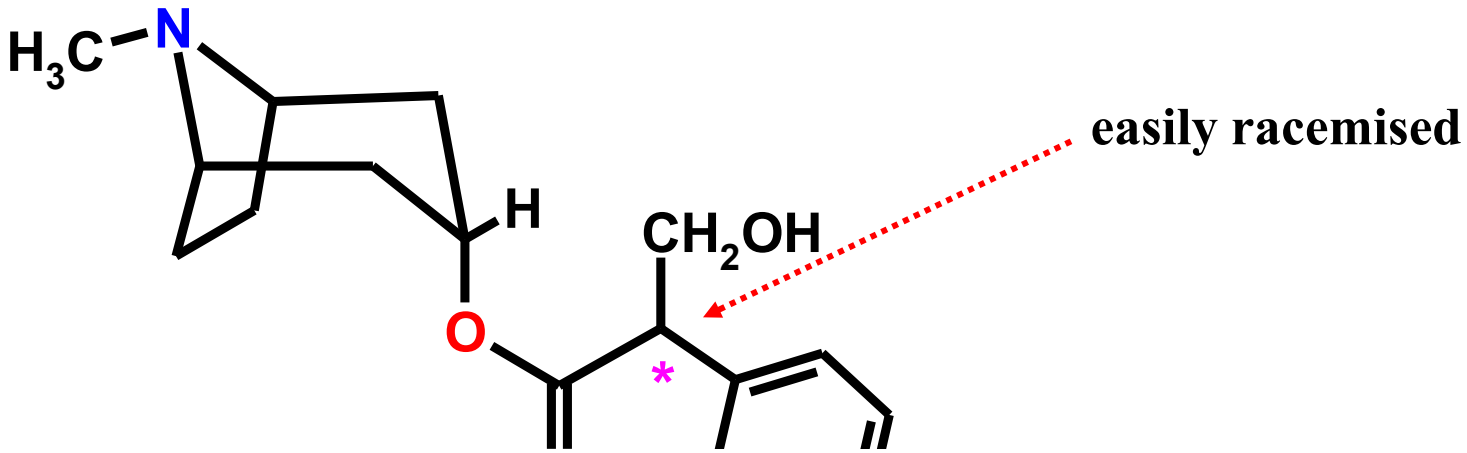
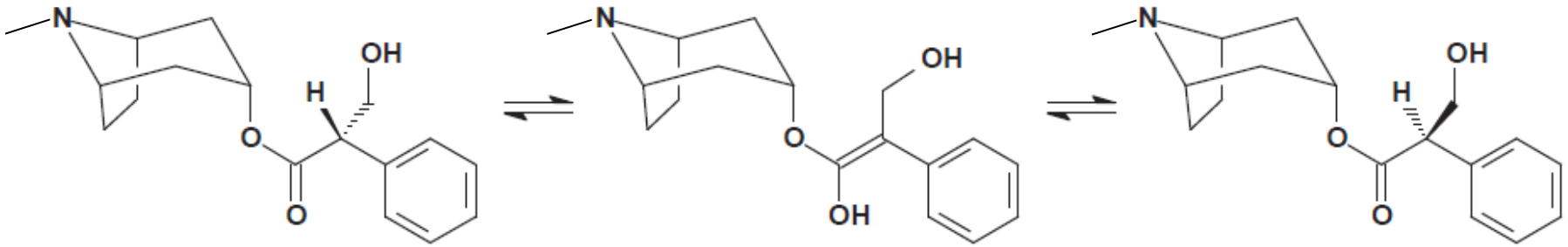
12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine… or D/L Hyscymine

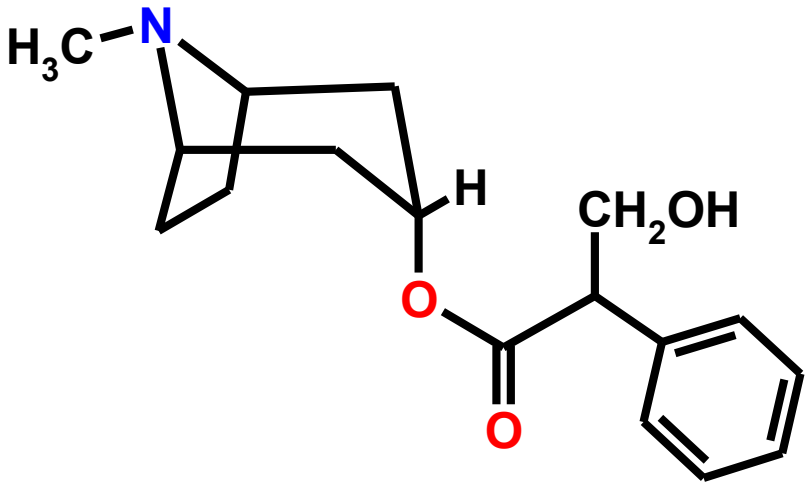




Atropina

12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine



- **Racemic form of hyoscyamine (*R* form)**
- **Source - roots of belladonna (1831) (*Atropa Belladonna*)**
- **Used as a poison**
- **Used as a medicine**
  - **decreases GIT motility**
  - **antidote for anticholinesterase poisoning**
  - ***resuscitation***
  - ***dilation of eye pupils***
- **CNS side effects - hallucinations**

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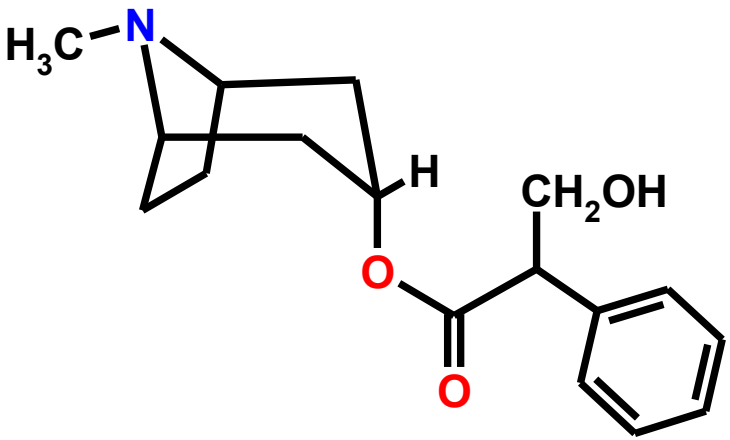
12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine



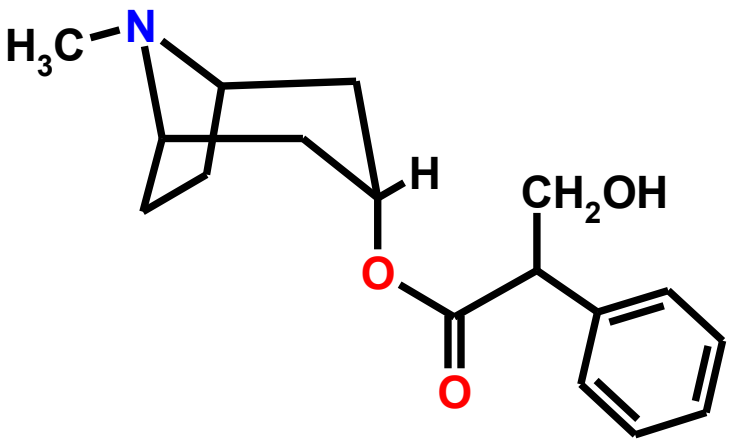
A common mnemonic used to describe the physiologic manifestations of Atropine overdose is:

hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hatter!

These associations reflect the specific changes of warm, dry skin from decreased sweating, blurry vision, decreased sweating/lacrimation, vasodilation, and central nervous system effects on muscarinic receptors, type 4 and 5. This set of symptoms is known as **anticholinergic toxidrome**, and may also be caused by other drugs with anticholinergic effects, such as scopolamine, diphenhydramine, phenothiazine antipsychotics and benztropine.

12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine



Resuscitation!

The action of this drug is to block the effect of the vagus nerve on the heart. This nerve normally slows heart rate and, during cardiac arrest, is a common cause of asytole. Atropine also acts on the conduction system of the heart and accelerates the transmission of electrical impulses through cardiac tissue.

In cardiac arrest it is given to reverse asystole and severe bradycardia. The *Resuscitation Council* recommends that atropine be given for pulseless electrical activity with a rate of less than 60 beats per minute or in complete asystole.

This drug should be administered intravenously and the dose depends on the heart rhythm. For bradycardia a dose of 0.5mg should be given and repeated every five minutes until a satisfactory heart rate is achieved. In asystole a single dose of 3mg should be given and this should not be repeated unless the cardiac rhythm changes to bradycardia or pulseless electrical activity.

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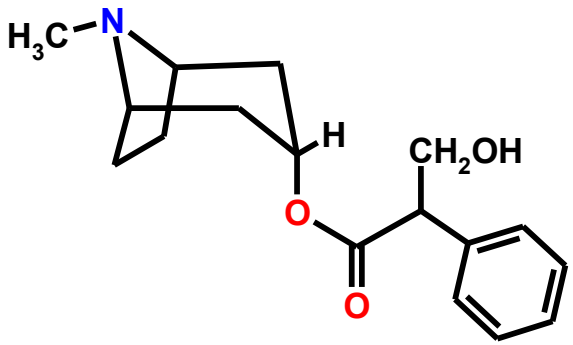
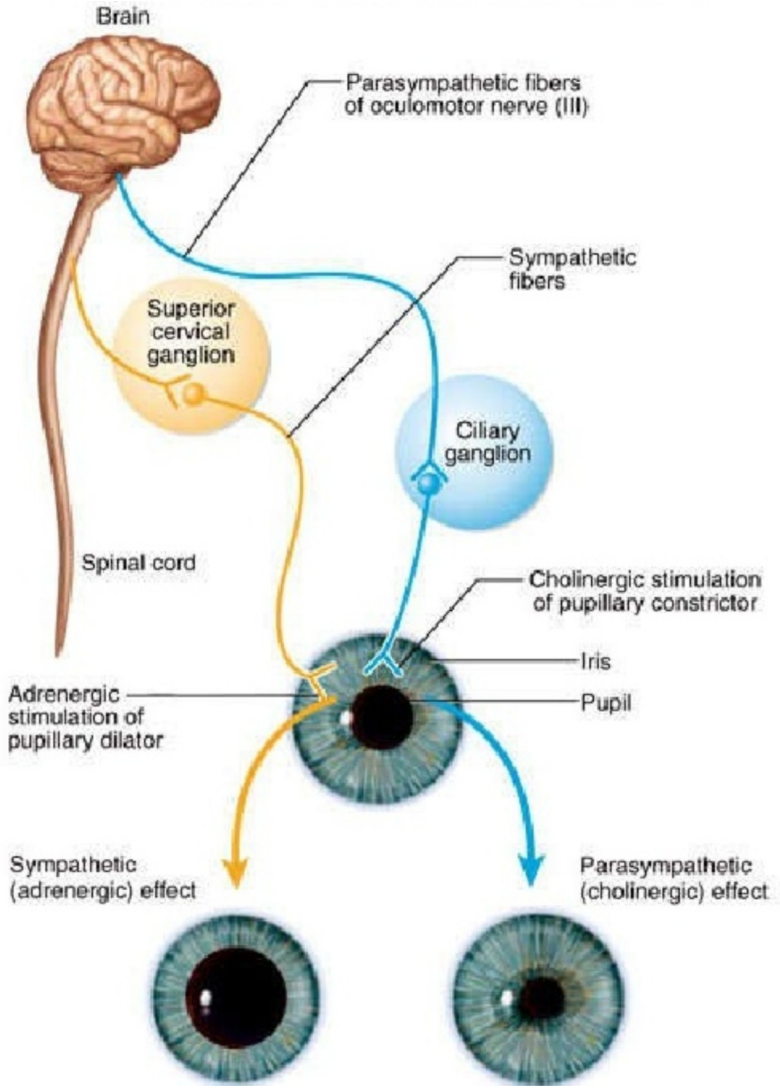
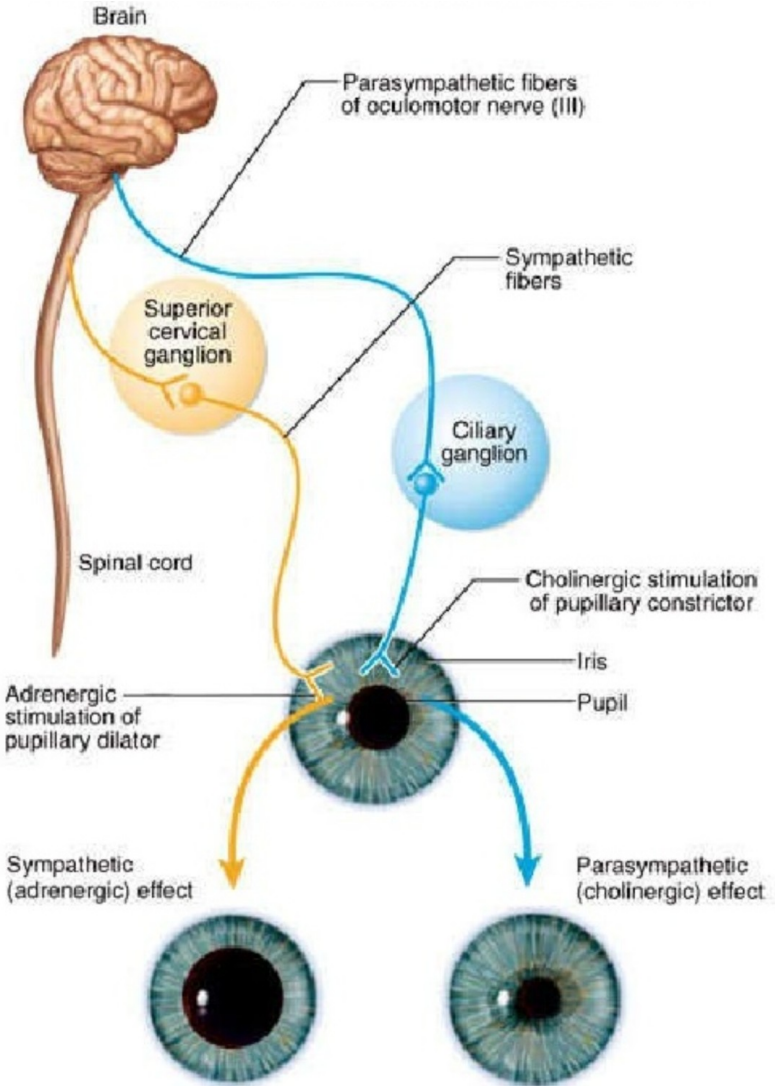
12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine





The eyes don't lie!!!



Pinned Out Pupils

Opiods, Benzodiazapines, and Barbiturates cause pupil constriction.

Opioids: Percocet, vicodin, oxycodone, heroin.
Benzodiazepines alleviate anxiety. [Xanax, valium]
Barbiturates also called tranquilizers or sedatives.

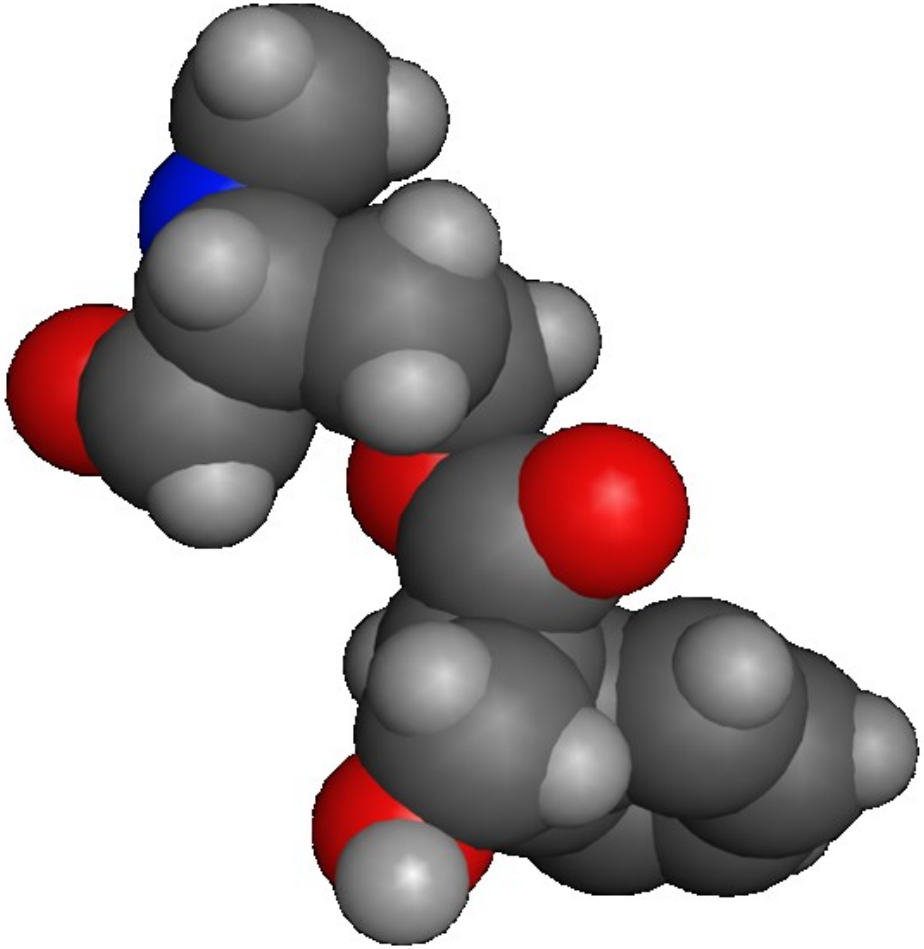
Dilated Pupils

Hallucinogens & Stimulants are known to cause pupil dilation.

Hallucinogens: Pot, LSD [Mushrooms, Acid]
Stimulants: Cocaine, crack, crystal meth.
Antidepressants can also cause dilation.

12. Cholinergic Antagonists (Muscarinic receptor)

12.2 Hyoscine (scopolamine)



a Japonica (Solanaceae)

g P = 1.0

IW = 303.3

SA ≅ 62Å²

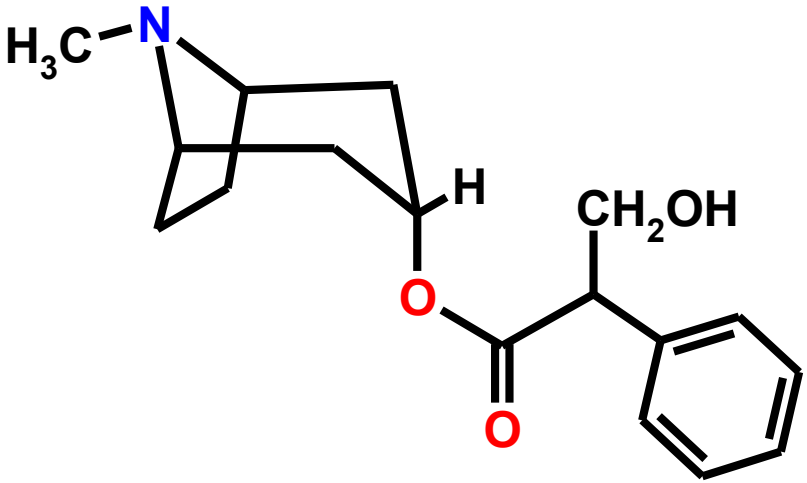
+ N = 5

Ka = 7.7

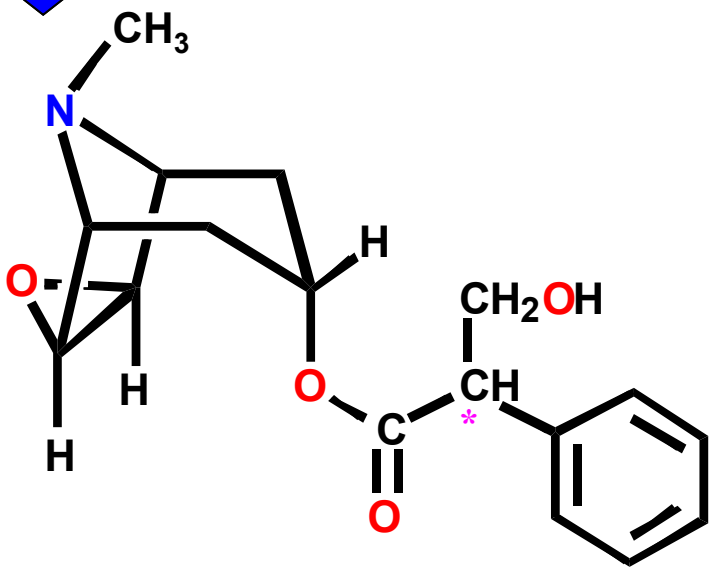
12. Cholinergic Antagonists (Muscarinic receptor)

12.2 Hyoscine (scopolamine)

pKa = 9.7



pKa = 7.7



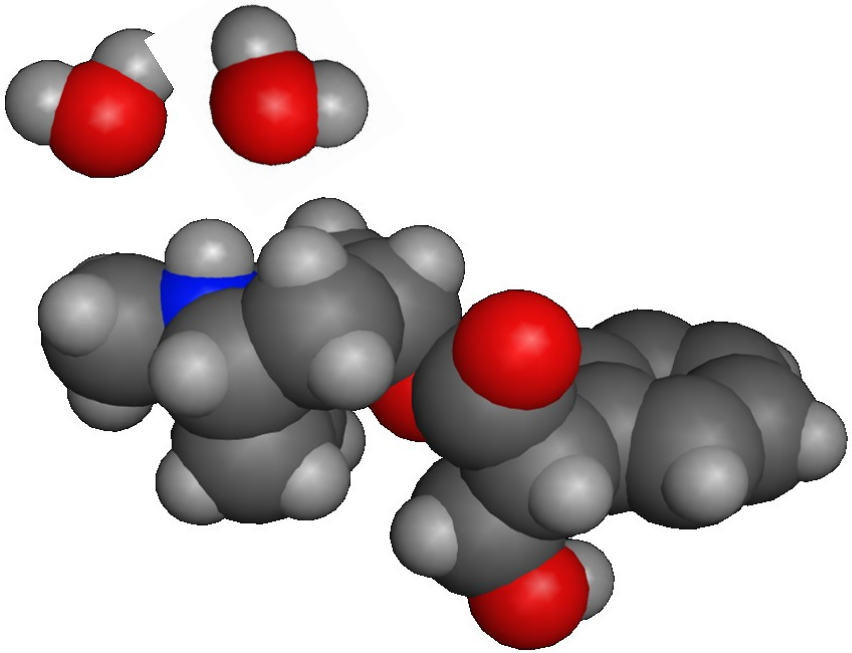
12. Cholinergic Antagonists (Muscarinic receptor)

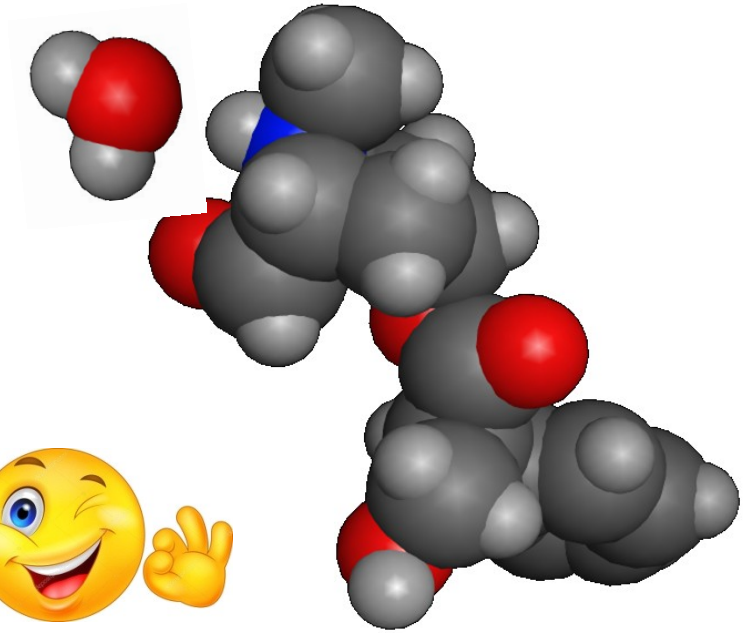
12.2 Hyoscine (scopolamine)

pKa = 9.7

pKa = 7.7

The accessibility of the water molecules to the ammonium salt is facilitated by the smaller steric hindrance present in the atropine molecule compared to that of scopolamin





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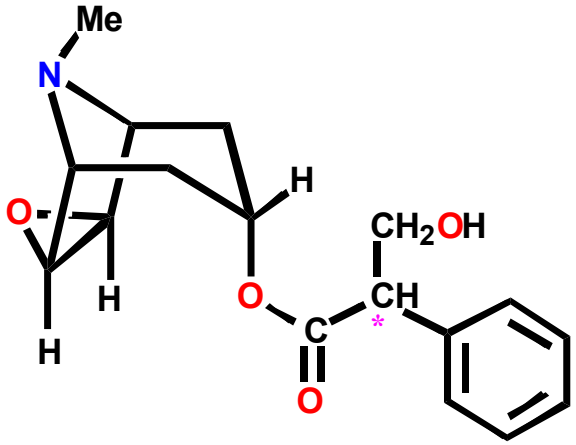
12. Cholinergic Antagonists (Muscarinic receptor)

12.2 Epoxide = Reactive site = Instability = Toxicity ???

SN2… backside attack!!!

12. Cholinergic Antagonists (Muscarinic receptor)

12.2 Hyoscine (scopolamine)



- **It is mostly a M1 muscarinic antagonist**
- **Treatment of nausea and motion sickness (*transdermal route*).**
- **To reduce motility and secretions in the GI tract.**
- **Treatment of intestinal cramping.**
- **As an adjunct to opioid analgesia, such as the product *Twilight Sleep* which contained morphine and scopolamine. This combination induces a semi-narcotic state which produces the experience of childbirth without pain, or without the memory of pain. *It is now merely a chapter in the past history of obstetrics.***

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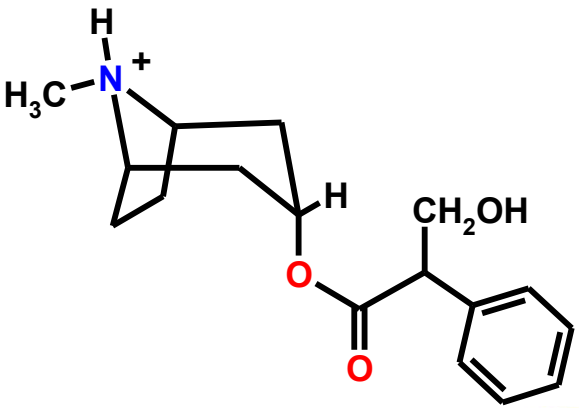
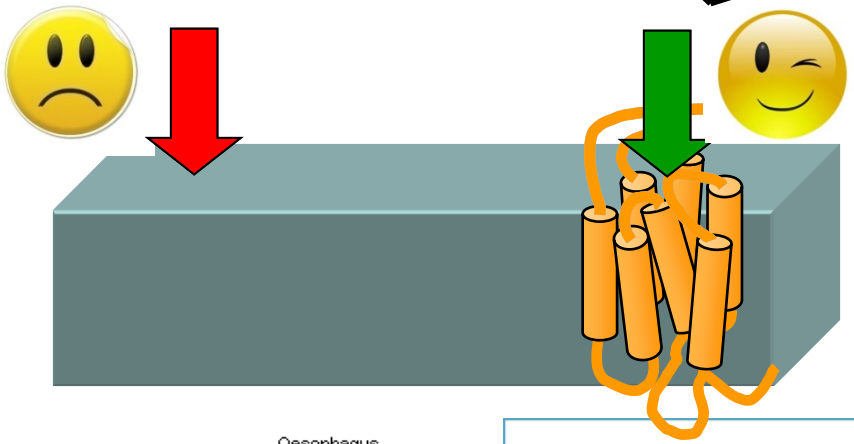
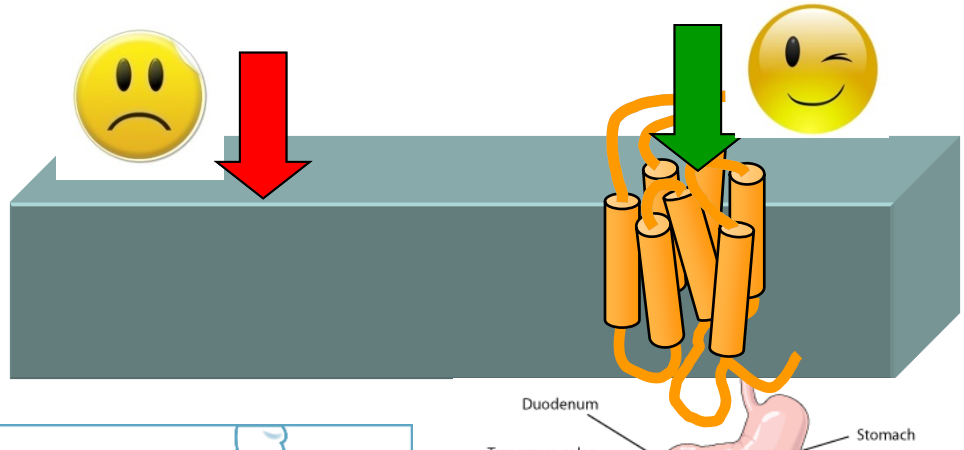
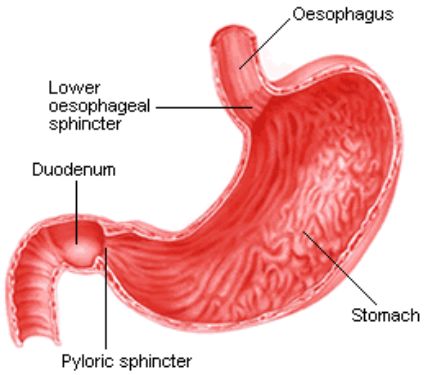
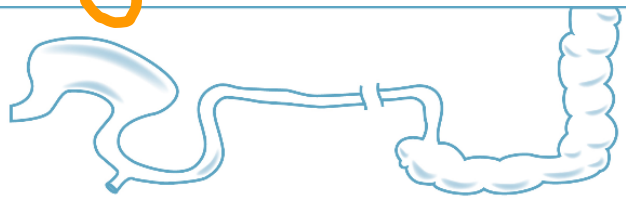
To cross… or not to cross, this is the dilemma!



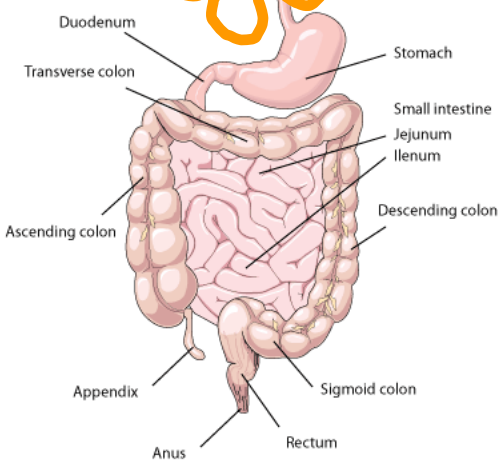








	Stomach	Jejunum	Ileum	Colon	
pH	1.4-2.1	4.4-6.6	6.8-8.6	5-8	fasting
	3-7	5.2-6.2	6.8-8.0	5-8	fed



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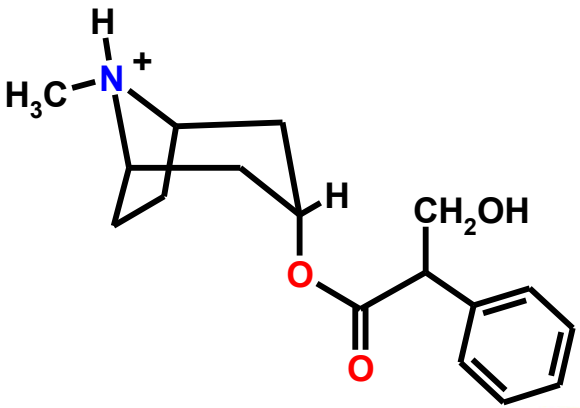
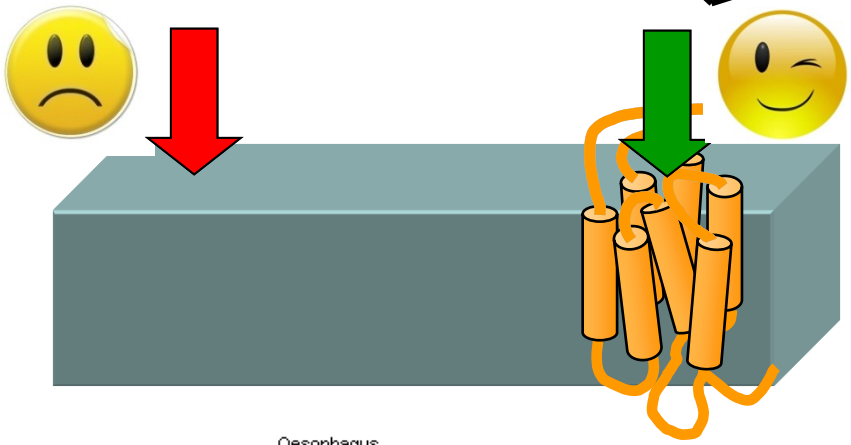
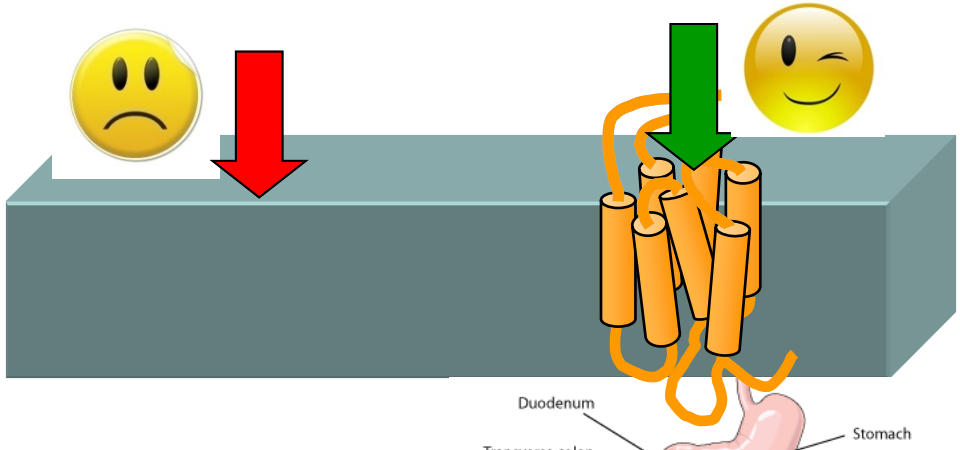
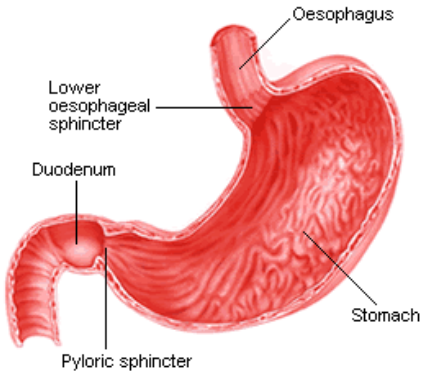
To cross… or not to cross, this is the dilemma!

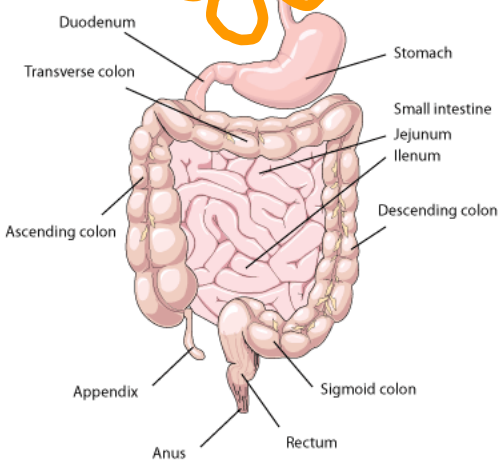








without peripheral and SNC side effects!!!



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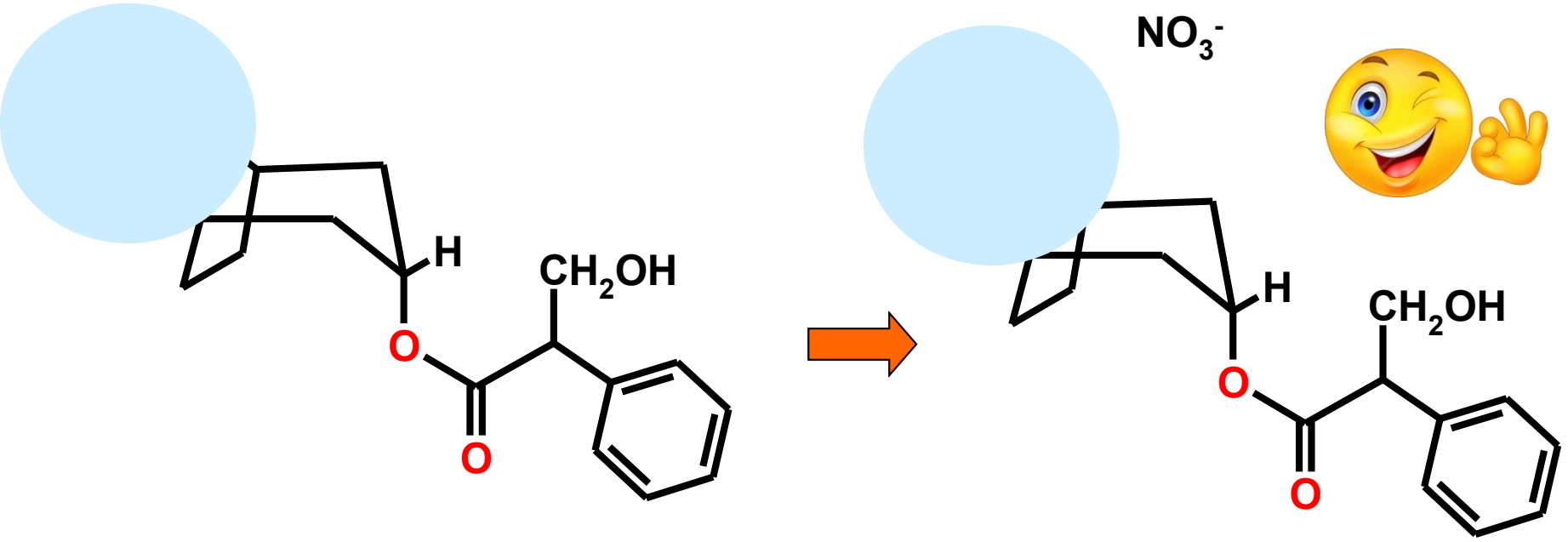
12. Cholinergic Antagonists (Muscarinic receptor)

12.4 The first good idea: the analogues of atropine

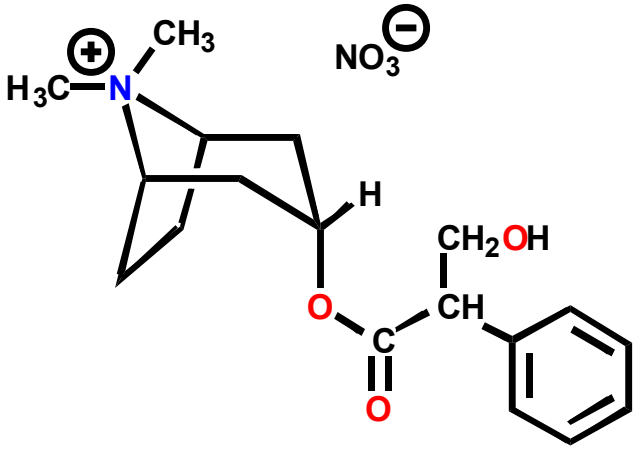


Atropine methonitrate

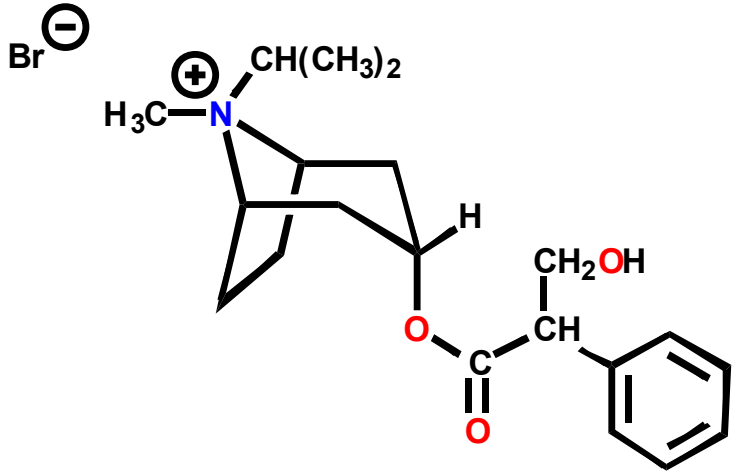
- **Analogues are fully ionised**
- **Analogues unable to cross membranes including BBB**
- **No CNS side effects**

12. Cholinergic Antagonists (Muscarinic receptor)

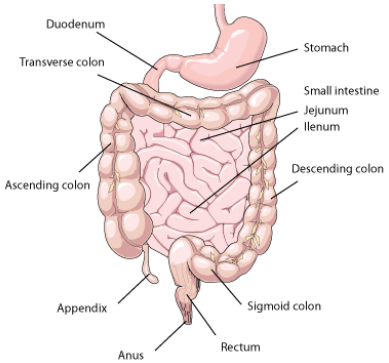
12.4 The quaternary nitrogen analogues of atropine



Atropine methonitrate

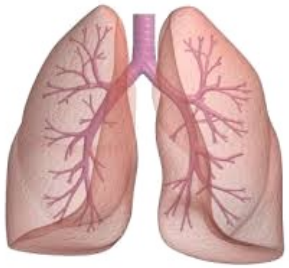


Ipratropium



Oral administration:

1. treat pain and discomfort caused by abdominal cramps, or other spasmodic activity in the digestive system.



Inhalation administration:

1. treat and prevent minor and moderate bronchial asthma;
2. treat of chronic obstructive pulmonary disease (COPD).
3. It is also combined with **Salbutamol** (beta$_2$ adrenergic agonist) for the management of COPD and asthma.

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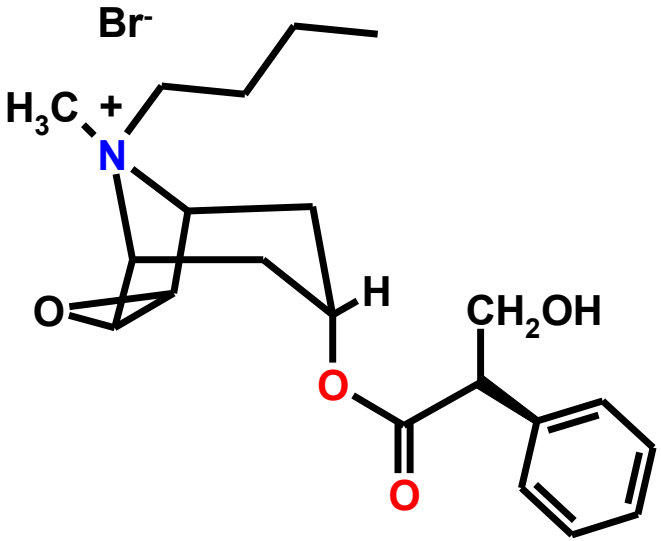
12. Cholinergic Antagonists (Muscarinic receptor)

12.4 The most famous quaternary nitrogen analogue!



Butylscopolamine (Buscopa

- **Butylscopolamine** is used to treat pain and discomfort caused by abdominal cramps, menstrual cramps, or other spasmodic activity in the digestive system. It is *not* an analgesic in the normal sense, since it doesn't 'mask' or 'cover over' the pain, but rather works to prevent painful cramps and spasms from occurring in the first place.

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Mather nature…

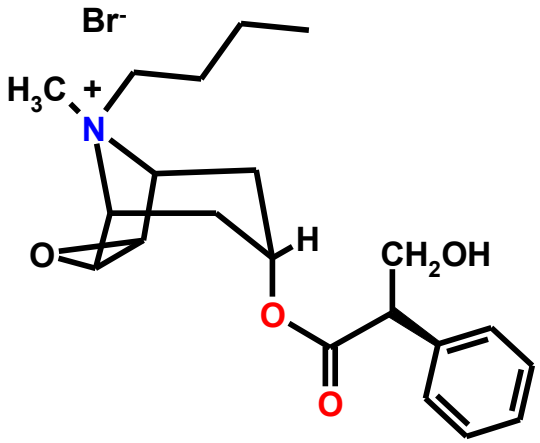
Duboisia and the development of Buscopan®

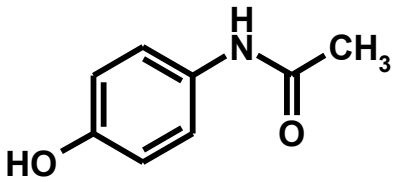
In the search for a safe and effective treatment for the pain of abdominal cramps, Boehringer Ingelheim learnt from the healing arts of some of the world's oldest cultures. Ancient Hindu physicians in India knew of the antispasmodic effects of a relative of *Duboisia*: the plant *Datura*. Today, the Buscopan® story starts in Ingelheim, Germany, where elite *Duboisia* plants are grown in greenhouses. These plants are bred to be resistant against nematodes and beetles. The best seeds are harvested and then delivered to the company´s plantations in South America and Australia for further on-site selection. Here, the shrubs grow on a large scale. The pharmaceutically important alkaloid scopolamine which is contained in the dried leaves and stalks is isolated and purified. Finally, the active precursor substance scopolamine is converted in a single chemical process into hyoscine butylbromide, the active ingredient of Buscopan®.

In 1951, the new medication was ready for commercial production. Buscopan® was launched in 1952. Today, with more than half a century of proven expertise in safe antispasmodic effectiveness, Buscopan® is the world's leading and most trusted treatment for abdominal pain.

12. Cholinergic Antagonists (Muscarinic receptor)

12.4 … and in association with Paracetamol

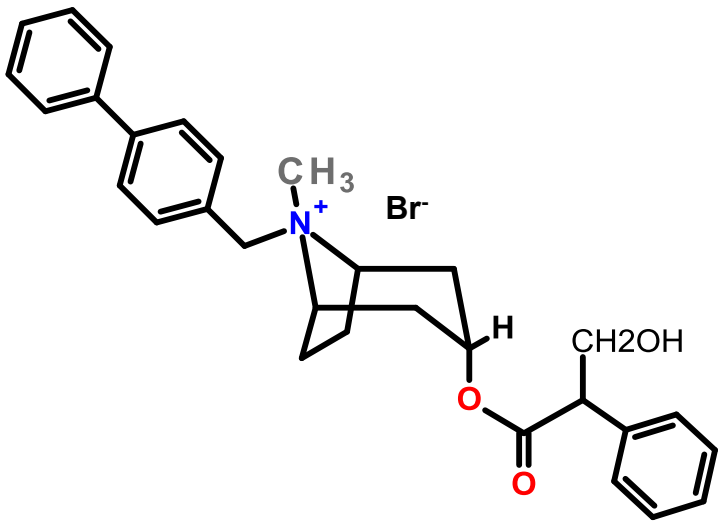


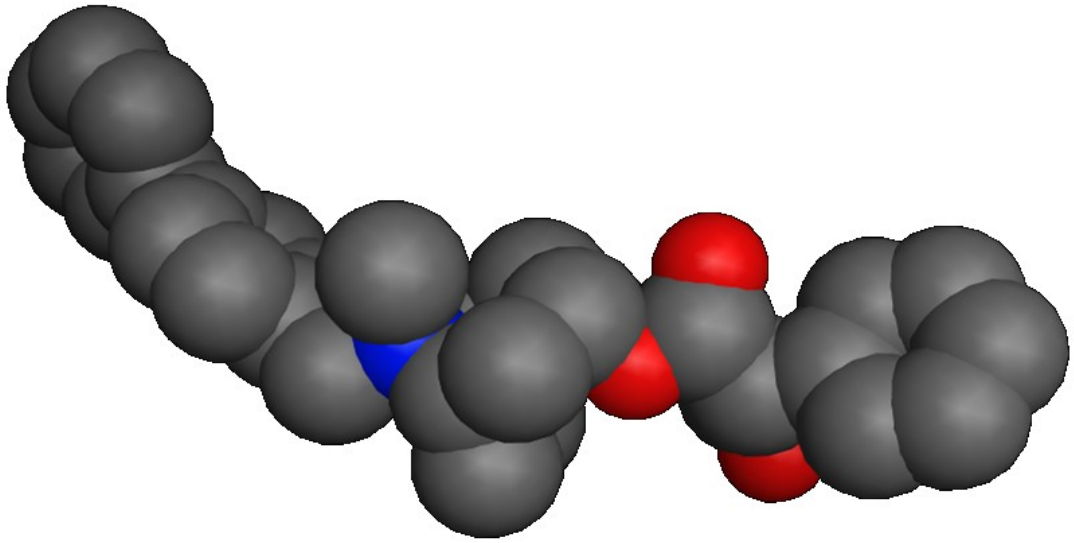


Buscopan® Plus (also known as **Buscapina®** Compositum N in some countries) has a dual effect. Paracetamol, a proven analgesic, reduces the pain of uterine cramps. At the same time, Butylscopolamine relieves the painful cramps of the colon and intestine that often accompany menstrual pain. In this way, **Buscopan®** Plus quickly and effectively relieves the pain of menstrual cramps, without interfering in the body's natural menstrual rhythm.

12. Cholinergic Antagonists (Muscarinic receptor)

12.5 … thanks Giovanni!!! The biggest substitution on N

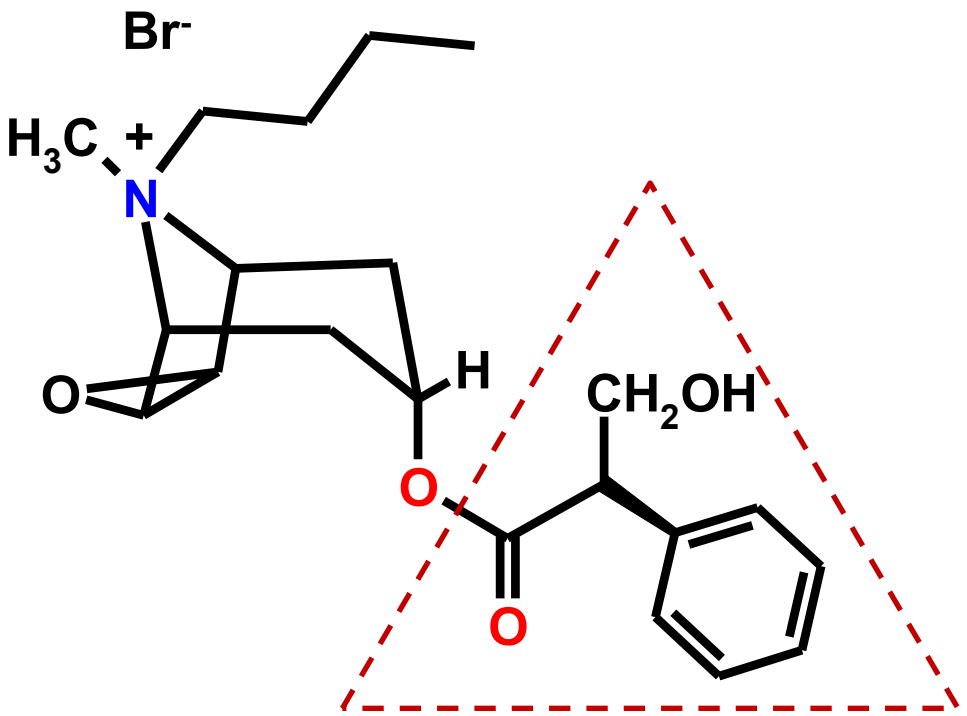




8-methyl-8-[(4-phenylphenyl)methyl]-8-azoniabicyclo[3.2.1]octan-3-yl] 3-hydroxy-2-phenylpropanoate bromide

(Gastropin®)

and now… bioisosterism!



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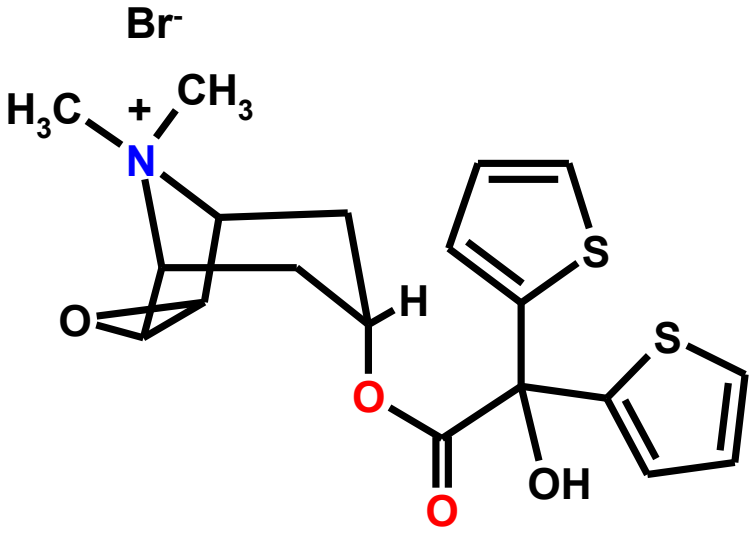
12. Cholinergic Antagonists (Muscarinic receptor)

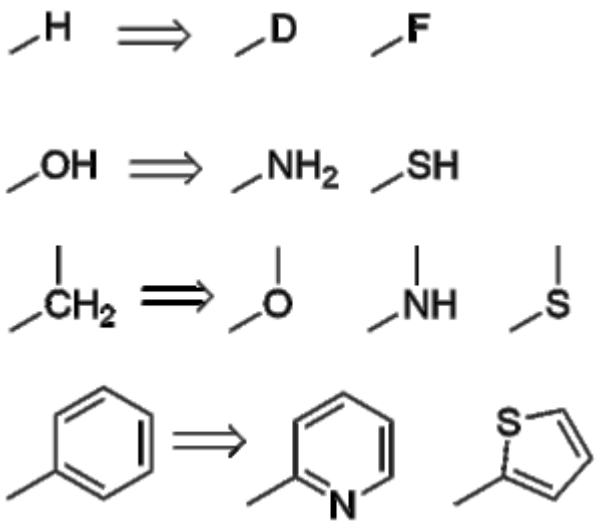
12.4 … and an interesting analog.



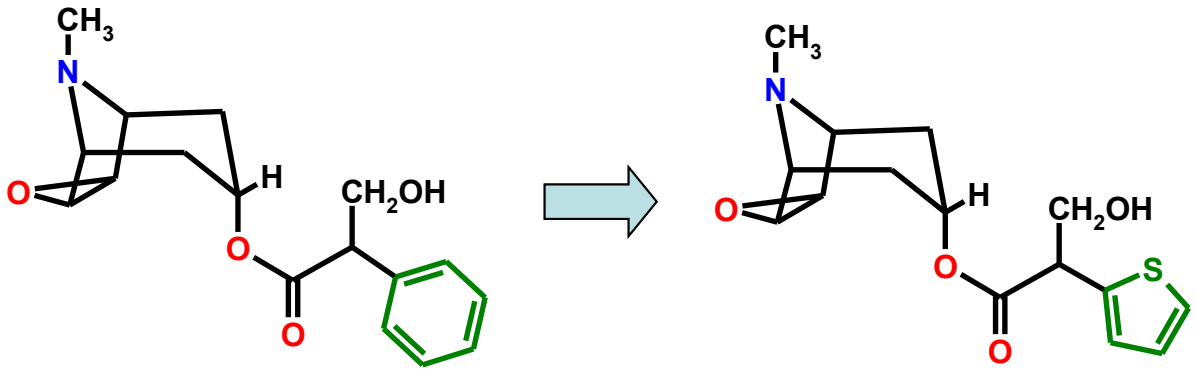
Tiotropium bromide

Tiotropium bromide is a muscarinic receptor antagonist, often referred to as an antimuscarinic agent. Although it does not display selectivity for specific muscarinic receptors, when topically applied it acts mainly on M3 muscarinic receptors located on smooth muscle cells and submucosal glands. This leads to a reduction in smooth muscle contraction and mucus secretion and thus produces a bronchodilatory effect.
Tiotropium bromide is a long-acting, 24 hour, bronchodilator used in the management of chronic obstructive pulmonary disease (COPD).

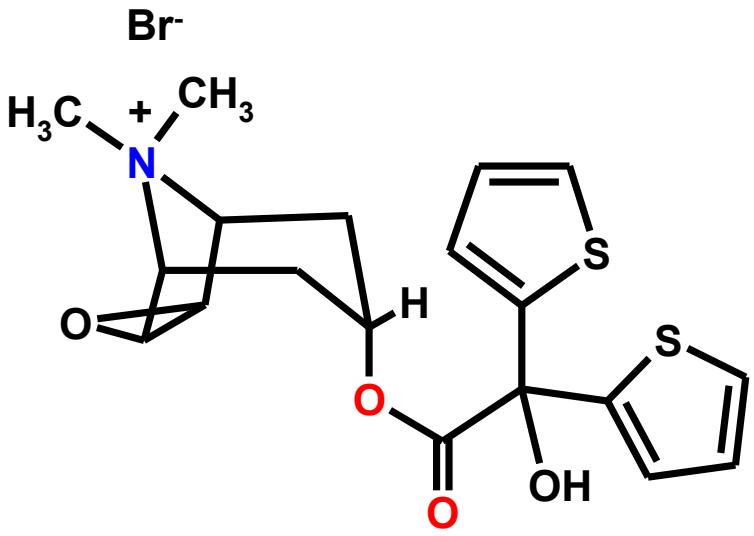
Do you remember *bioisostere* concept?

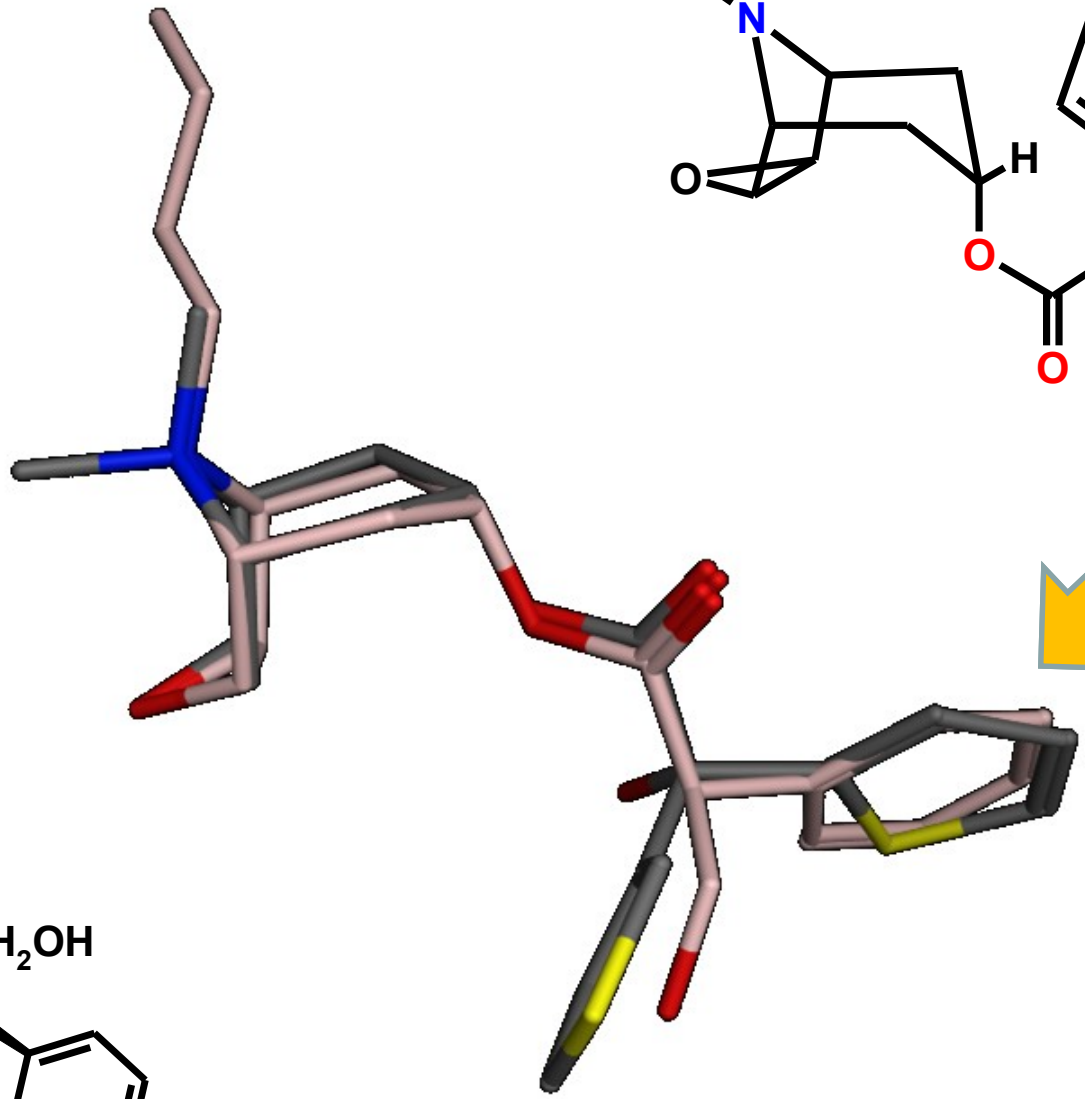


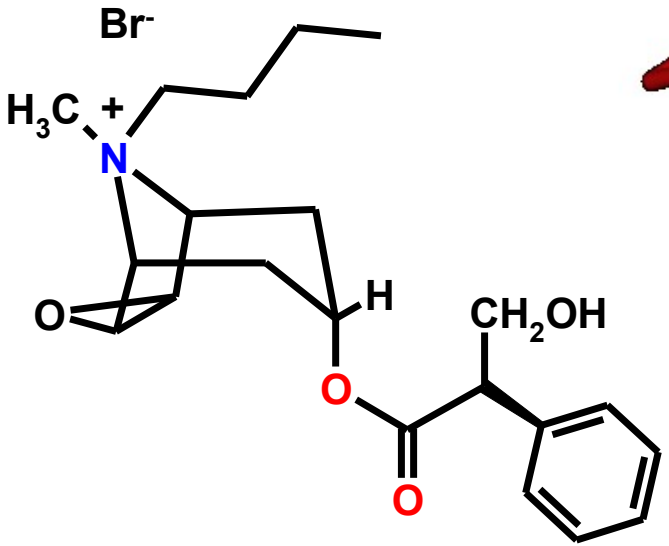
here is a simple example:



Wonderful!!!







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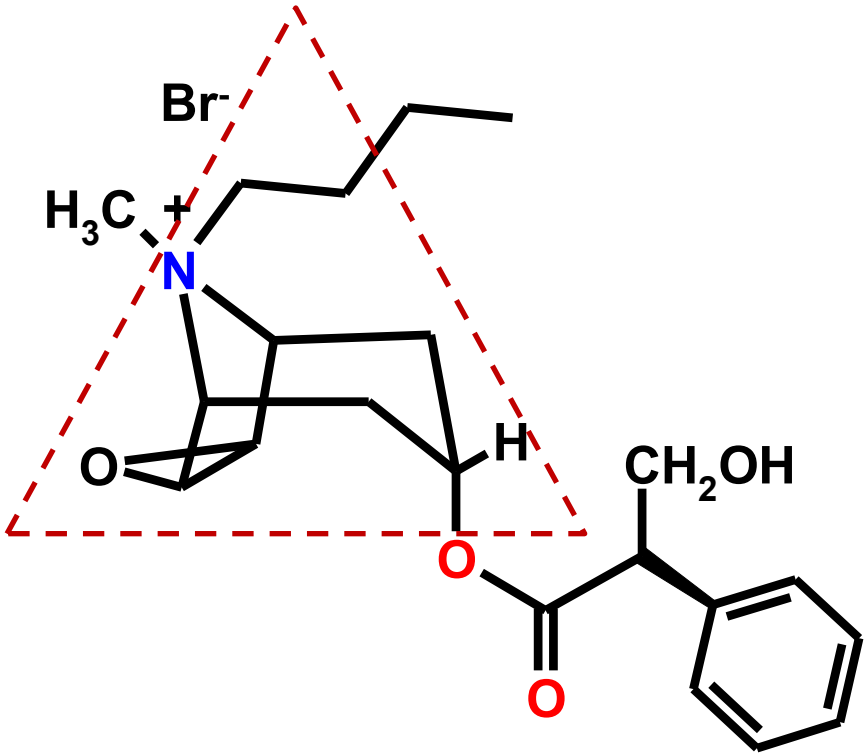
and now… ring demolition!



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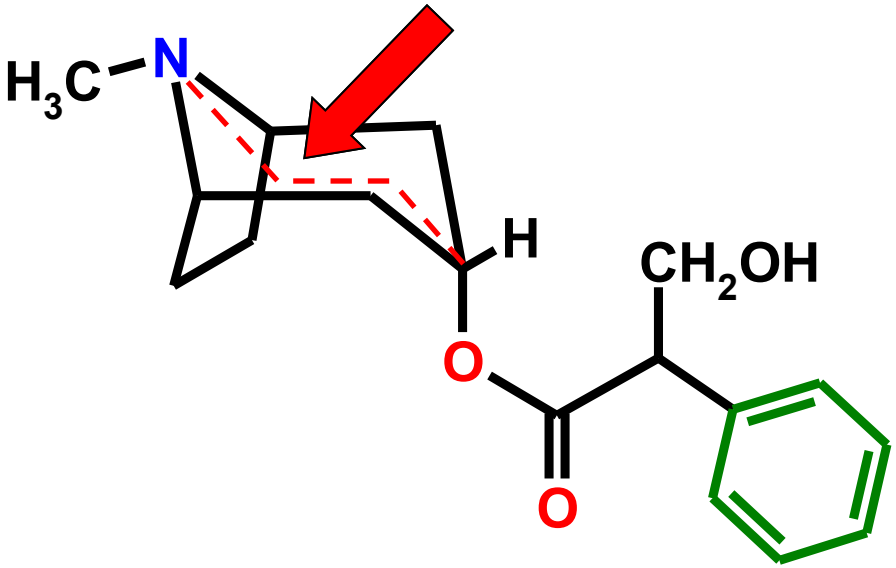
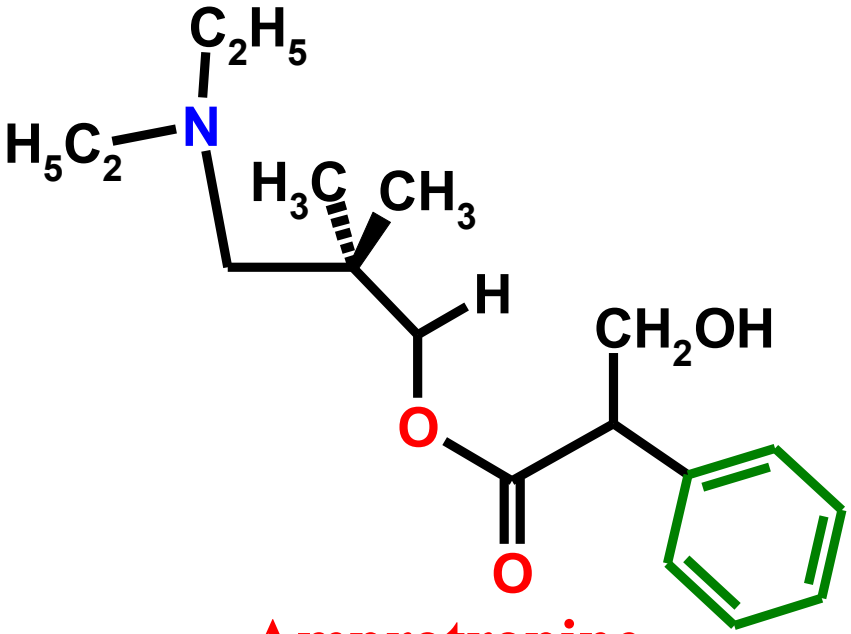
12. Cholinergic Antagonists (Muscarinic receptor)

12.5 Simplified Analogues

Pharmacophore = ester + basic amine + aromatic ring





Amprotropine

[3-(diethylamino)-2,2-dimethylpropyl] 3-hydroxy-2-phenylpropanoate

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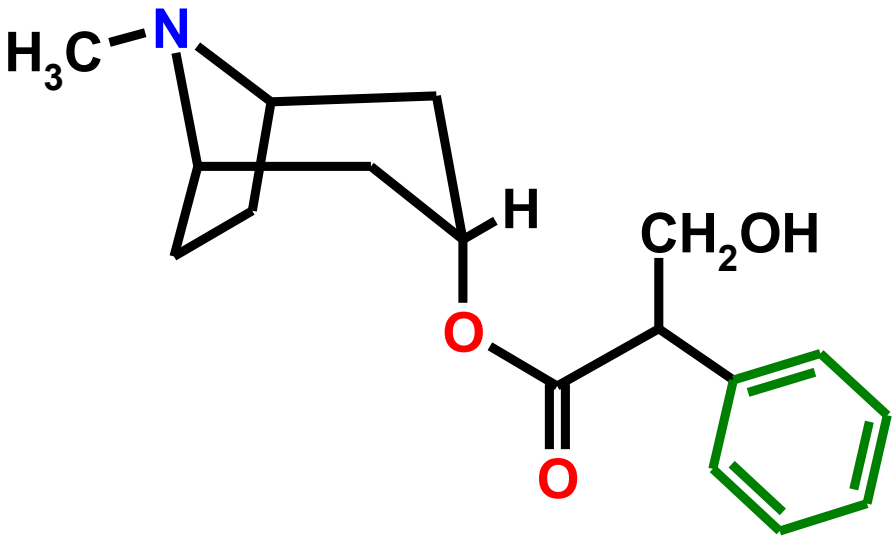
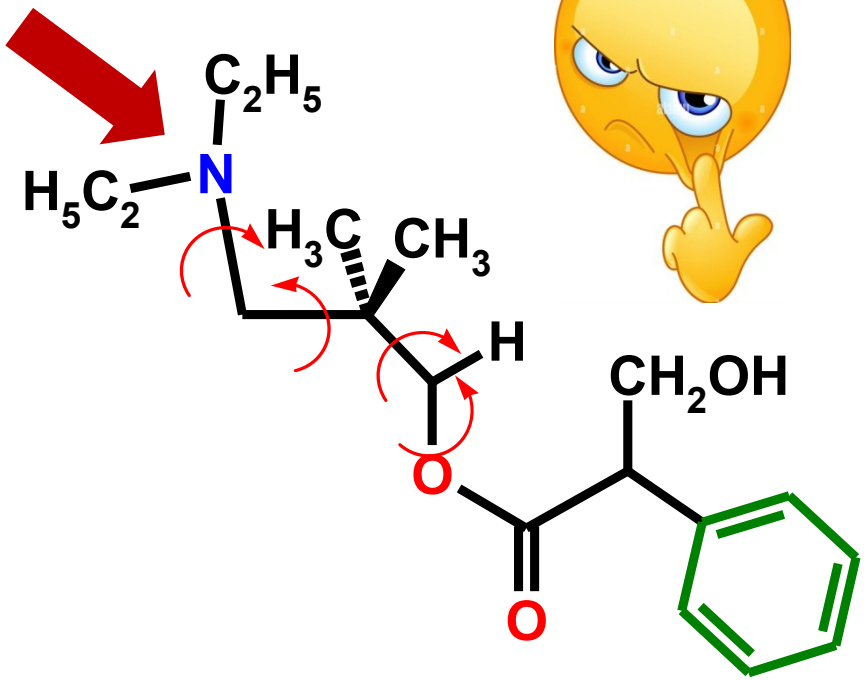
I need your guess: more or less active than…





Amprotropine
(logP = 3.0)

Amprotropine is ≈1/100 less potent as muscarinic antagonist compare to atropine, why?

BRAVI!!!

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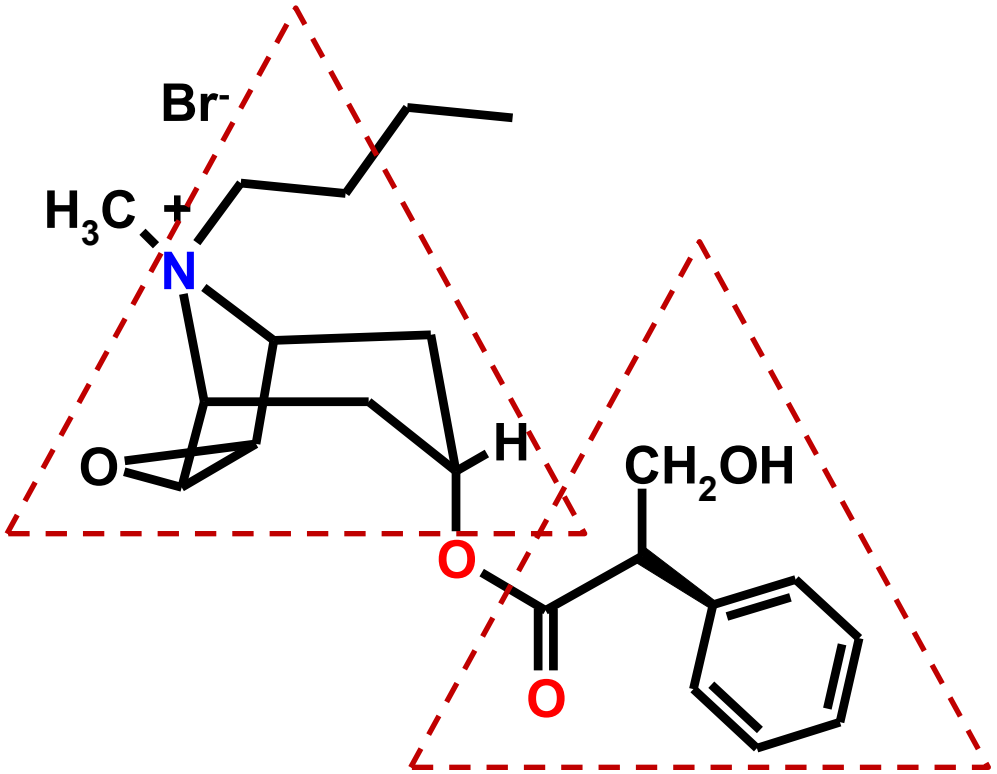
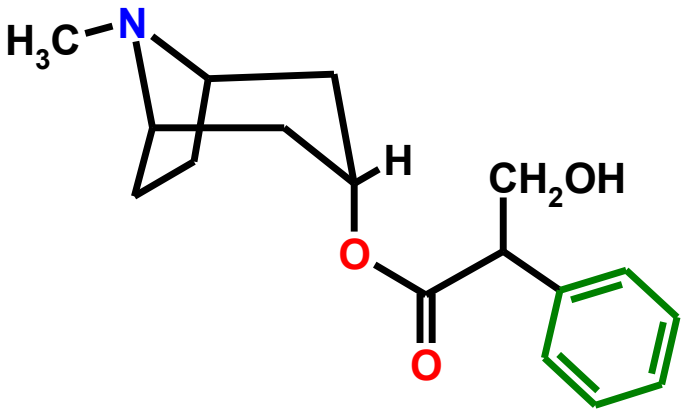
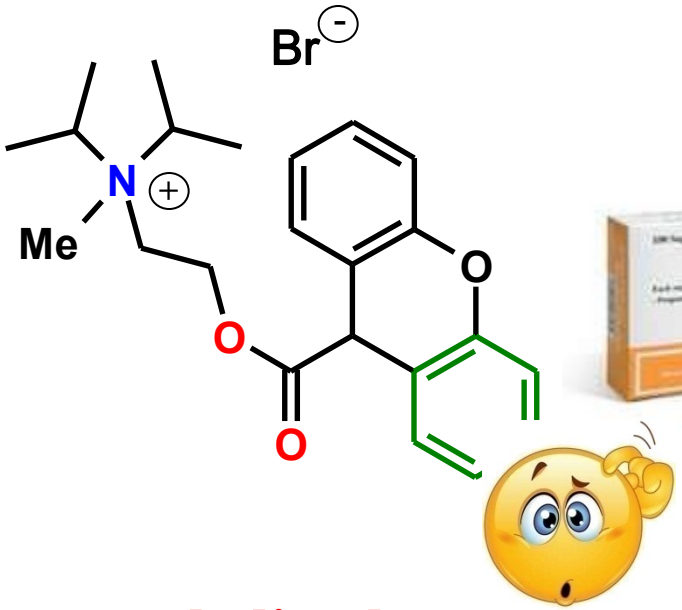
and finally… both of them!



12. Cholinergic Antagonists (Muscarinic receptor)

12.5 Simplified Analogues



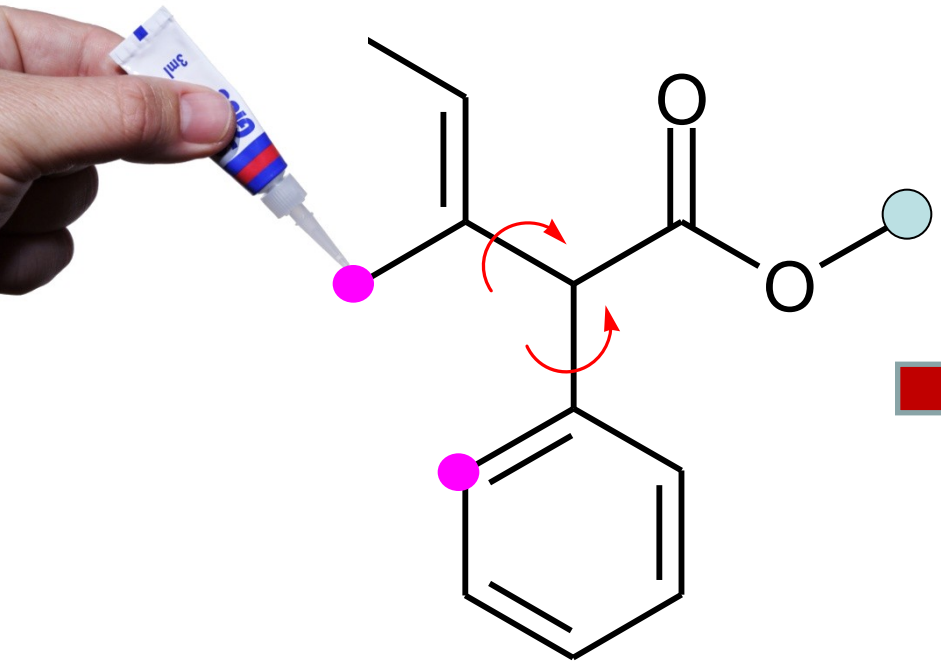


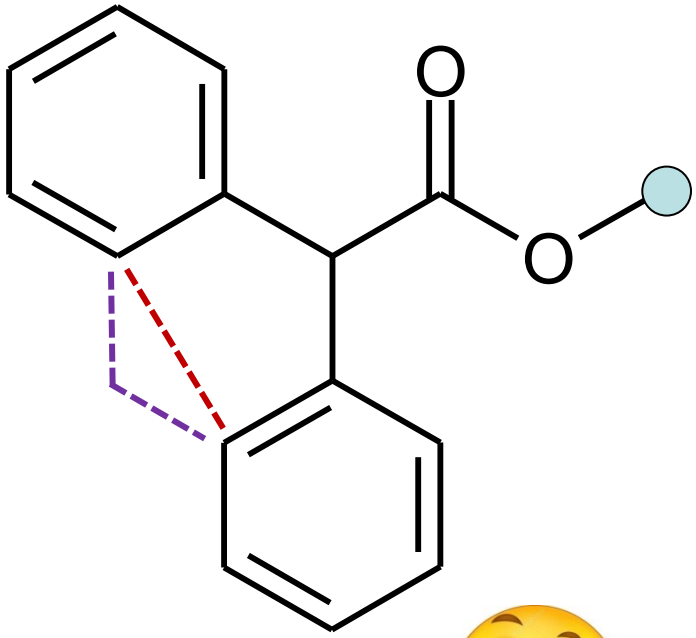
Propantheline bromide

N-isopropyl-N-methyl-N-{2-[(9H-xanthen-9-ylcarbonyl)oxy]ethyl}propan-2-aminium bromide

Used for the treatment of excessive sweating (hyperhidrosis), cramps or spasms of the stomach, intestines (gut) or bladder, and involuntary urination (enuresis).

Remembe, if possible…





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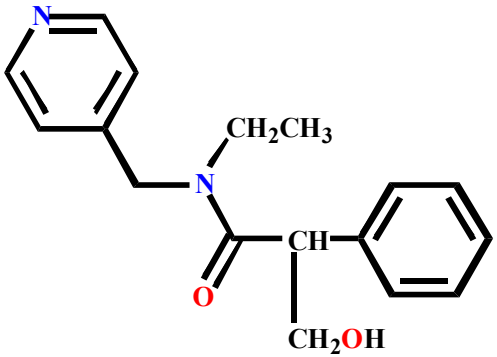
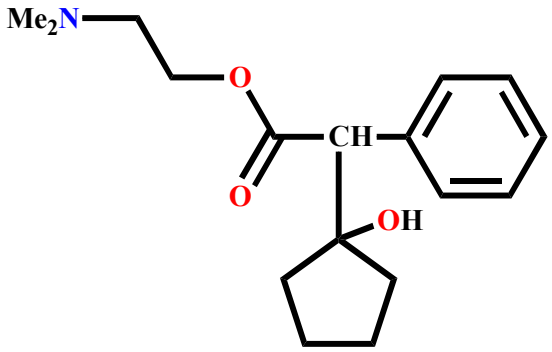
12. Cholinergic Antagonists (Muscarinic receptor)

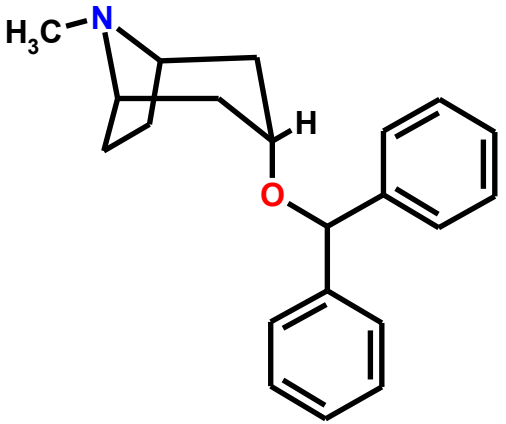
12.5 Simplified Analogues



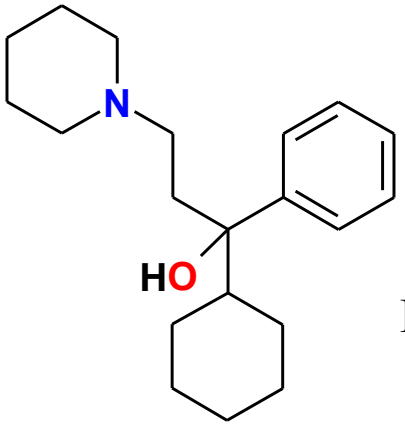
Tropicamide (logP = 1.3)
(opthalmics)



Cyclopentolate (logP = 2.4)
(opthalmics)



Benztropine (logP = 4.3)
(Parkinsons disease)



Benzhexol (logP =4.5)
(Parkinsons disease)

role of cholinergic and dopaminergic signalling in Parkinson

Pathophysiology

Parkinsonism (paralysis agitans) is a common movement disorder that involves dysfunction in the basal ganglia and associated brain structures. Signs include rigidity of skeletal muscles, akinesia (or bradykinesia), flat facies, and tremor at rest (mnemonic **RAFT**).

Naturally occurring parkinsonism

The naturally occurring disease is of uncertain origin and occurs with increasing frequency during aging from the fifth or sixth decade of life onward.
Neural network regulating extrapyramidal motor functions and Parkinson's disease. Striatal GABAergic GABA output neurons receive glutamatergic Glu excitatory inputs from the cerebral cortex and excitatory inputs from acetylcholinergic ACh interneurons within the striatum. Dopaminergic DA neurons from the *substantia nigra pars compacta* negatively regulate both striatal output neurons and ACh interneurons. In patients with Parkinson's disease, the nigro-striatal dopaminergic neurons are degenerated, which causes hyperexcitation of both GABA and ACh striatal neurons. The serotonergic 5-HT neurons derived from the raphe nuclei project to the striatum, substantia nigra and cerebral cortex, and modulate the expression of extrapyramidal motor disorders.

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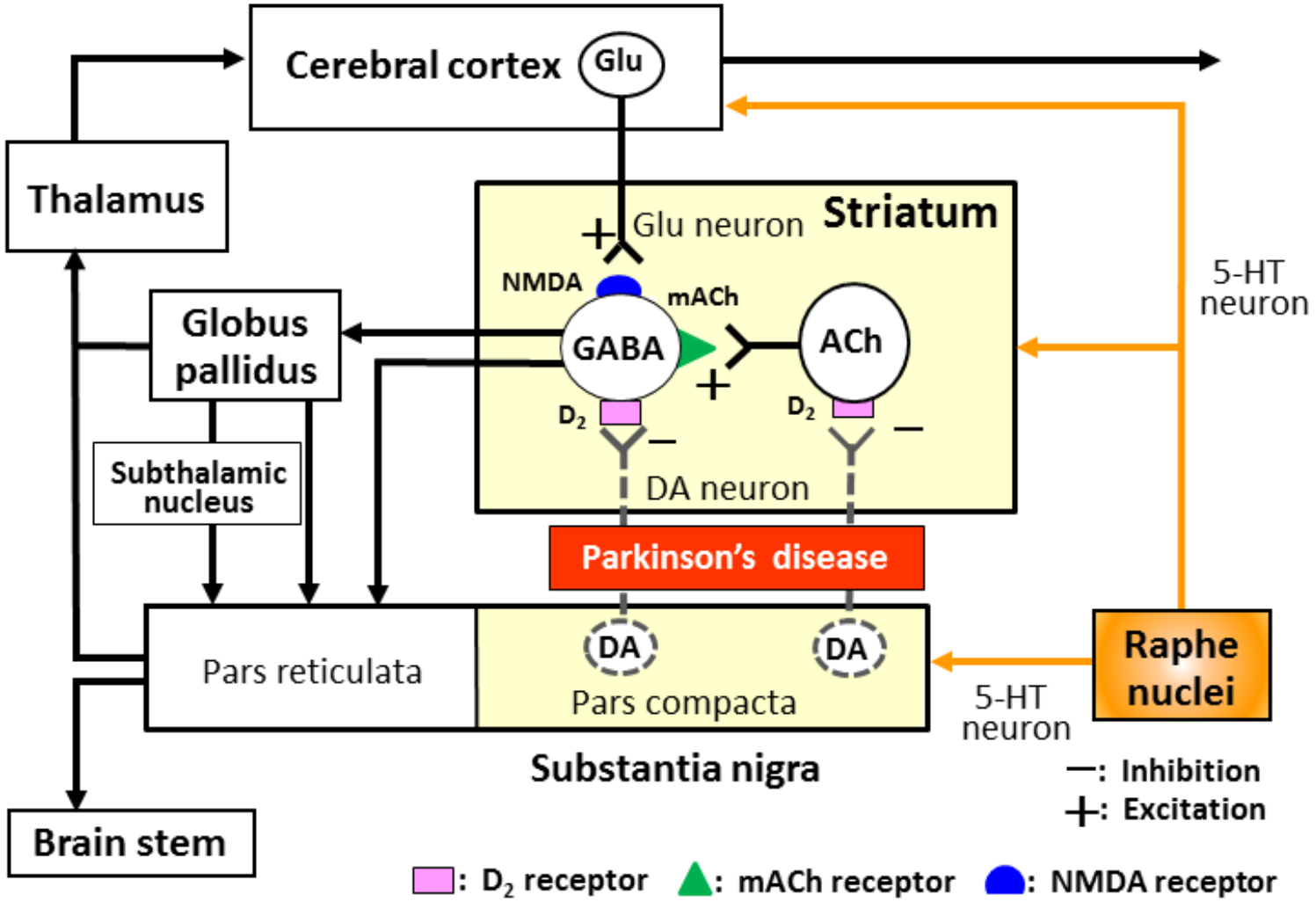
role of cholinergic and dopaminergic signalling in Parkinson



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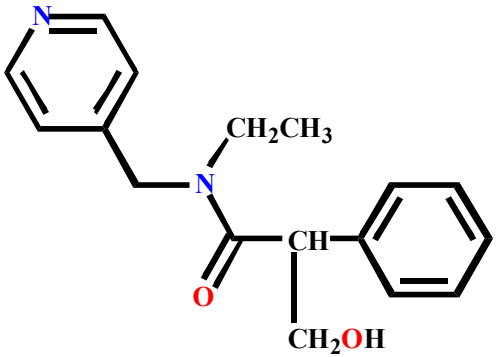
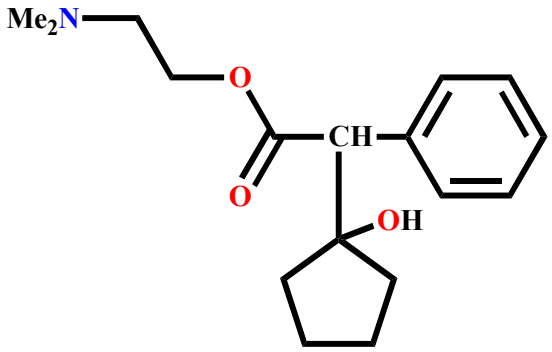
12. Cholinergic Antagonists (Muscarinic receptor)

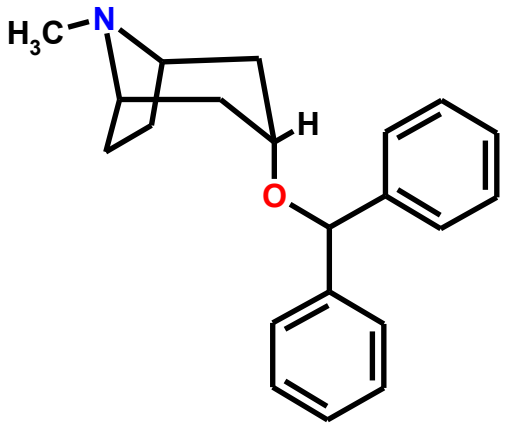
12.5 Simplified Analogues



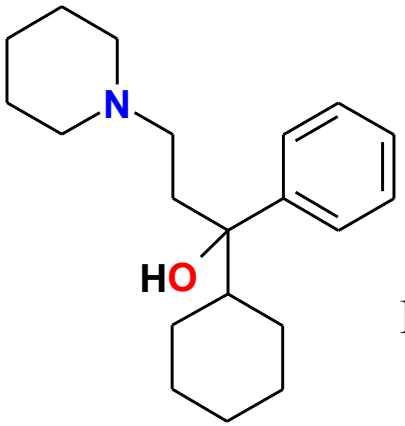
Tropicamide (logP = 1.3)
(opthalmics)



Cyclopentolate (logP = 2.4)
(opthalmics)



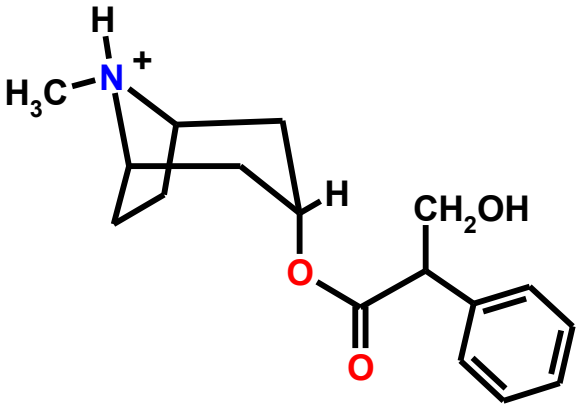
Benztropine (logP = 4.3)
(Parkinsons disease)

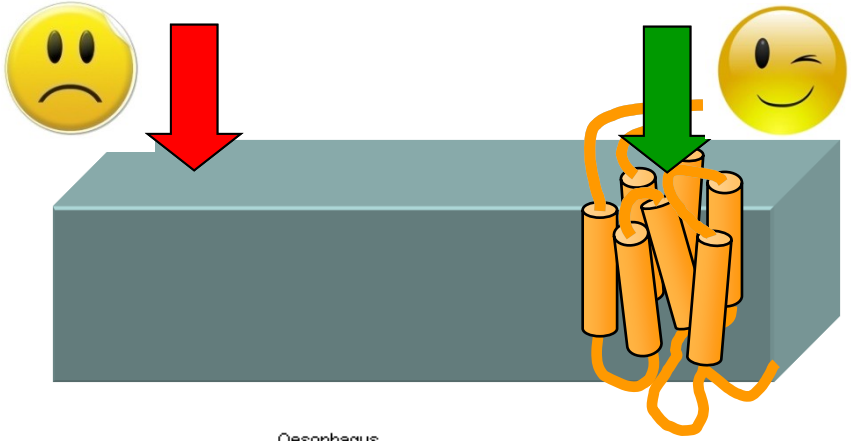


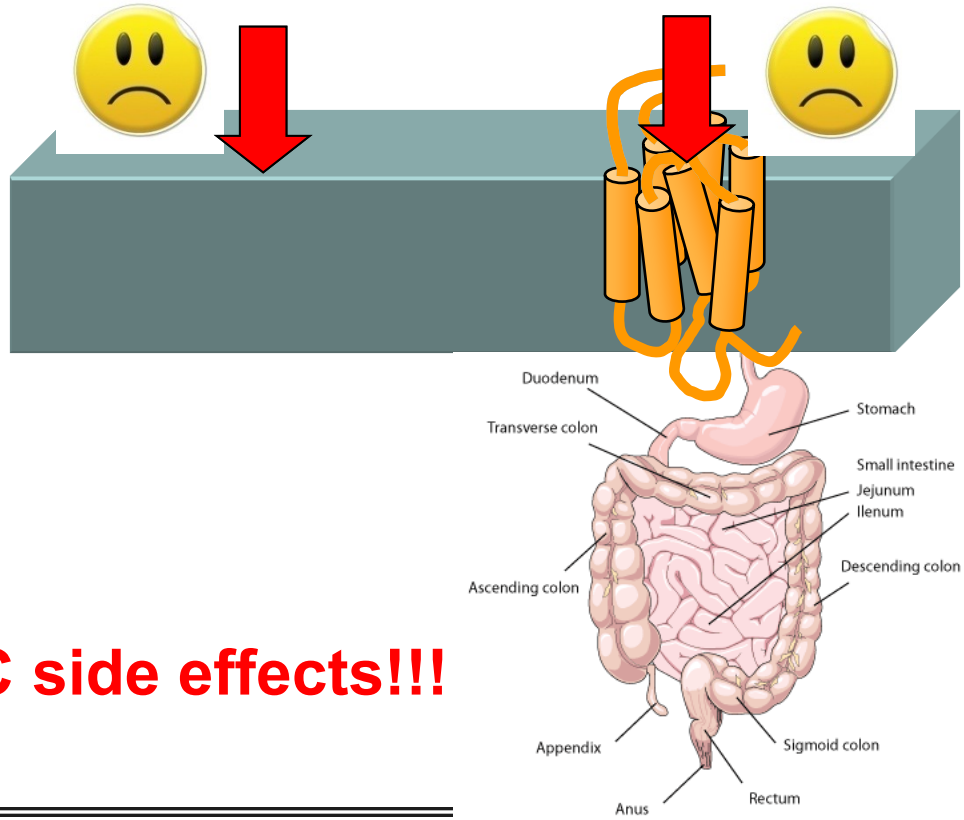
Benzhexol (logP =4.5
(Parkinsons disease)

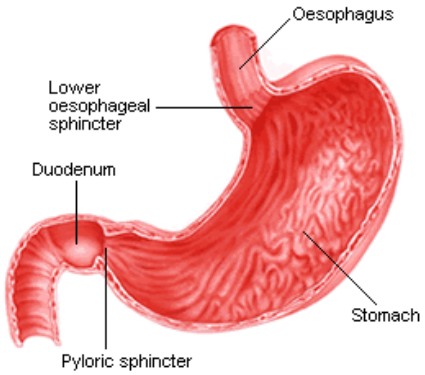
ne (logP = …)
i-ulcer)

Give me another good idea!









without SNC side effects!!!

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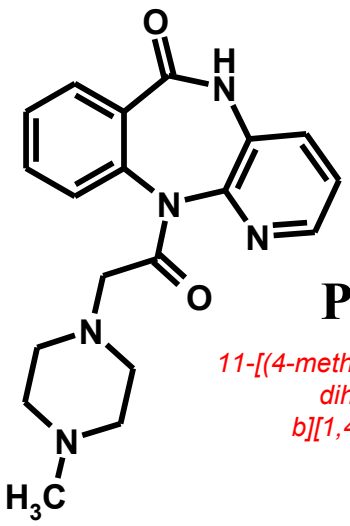
12. Cholinergic Antagonists (Muscarinic receptor)

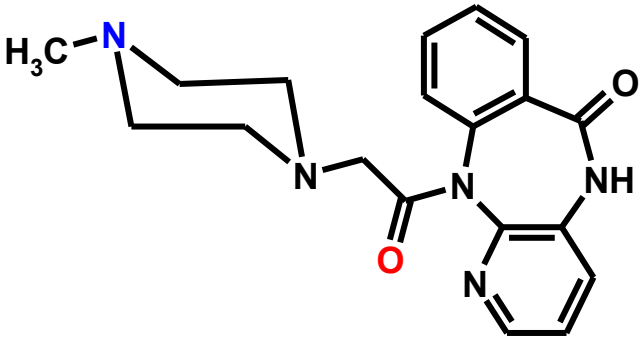
12.5 Simplified Analogues: Pirenzepine…

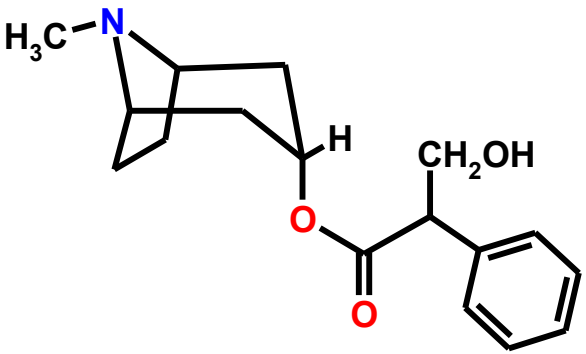


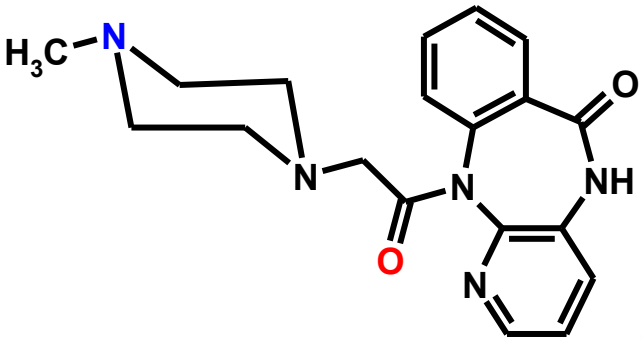
Pirenzepine

11-[(4-methylpiperazin-1-yl)acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

redrawing

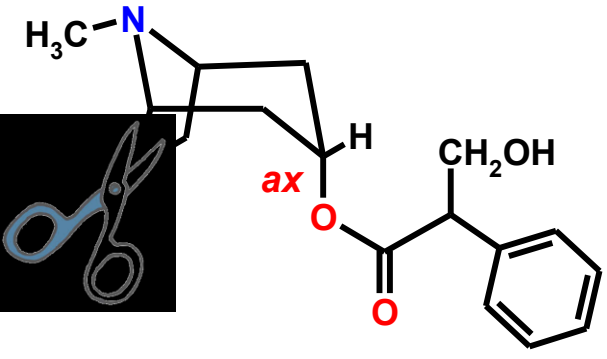


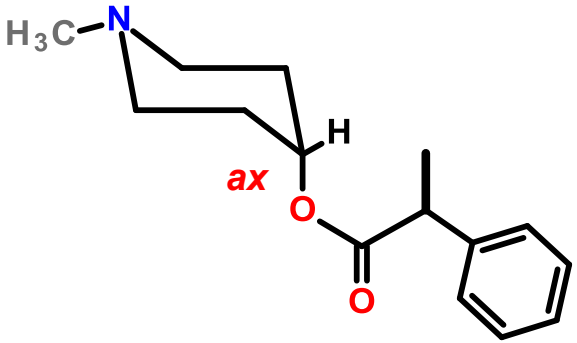


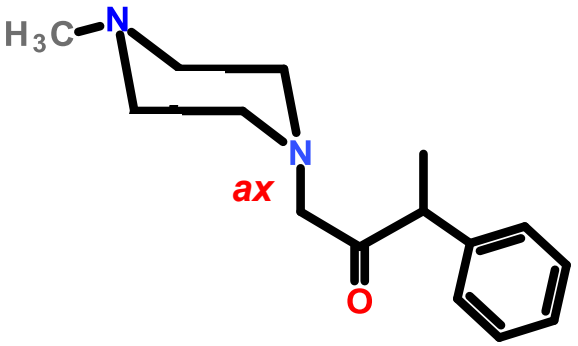


12. Cholinergic Antagonists (Muscarinic receptor)

12.5 Pirenzepine versus Atropine

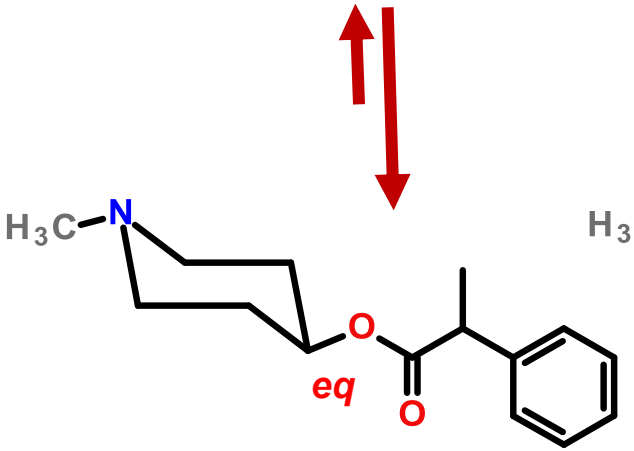


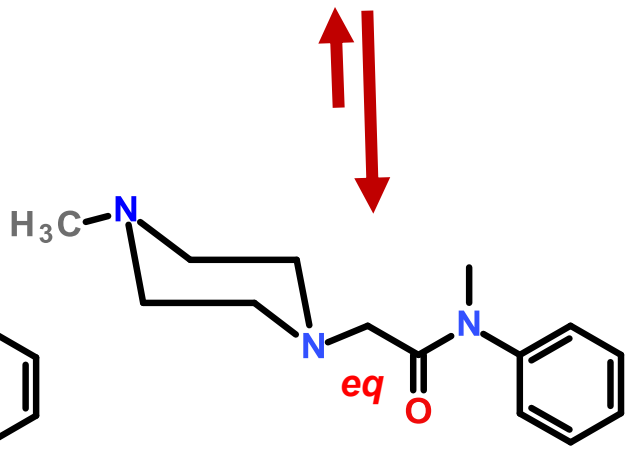




piperidine analogs

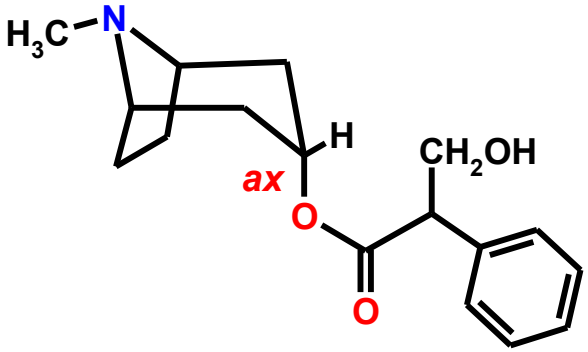
piperazine analogs

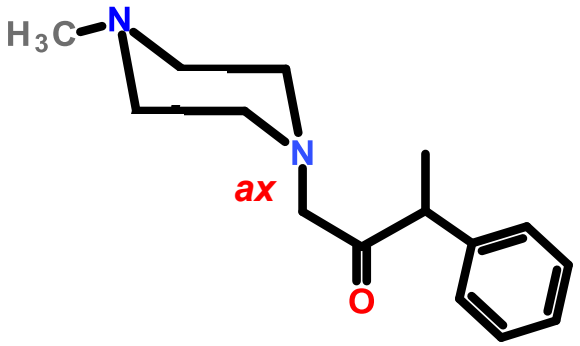


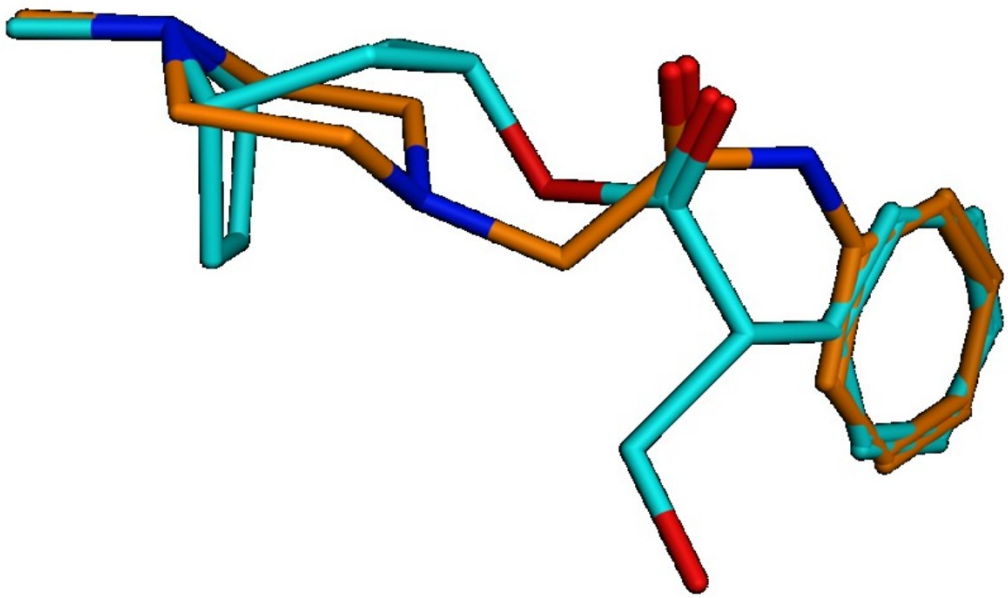


12. Cholinergic Antagonists (Muscarinic receptor)

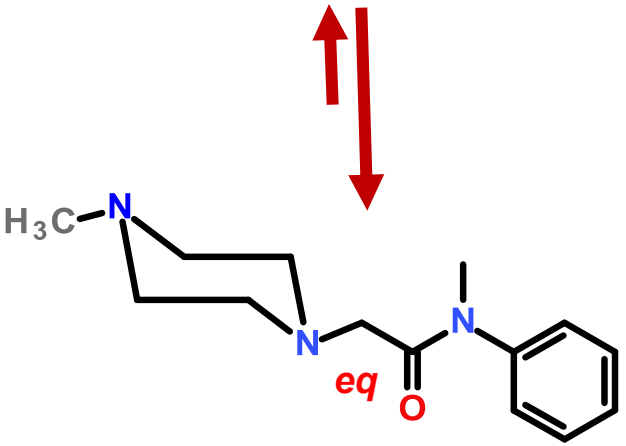
12.5 Pirenzepine versus Atropine







piperazine analogs



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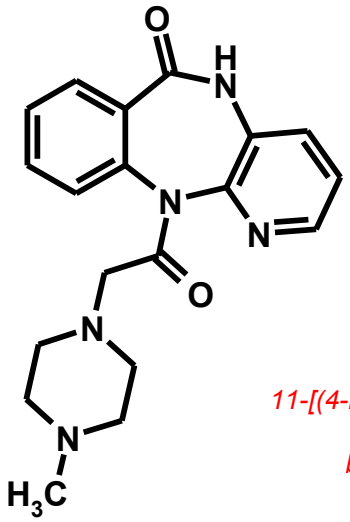
12. Cholinergic Antagonists (Muscarinic receptor)

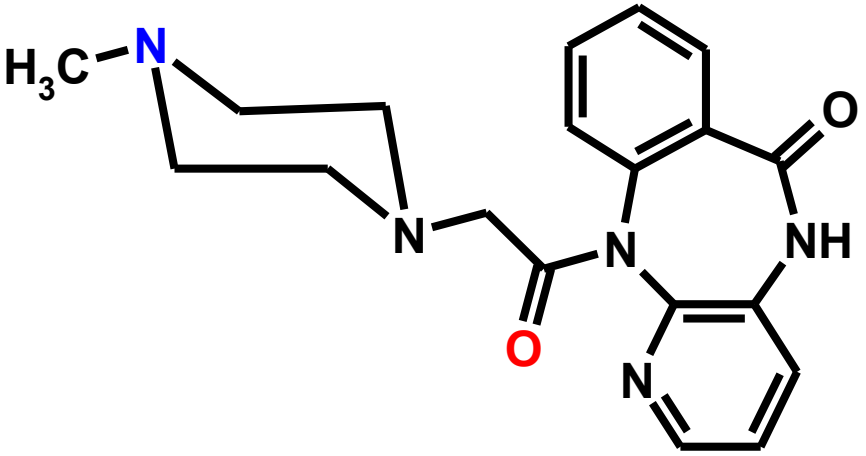
12.5 Simplified Analogues



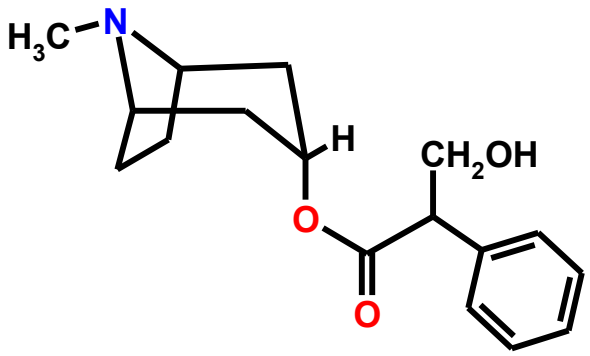
Pirenzepine (anti-ulcer)

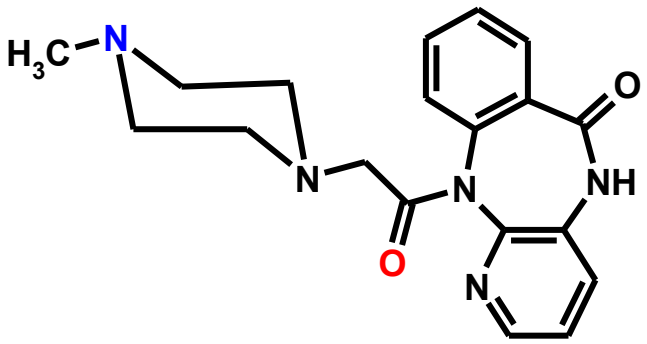
11-[(4-methylpiperazin-1-yl)acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

- **It is a M1 muscarinic antagonist**
- **Medical use - treatment of motion sickness (kinetosis), nausea, intestinal cramping**
- ***It has no effects on the brain and spinal cord as it cannot diffuse through the blood-brain barrier***

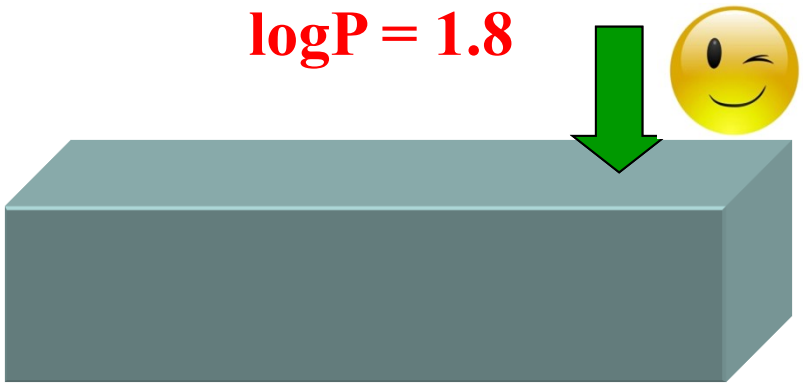


… now it is clear!

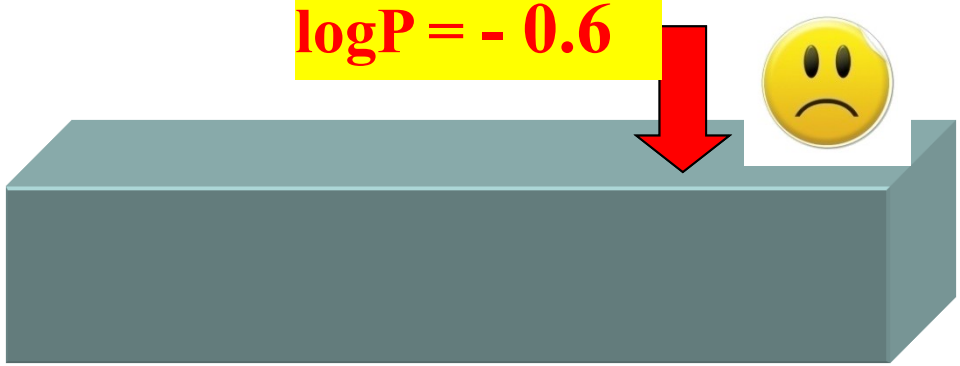


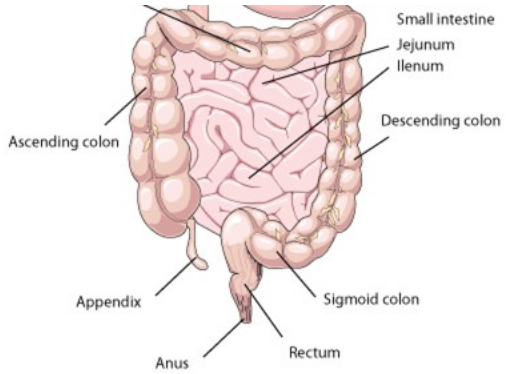


logP = 1.8



logP = - 0.6





without periferal and SNC side effects!!!

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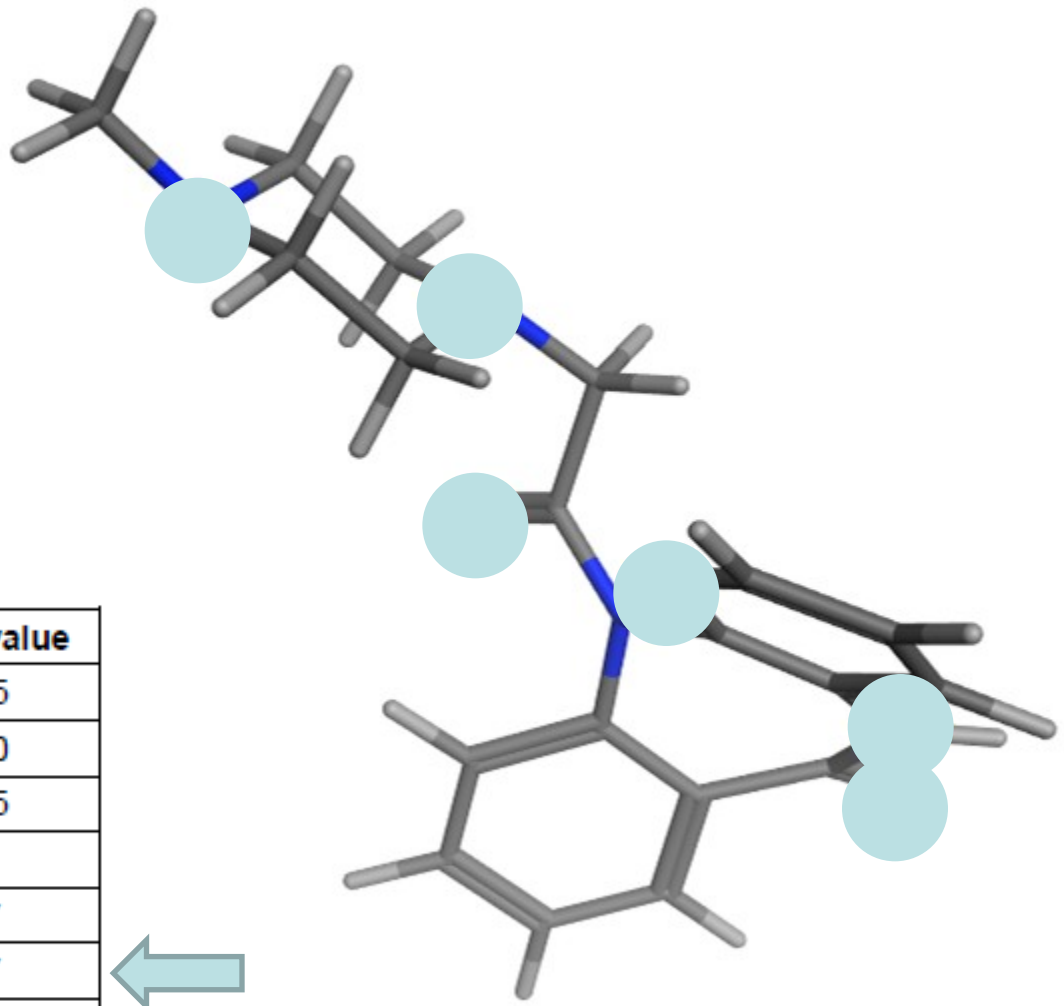
Why? Count the number of hetero-atoms!!!



*

Fragments	Pi value
C	+0.5
phenyl/benzene/aromatic ring	+2.0
Cl	+0.5
S	0.0
carboxylic acid or ester	-0.7
amide or imide	-0.7
O (hydroxyl, phenol, ether)	-1.0
N (amine)	-1.0

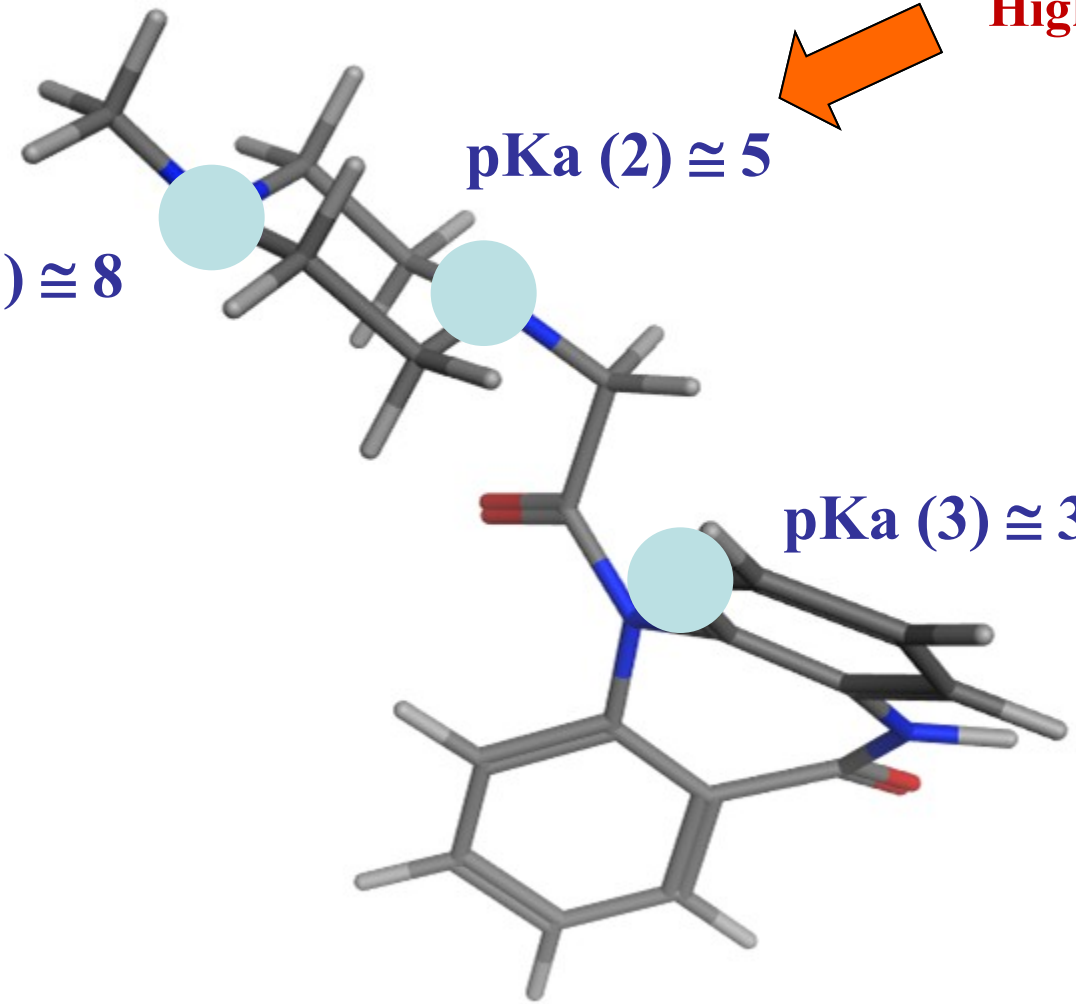
Less steric hindrance... Higher basicity!!!

Higher steric hindrance

pKa (2) ≅ 5

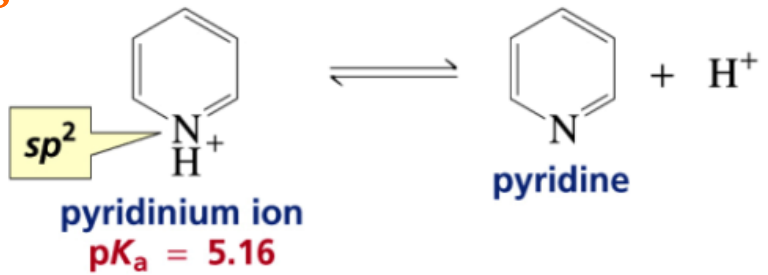
pKa (1) ≅ 8

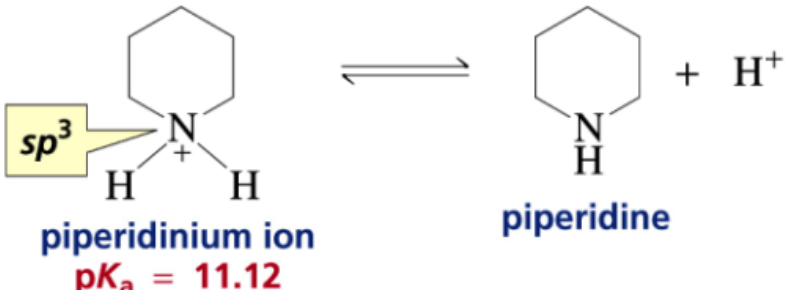
pKa (3) ≅ 3 (sp^2 !!!)

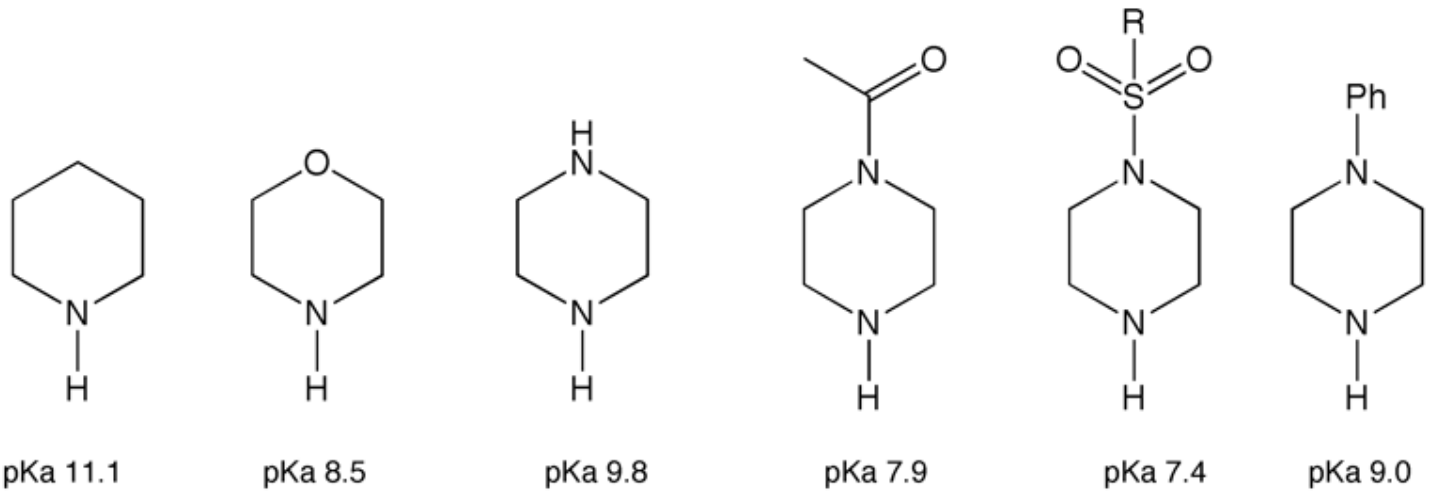


12. Cholinergic Antagonists (Muscarinic receptor)

Please… don't forget:

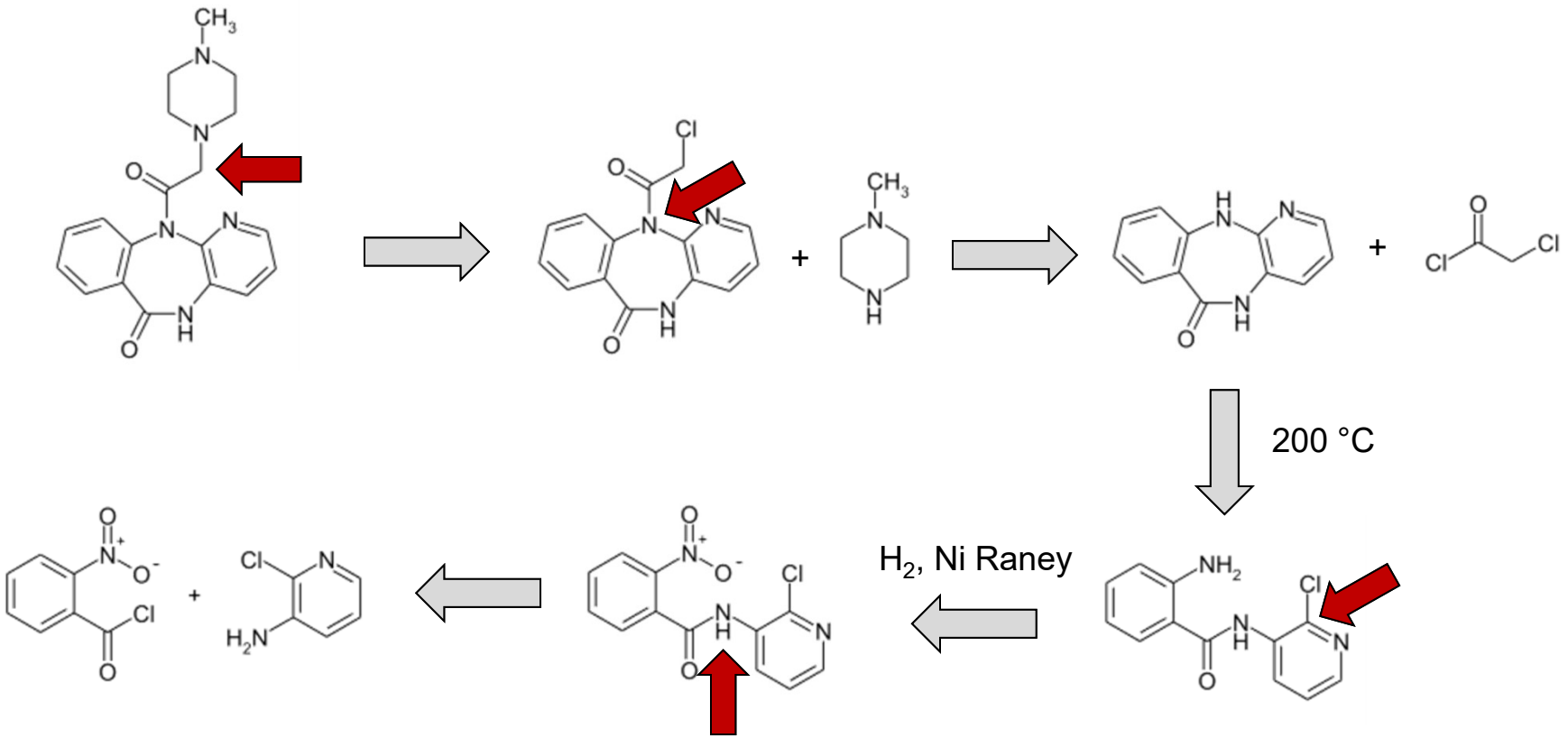






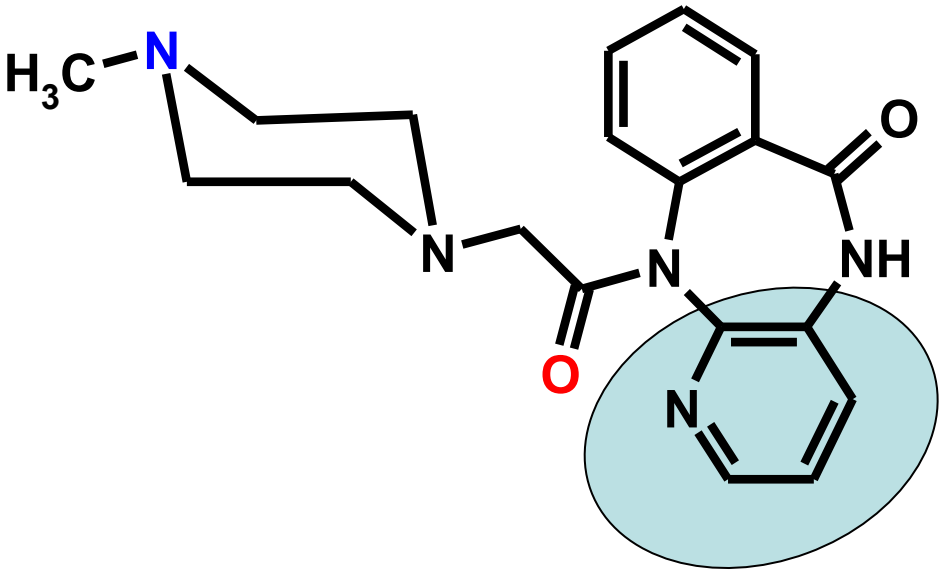
Back to chemistry…

A possible retro synthesis path:

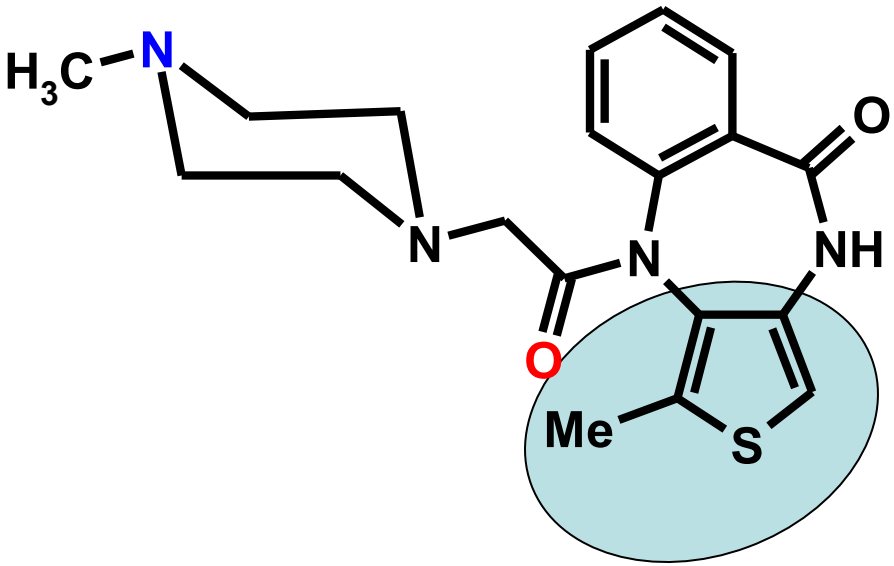


12. Cholinergic Antagonists (Muscarinic receptor)

12.5 Simplified Analogues



Pirenzepine
(anti-ulcer, M1 selective)
logP = -0.61

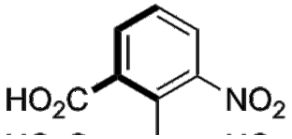


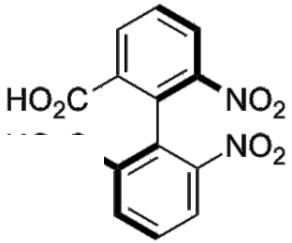
Telenzepine
(anti-ulcer, M1 selective)
logP = 0.37

Telenzepine is 25 folds more potent than pirenzepine.

Do you remember: atropisomers?

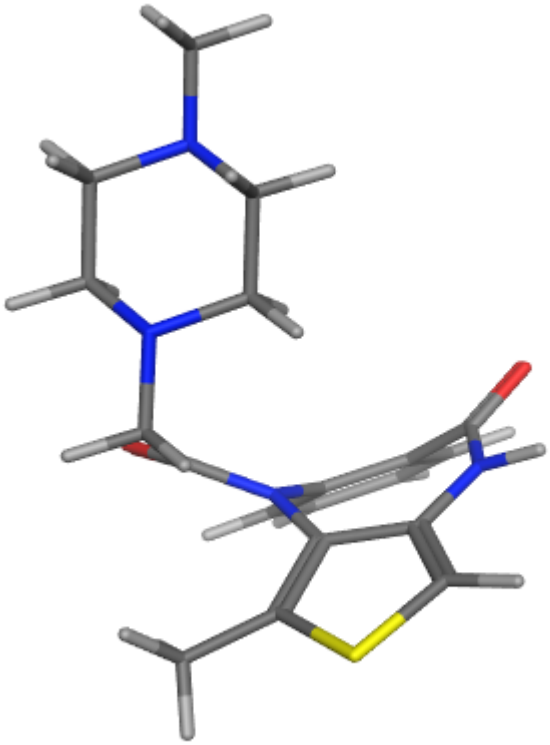
Atropisomers **are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough**

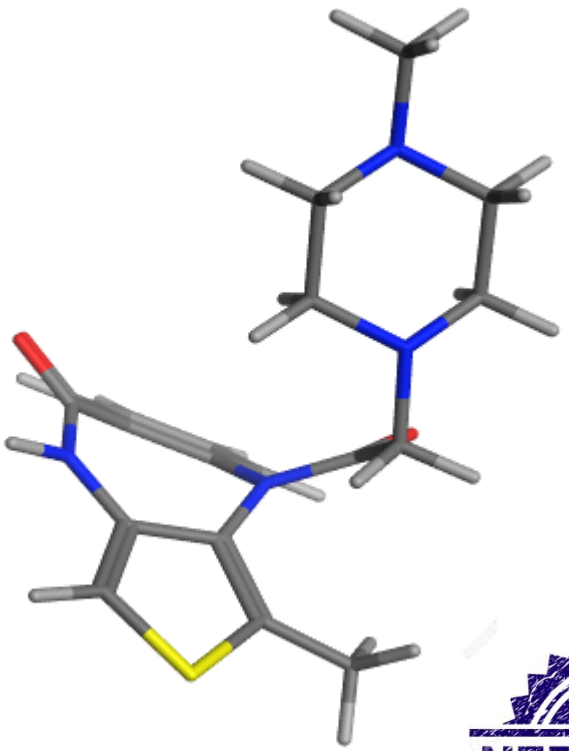


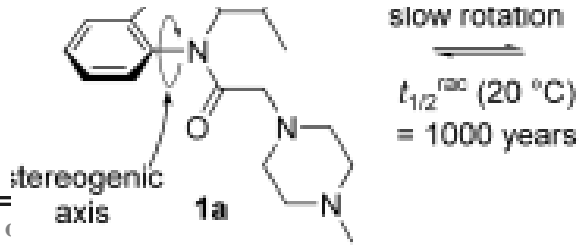


R_a

Telenzepin al aqueous solution it separation of the ena affinity for muscarinic much lower selectivity opisomers was seen a

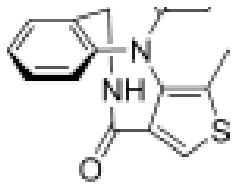




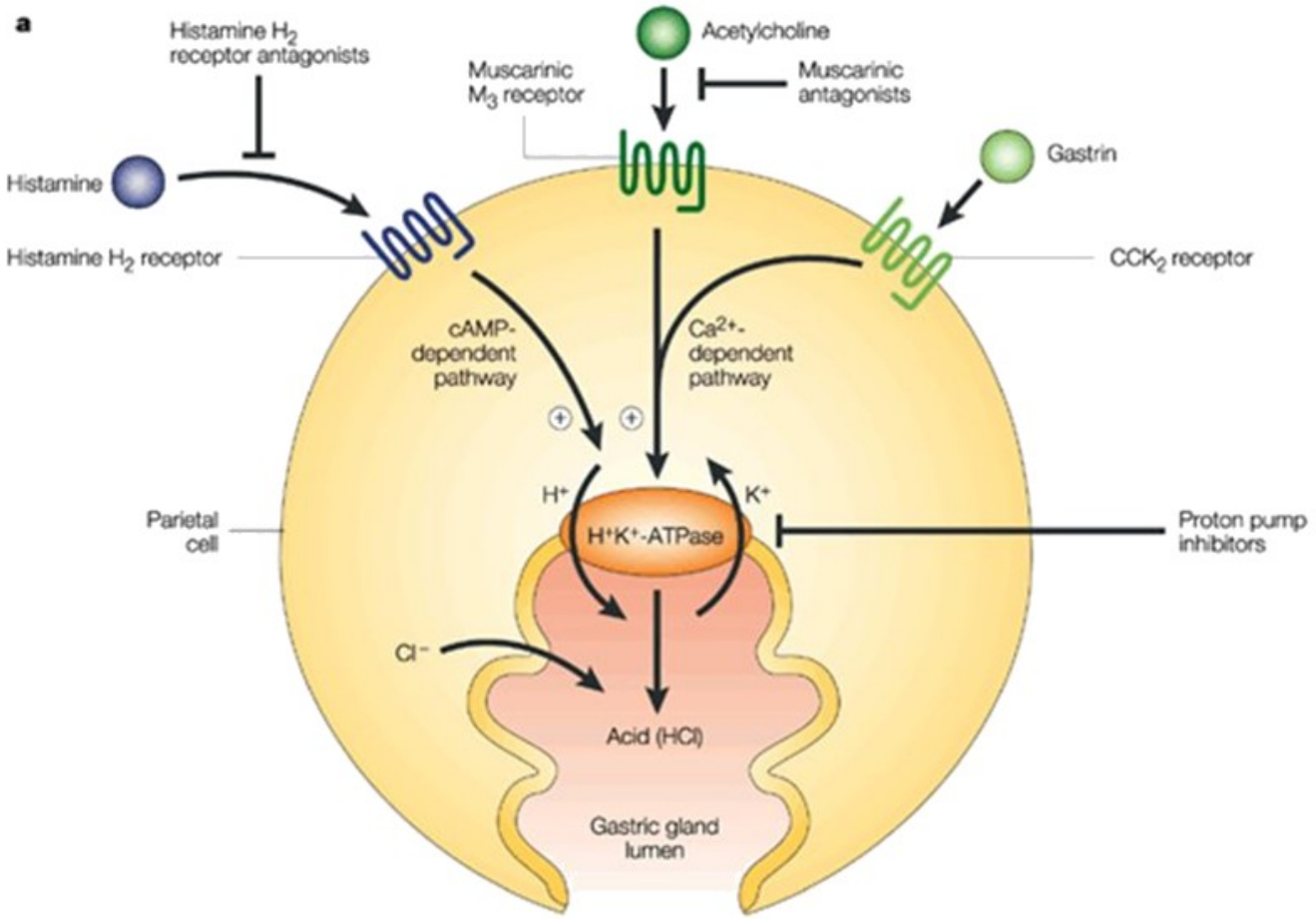


slow rotation

$t_{1/2}^{rac}$ (20 °C) = 1000 years

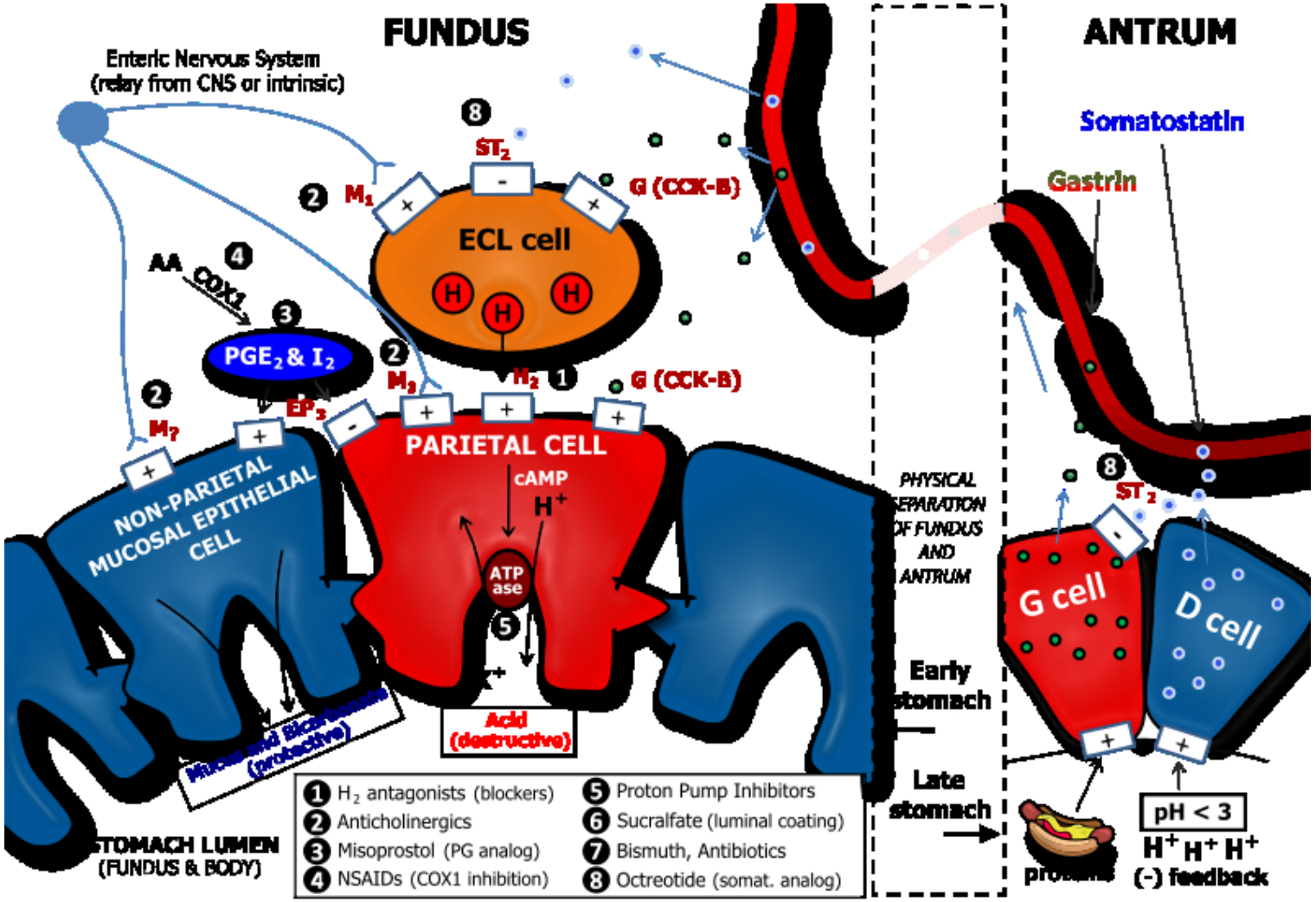


A very intricate control of HCl release from the gastric parietal cells:



12. Cholinergic Antagonists (Muscarinic receptor)

12.6 Determinants of Gastric Acid Secretion



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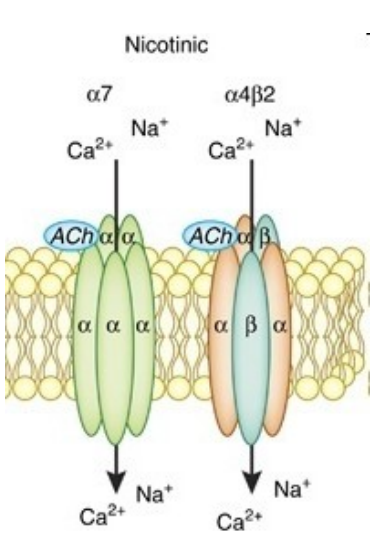
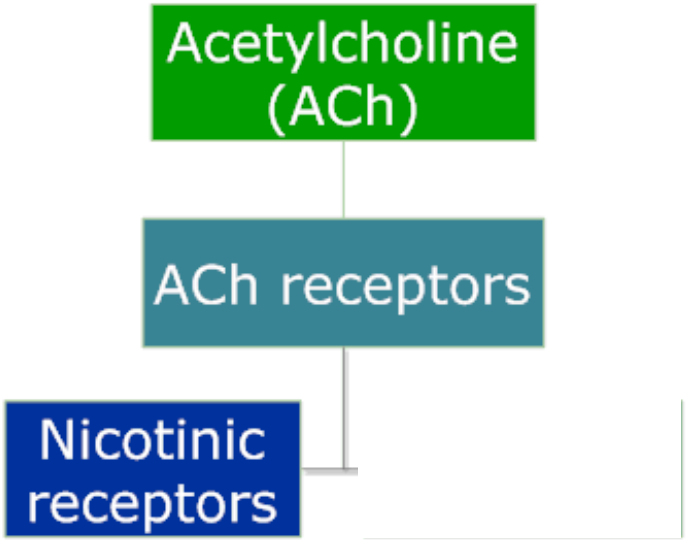
From muscarinic to nicotinic antagonists!!!

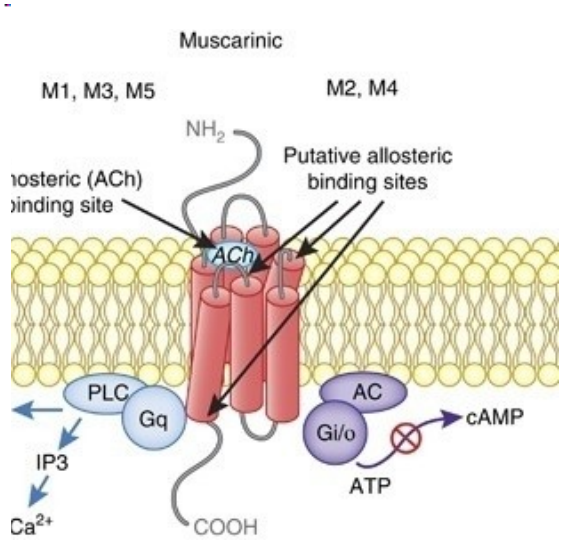
12. Cholinergic receptors

Receptor types

- Not all cholinergic receptors are identical
- Two types of cholinergic receptor - *nicotinic* and *muscarinic*
- Named after natural products showing receptor selectivity







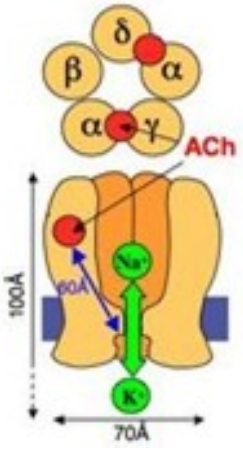
Ligand-gated ion channels (ionotropic receptors)

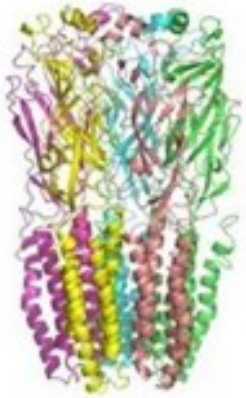
G protein-coupled receptors (metabotropic receptors)

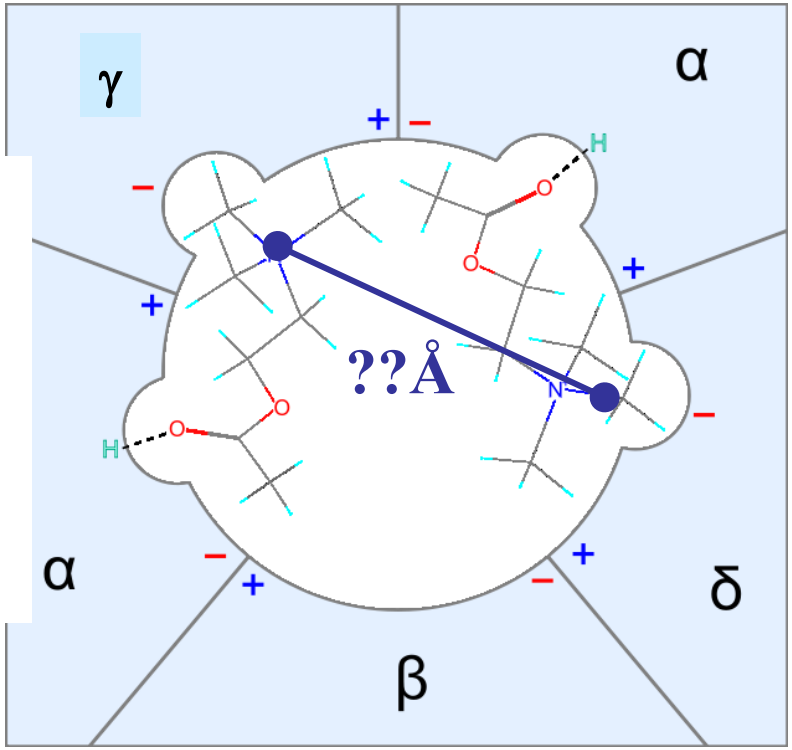
13. Cholinergic Antagonists (Nicotinic receptor)

Pharmacophore

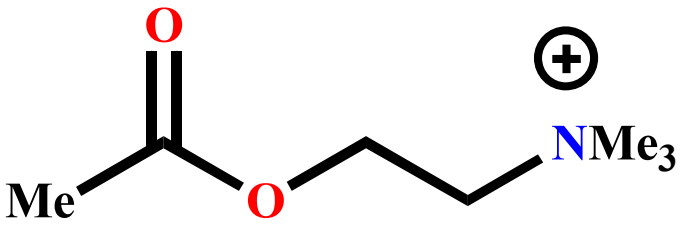
- **Two quaternary centres at specific separation**
- **Different mechanism of action from atropine based antagonists**
- **Different binding interactions**



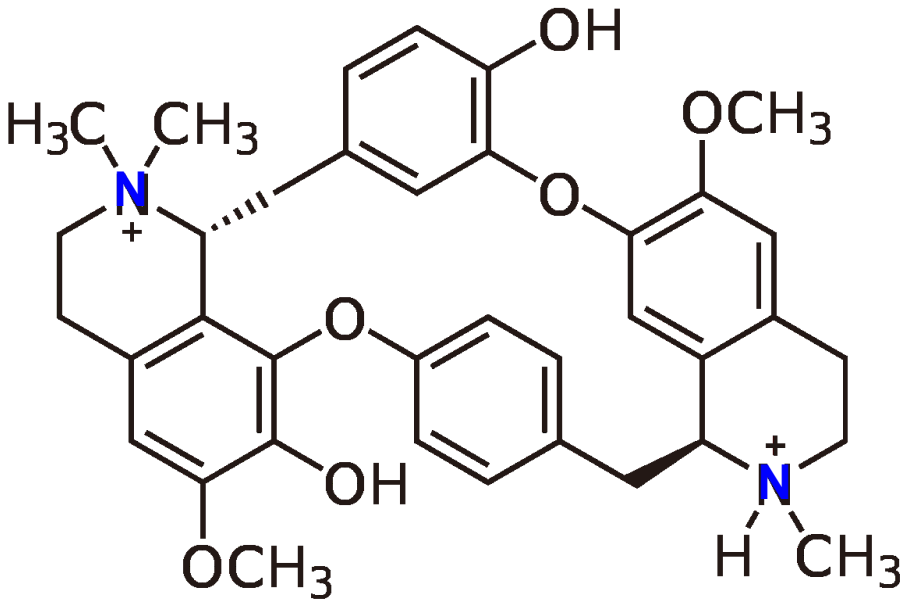




As usual, let's start by learning from mother nature …



Ach



***d* - Tubocurarine (dTc)**

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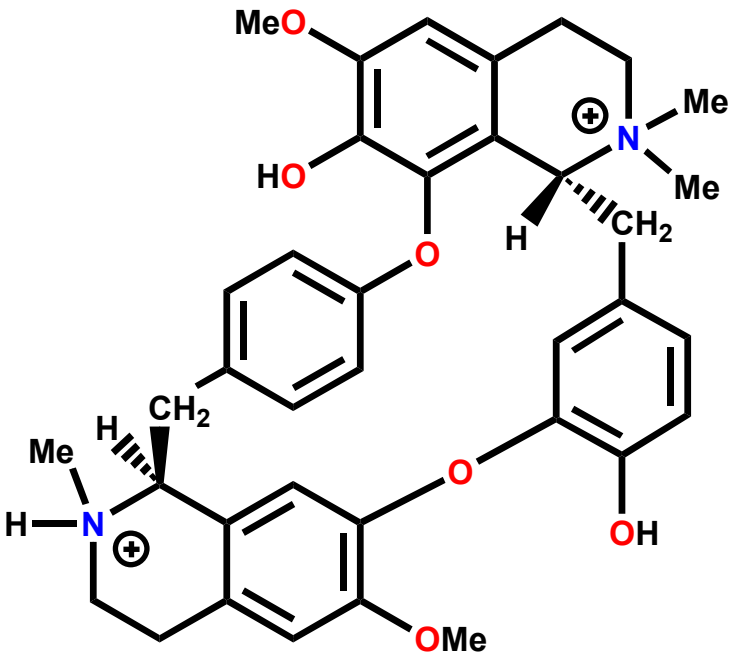
13. Cholinergic Antagonists (Nicotinic receptor)

13.1 Curare

- Extract from *curari* plant
- Used for poison arrows
- Causes paralysis (blocks acetylcholine signals to muscles)
- Active principle = tubocurarine



d-Tubocurarine (dTc)

chondrodendron tomentosum

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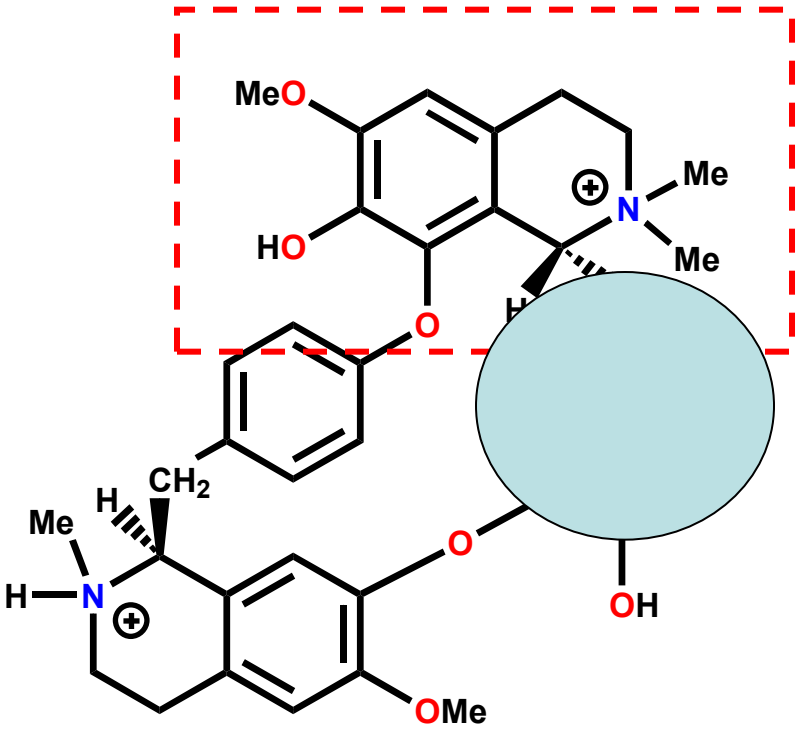
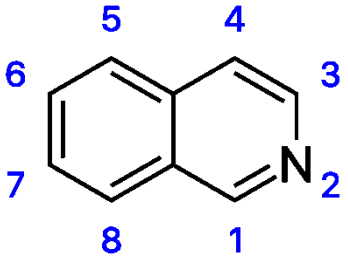
13. Cholinergic Antagonists (Nicotinic receptor)

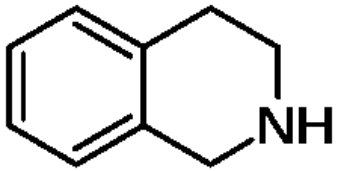
1,2,3,4-tetrahydro-1-benzyl-isoquinoline



d-Tubocurarine (dTc)

Isoquinoline derivatives





1,2,3,4-tetrahydro-isoquinoline

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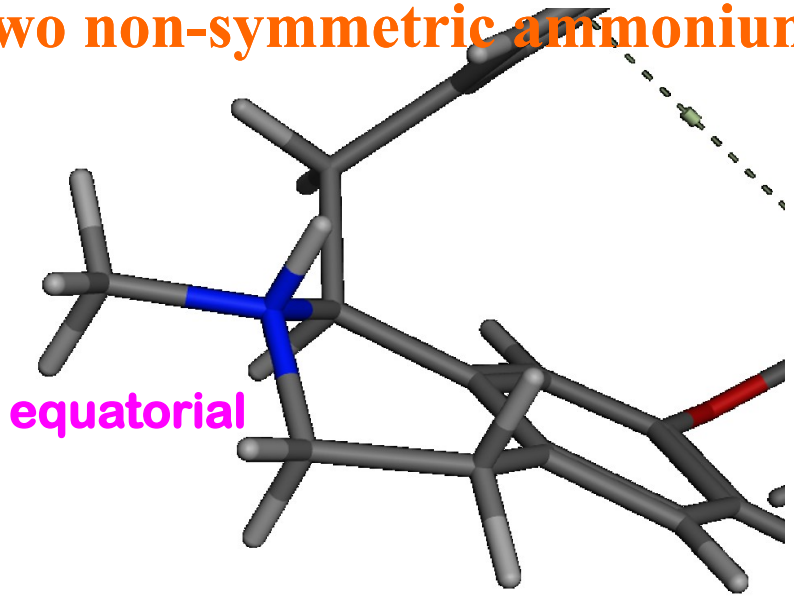
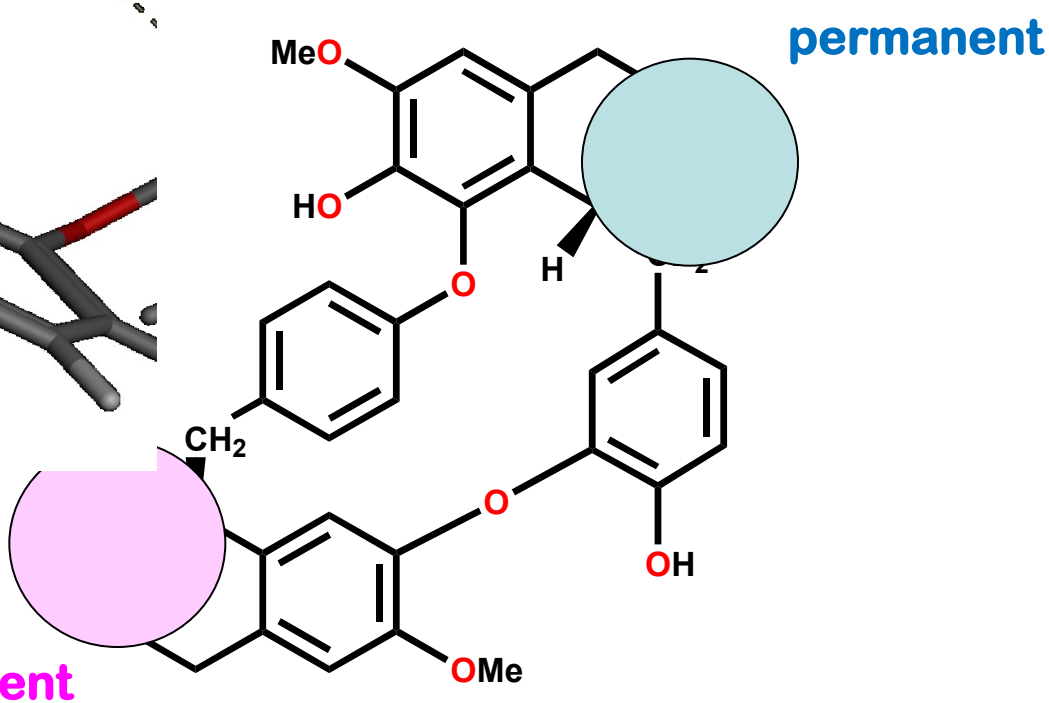
13. Cholinergic Antagonists (Nicotinic receptor)

Two non-symmetric ammonium salts



equatorial



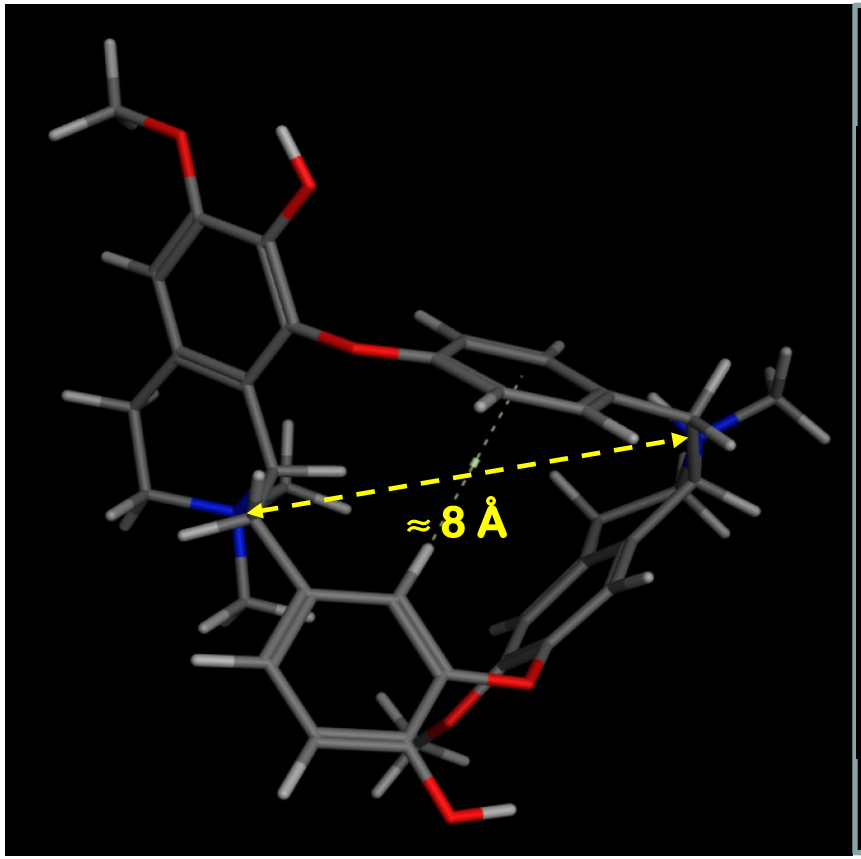
permanent

pH-dependent

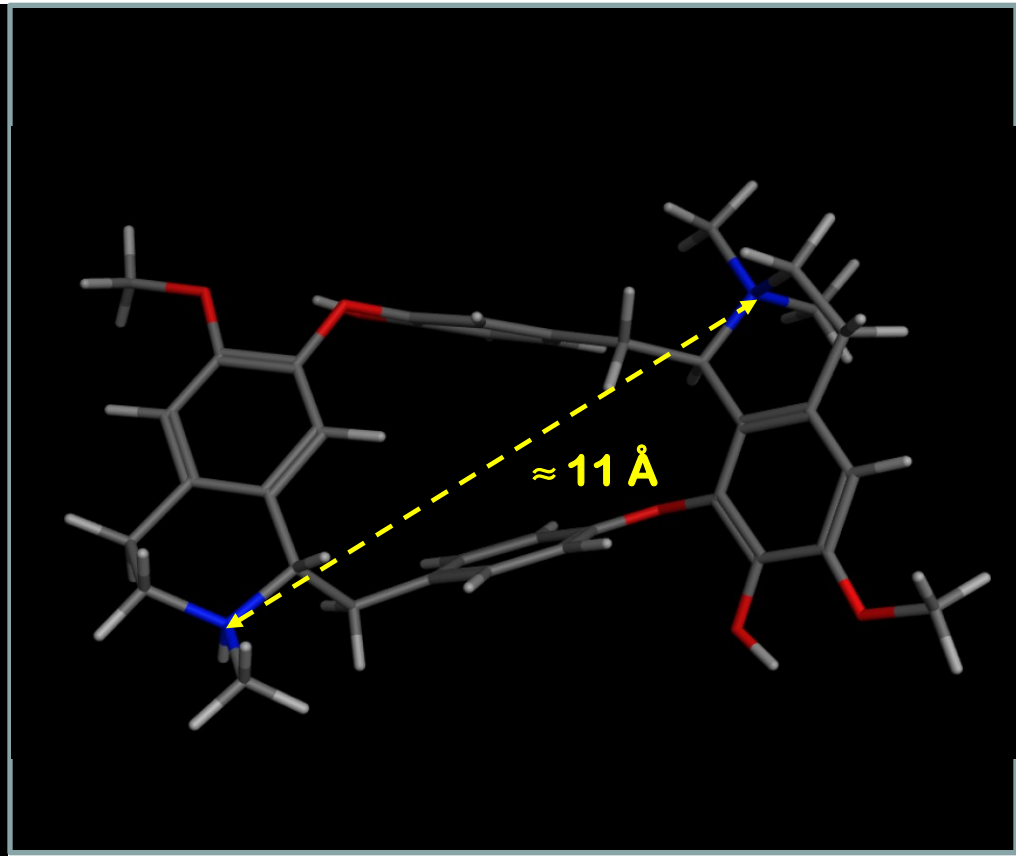
***d*-Tubocurarine (dTc)**

13. Cholinergic Antagonists (Nicotinic receptor)

Two non-equivalent conformations (π–π interactions!)



T-shape

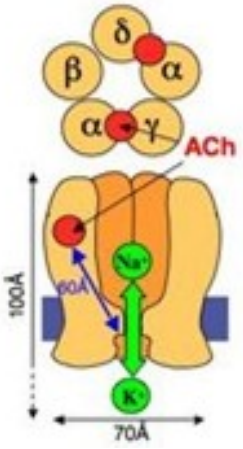


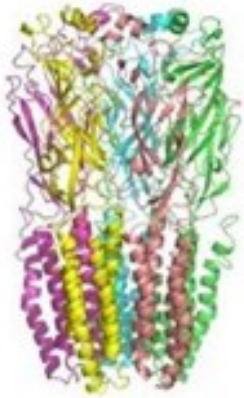
face2face

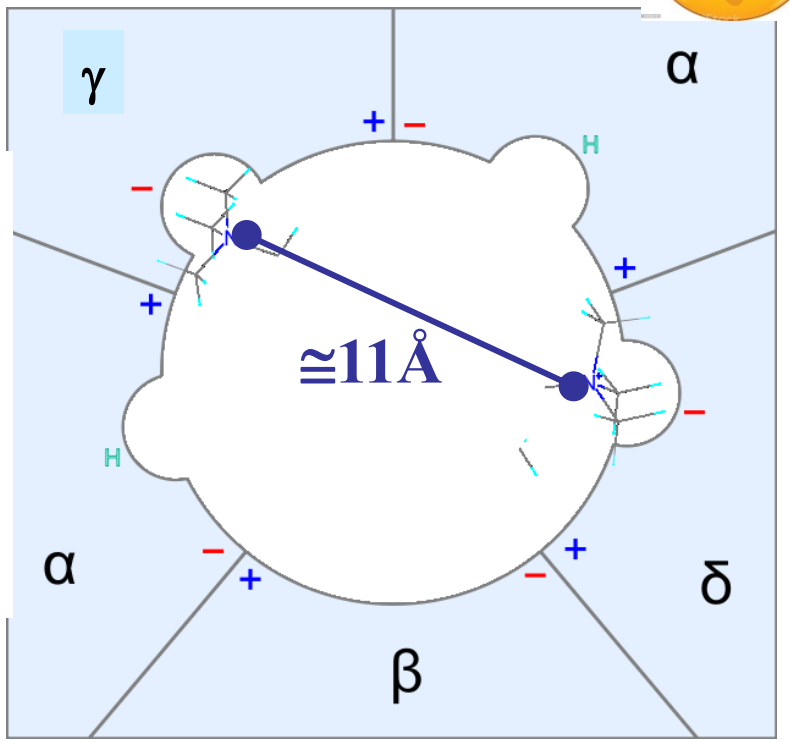
13. Cholinergic Antagonists (Nicotinic receptor)

Pharmacophore

- **Changing of the Ach:NicRec stoichiometry 2:1 to 1:1**







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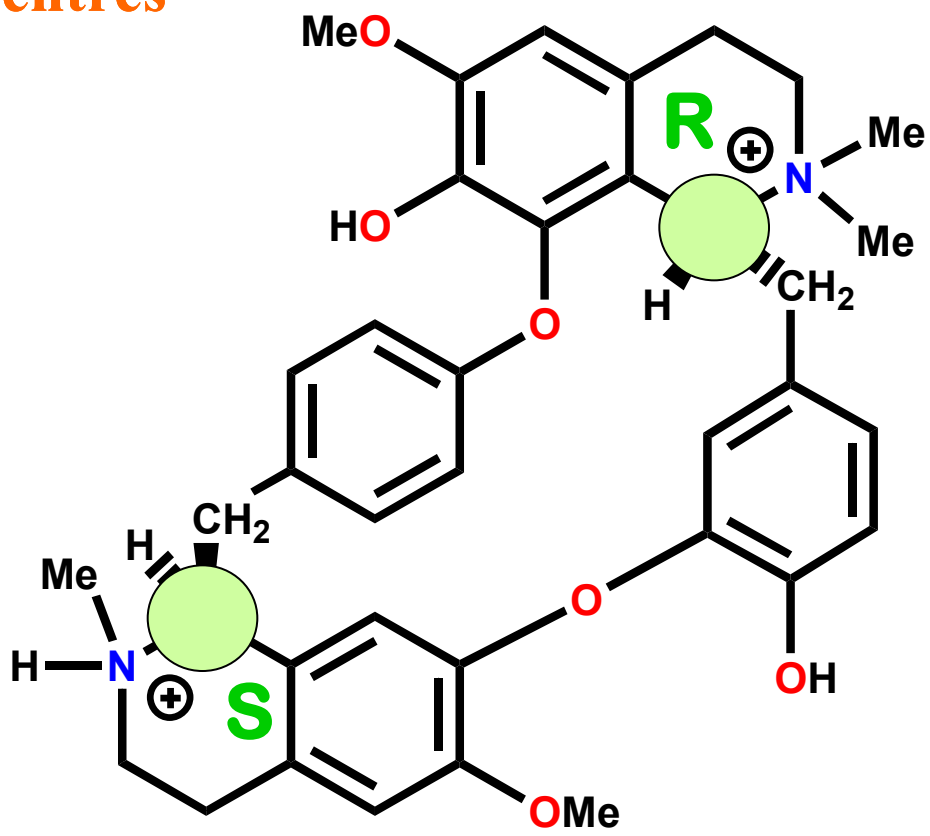
13. Cholinergic Antagonists (Nicotinic receptor)

Two asymmetric centres



***d*-Tubocurarine (dTc)**

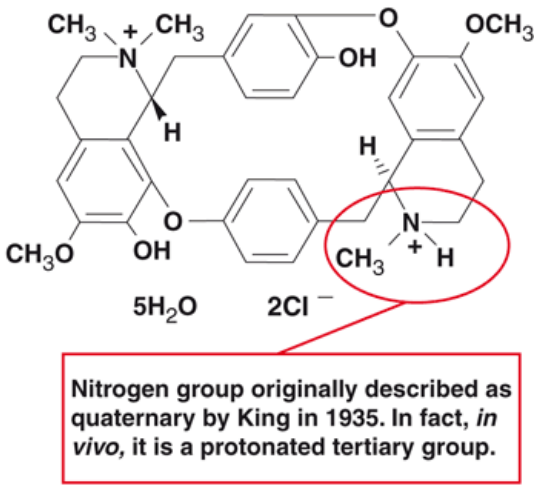
(+)- Tubocurarine

d **:** An enantiomer can be named by the direction in which it rotates the plane of polarized light. Clockwise rotation of the light traveling toward the viewer is labeled (+) enantiomer. Its mirror-image is labeled (−). The (+) and (−) isomers have been also termed *d*- and *l*- (for *dextrorotatory* and *levorotatory*); but, naming with *d*- and *l*- is easy to confuse with D- and L- labeling and is therefore discouraged by IUPAC.[1]

A nice piece of medicinal chemistry history:

In 1935, **Harold King** (1887–1956) extracted tubocurarine from a crude preparation of unknown origin. From the information he gathered, he published an erroneous chemical structure of tubocurarine. King proposed that curare had quaternary nitrogen groups at each end of the molecule (i.e. it was bis-quaternary). This notion underlay the subsequent development of new muscle relaxants. Discovery of this error in 1970 facilitated development of a new generation of mono-quaternary relaxants, the prototype being vecuronium. Although in 1935, large-scale production of tubocurarine was not possible, there followed a string of fortunate circumstances, leading to the first public demonstration of curare in humans.

In 1935, King had described the structure he thought was required in a neuromuscular blocking drug: two quaternary nitrogen groups separated by a distance (interonium) of 1.4 to 1.5 nm. The interonium distance proved to be more flexible than King predicted, for pancuronium being 1.05 nm and for fazadinium 0.7 nm.



credits: https://aneskey.com/a-history-of-neuromuscular-block-and-its-antagonism/

13. Cholinergic Antagonists (Nicotinic receptor)

Clinical uses

- **Neuromuscular blocker for surgical operations**
- **Permits lower and safer levels of general anaesthetic**
- **Tubocurarine used as neuromuscular blocker but side effects in particular *hypotension* and *bronchoconstriction* (by histamine release from mast cells)**
- **Currently, tubocurarine is rarely used as an adjunct for clinical anesthesia because safer alternatives**

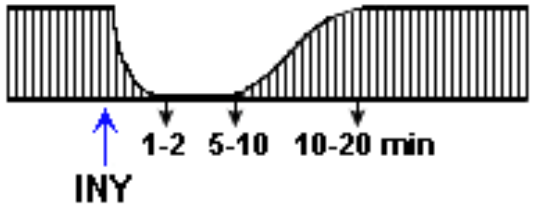
Time to onset: 300 seconds or more

(which is relatively slow among neuromuscular-blocking drugs)

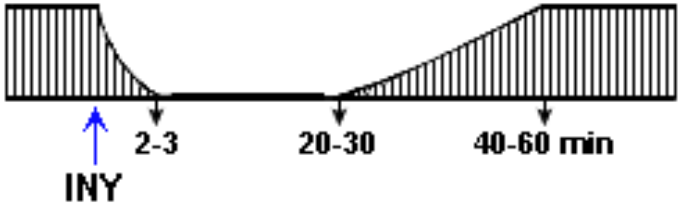
Duration: 60 -120 minutes

(which is relatively long time)

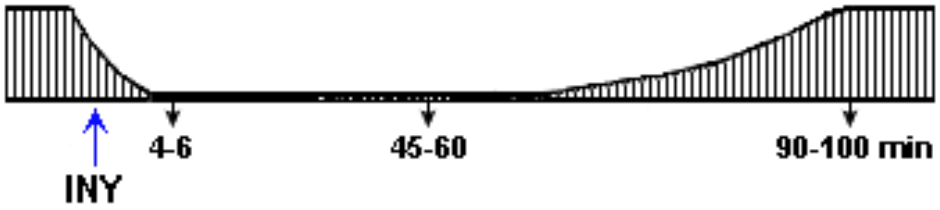
Common classification… on set & duration



Short duration



Intermediate duration



Long duration

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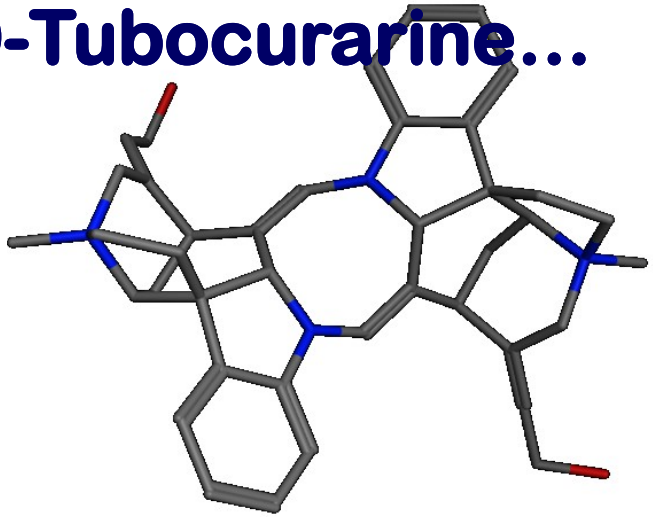
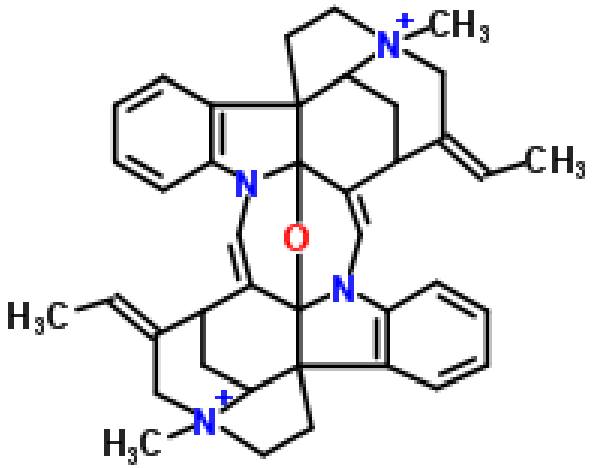
Not only D-Tubocurarine…

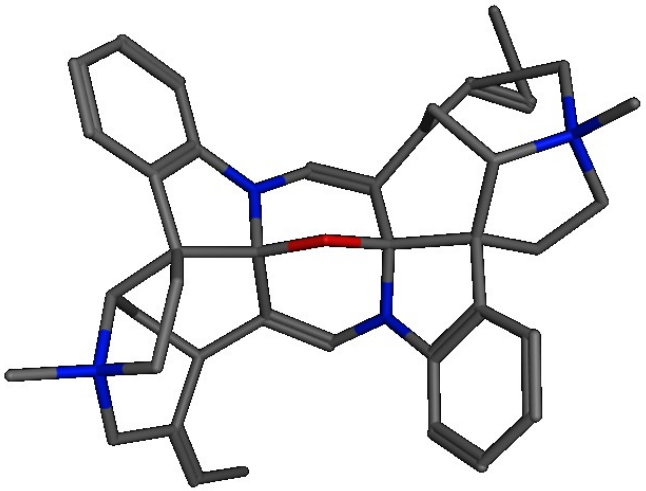


Toxiferine

$d(N^+\text{-}N^+) \cong 9.9$ Å

Strychnos toxifera

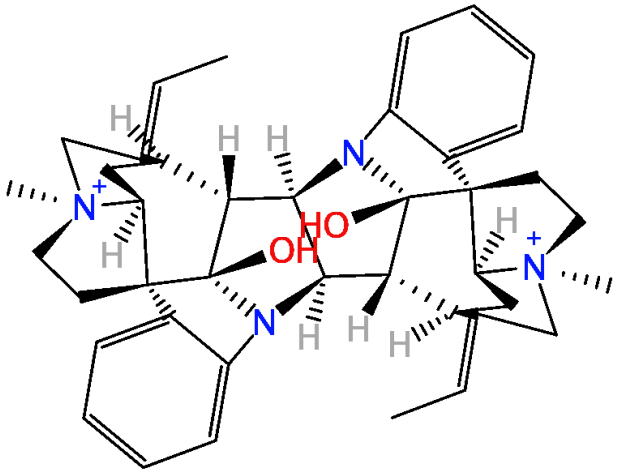


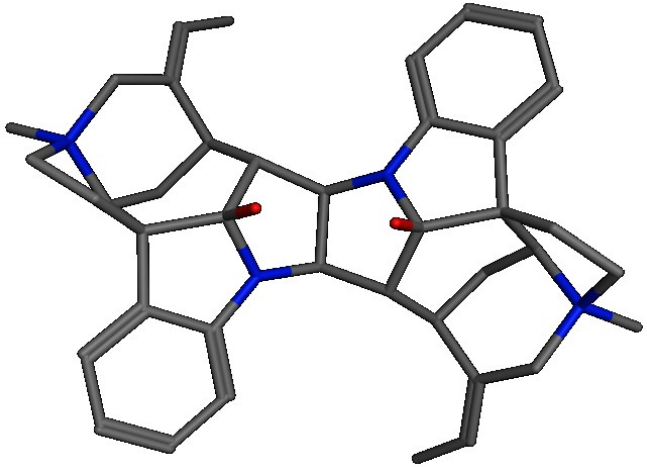


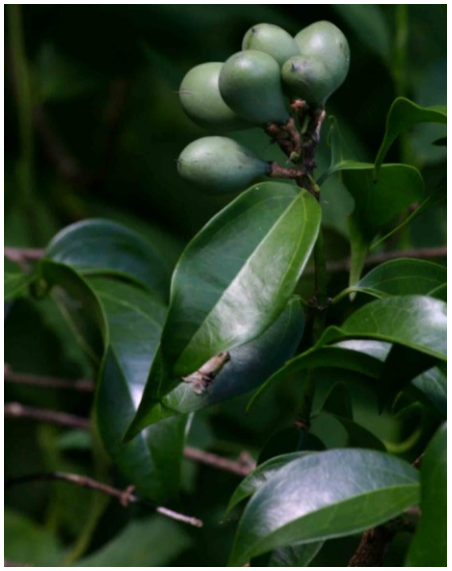
C-Curarine

$d(N^+\text{-}N^+) \cong 9.5$ Å

Lagenaria siceraria



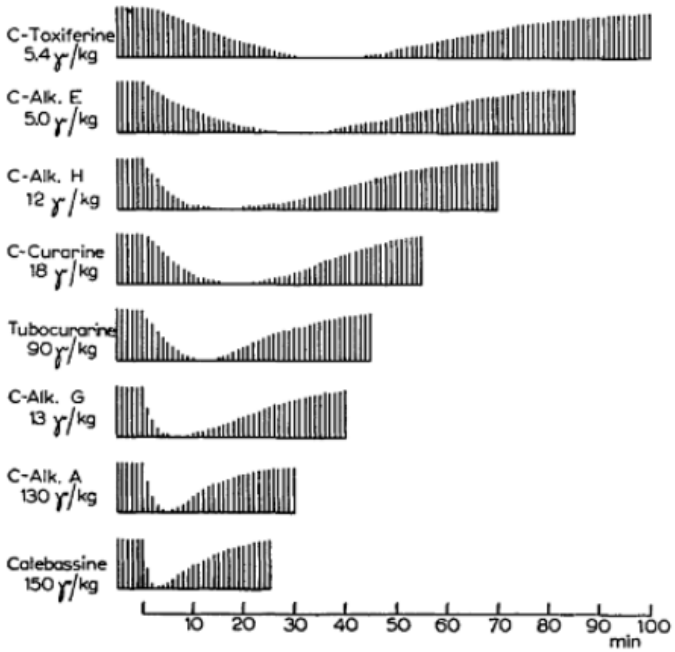




Calebassine

$d(N^{+}\text{-}N^{+}) \cong 10.2$ Å

Strychnos usambarensis



Duration of paralysis (paralytic dose i.v.), contraction of cat gastrocnemius by electrically stimulated sciatic nerve (4 x /min). [J.E. Saxton "The Alkaloids" Vol. 1, p.330, 1970]

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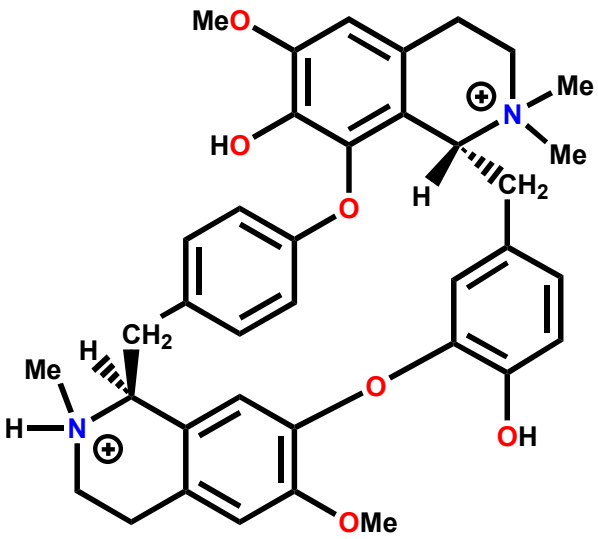
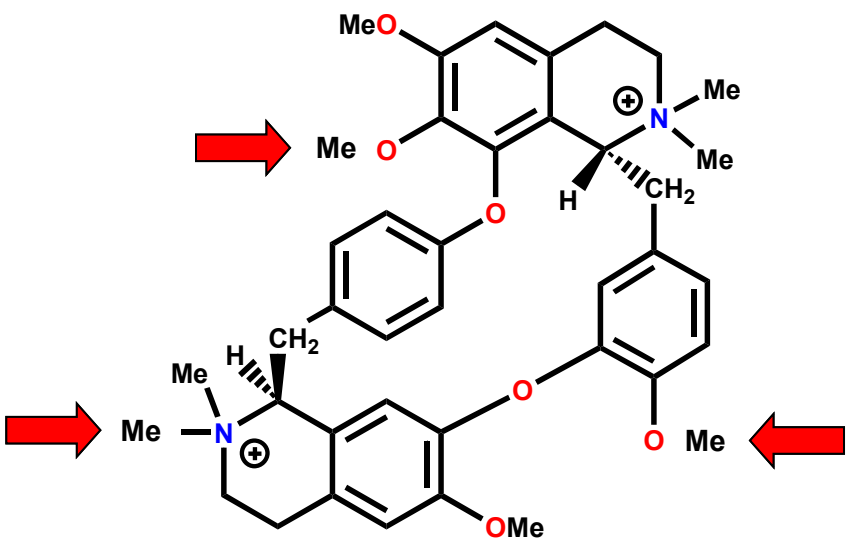
13. Cholinergic Antagonists (Nicotinic receptor)

From *d*-Tubocurarine to Metocurine



***d*-Tubocurarine (dTc)**



Metocurine

Metocurine is a semisynthetic derivative of DTc, first synthesized by King in 1935 as part of the work that first suggested a chemical structure for DTc. It is the N,O,O-trimethylated compound. Unlike DTc, it is a *bisquaternary molecule*. **Metocurine is about twice as potent as curare in human subjects**, with a similarly long duration of action. Its principal advantage over curare is its weaker histamine-releasing property-less than one-half that of DTc. Metocurine is indicated for longer operations (3–4 hours). Metocurine is excreted only by the kidney. It has no alternate biliary pathway, and no metabolism occurs in the liver.

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13. Cholinergic Antagonists (Nicotinic receptor)

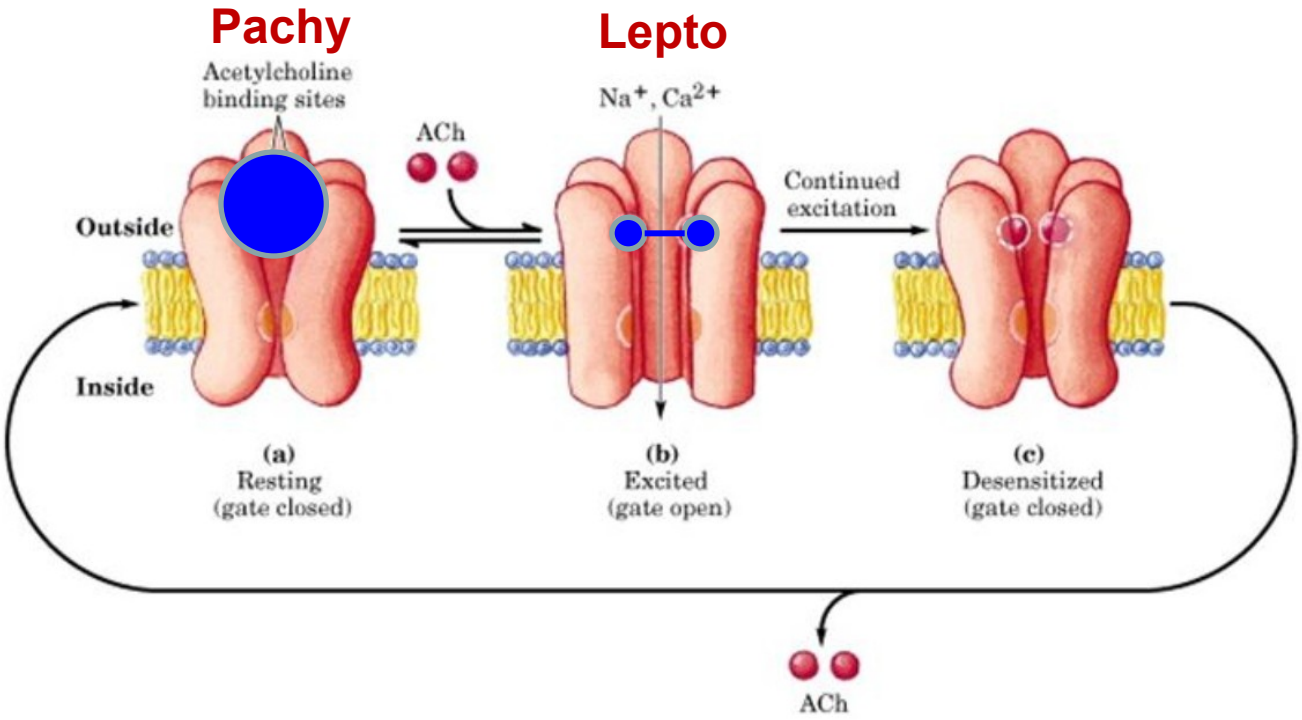
13.3 Analogues of tubocurarine (simplification strategy)

Neuromuscular blocking drugs are often classified into two broad classes:

***Pachycurares*, which are bulky molecules, fully competitive antagonits of acetylcholine with non-depolarizing activity because they bind the closed form of the channel;**

***Leptocurares*, which are thin and flexible molecules that tend to have depolarizing activity because they bind the open form of the channel.**

the apparently strange behavior between pachy and lepto…



Leptocurares produce muscle relaxation not by preventing the opening of the Ach-activated channels but by keeping them open too long… or in other words keep the muscle membrane depolarized and refractory to a new impulse initiation.

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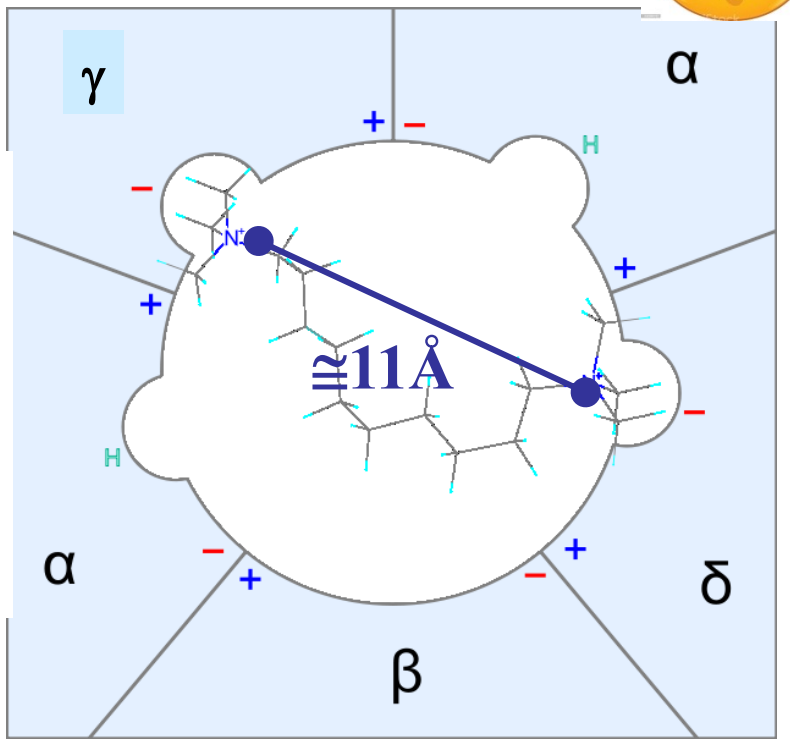
13. Cholinergic Antagonists (Nicotinic receptor)

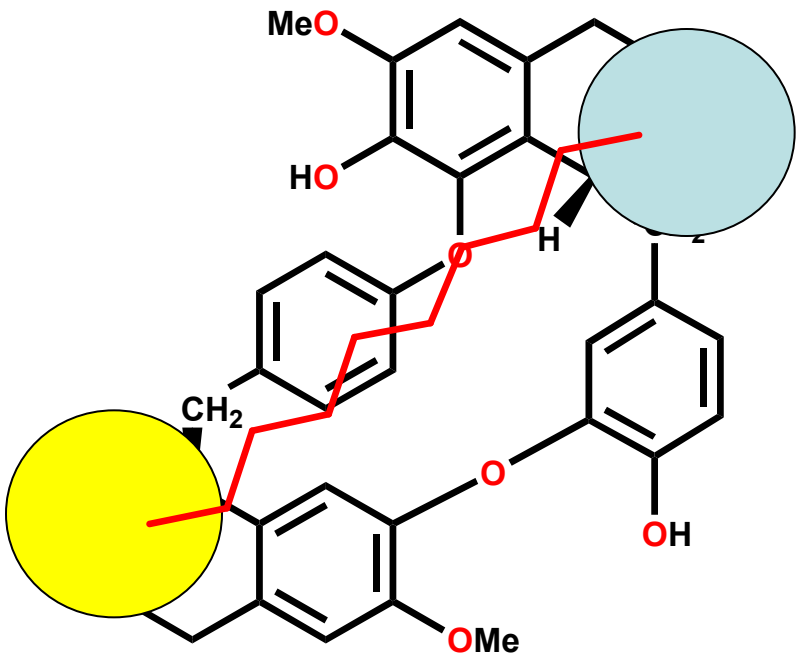
Pharmacophore

- **Changing of the Ach:NicRec stoichiometry 2:1 to 1:1**



13. Cholinergic Antagonists (Nicotinic receptor)

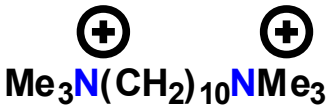
13.3 Analogues of tubocurarine (simplification strategy)



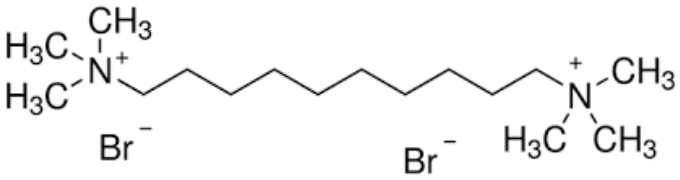
from pachy to lepto…

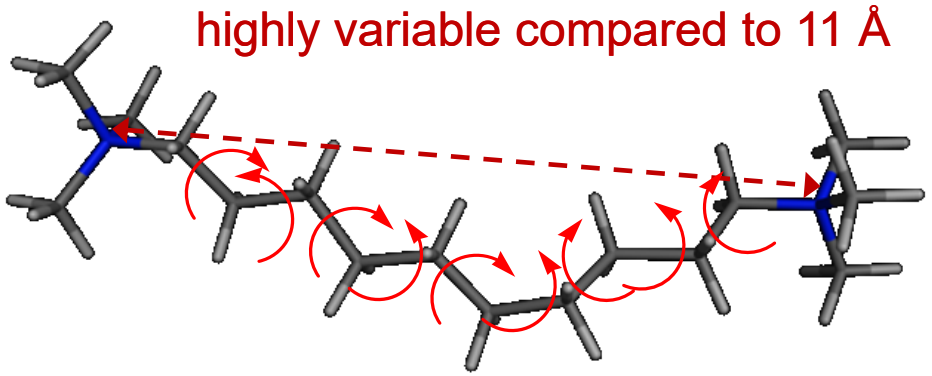
13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (leptocurares)



Decamethonium

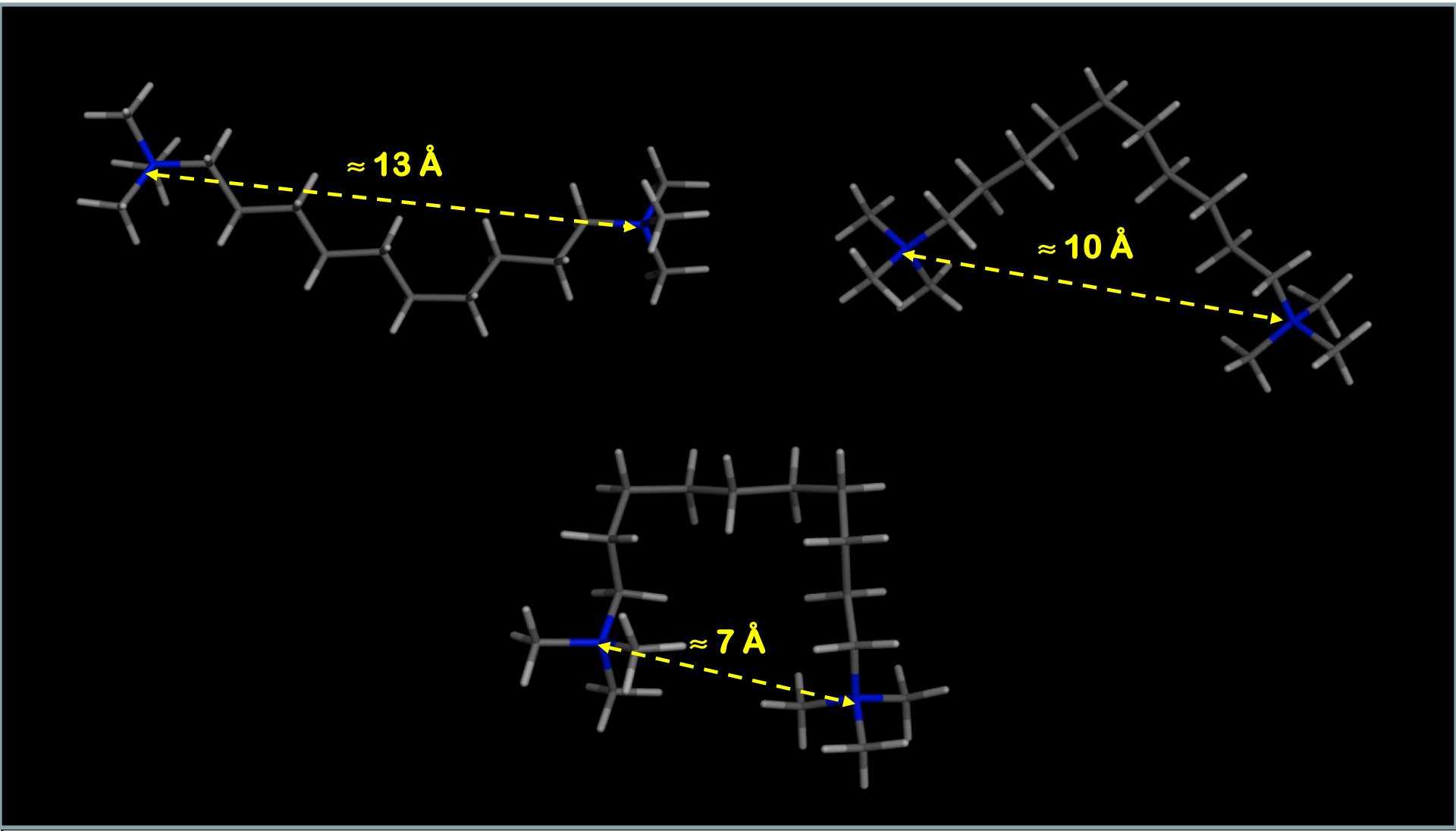




- **Long lasting**
- **Long recovery times**
- **Side effects on heart**
  (*VOC blocker*)

13. Cholinergic Antagonists (Nicotinic receptor)

Conformational variability of Decamethonium:



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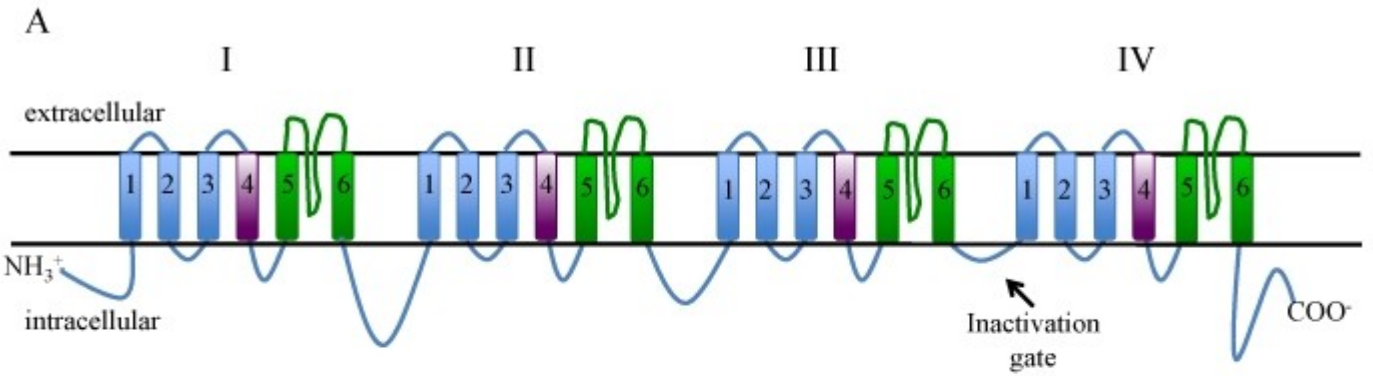
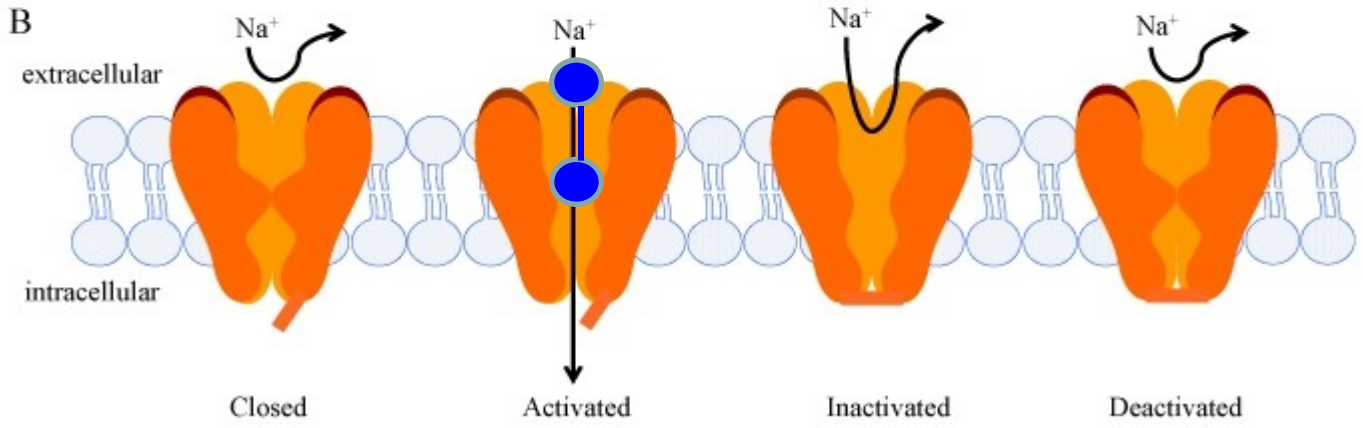
VOC blockers: lepto… and several other small ammonium cations



Lepto



Welcome to a great scientist: the most brilliant ideas are sometimes the simplest ones!

Daniel Bovet, (born March 23, 1907, Neuchâtel, Switz.- died April 8, 1992, Rome, Italy), Swiss-born Italian pharmacologist who received the 1957 Nobel Prize for Physiology or Medicine for his discoveries of certain chemotherapeutic agents - namely, sulfa drugs, antihistamines, and muscle relaxants.

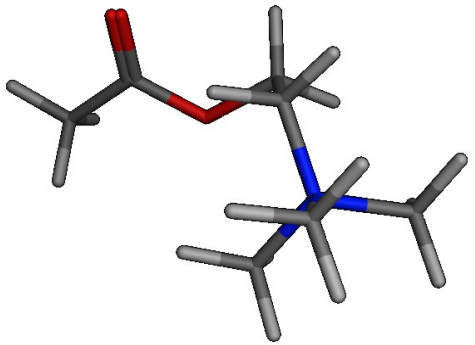
Bovet studied at the University of Geneva, graduating with a doctorate in science in 1929. That same year, he went on to the Pasteur Institute in Paris and became head of the therapeutic chemistry laboratory there in 1939. In 1937 Bovet discovered the first antihistamine substance, which (in counteracting the effect of histamine) is effective in treating allergic reactions. This discovery led to development of the first antihistamine drug for humans in 1942, and in 1944 one of Bovet's own discoveries, pyrilamine, was produced as a drug.

In 1947 Bovet was invited to establish a laboratory of chemotherapeutics at the Superior Institute of Health in Rome, and eventually he took Italian citizenship. There he turned his attention to curare, a drug used to relax muscles during surgery. Because the drug was expensive and somewhat unpredictable in its effects, a low-cost dependable synthetic alternative was desired. Bovet produced hundreds of synthetic alternatives, of which gallamine and succinylcholine came into widespread use.

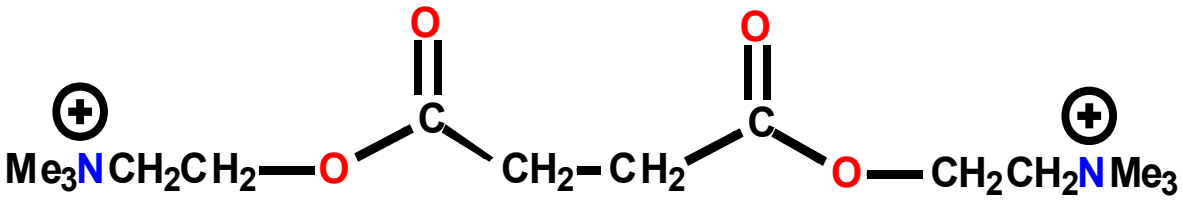
In 1964 Bovet became professor of pharmacology at the University of Sassari, on the Italian island of Sardinia. He served as the head of the psychobiology and psychopharmacology laboratory of the National Research Council (Rome) from 1969 until 1971, when he became professor of psychobiology at the University of Rome (1971–82).

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (leptocurares)



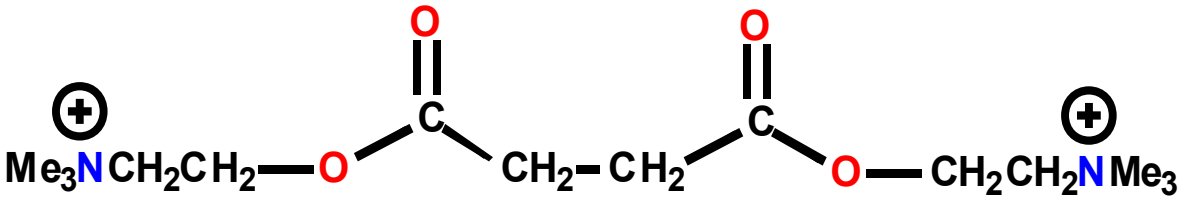
gauche



Suxamethonium or succinylcholine

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (leptocurares)



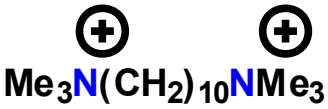
Suxamethonium or succinylcholine

Suxamethonium chloride **(otherwise known as succinyl chloride or "sux") is a drug used to create short-term muscle paralysis. The drug can effectively stop the action of all skeletal muscles in the body in 30-60 seconds enabling doctors to perform a Tracheal Intubation (placing a flexible plastic tube into the trachea to maintain an open airway as shown in the diagram) without the patient struggling. The effect typically lasts 5-10 minutes meaning that the patient does not need to have artificial breathing for too long.**

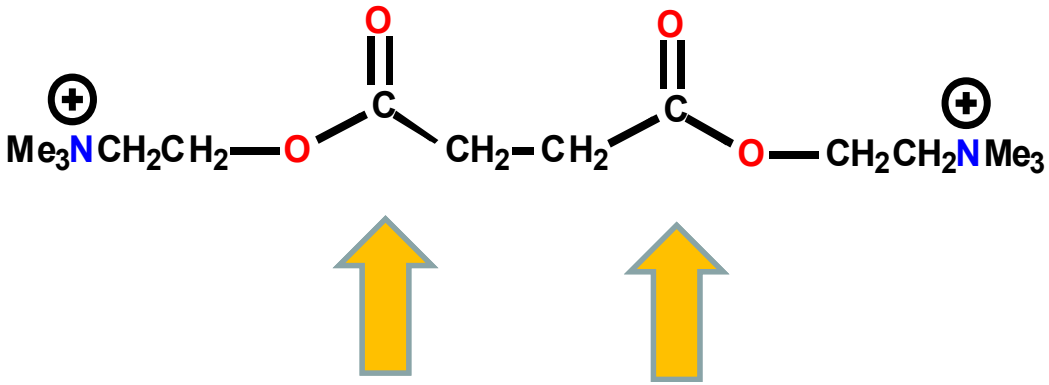
The discovery and development of suxamethonium led to a Nobel Prize in medicine for Daniel Bovet in 1957.

why long… why short…

Decamethonium

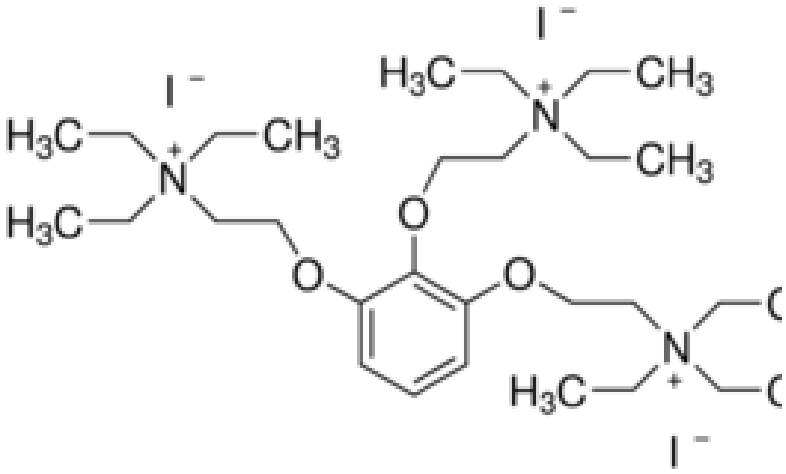


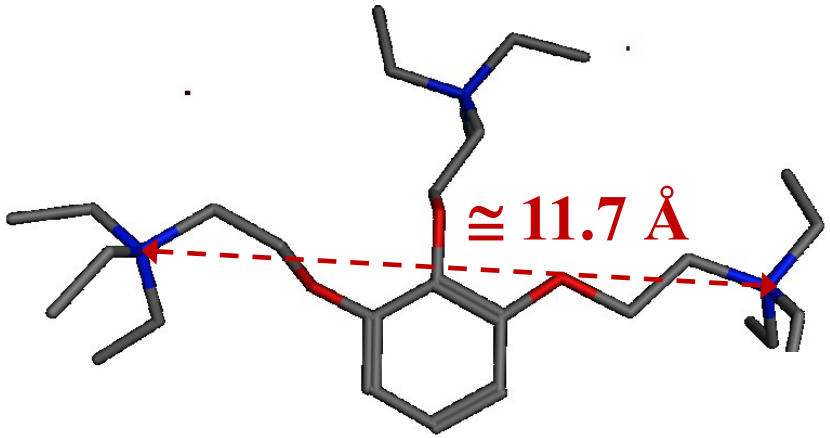
Suxamethonium



13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)





Gallamine triethiodide

Gallamine triethiodide (**Flaxedil**) is a non-depolarising muscle relaxant. It was developed by Daniel Bovet in 1947. The pharmaceutical is no longer marketed.

and from lepto back to pachy…

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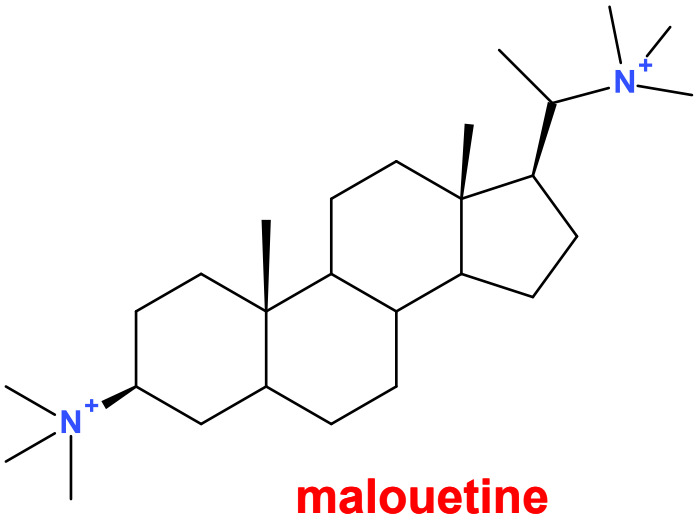
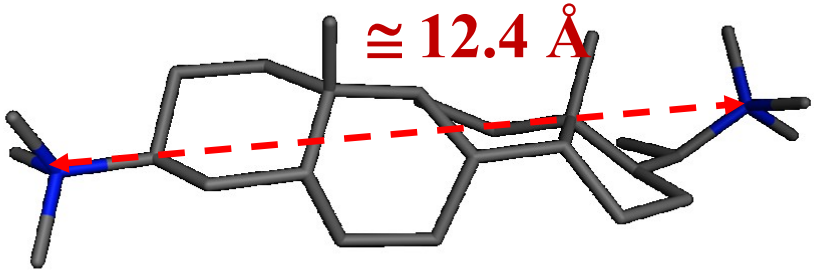
Back to mother nature…

The discovery of a steroidal alkaloid **malouetine** prompted development of steroid molecules with curare-like effects. The general structure had two acetylcholine-like groups separated by an appropriate distance, and had to be bulky (pachycurare) to confer non-depolarizing characteristics. William “Bill” Bowman was a gifted pharmacologist at the University of Strathclyde in Glasgow, Scotland, who had worked with Paton on curare-like drugs. Bowman considered that the rigid steroidal **androstane** molecule was the perfect skeleton on which to place the quaternary nitrogen groups to create a muscle relax



malouetine



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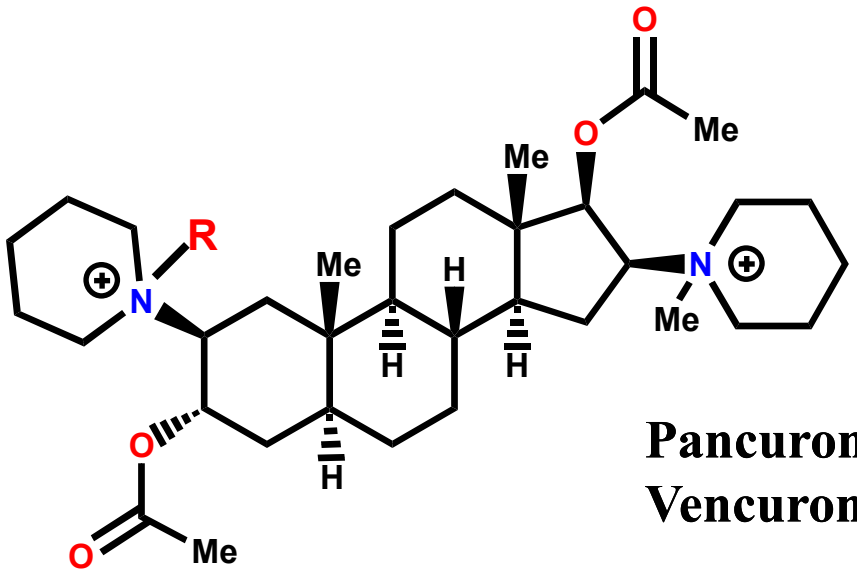
From malouetine to pancuronium:

It was these structural "rules" and Bowman's idea to use the androstane nucleus that led to the development of the aminosteroid relaxant pancuronium by Hewett and Savage. Pancuronium obeyed the rules except for its short interonium distance. This shortness conferred high potency and was long enough to avoid producing ganglionic blockade. Soon after the report of its clinical use in 1967, **pancuronium** supplanted curare and gallamine for use in patients. Although devoid of ganglionic blocking effects, it had both vagolytic and sympathomimetic activity, but did not produce the hypotension associated with d-tubocurarine, or as much tachycardia as seen with gallamine.

David Savage



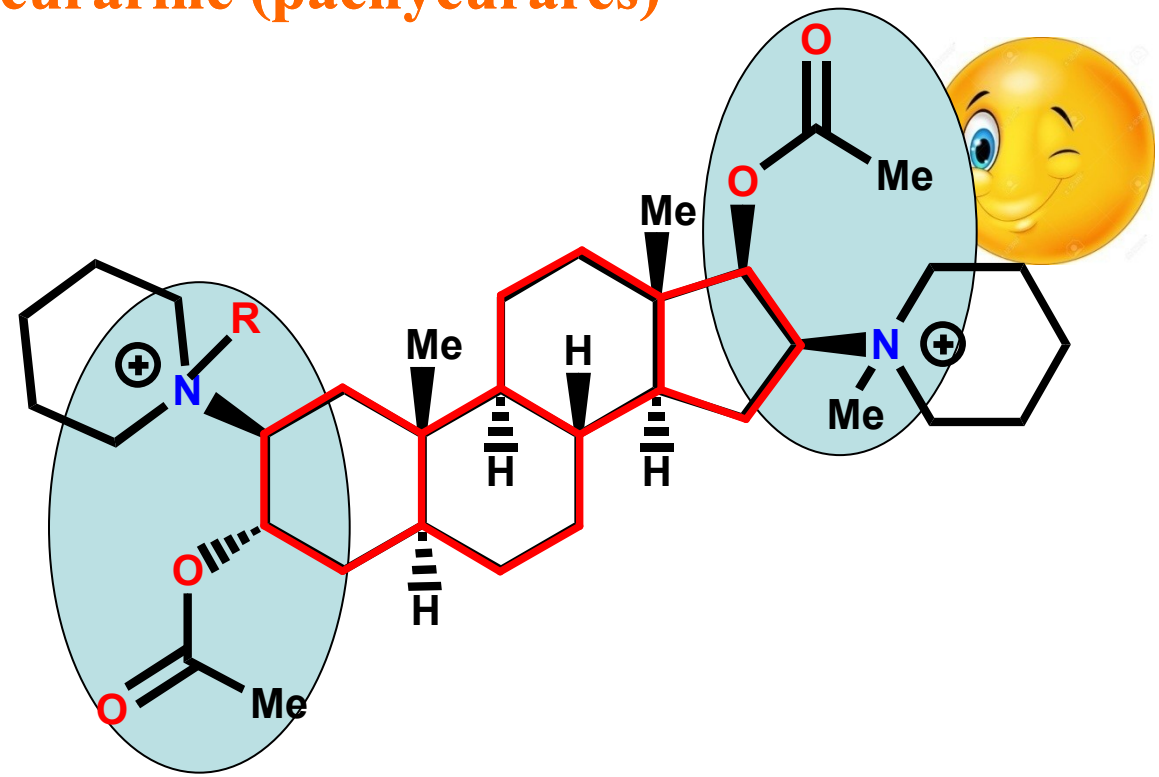
Pancuronium (R=Me)
Vencuronium (R=H)

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)

Pancuronium (R=Me)

Vecuronium (R=H)



- **Steroid acts as a spacer for the quaternary centres (≈ 11Å)**
- **Acyl groups are added to introduce the Ach skeleton**
- **Faster onset then tubocurarine but slower than suxamethonium**
- **Longer duration of action than suxamethonium (> 45 min)**
- **No effect on blood pressure and fewer side effects**

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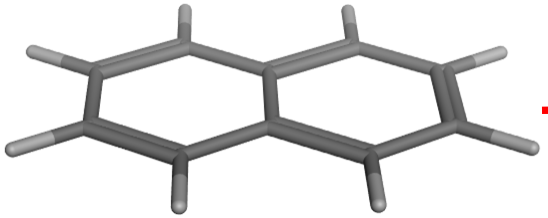
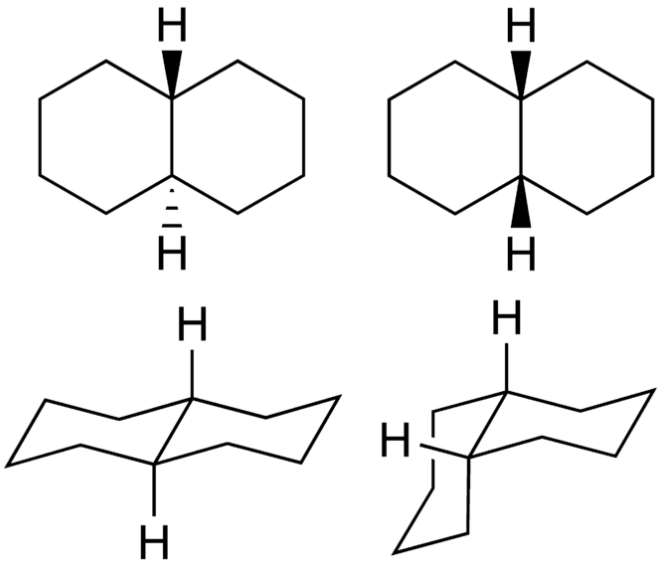
Do you remember?

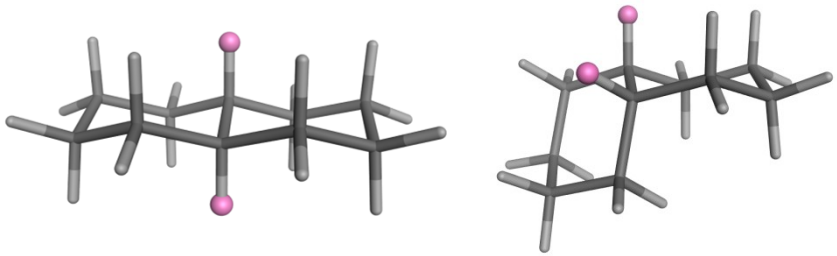
Decalin
(decahydronaphthalene)



Naphthalene

H_2

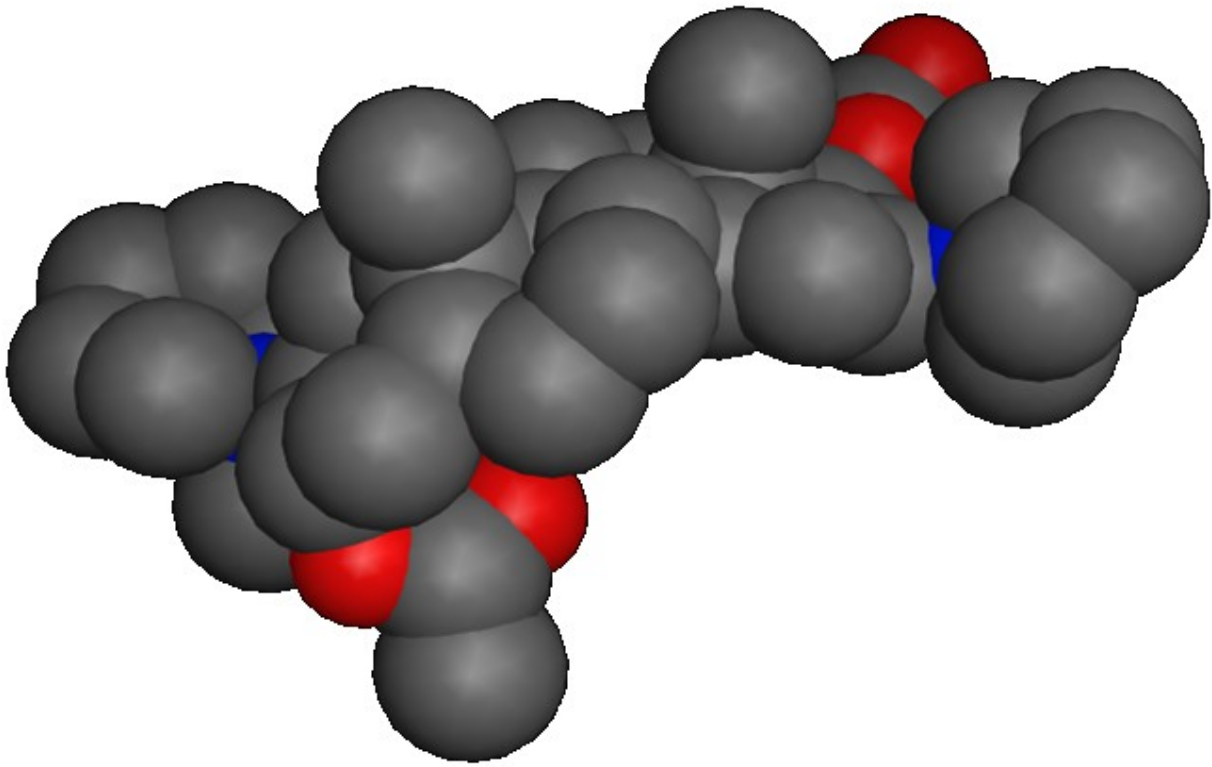




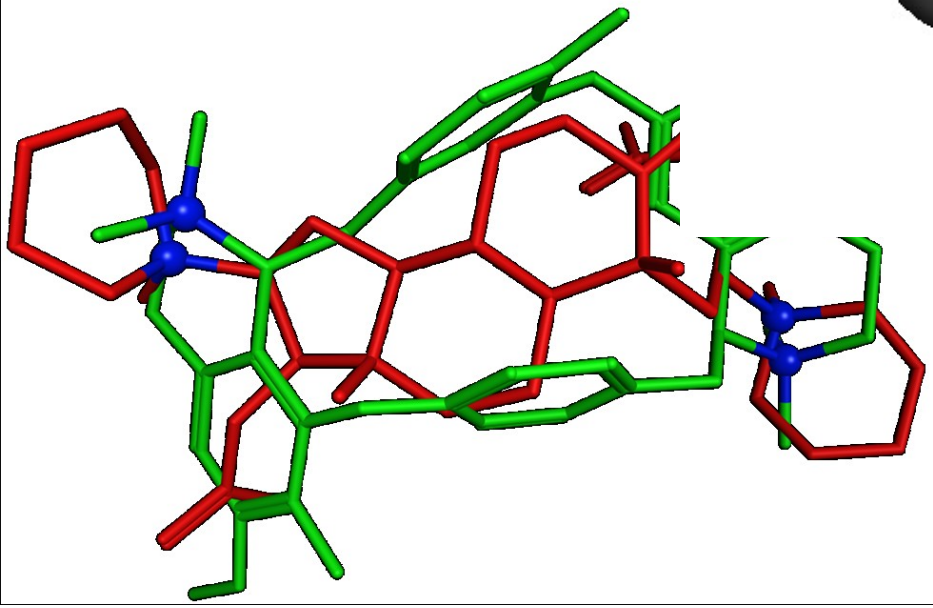
trans ***cis***

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tub



Time to onset: 240 (seconds)
Duration: 120 - 180 (minutes)



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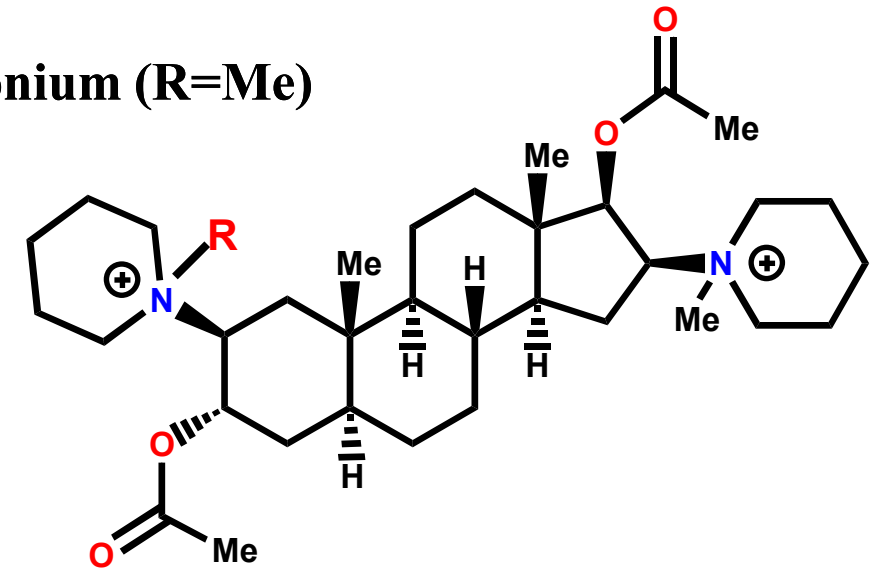
13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)

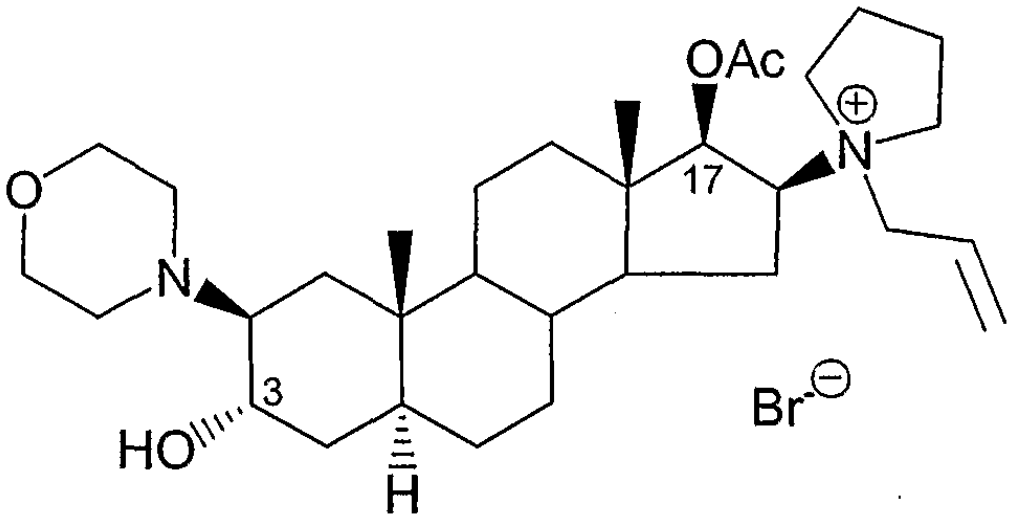
Pancuronium (R=Me)

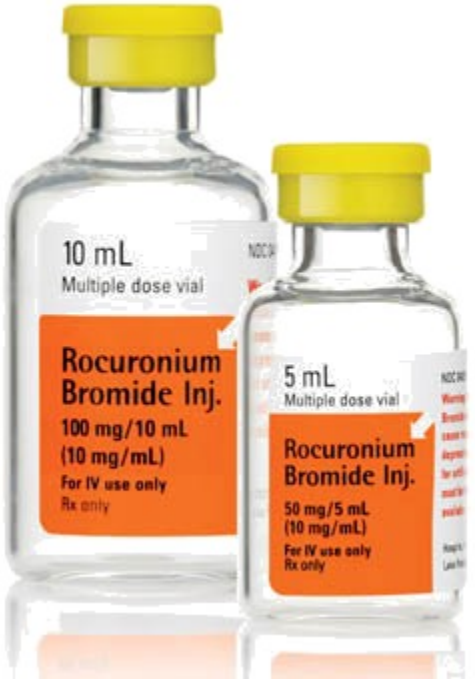


It is also used as one component of a **lethal injection** (typically a **barbiturate, pancuronium, and potassium solution)** in administration of the **death penalty** in some parts of the United States.

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)





Rocuronium bromide

Time to onset: 75 (seconds)

Duration: 45 - 70 (minutes)

It was introduced in 1994, and is marketed under the trade name of Zemuron in the United States and Esmeron in most other countries. t was designed to be a weaker antagonist at the neuromuscular junction than pancuronium; hence its monoquaternary structure and its having an allyl group and a pyrrolidine group attached to the D ring quaternary nitrogen atom. Rocuronium has a rapid onset and intermediate duration of action.

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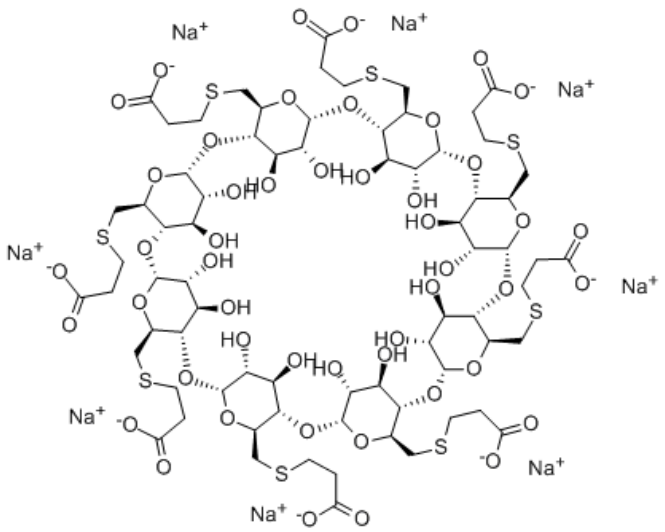
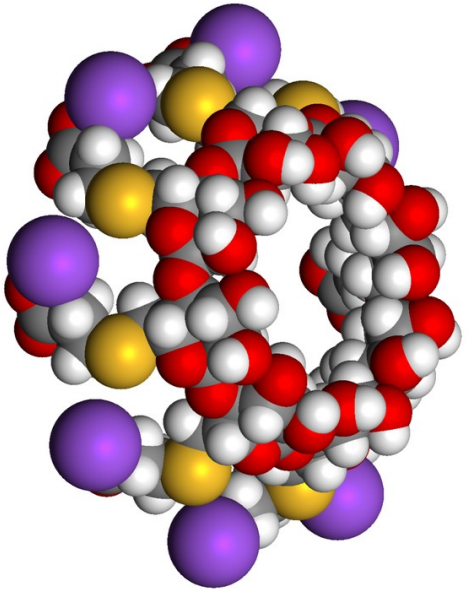
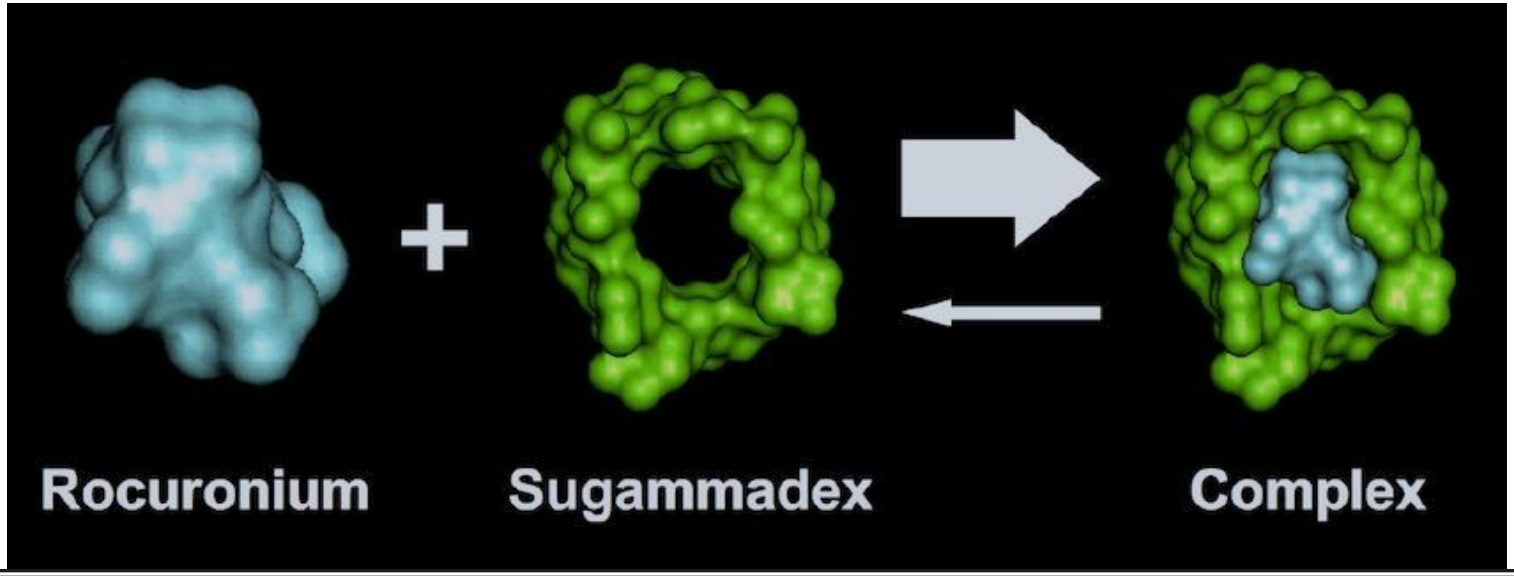
Suggamadex… a modified γ-cyclodextrin:







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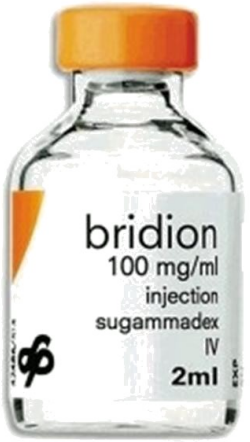
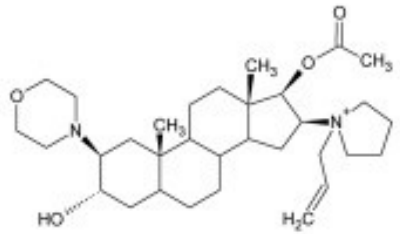
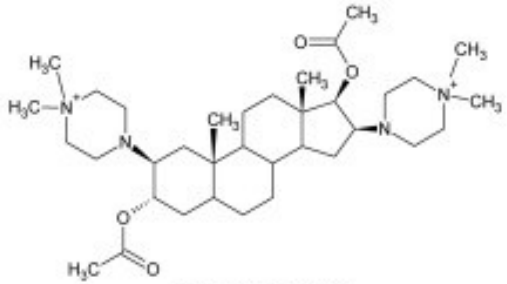
Suggamadex… a modified γ-cyclodextrin:



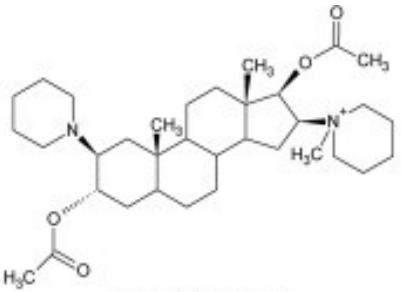
Sugammadex is used to reverse neuromuscular blockade after administration of the aminosterioid non-depolarizing neuromuscular-blocking agents such as vecuronium, pancuronium or rocuronium.



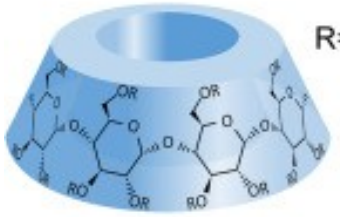
Rocuronium



Pipecuronium

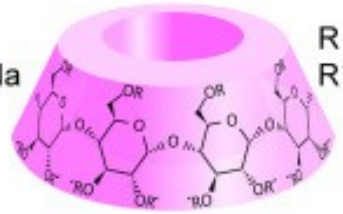


Vecuronium



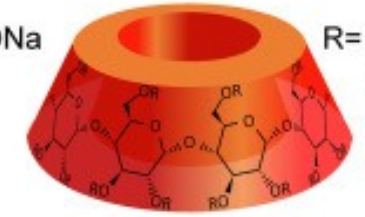
R= -H
-CH_2COONa
(DS~3.5)

Carboxymethyl-γCD



R = -CH_2COONa
R´= -CH_3

DMCMGCD



R= -H
-$(CH_2)_4SO_3Na$
(DS~6.3)

Sulfobutylether-γCD

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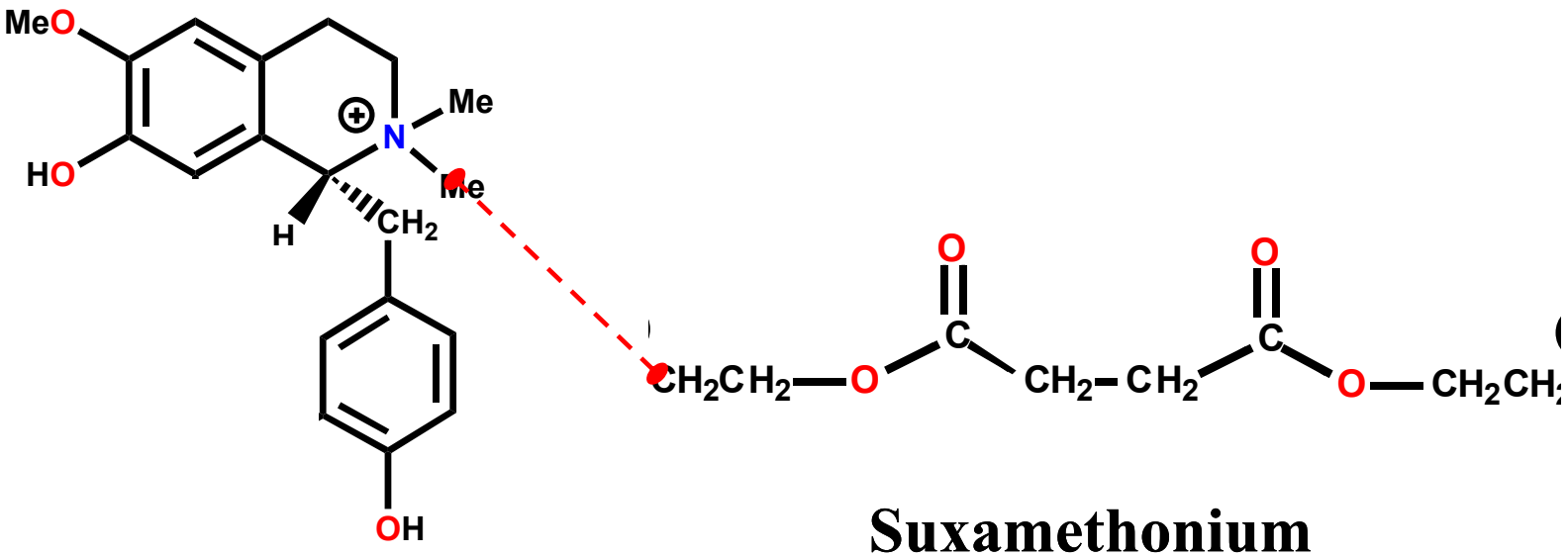
Another great idea... by a Ph.D. student in Pharmacy and Medicinal Chemistry

Atracurium (originally classified as 33A74) was the culmination of a rational approach to drug design to produce the first non-depolarizing, non-steroidal skeletal muscle relaxant that undergoes **chemodegradation *in vivo***.

Dewar GH (1976). "Potential short-acting neuromuscular blocking agents". Ph.D. Thesis - the Department of Pharmacy, University of Strathclyde, Scotland.

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)



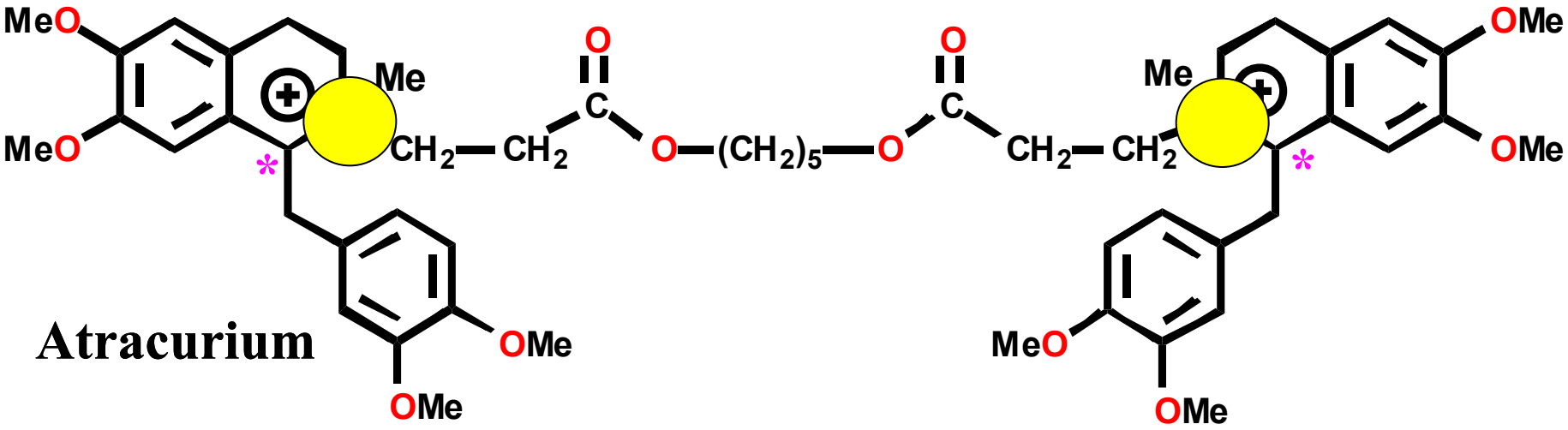
Suxamethonium

***d*-Tubocurarine**

tetrahydropapaverine …

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)

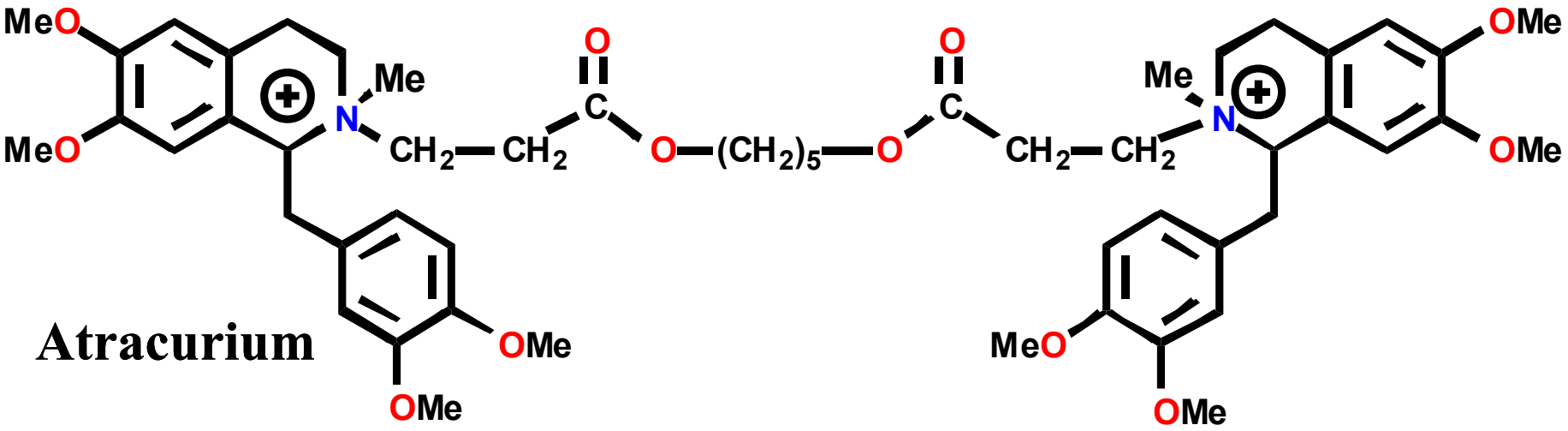


Atracurium

- **Stereochemical problem: also ammonium salts become chirals!**
- **Atracurium has been utilized as a mix of all stereoisomers!**

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)



Atracurium

- Design based on tubocurarine and suxamethonium
- *Lacks cardiac side effects*
- Rapidly broken down in blood both chemically and metabolically
- Avoids patient variation in metabolic enzymes
- Administered as an i.v. drip
- Self destruct system limits lifetime

Time to onset: 90 or more (seconds)
Duration: 30 or less (minutes)

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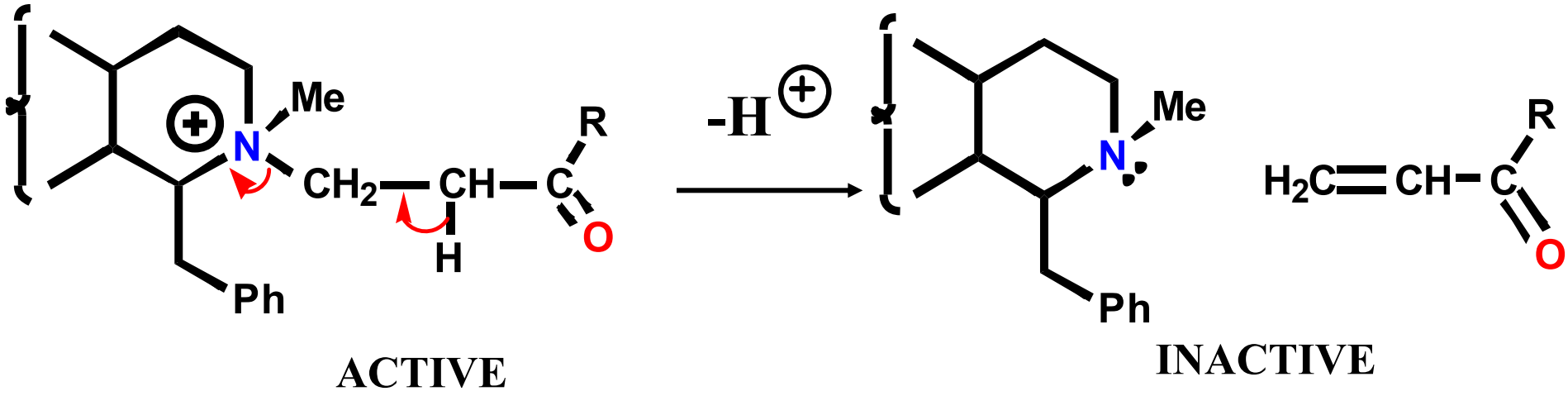
13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Chemodegradation *in vivo*... amazing!!!

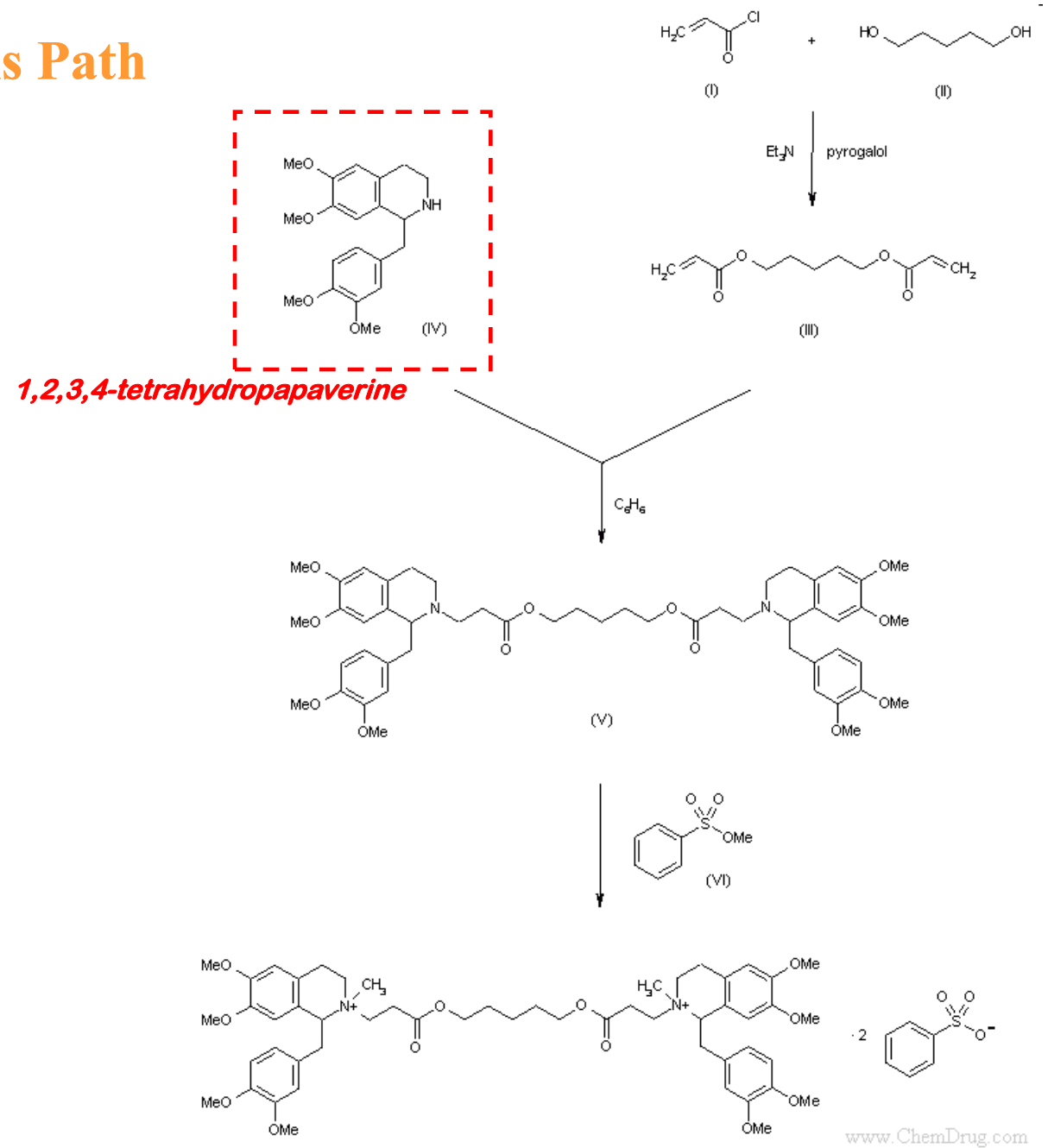


ACTIVE

INACTIVE

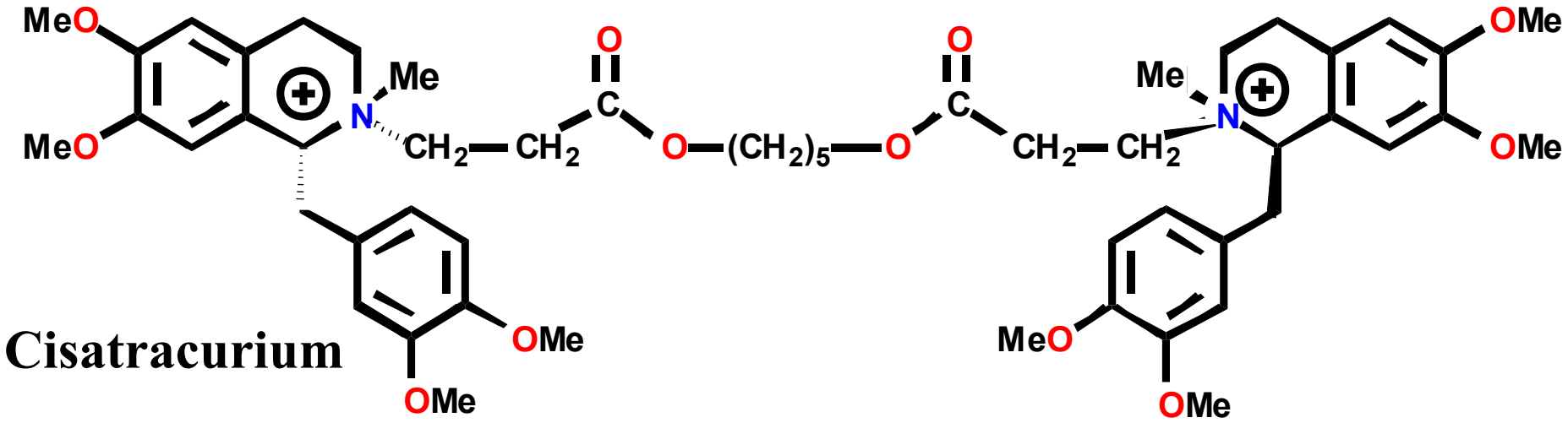
Hofmann elimination at blood pH (7.4): **Hofmann elimination provided precisely this basis: it is a chemical process in which a suitably activated quaternary ammonium compound can be degraded by the mildly alkaline conditions present at physiological pH and temperature. In effect, Hofmann elimination is a retro-Michael addition chemical process.**

Synthesis Path



13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)



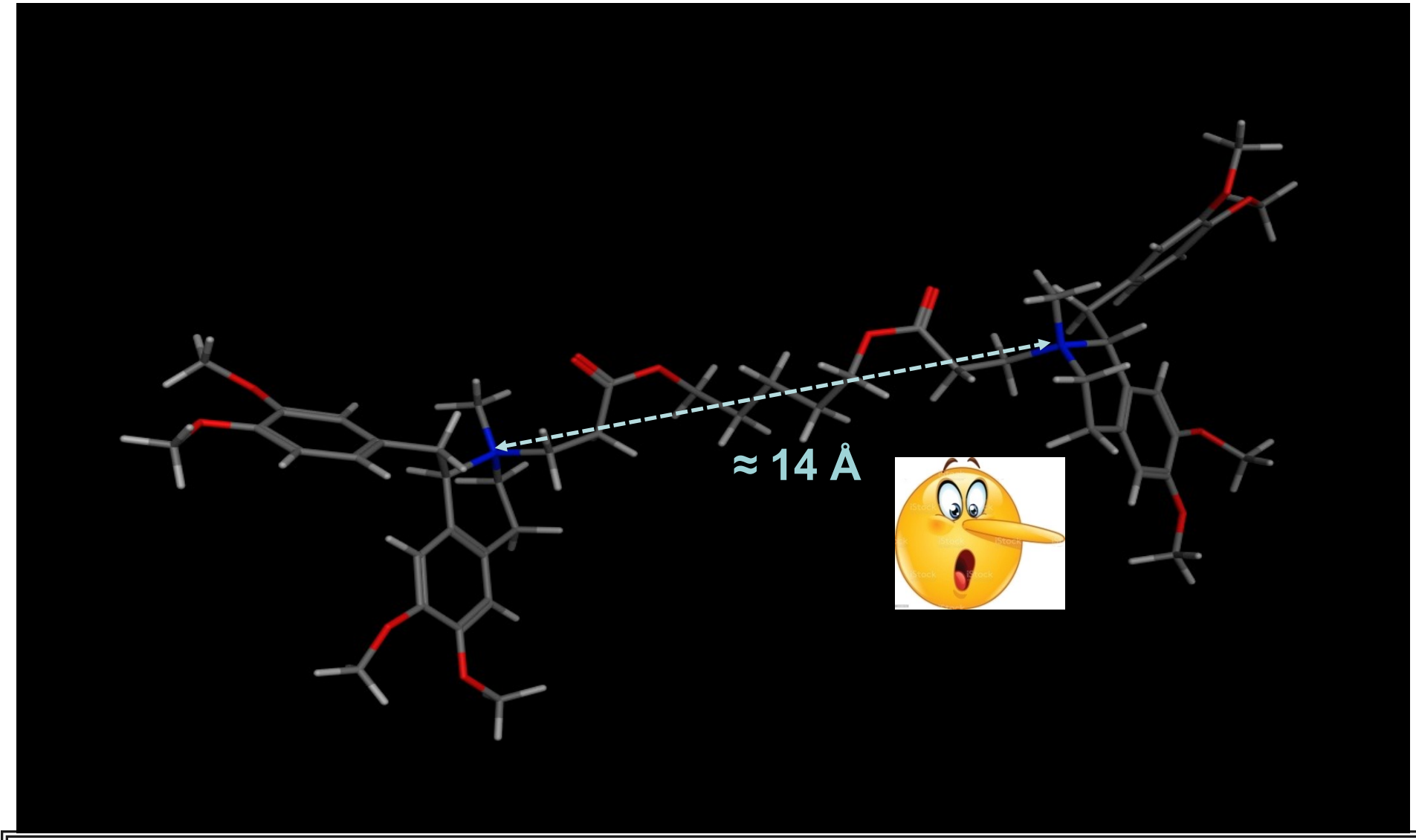
Cisatracurium

5-[3-[(1R,2R)-1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-1H-isoquinolin-2-ium-2-yl]propanoyloxy]pentyl 3-[(1R,2R)-1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-1H-isoquinolin-2-ium-2-yl]propanoate

Time to onset: 90 (seconds)
Duration: 60 - 80 (minutes)

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine (pachycurares)



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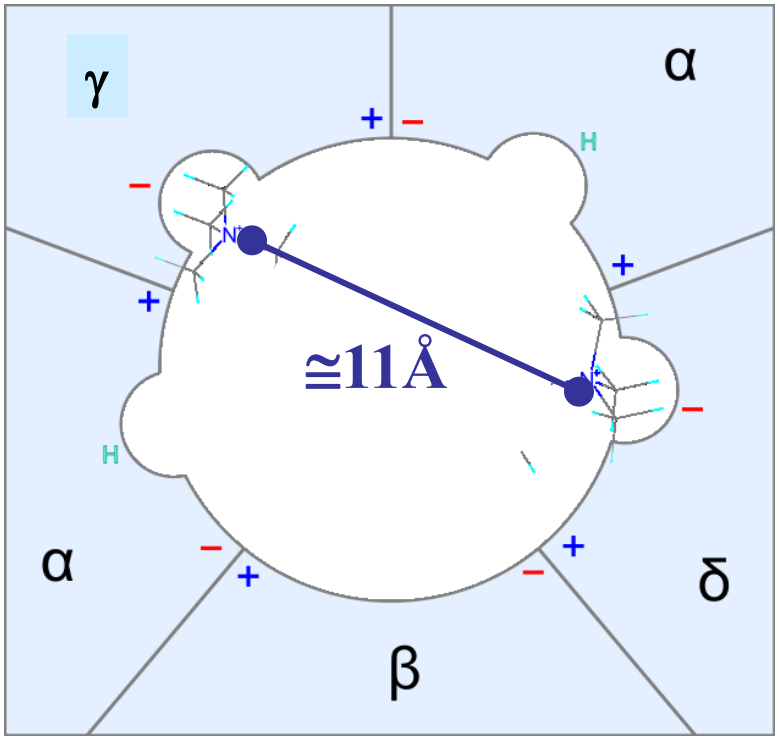
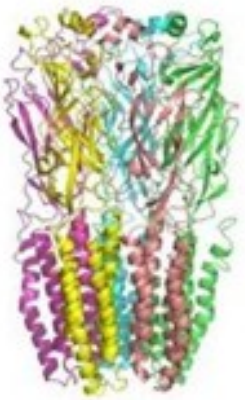
13. Cholinergic Antagonists (Nicotinic receptor)

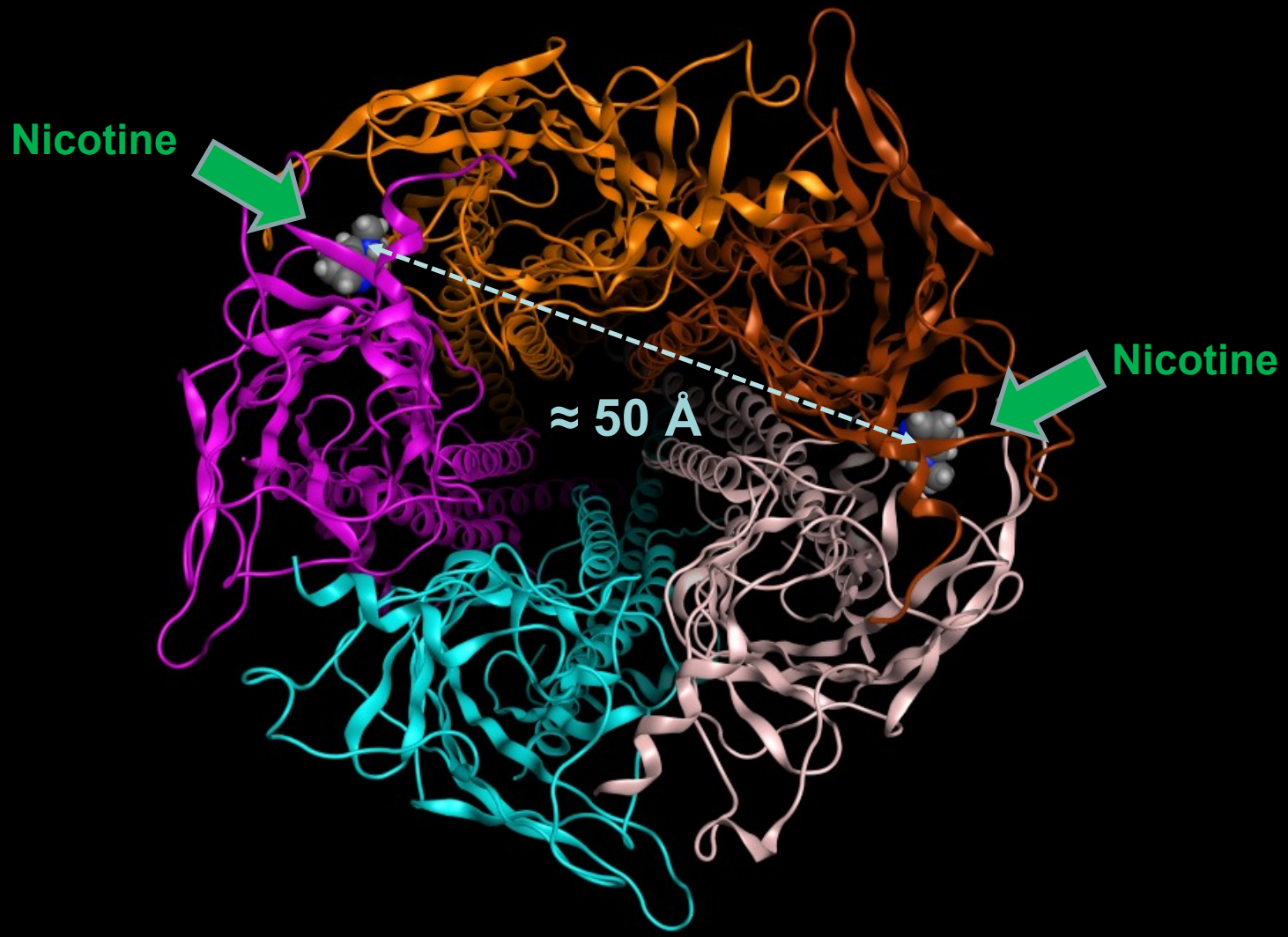
Pharmacophore

- **Changing of the Ach:NicRec stoichiometry 2:1 to 1:1**
- ***Is it really true?***





… judge by for yourself:



https://www.rcsb.org/structure/6PV7

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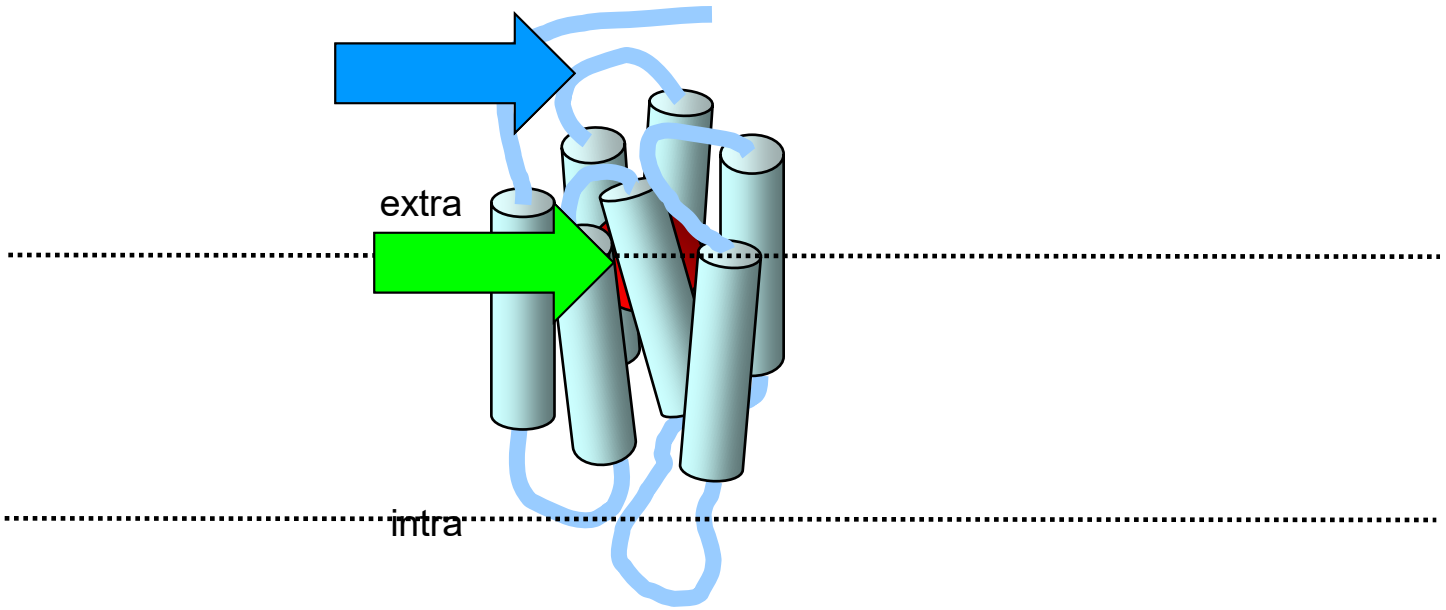
Adverse effects:

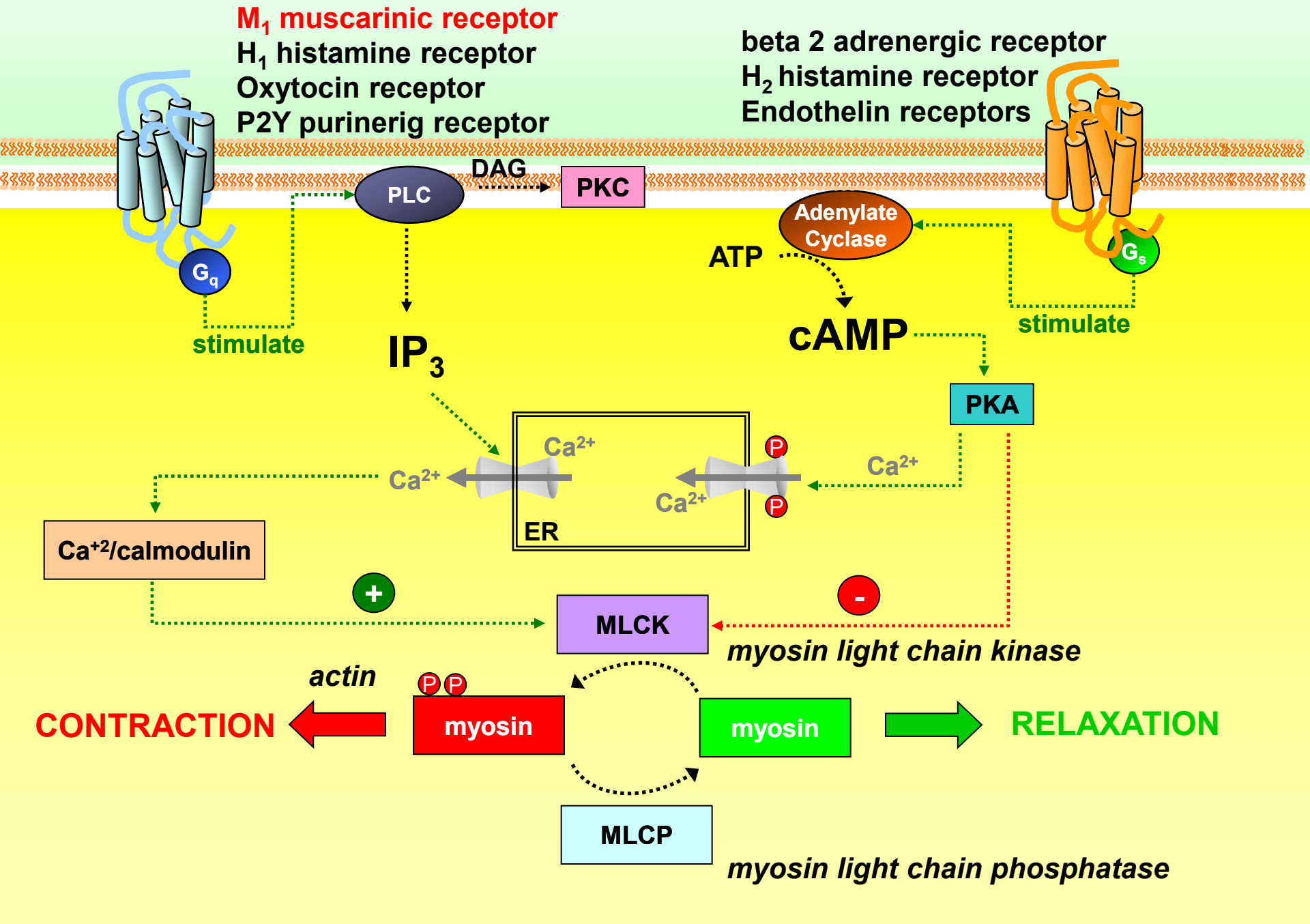
In addition, these drugs may exhibit ***cardiovascular effects***, since they are not fully selective for the nicotinic receptor and hence may have effects on muscarinic receptors, ***as allosteric modulators.***

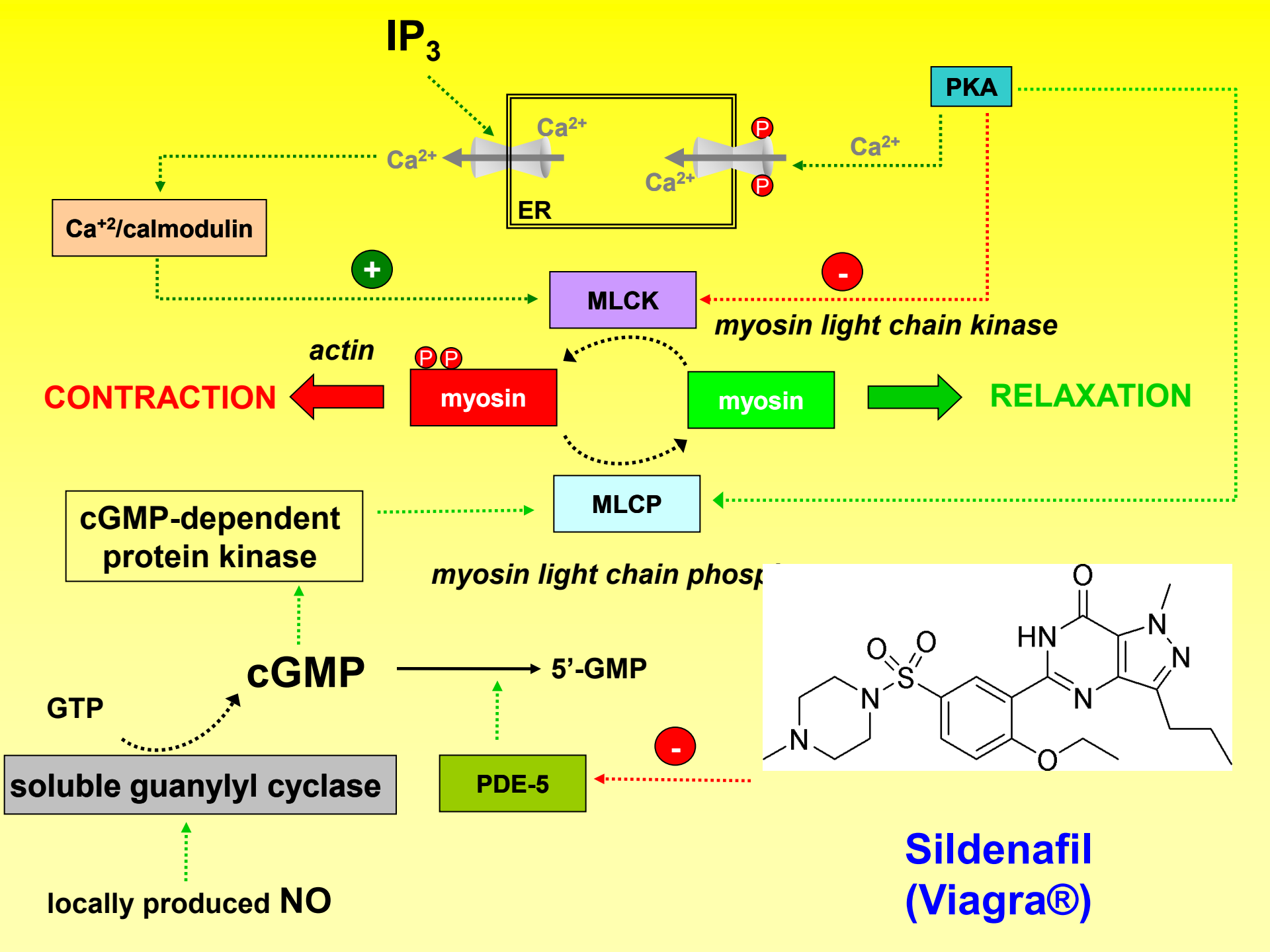


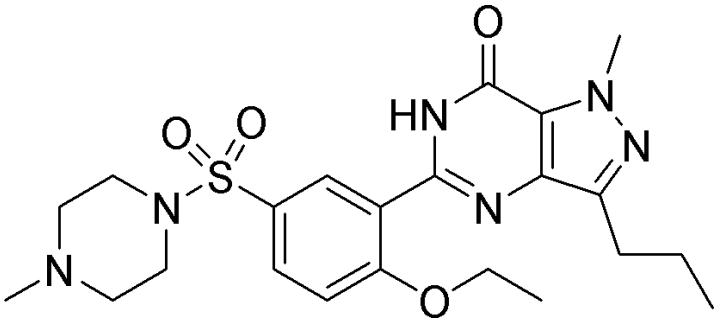
Family A

ORTHOSTERIC SITE **ALLOSTERIC SITE**

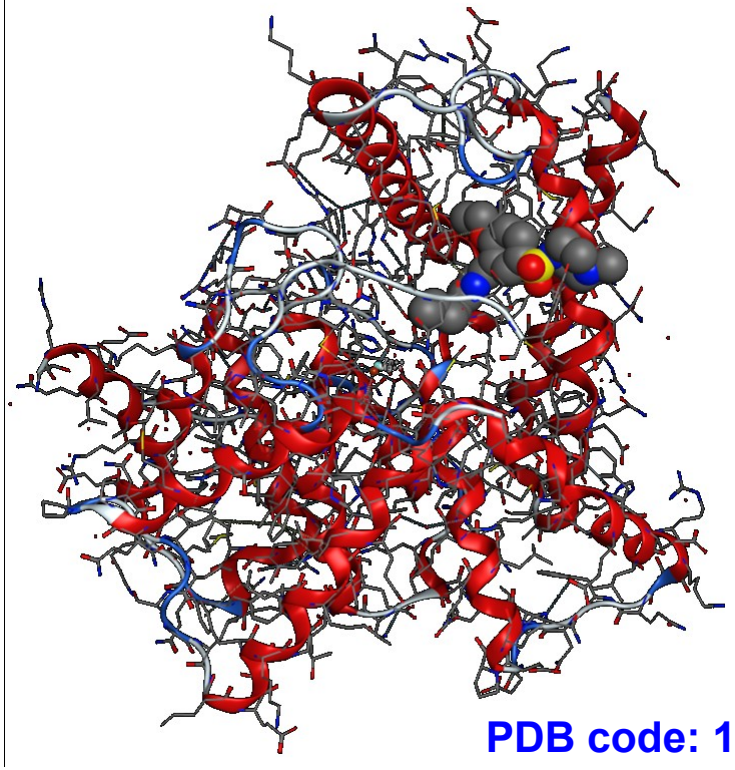
Smooth muscle signal trasduction:




IP3
PKA
Ca2+
Ca2+
Ca2+
Ca2+
ER
P
P
Ca+2/calmodulin
+
-
MLCK
myosin light chain kinase
actin
P P
CONTRACTION
myosin
myosin
RELAXATION
MLCP
cGMP-dependent protein kinase
myosin light chain phosp
cGMP
5'-GMP
GTP
soluble guanylyl cyclase
PDE-5
-
locally produced NO
O
HN
N
N
O S O
N
N
N
O
Sildenafil (Viagra®)



Sildenafil (Viagra®)



PDB code: 1UDT

log P = 1.9

MW = 474.5

PSA ≅ 110Å²

O + N = 10

pKa = 8.7

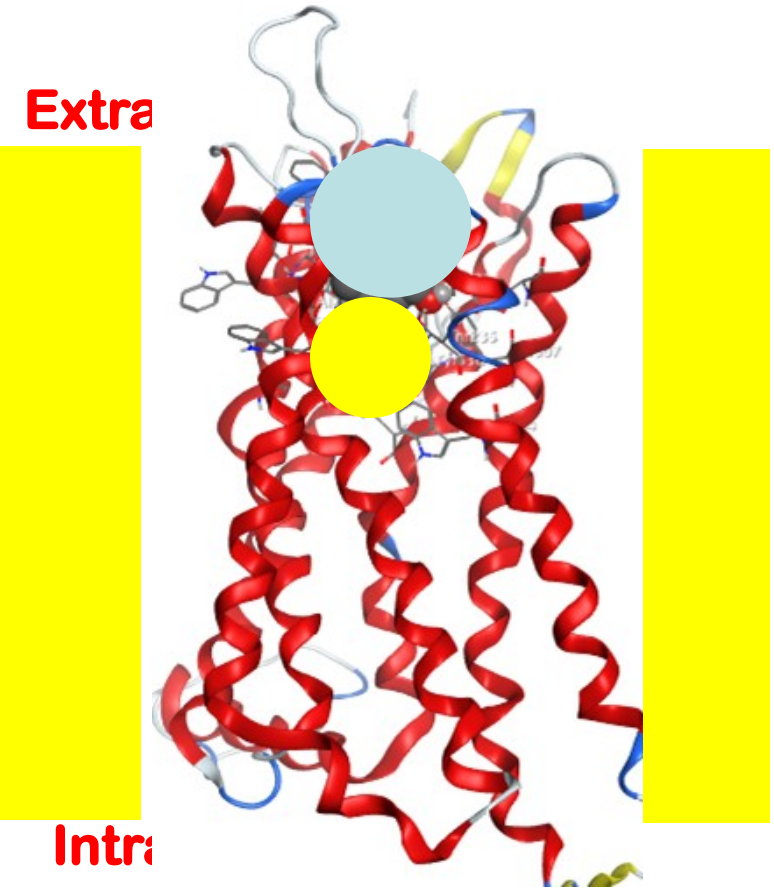
The mechanism of action of Sildenafil involves the protection of cyclic guanosine monophosphate (cGMP) from degradation by cGMP-specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, leading to smooth muscle relaxation (vasodilatation) of the intimal cushions of the *helicine arteries*. This smooth muscle relaxation leads to vasodilation and increased inflow of blood into the spongy tissue of the penis, causing an erection.

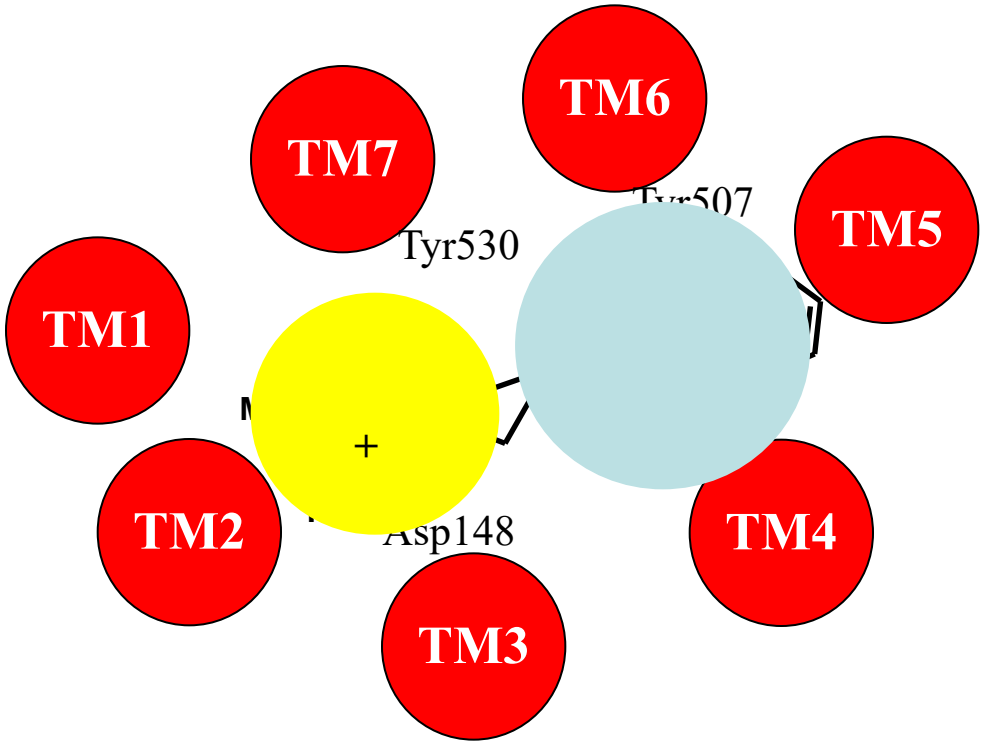
Other drugs that operate by the same mechanism include Tadalafil (Cialis) and Vardenafil (Levitra).

Sildenafil is metabolized by liver enzymes and excreted by both the liver and kidneys.

12. Cholinergic Antagonists (Muscarinic receptor)

12.8 Muscarinic binding site





Muscarinic M3