تفريغ ميديسينال

محاضرة: cholinergic antagonist

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لجان الدفعات

Soul Academy

Patrick
An Introduction to Medicinal Chemistry 3/e

Chapter 22

CHOLINERGICS, ANTICHOLINERGICS & ANTICHOLINESTERASES

Part 2: Cholinergics antagnoists

updated by:Dr Dana Atoum

* لما حكينا عن الـ muscarinic receptor حكينا انهم موجودين بكل

Cardiac muscel
Smooth muscel
Gland

* لما نحكي muscarinic antagonist يعني انهم يتنافسوا (Compete) مع الـ Ach فلما يرتبطوا بالـ muscarinic receptor ح يعملوا blocking

للـ receptor يوقف ح يصير الـ receptor inactive ← ووضعه لا يمنع ارتباط الـ Ach بالـ receptor

لما الـ antagonist يعمل blocking لهذا الـ cholinergic receptor ح يعطي opposit clincal effect for Ach

* ما بأثر على الـ muscarinic antagonist الـ Nicotinic

smooth muscle → relaxation

Gland → decreas of secretion

12. Cholinergic Antagonists (Muscarinic receptor)

Drugs which bind to cholinergic receptor but do not activate it

Prevent acetylcholine from binding

Opposite clinical effect to agonists - lower activity of acetylcholine

- Muscarinic antagonists **do not affect nicotinic receptors** (like those in skeletal muscle). Instead, they target:
- **Glands** (e.g., salivary, gastric)
- **Central Nervous System (CNS)**
- **Smooth muscle** in:Gastrointestinal tract (GIT), Urinary tract, Eyes (iris muscles)

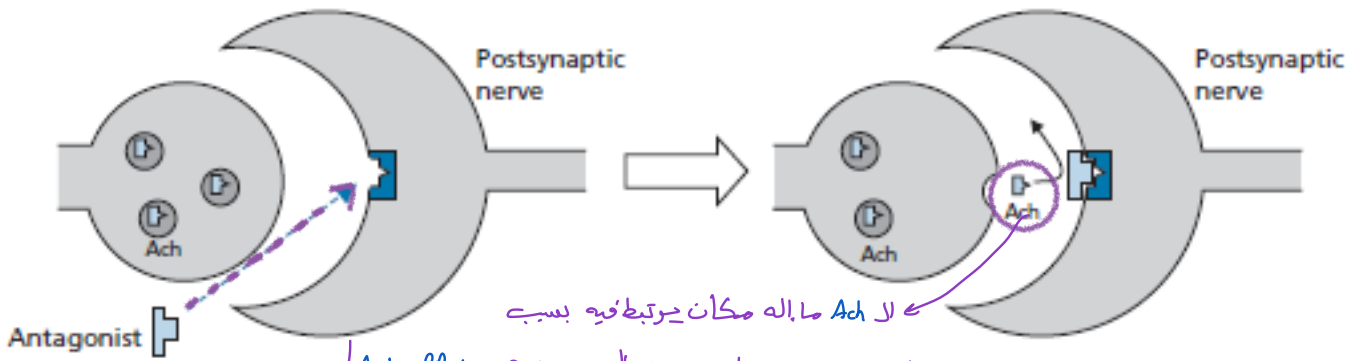


FIGURE 22.24 Action of an antagonist to block a receptor.

12. Cholinergic Antagonists (Muscarinic receptor)

Clinical Effects

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

Uses

1- Shutting down digestion for surgery
2- Ophthalmic examinations
3- Relief of peptic ulcers → GI secretion لانه بقلل ال
4- Treatment of Parkinson's Disease
5- Anticholinesterase poisoning
6 Motion sickness

12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine

Atropine: Found in *Atropa belladonna* (deadly nightshade). Historically used by Italian women to dilate pupils—hence the name belladonna ("beautiful lady").

Atropine exists as a racemate (equal mix of enantiomers), but:

الـ atropin تعتبر مادة مهمة

Naturally found as (S)-hyoscyamine, a single enantiomer.

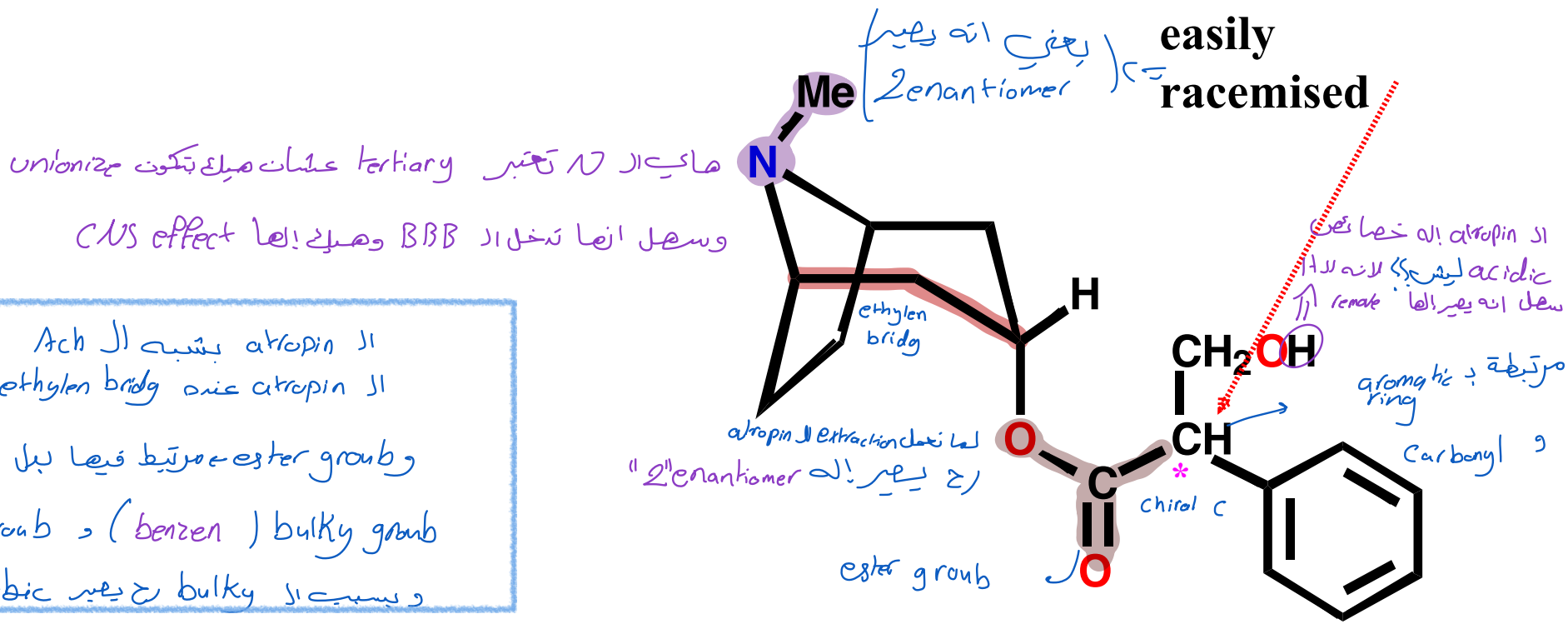
Upon extraction into solution, racemization occurs due to:

The asymmetric center being adjacent to a carbonyl group and aromatic ring.

This makes the attached proton acidic and easily removed, allowing for rapid interconversion between enantiomers

Used as a medicine

1. dilation of eye pupils
2. decreases GIT motility
3. antidote for anticholinesterase poisoning
4. CNS side effects - hallucinations



الـ atropin بشبه الـ Ach

N و ethylen bridg عنده atropin الـ

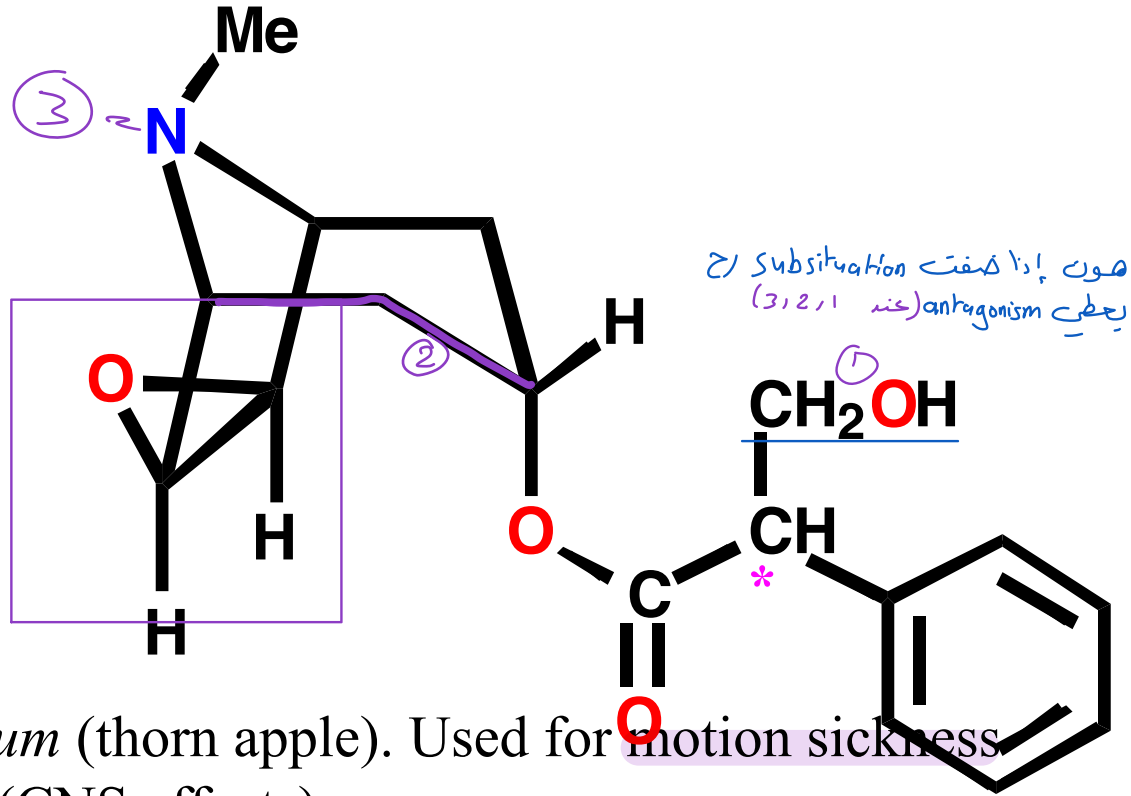
Me بدل الـ ester group مرتبط فيها

other group و (benzen) bulky group

hydrophobic رح يصير bulky و بسبب الـ

12. Cholinergic Antagonists (Muscarinic receptor)

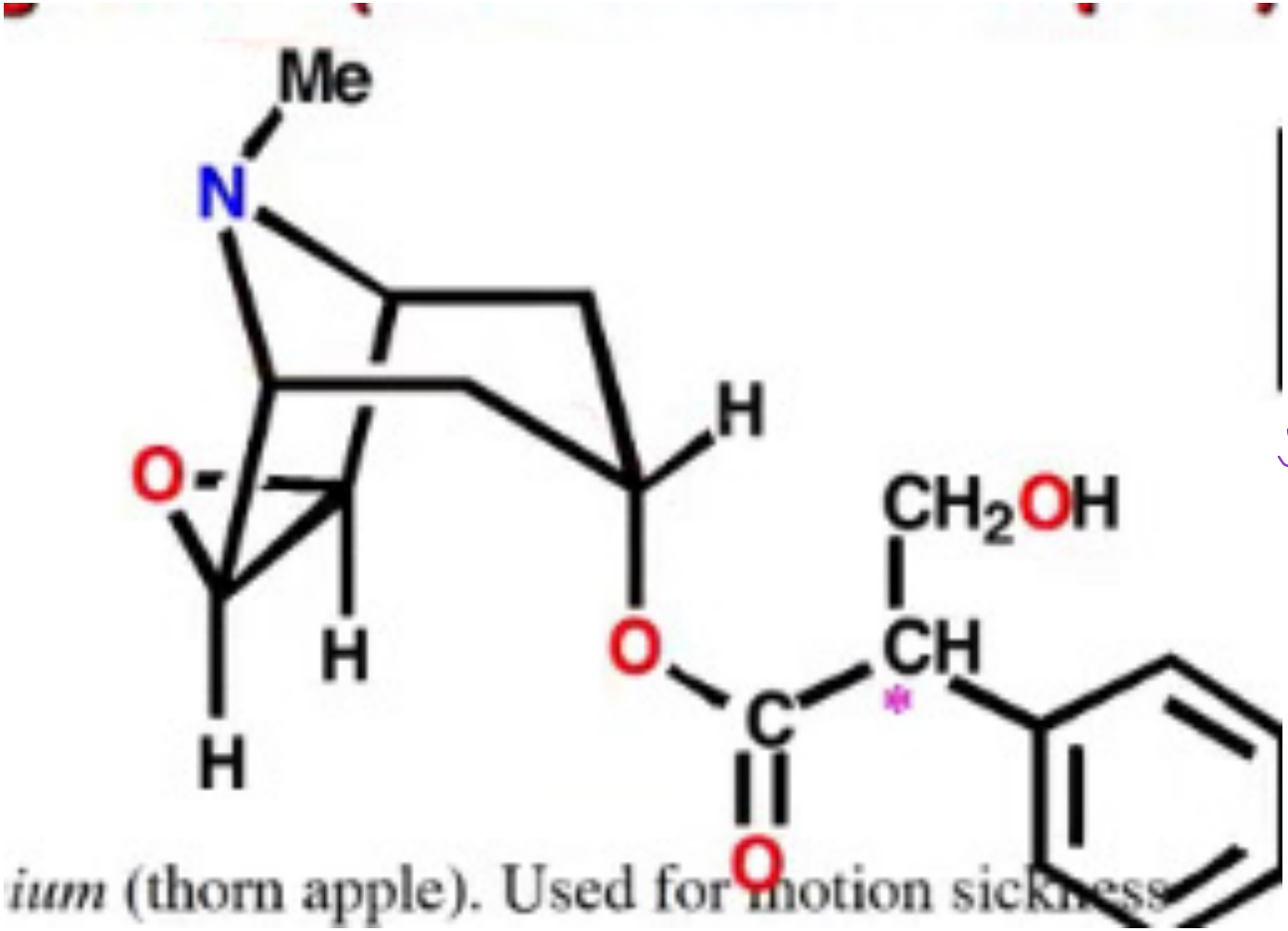
12.2 Hyoscine (scopolamine)



Extracted from *Datura stramonium* (thorn apple). Used for motion sickness and nausea. Used as a truth drug (CNS effects)

Both atropine and hyoscine are tertiary amines, meaning:

- They are lipophilic enough in their free base form to cross the blood-brain barrier.
- Once inside the CNS, they become protonated and bind muscarinic receptors.
- High doses can cause hallucinogenic effects, historically associated with "witches' brews."



ium (thorn apple). Used for motion sickness

antagonist الـ antagonist الـ بموضوع
strongly binding to receptor more بكون
than the acytlchdin •
يسبب الـ hydrophobic group تعمل
binding site الـ مع الـ van-der bond بشكل

agonist اقوى من الـ

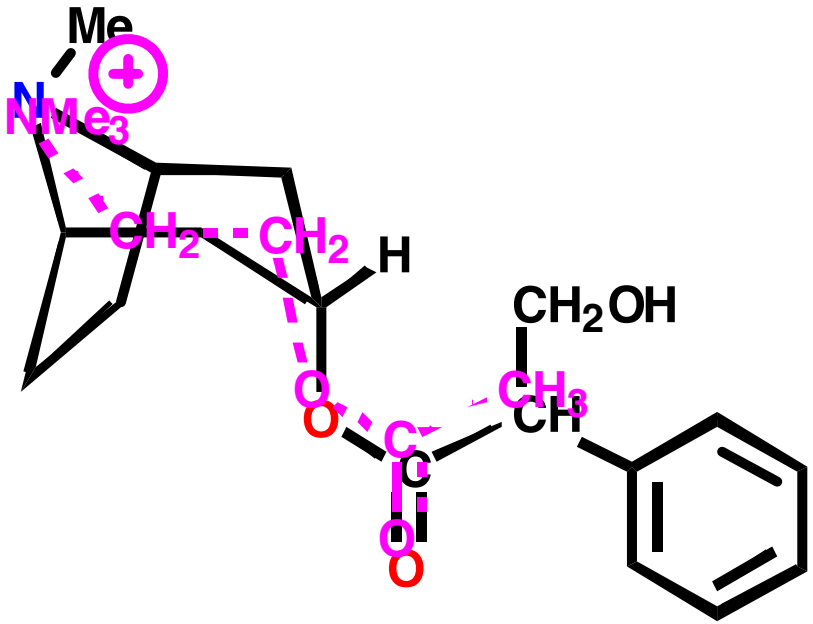
12. Cholinergic Antagonists (Muscarinic receptor)

اللون الزهري هو الـ Ach
اللون الأسود هو الـ atropin

12.3 Comparison of atropine with acetylcholine

مقارنة بين الـ Ach والـ atropin

الأفضل تقارنوا بينهم بالرسمات
بس يكونوا جنب بعض لش
فوق بعض

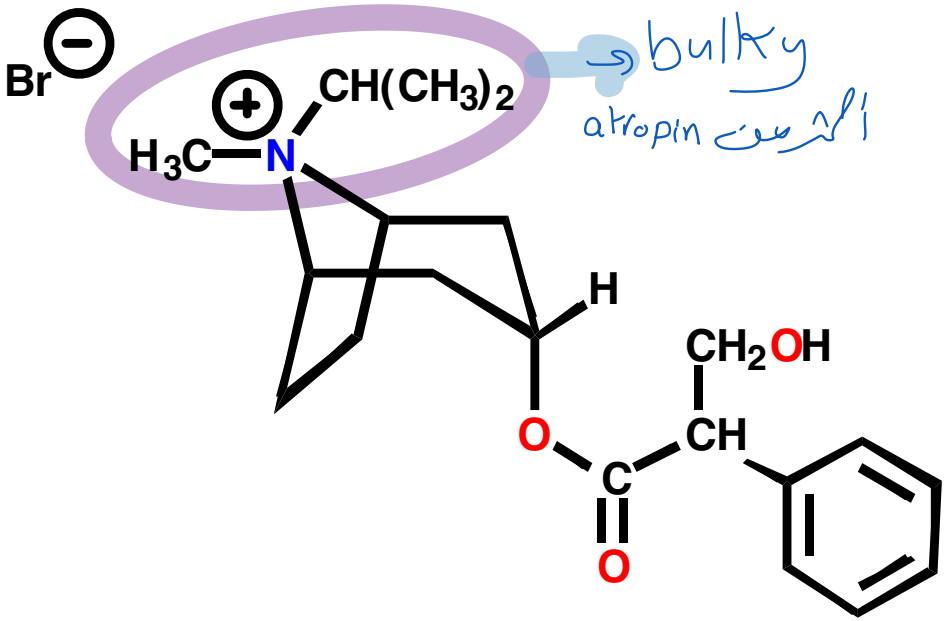


المسافة بين الـ N والـ O
بالـ atropin والـ Ach هي نفسها

1. Relative positions of ester and nitrogen similar in both molecules
2. Nitrogen in atropine is ionised → 4° Amin
3. Amine and ester are important binding groups (ionic + H-bonds) (Asp, Asn)
4. Aromatic ring of atropine is an extra binding group (vdW)
5. Atropine binds with a different induced fit - no activation
6. Atropine binds more strongly than acetylcholine

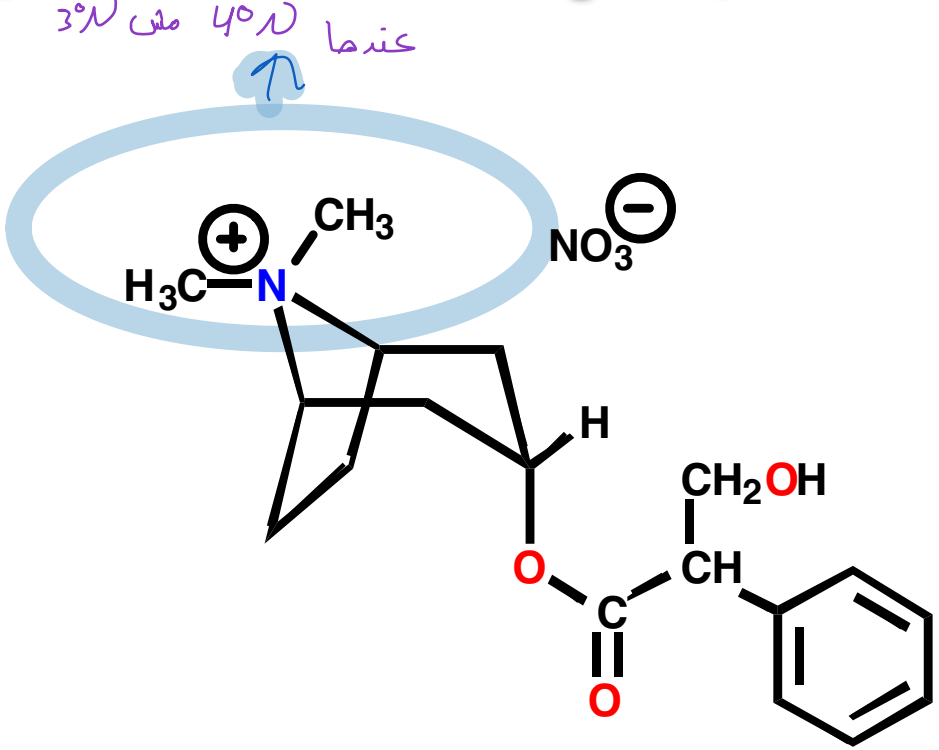
12. Cholinergic Antagonists (Muscarinic receptor)

12.4 Analogues of atropine



bulky

atropin الأصل



عندما N 3° من N 4°

Ipratropium
(bronchodilator for COPD & anti-asthmatic)

or recpiraroy infection

Atropine methonitrate
Used to relieve **intestinal spasms**

- **Analogues are fully ionised**
- **Analogues unable to cross the blood brain barrier**
- **No CNS side effects**

بسبب الـ (+) charg الي على الـ N

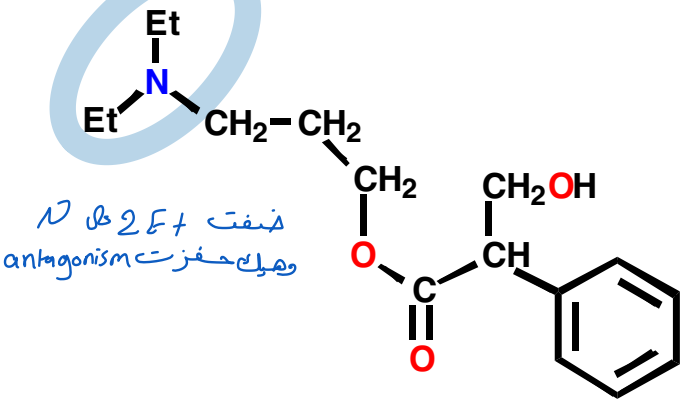
12. Cholinergic Antagonists (Muscarinic receptor)

الاشياء اي محدد عليها
antagonism هي اي رح تزيد

12.5 Simplified Analogues

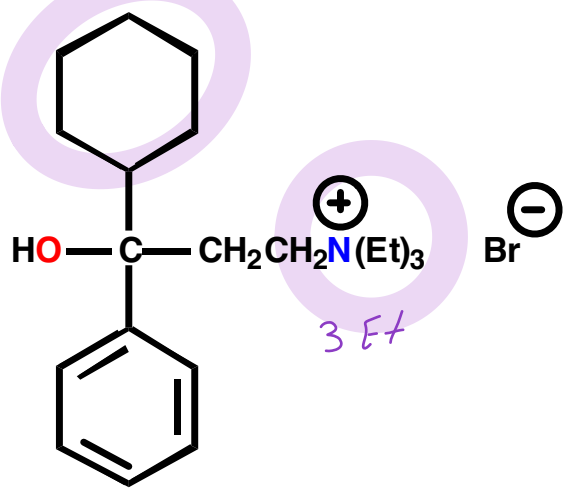
Pharmacophore = basic amine +ester + aromatic ring

The complex ring system is not necessary for antagonist activity
Chain contraction to two carbon atoms can be carried out without loss of activity



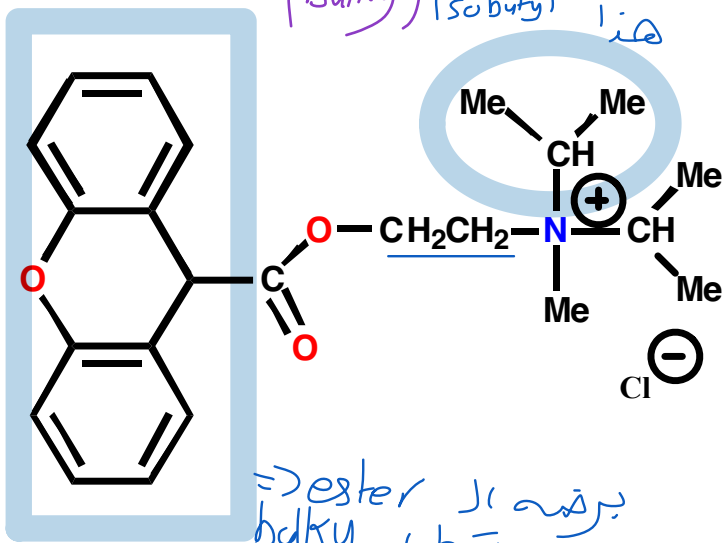
خففت 2 Et
antagonism وهيك حفزت

Amprotropine



3 Et

Tridihexethyl bromide



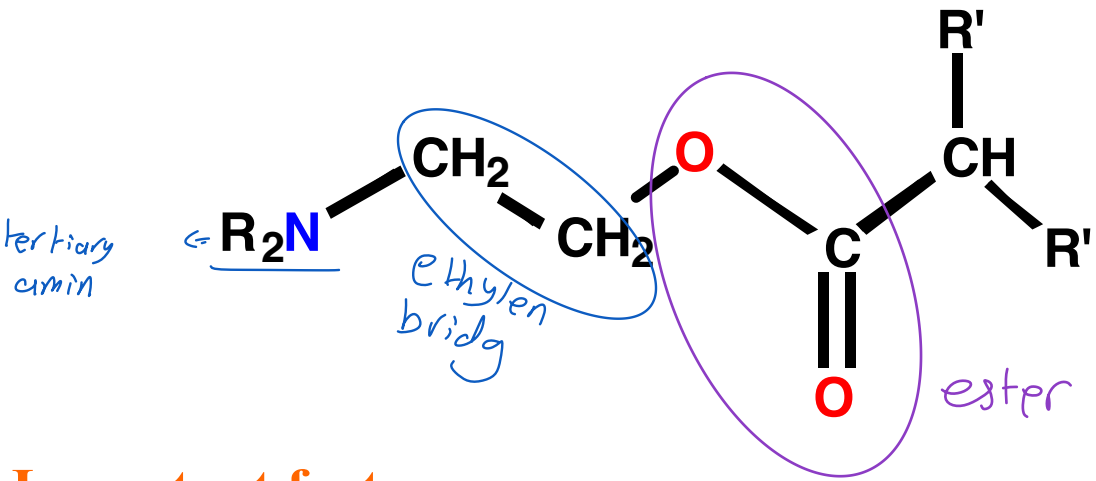
(bulky) isobutyl هذا

ester برتبط ال
bulky مرتبط
group

Propantheline chloride

12. Cholinergic Antagonists (Muscarinic receptor)

12.6 SAR for Antagonists



R' = Aromatic or Heteroaromatic

Important features

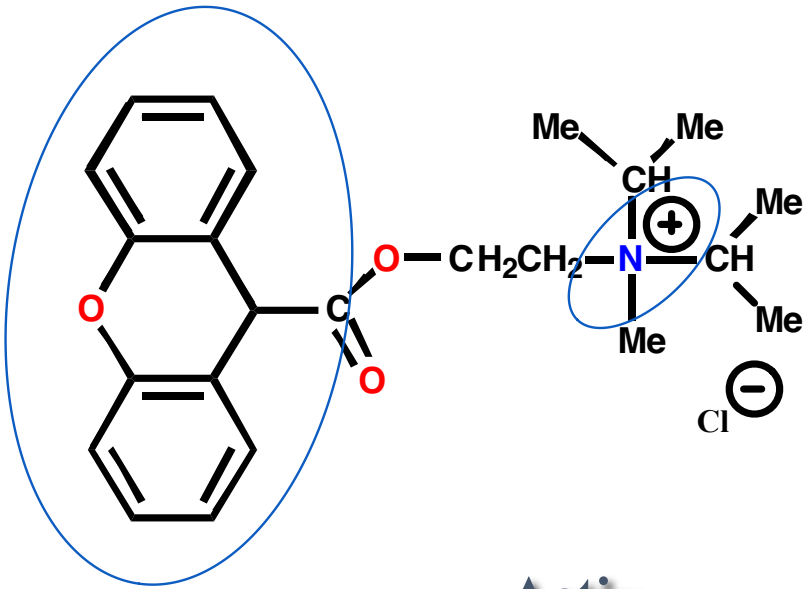
- **Tertiary amine (ionise at physiological pH) or a quaternary nitrogen**
- **Ester**
- ***N*-Alkyl groups (R) can be larger than methyl (unlike agonists)**
- **Large branched acyl group**
- **R' = aromatic or heteroaromatic ring**
- **Branching of aromatic/heteroaromatic rings is important**

* ال alkyl groub كل ما كانت bulky كل ما كانت fit مع ال receptor أكثر يعني blocked for muscarinic

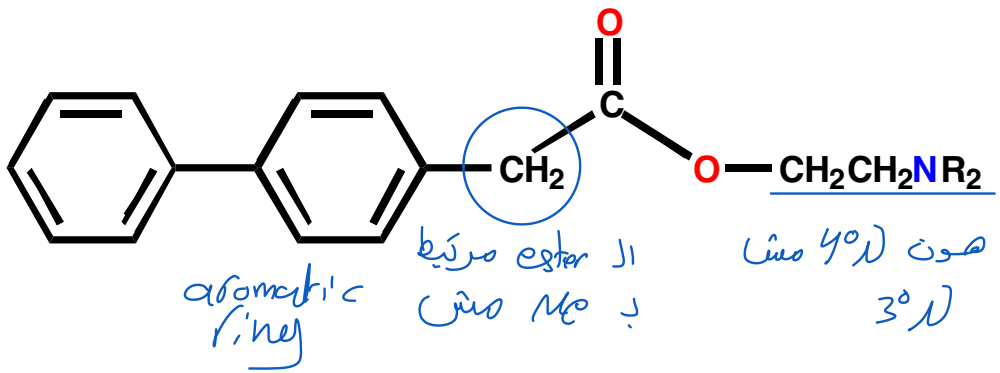
* ال ester لازم يكون مربط aromatic ring عشان يعطي antagonism effect لانها رح تعطل vdw وهاد رح يكون اقوى binding وهيك ال receptor

12. Cholinergic Antagonists (Muscarinic receptor)

12.6 SAR for Antagonists



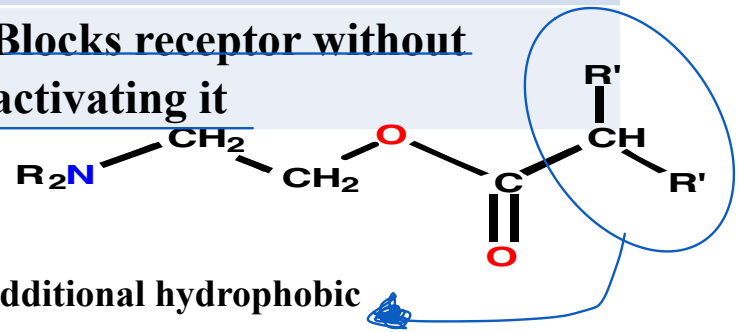
Activ
e



Inactive

SAR Comparison: Antagonists vs. Agonists

Feature	Agonists (e.g., ACh)	Antagonists (e.g., Atropine analogues)
Nitrogen	Quaternary only	Tertiary or quaternary (charged when bound)
Acyl group	Small (acetyl)	Large, branched, hydrophobic 2–3 carbon atoms between ester and nitrogen still work
Ring system	Not present R' = H	R' = aromatic or heteroaromatic Branching of Ar rings important
Function	Activates receptor	Blocks receptor without activating it



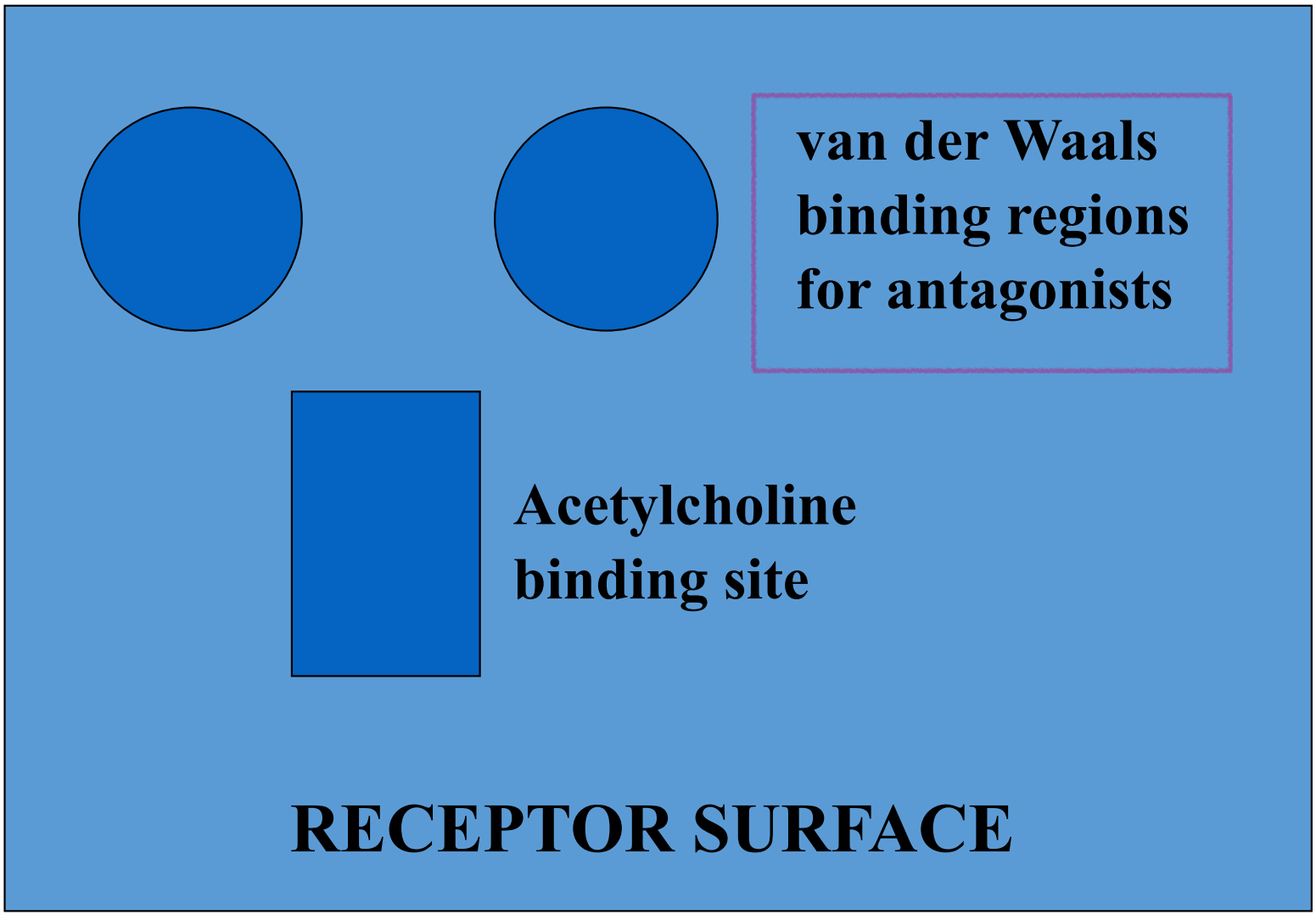
Antagonists like atropine can **bind more strongly** than acetylcholine due to **additional hydrophobic interactions**.

This causes a **different induced fit** → the receptor **fails to activate** and instead remains blocked.

The **bulk and branching** of the acyl group are crucial → this supports a **T- or Y-shaped binding site model**, suggesting extra hydrophobic pockets near the ACh site.

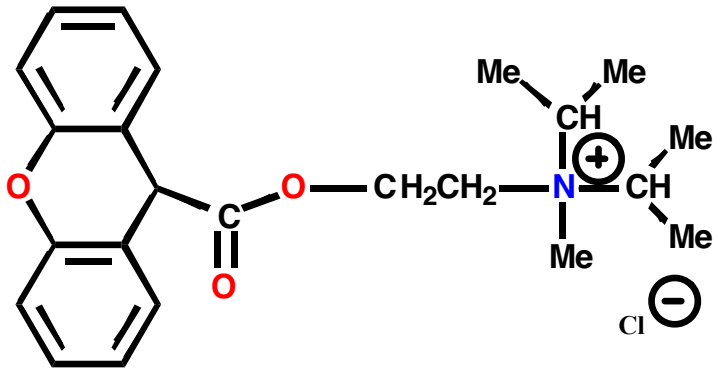
12. Cholinergic Antagonists (Muscarinic receptor)

12.7 Binding Site for Antagonists

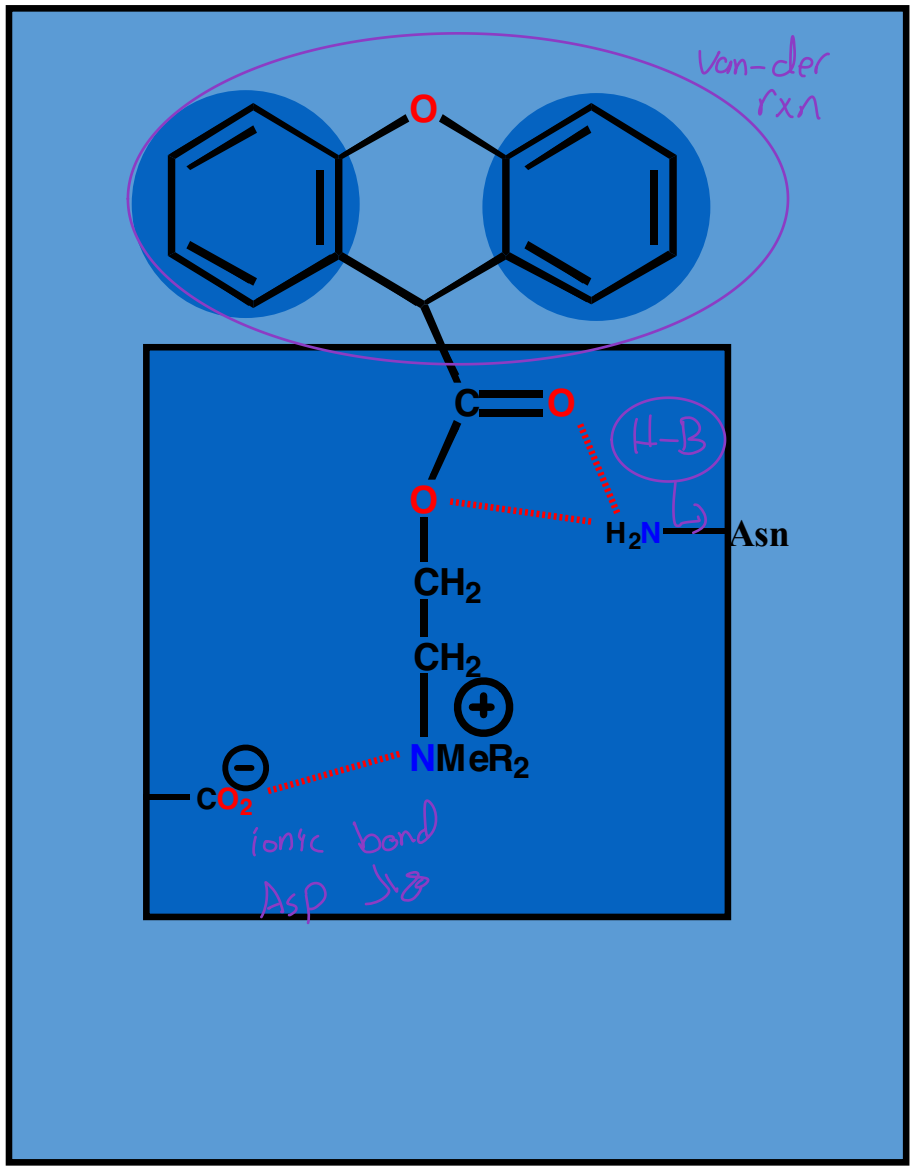


12. Cholinergic Antagonists (Muscarinic receptor)

12.7 Binding Site for Antagonists



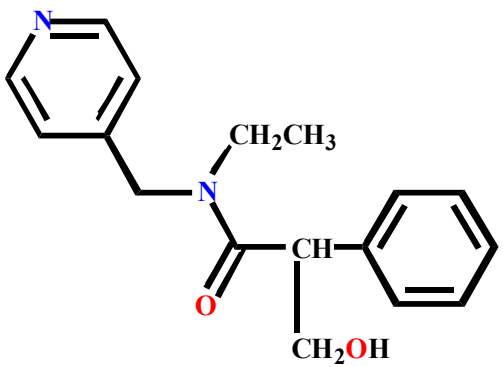
Propantheline chloride



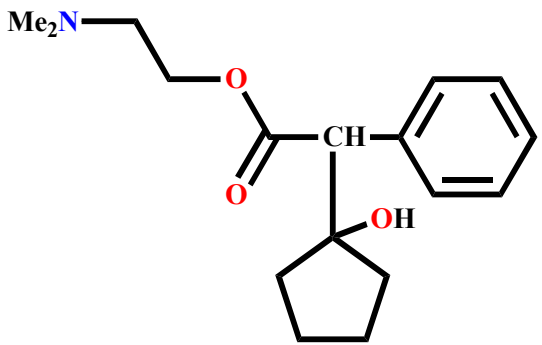
12. Cholinergic Antagonists (Muscarinic receptor)

هدون ال structur مش مطلوب

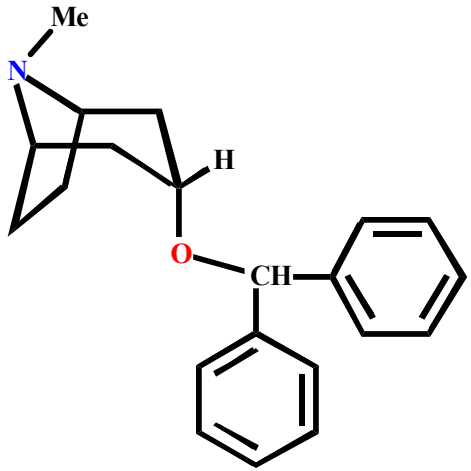
12.5 Simplified Analogues



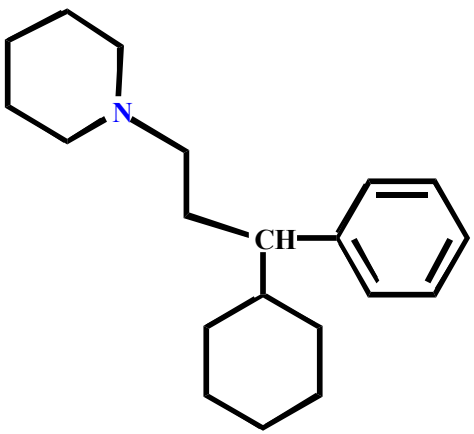
Tropicamide
(opthalmics)



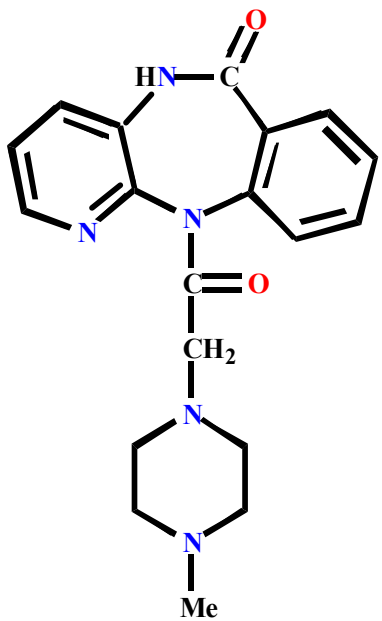
Cyclopentolate
(opthalmics)



Benztropine
(Parkinsons disease)



Benzhexol
(Parkinsons disease)



Pirenzepine
(anti-ulcer)

13. Cholinergic Antagonists (Nicotinic receptor)

13.1 Curare

كانوا يستخدموه الصيادين على السهم ويرموه على الحيوان درج يصيبه Paralysis ويقدرو يمسكوه

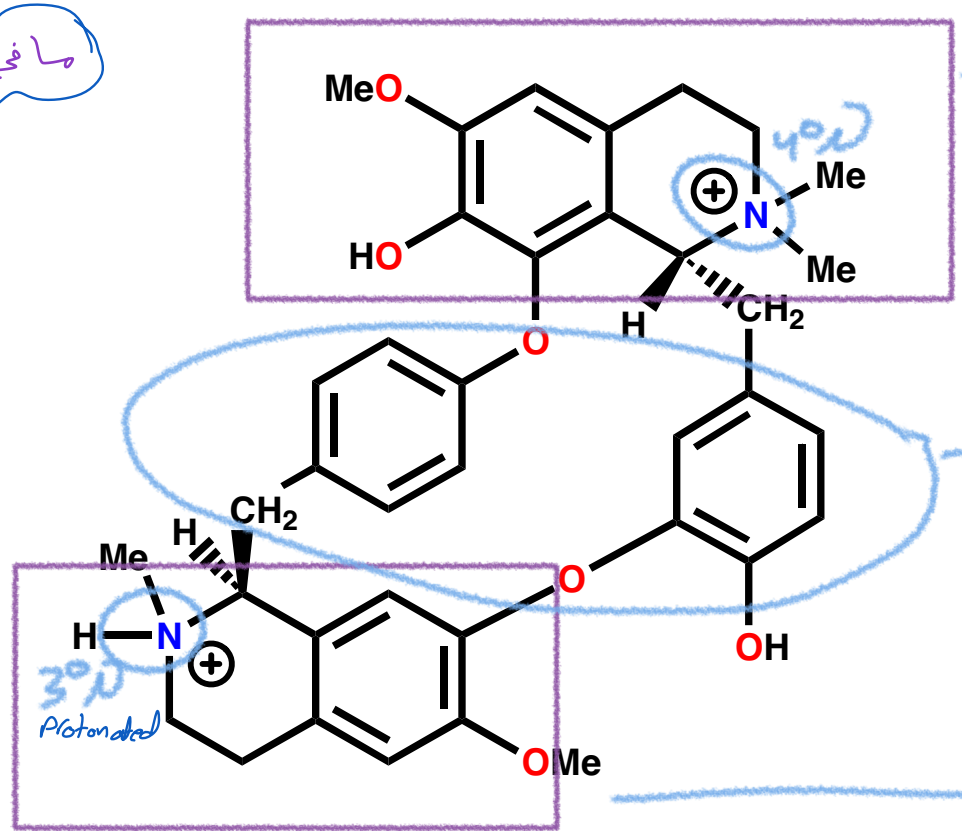
Extract from curare plant

Used for poison arrows

Causes paralysis (blocks acetylcholine signals to muscles)

Active principle = tubocurarine

ester مافي



Tubocurarine

عبارة عن حلقه benzen مع حلقه فيها N

2 benzyl بيتهم

حلقه benzen وحلقه فيها N

13. Cholinergic Antagonists (Nicotinic receptor)

المسافه بينهم fit عشان تدخل ال Nicotinic receptor

Pharmacophore

Two quaternary centres at specific separation (1.15nm)

Different mechanism of action from atropine based antagonists

Different binding interactions

MOA :- blocked for 5 glycoprotin

Clinical uses

Acts as a **neuromuscular blocking agent**, helpful in:

Surgery (muscle relaxation)

Reducing general anesthetic dose

Problem: It also **blocks autonomic ganglia nicotinic receptors**, causing **side effects** (e.g., hypotension).

Now largely replaced by safer, more selective agents (e.g., rocuronium, atracurium).

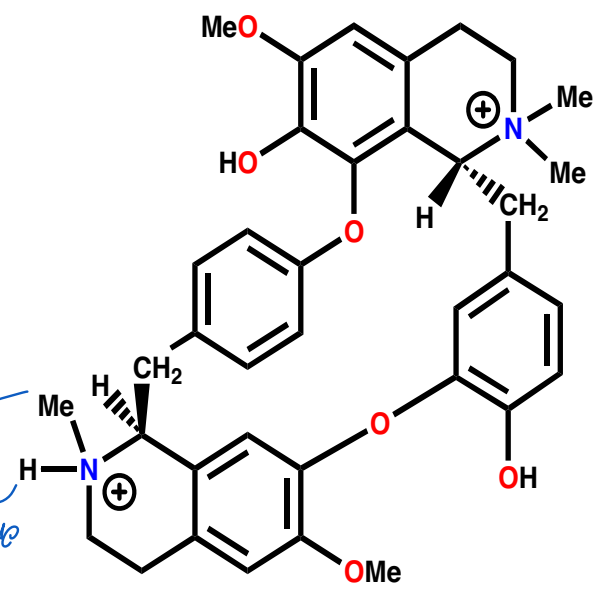
Tubocurarine:

Has **two positively charged nitrogens**:

One **quaternary ammonium**

One **protonated tertiary amine**

No ester group, unlike acetylcholine or muscarinic antagonists.

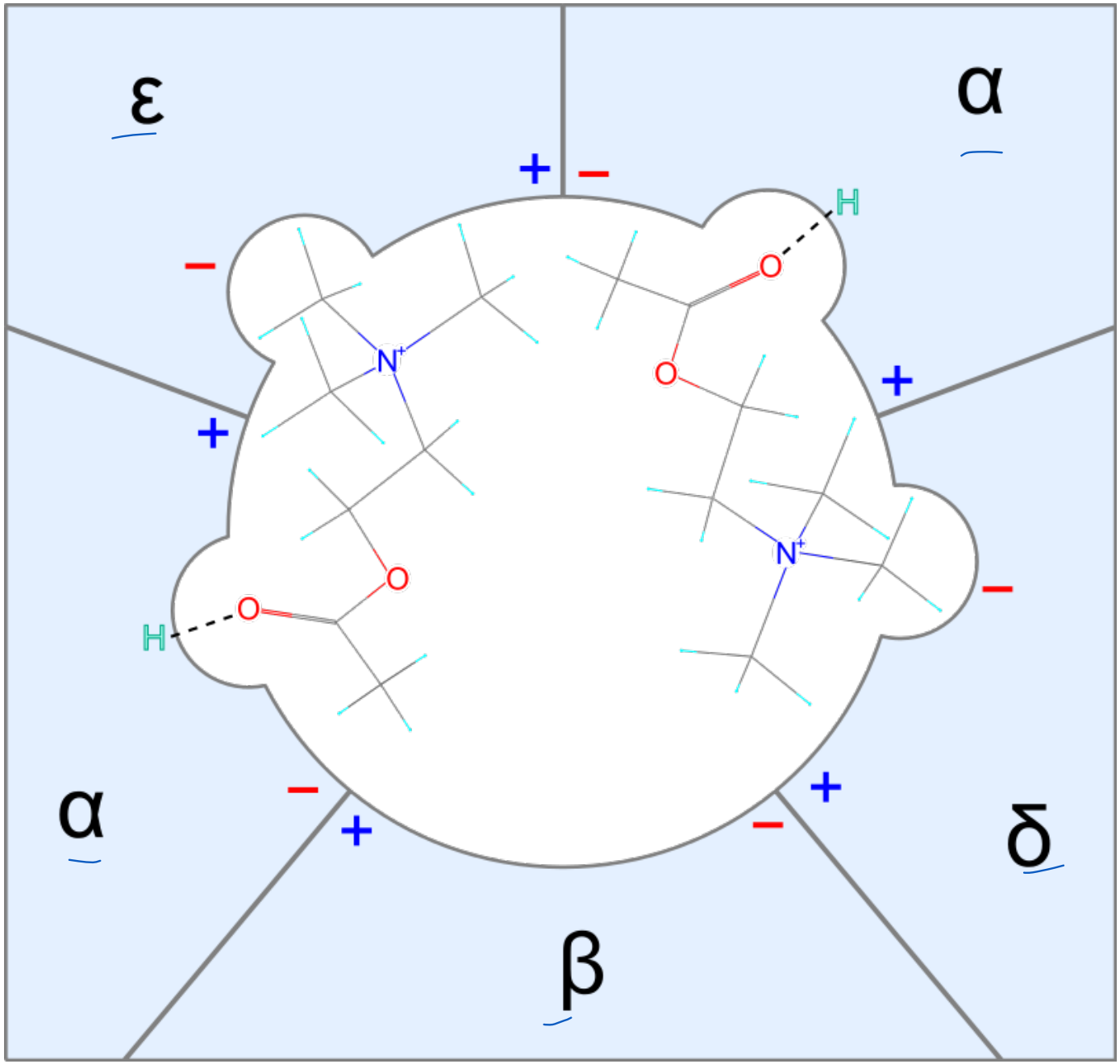


Tubocurarine

Current Binding Theory

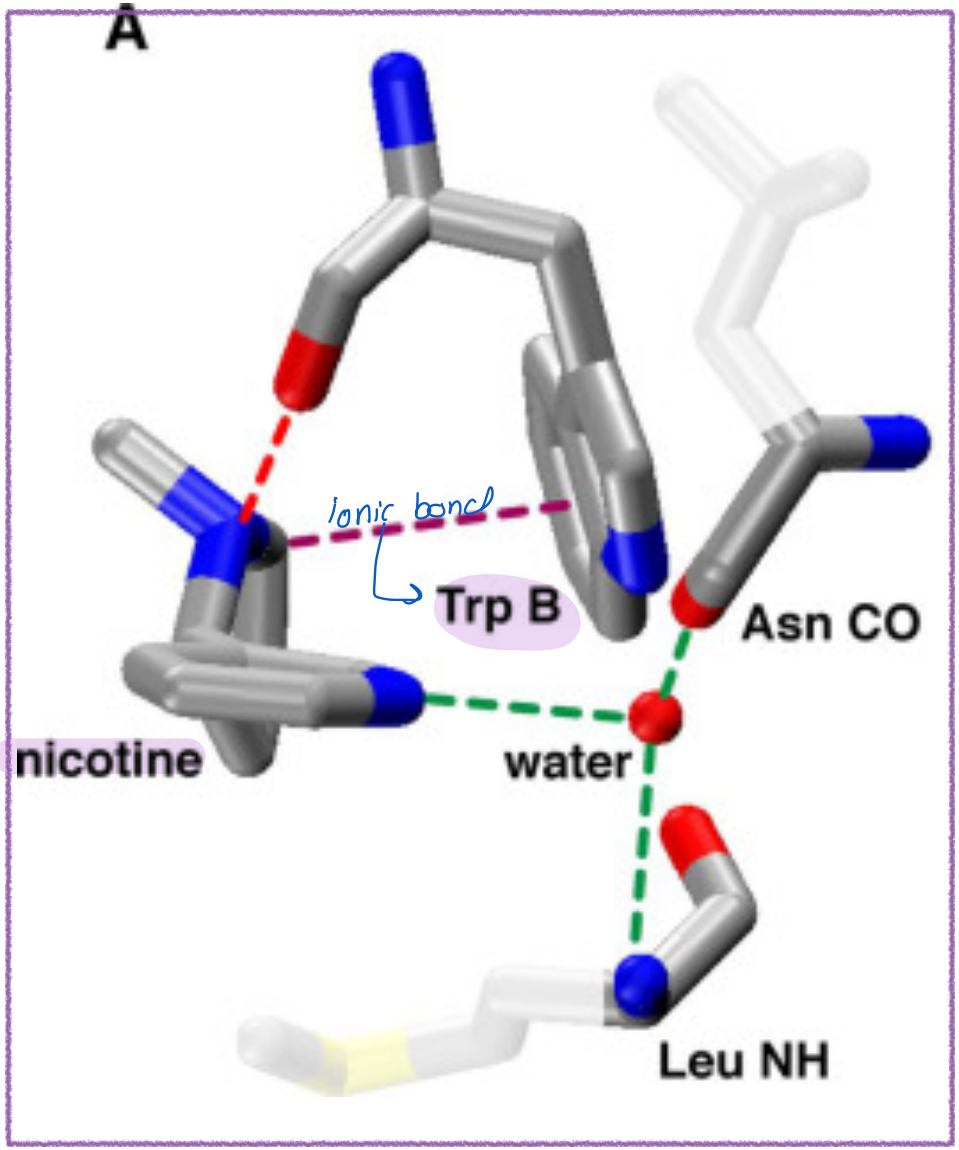
- **One charged nitrogen** binds the **anionic ACh binding site** (like ACh does).
- The **second charged nitrogen** interacts with a **nearby cysteine residue**, 0.9–1.2 nm away.
- This **dual-point binding** model helps explain:
  - Strong binding
  - Lack of receptor activation (due to altered induced fit)
  - Blockade of ion channel opening

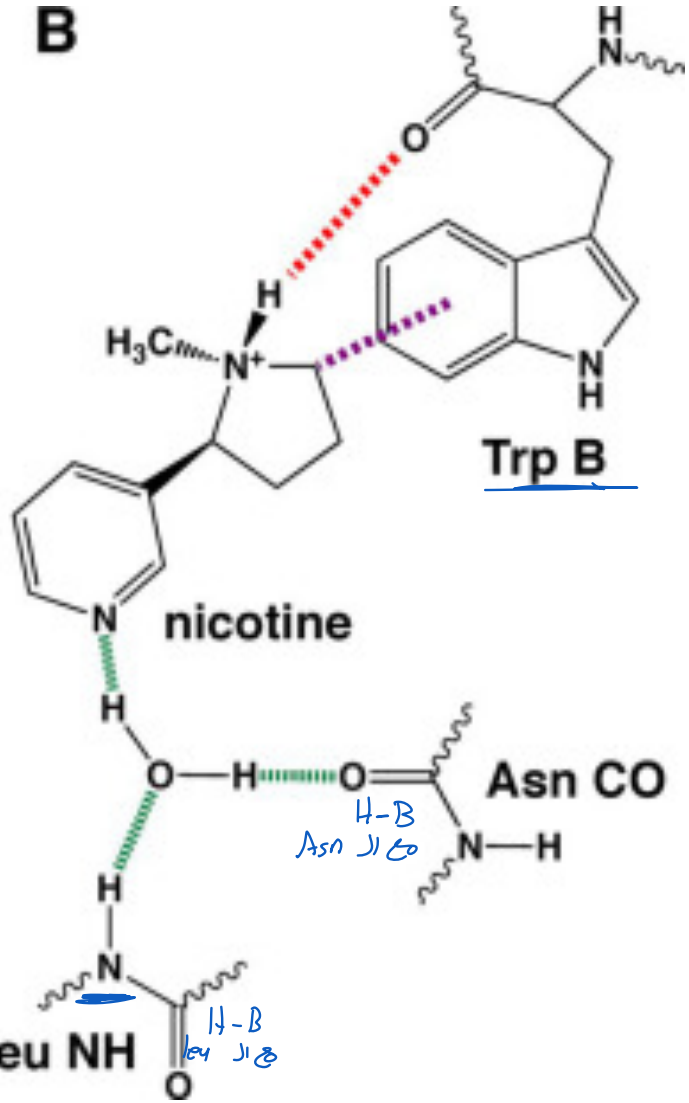
Binding site of acetylcholine- cholinergic receptors



receptor إذا إرتبط بال
blocking يعني راح يصير antagonist
ion channel لل

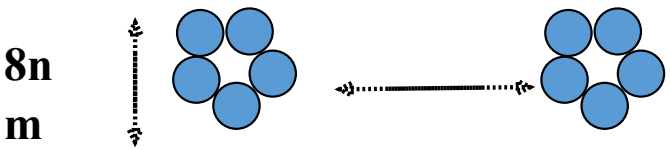
Binding of nicotine to nicotinic receptors



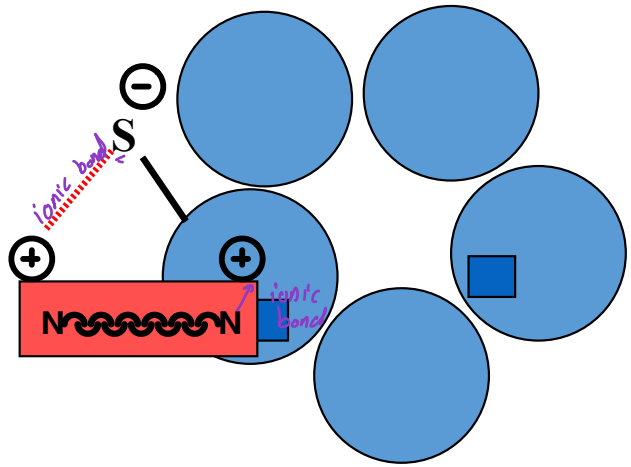


13. Cholinergic Antagonists (Nicotinic receptor)

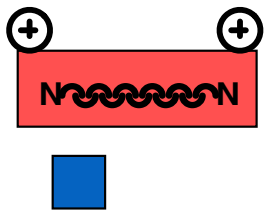
13.2 Binding



a) Receptor dimer



b) Interaction with tubocurarine



Tubocurarine

Acetylcholine binding site

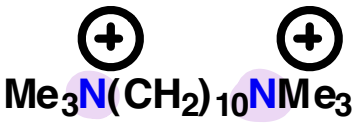
13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine

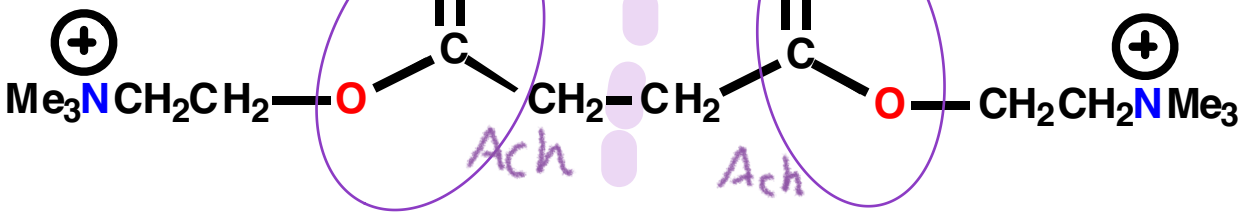
2 Ach تتكون من مرتبطين ببعض ester group

ester الـ metabolism بخلو المركب يصير ايله بسهوله

2(4N)



Decamethonium



Suxamethonium

analogus of tubocurarine

بس اشوفها بحرف انها

- **Long lasting (unmetabolized)** → un metabolize لانه
- **Long recovery times**
- **Side effects on heart**

Structure: Simple, straight-chain molecule with two **positively charged nitrogen atoms**.

Flexibility: Can adopt a **fully extended** form (between nitrogens) or a **folded conformation** mimicking **tubocurarine** spacing.

المسافه بين الـ 2N بالـ decamethonium تساوي المسافه بين الـ 2N بالـ tubocurarine

- **Esters incorporated**
- **Shorter lifetime (5 min)**
- **Fast onset and short duration**
- **Side effects at autonomic ganglia**

Long duration of action مابدي اياه لانه ح يأثر على الـ Heart عشان هيك بضيف Ester ليصير short duration of action

- Designed to **overcome decamethonium's long action**.
- Structurally: Two **acetylcholine molecules linked together**, with **two ester groups**.
- **Nitrogen–nitrogen distance** preserved allowing effective receptor binding.

المسافه بين 2N عند tubocurarine بالـ 2N تساوي المسافه بين الـ binding affinity ح تزيد

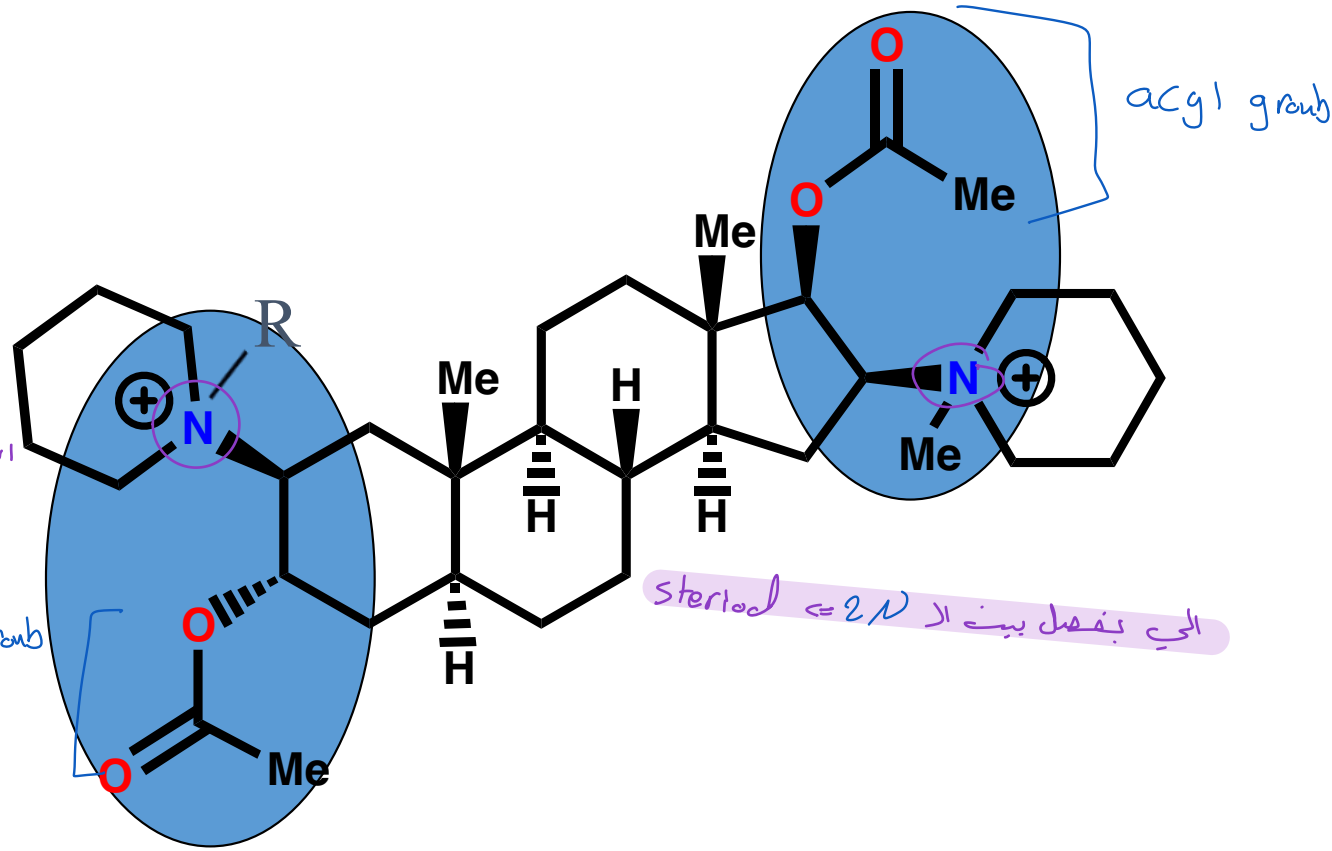
13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine

Pancuronium (R=Me)

Vecuronium (R=H)

Steroidal Nicotinic Antagonist اسمهم



acyl group الـ
خلت المركب يشبه (methyl ester) الـ Ach
وهيك زادت الـ Affinity

عشان 2 acyl group صفت ⇐ acyl group
binding affinity ازيد الـ

Steroid ⇐ 2N الي بفصل بين الـ

Steroid acts as a spacer for the quaternary centres (1.09nm)

Acyl groups are added to mimic the Ach skeleton enhancing receptor affinity

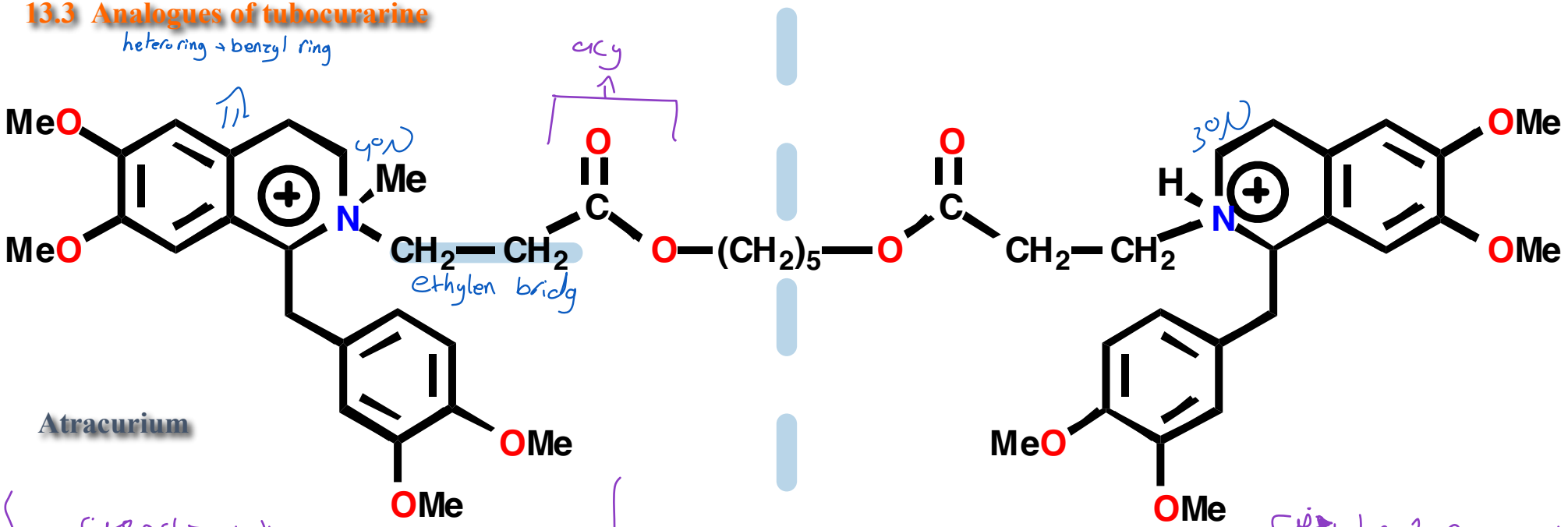
Faster onset then tubocurarine but slower than suxamethonium ⇒ 2 ester عنده هذا

Longer duration of action than suxamethonium (45 min)

No effect on blood pressure and fewer side effects

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine



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
- Lifetime is 30 minutes
- Administered as an i.v. drip
- Self destruct system limits lifetime

13. Cholinergic Antagonists (Nicotinic receptor)

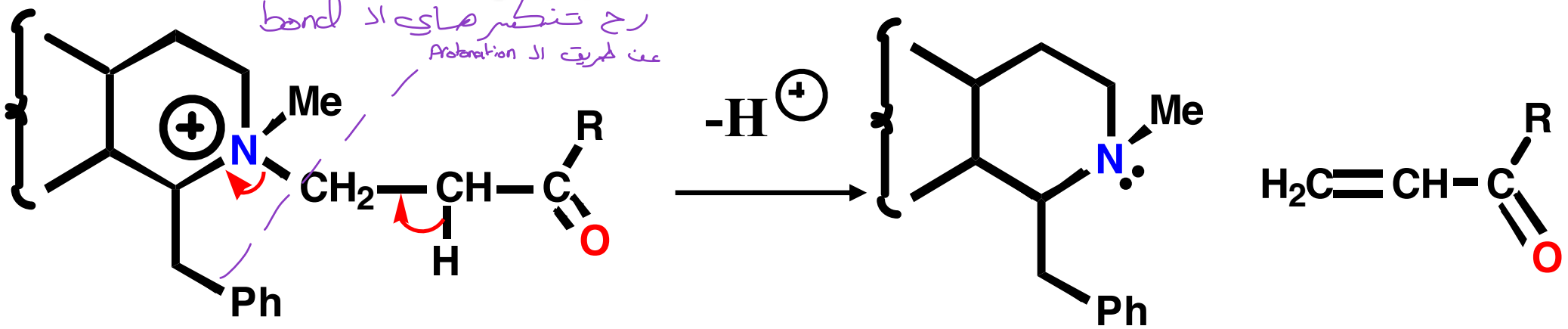
هذا الـ drug بصير إله elimination بسرعة لانه ما يحتاج لحرارة او enzym

ليصير إله metabolism.

13.3 Analogues of tubocurarine

Atracurium stable at acid pH
Hofmann elimination at blood pH (7.4)

رح تنكسر هاي الـ bond عن طريق الـ Protonation



ACTIVE

acidic drug

INACTIVE

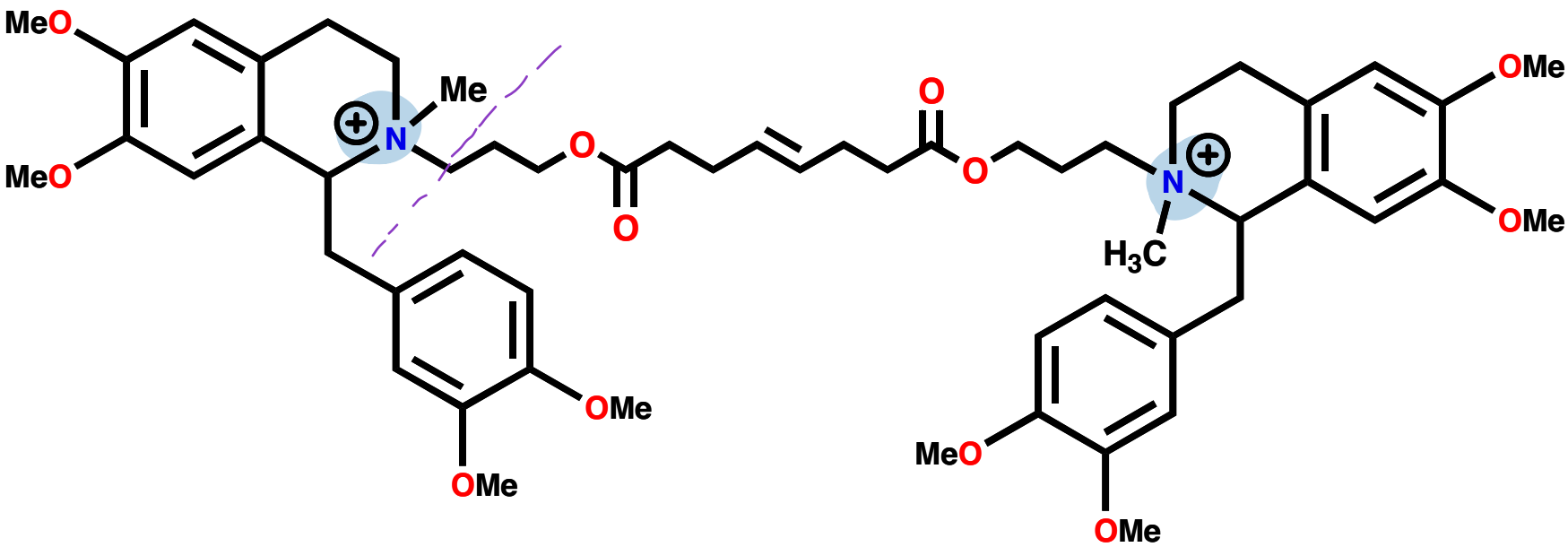
Hofmann elimination is used to design **short-acting neuromuscular blockers** like **atracurium** and **cisatracurium**. These drugs contain ester groups and a quaternary nitrogen, allowing them to break down spontaneously in the bloodstream under **mild alkaline conditions (pH 7.4)**. The ester group increases the acidity of a nearby hydrogen, enabling elimination without the need for enzymes or heat. This makes the drug **fast-acting and short-lived (≈30 minutes)**. It's **stable in acidic solution (pH 3–4)** for storage and can be safely administered during surgery via IV, with effects stopping quickly once the infusion ends.

ester → acidic خصائص عند drug الـ بتخلي

13. Cholinergic Antagonists (Nicotinic receptor)

13.3 Analogues of tubocurarine

Mivacurium



Mivacurium is a **short-acting neuromuscular blocker** similar to atracurium. It is inactivated **rapidly by both plasma enzymes and Hofmann elimination**, making it suitable for short procedures. It has a **faster onset of action (~2 minutes)** and a **shorter duration (~15 minutes)**.

ال 3° يعني tertiary amin

ال 4° يعني quaternary amin

لاتنسوا زميلنا ايهم من دعائكم