

Chapter 2: Drugs acting on Autonomic nervous system

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Objective

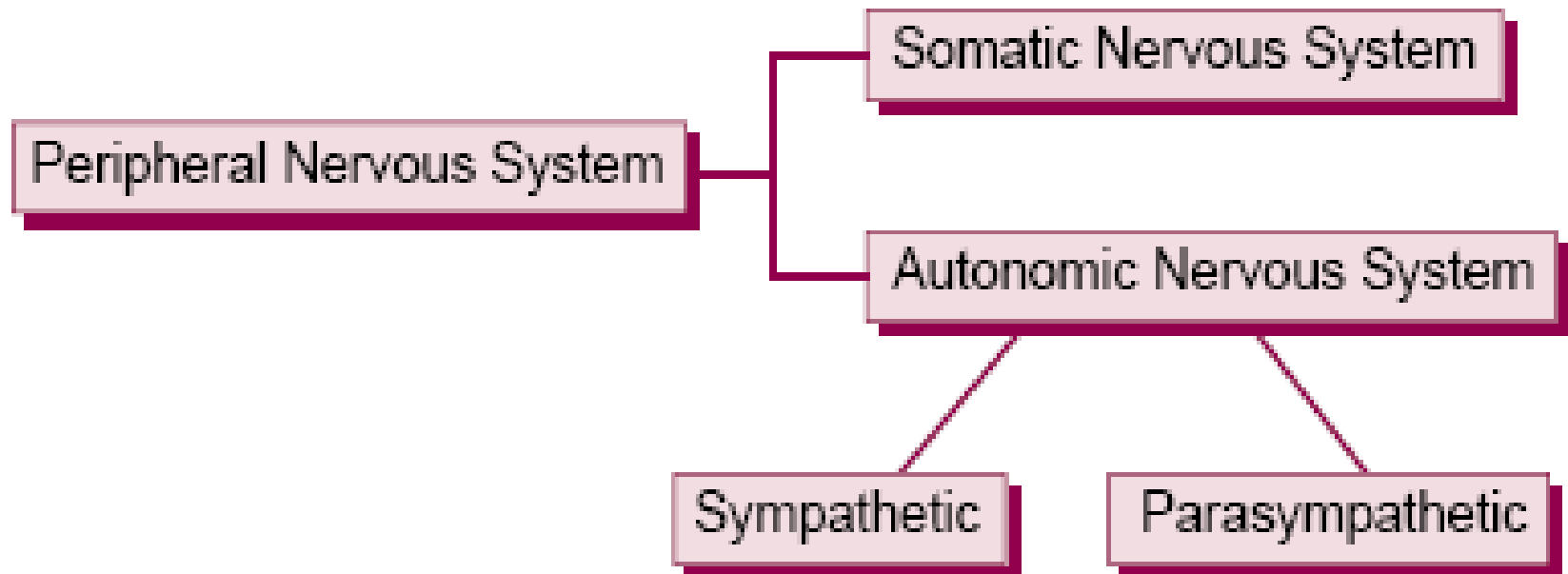
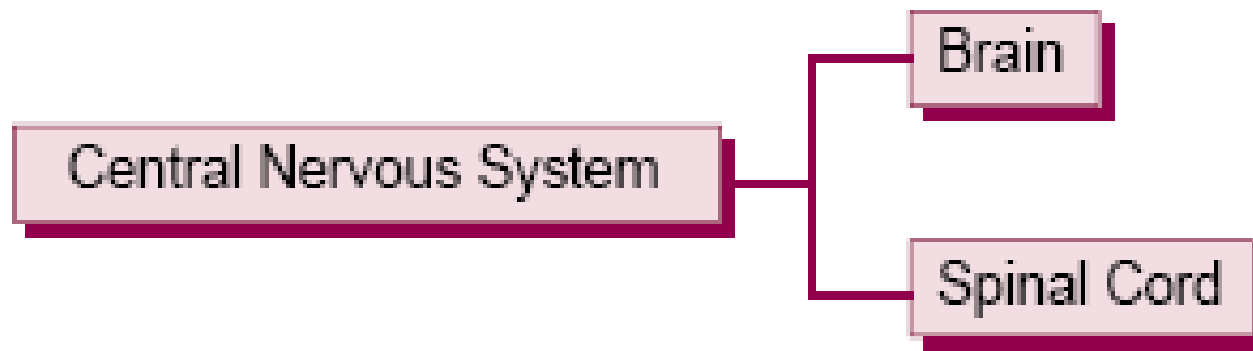
After completing this chapter, you will be able to understand the medicinal chemistry of drugs acting on the autonomic nervous system;

- Cholinergics
- Antimuscarinic drugs
- Neuromuscular blockers
- Ganglion blockers
- Adrenergic drugs
- Adrenergic blocking drugs

Introduction to the Autonomic Nervous system

The peripheral nervous system

- The peripheral nervous system is part of the nervous system which is outside of the central nervous system (CNS: the brain and spinal column).
- There are two subdivisions of the peripheral system:
 - Sensory nerves (nerves which take messages from the body to the CNS)
 - Motor nerves (nerves which carry messages from the CNS to the rest of the body)



Motor nerves of the peripheral nervous system

- These nerves take messages from the CNS to various parts of the body such as skeletal muscle, smooth muscle, cardiac muscle, and glands.
- Motor nerves of the peripheral nervous system have been divided into two sub-systems
 - The somatic motor nervous system
 - The autonomic motor nervous system

Somatic motor nervous system

- These are nerves which carry messages from the CNS to skeletal muscles.
- The neurotransmitter at the neuromuscular junction is acetylcholine.
- The final result of such messages is contraction of skeletal muscle.

The autonomic motor nervous system

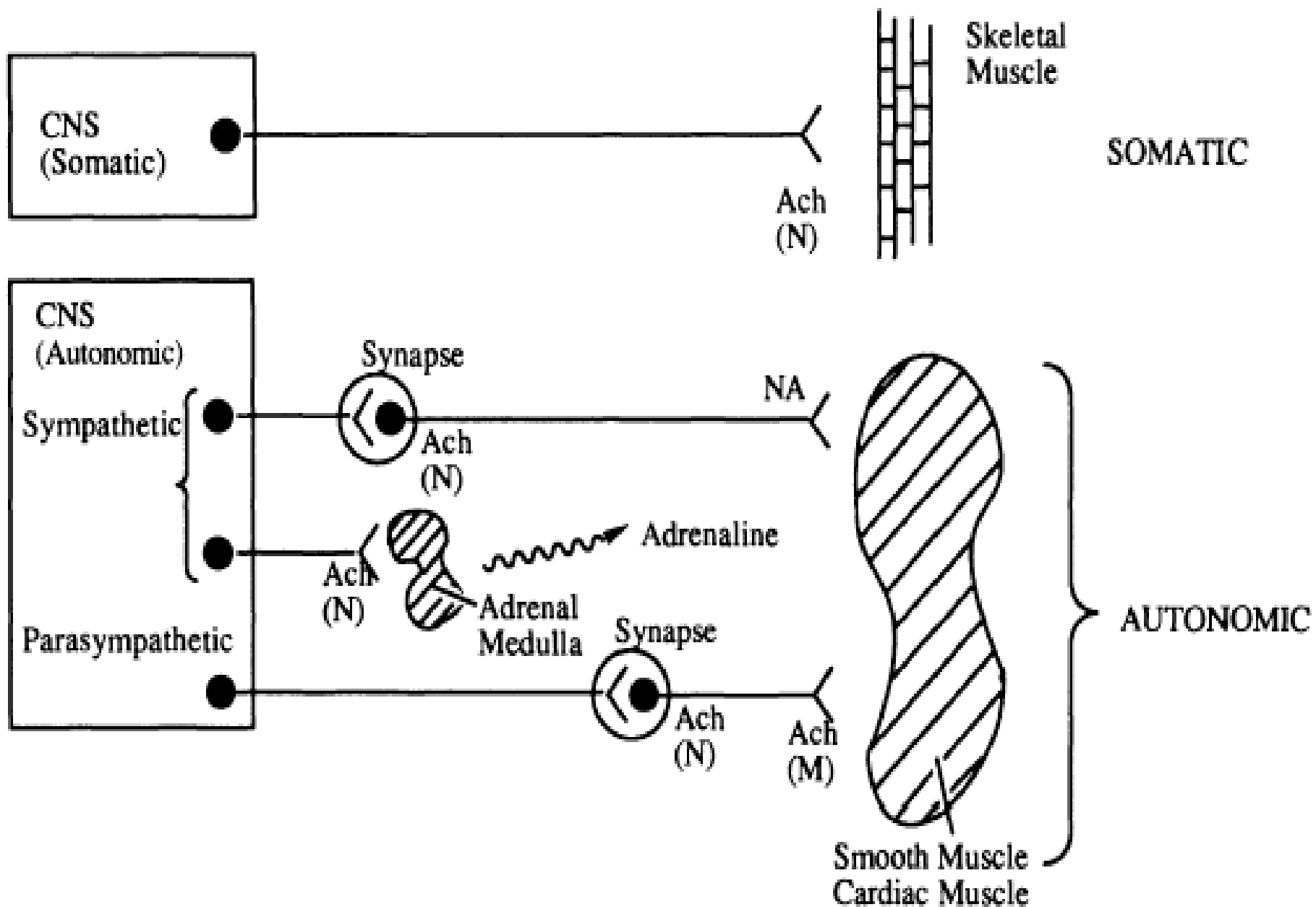
- These nerves carry messages from the CNS to smooth muscle, cardiac muscle, and the adrenal medulla.
- This system can be divided into two subgroups.
 - Sympathetic NS
 - Parasympathetic NS

Parasympathetic nerves

- These leave the CNS, travel some distance, then synapse with a second nerve which then proceeds to the final synapse with smooth muscle.
- The neurotransmitter at both synapses is acetylcholine.

Sympathetic nerves

- These leave the CNS, but almost immediately synapse with a second nerve (neurotransmitter—acetylcholine) which then proceeds to the same target organs as the parasympathetic nerves.
- However, they synapse with different receptors on the target organs and use a different neurotransmitter—noradrenaline



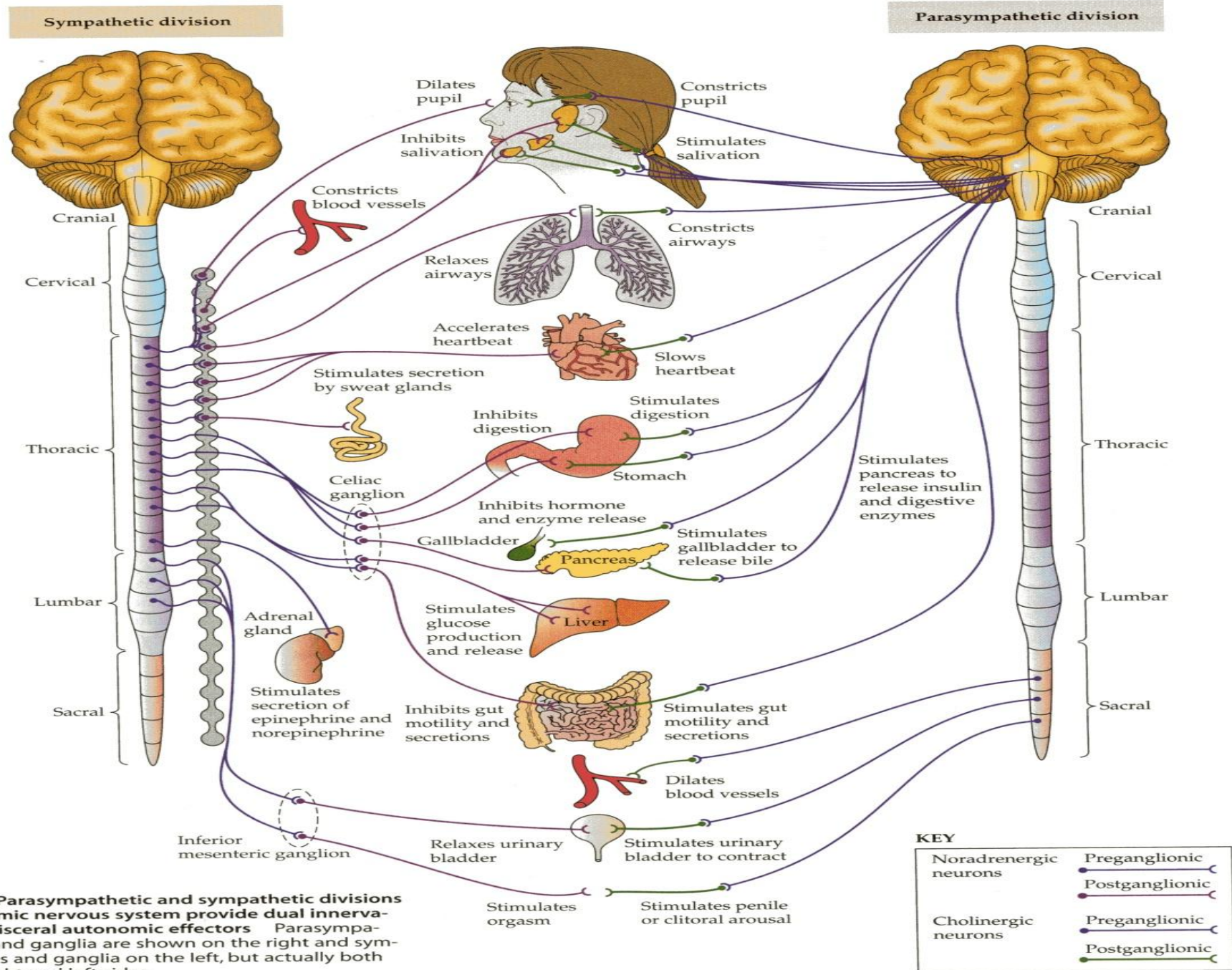
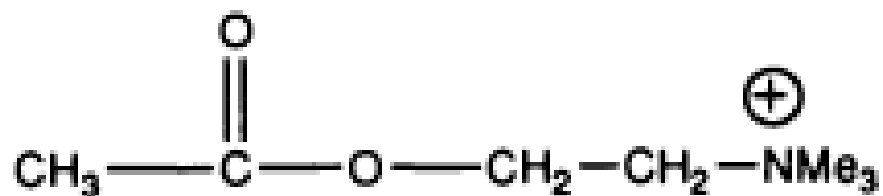


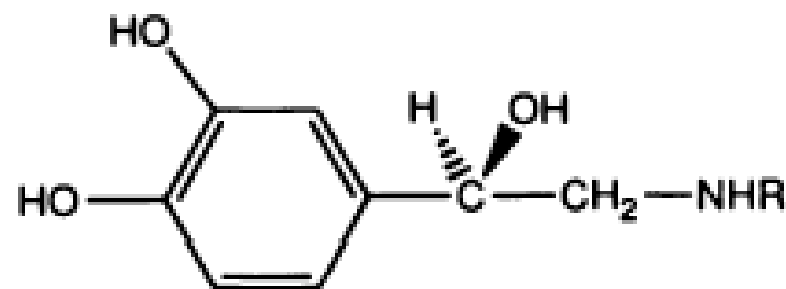
Figure 10.13 Parasympathetic and sympathetic divisions of the autonomic nervous system provide dual innervation of most visceral autonomic effectors. Parasympathetic nerves and ganglia are shown on the right and sympathetic nerves and ganglia on the left, but actually both have paired right and left sides.

The neurotransmitters

- There are a large variety of neurotransmitters in the CNS, but as far the peripheral nervous system is concerned we need only consider two—**acetylcholine** and **noradrenaline**



Acetylcholine



R = H Noradrenaline
(R = Me Adrenaline)

Actions of the peripheral nervous system

A. Somatic

- Stimulation leads to the contraction of skeletal muscle.

B. Autonomic

- **Sympathetic.**
 - Contraction of cardiac muscle and an increase in heart rate.
 - Relaxes smooth muscle and reduces the contractions of the GIT and urinary tracts
 - Reduces salivation and reduces dilation of the peripheral blood vessels.
 - **Fight or flight** response of the body

Parasympathetic.

- The stimulation of the parasympathetic system leads to the opposite effects from those of the sympathetic system.
 - **Rest and digest** role of the body (house keeping role)
- Acetylcholine is released at the target organs and reacts with receptors specific to it and not to noradrenaline

1. Cholinergic agents

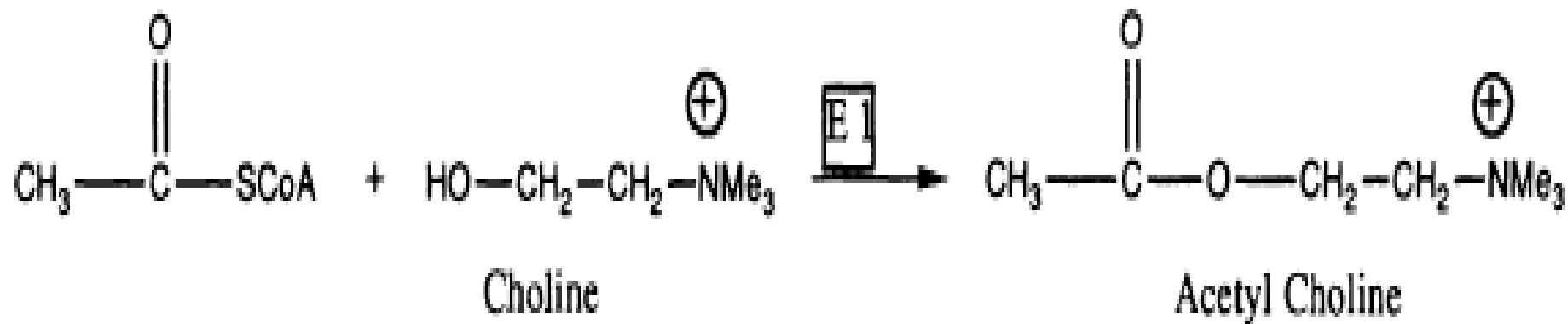
The cholinergic system

- What happens at synapses involving acetylcholine as the neurotransmitter?

Biosynthesis of acetylcholine

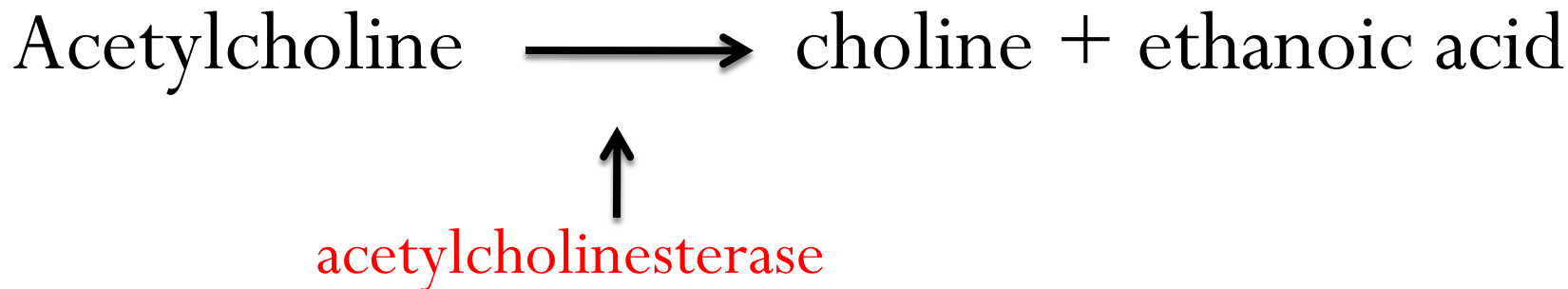
- Acetylcholine is synthesized in the nerve ending of the pre-synaptic nerve from choline and acetyl coA.

- The reaction is catalysed by the enzyme **choline-acetyltransferase, E1**.

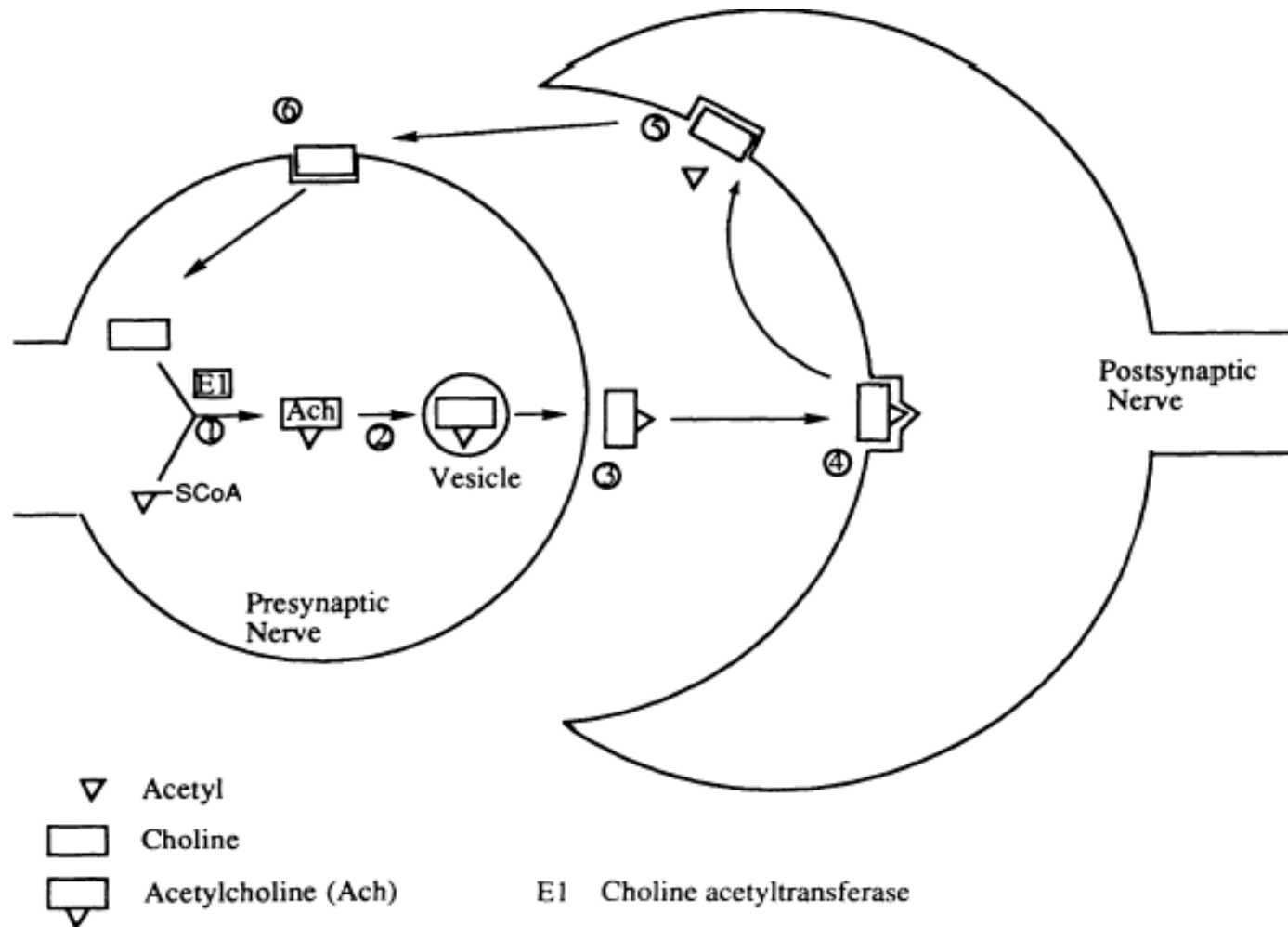


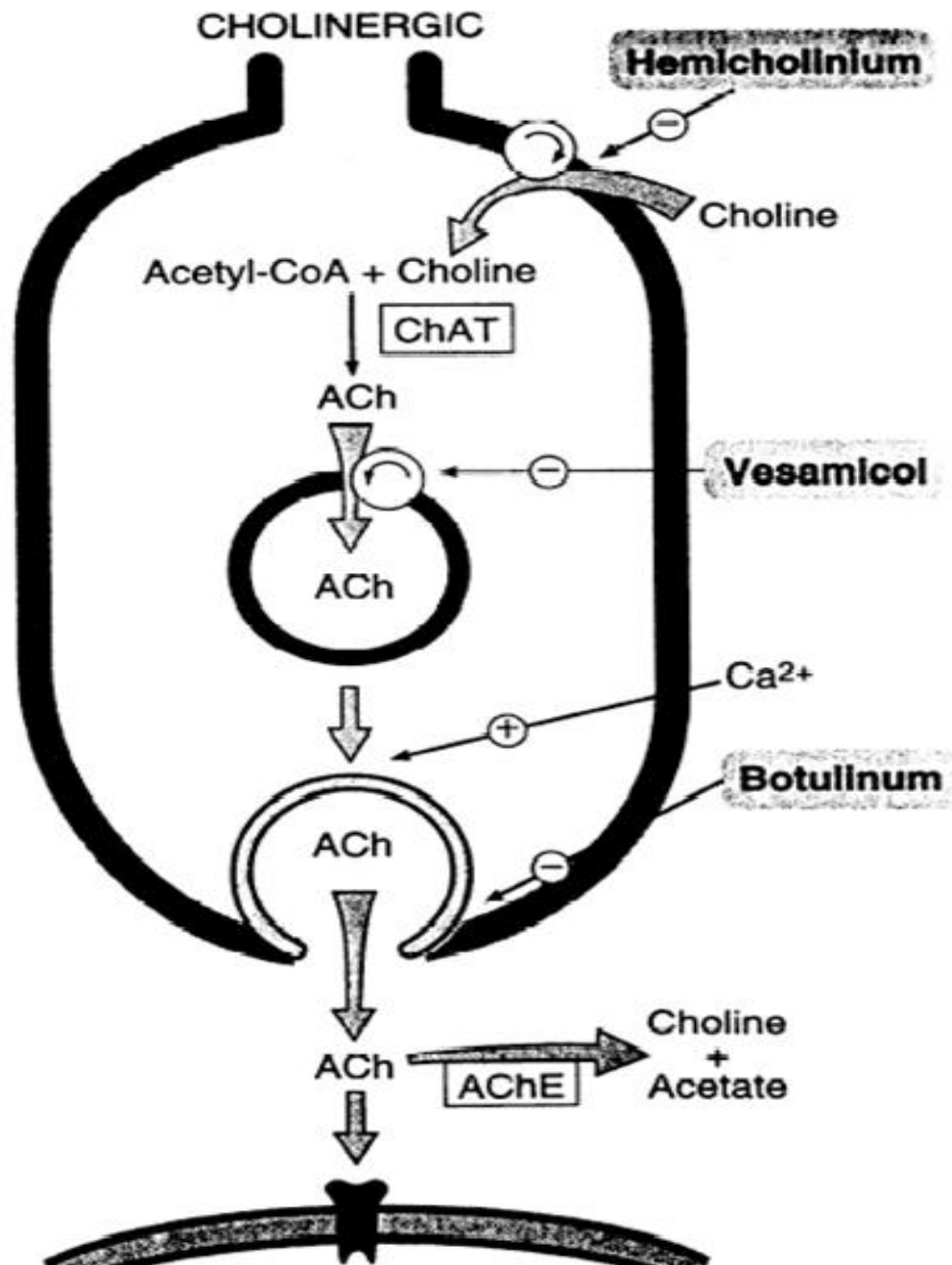
- Acetylcholine is incorporated into membrane-bound vesicles.
- The arrival of a nerve signal leads to the release of acetylcholine.
- Acetylcholine crosses the synaptic gap and binds to the cholinergic receptor leading to stimulation of the second nerve.

- Acetylcholine moves to an enzyme called **acetylcholinesterase** which is situated at the postsynaptic nerve and which catalyses the hydrolysis of acetylcholine to choline and ethanoic acid



Choline binds to the choline receptor on the postsynaptic nerve and is taken up into the cell by an efficient transport system to continue the cycle.





Agonists at the cholinergic receptor

- If there is a lack of acetylcholine acting at a certain part of the body, why do not we just give the patient more acetylcholine?
- After all, it is easy enough to make in the laboratory.
- There are three reasons why this is not feasible.
 1. Acetylcholine is easily hydrolysed in the stomach by acid catalysis and cannot be given orally.
 2. Acetylcholine is easily hydrolysed in the blood, both chemically and by enzymes (esterases and acetylcholinesterase).
 3. There is no selectivity of action. Acetylcholine will switch on all acetylcholine receptors in the body.

- Therefore, we need analogues of acetylcholine which are
 - More stable to hydrolysis
 - More selective with respect to where they act in the body.

There are two ways in which selectivity can be achieved.

- Firstly, some drugs might be distributed more efficiently to one part of the body than another.
- Secondly, cholinergic receptors in various parts of the body might be slightly different.

Acetylcholine

('Fits' both types of receptor)

Ach Analogue

'FIT'

Ach Analogue

Acetylcholine Receptor
Type 1?

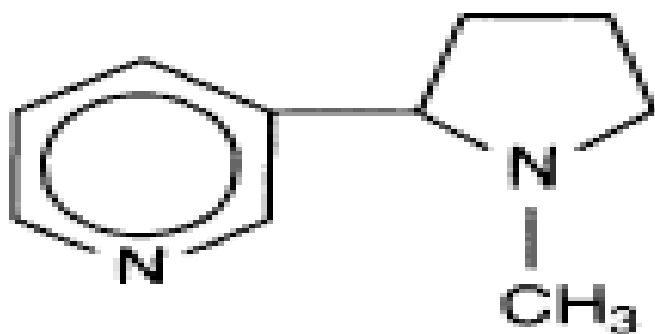
NO 'FIT'

Ach Analogue

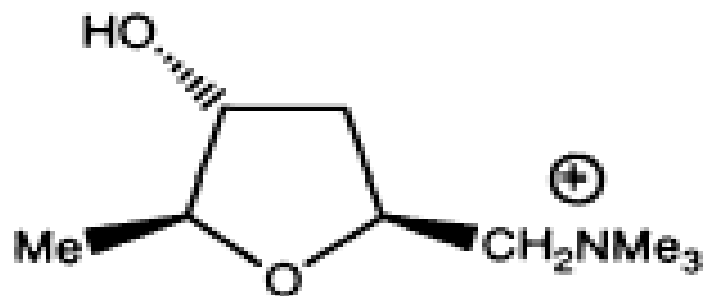
'Wall'

Acetylcholine Receptor
Type 2?

- This is not just a peculiarity of acetylcholine receptors.
 - Subtle differences have been observed for other types of receptors such as those for dopamine, noradrenaline, and serotonin.
- **How do we know if there are different subtypes of acetylcholine receptor?**
 - The first clue came from the action of natural compounds.
- It was discovered that the compounds **nicotine** and **muscarine** were both acetylcholine agonists, but that they had different physiological effects.



NICOTINE



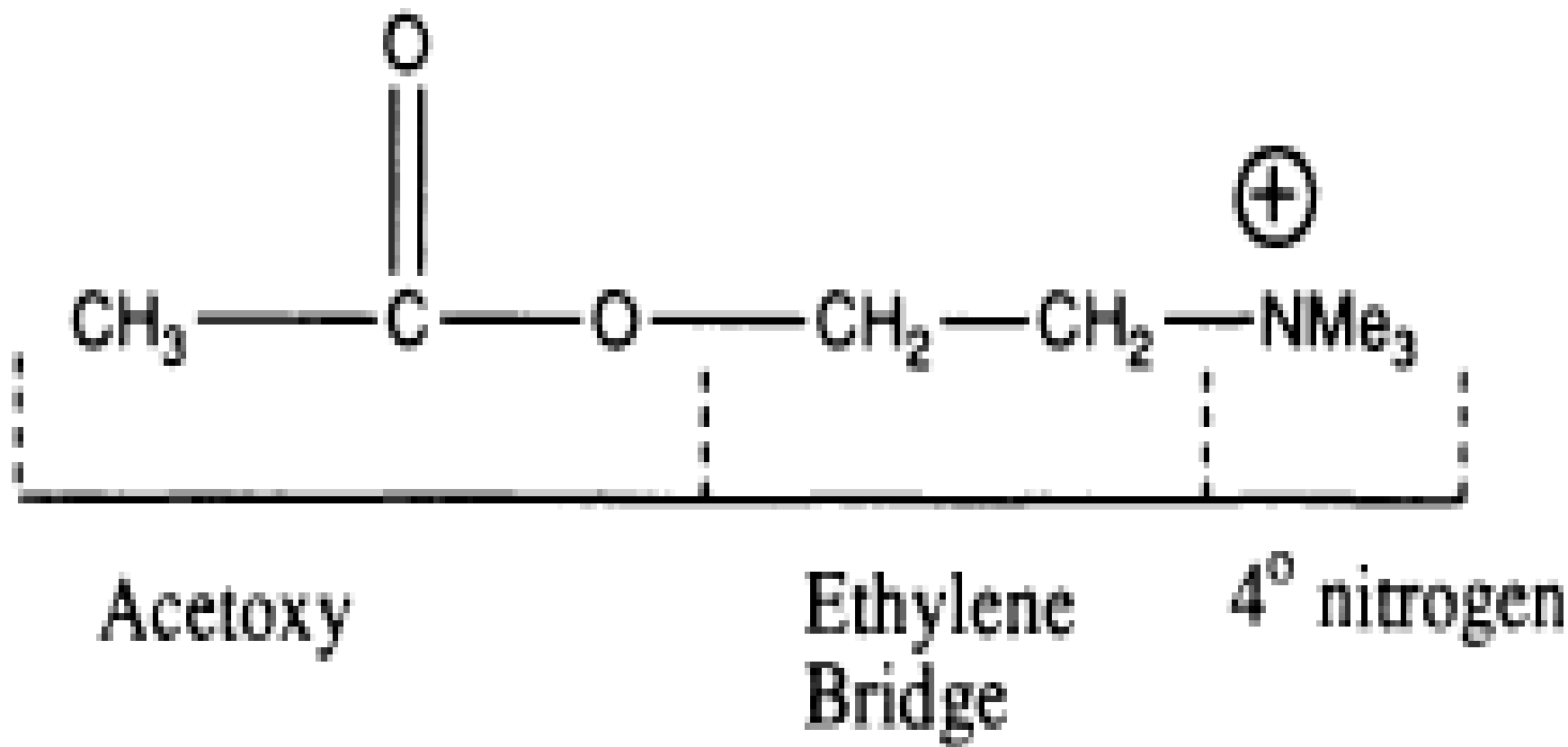
L (+) MUSCARINE

- **Nicotine** was found to be active at the synapses between
 - Two different nerves
 - Nerves and skeletal muscle,
 - But had poor activity elsewhere.

- **Muscarine** was active at the synapses of nerves with
 - Smooth muscle and
 - Cardiac muscle,
 - But showed poor activity at the sites where nicotine was active.
- From these results:
 - There is one type of acetylcholine receptor on skeletal muscles and at nerve synapses
 - Known as **nicotinic receptor, N**
 - There is a different sort of acetylcholine receptor on smooth and cardiac muscles
 - Known as **muscarinic receptor, M**

- Unfortunately, these two compounds are not suitable as medicines since they have **undesirable side-effects**.
- But they have served as a **lead compound** for further development

Acetylcholine: Structure, SAR, and receptor binding



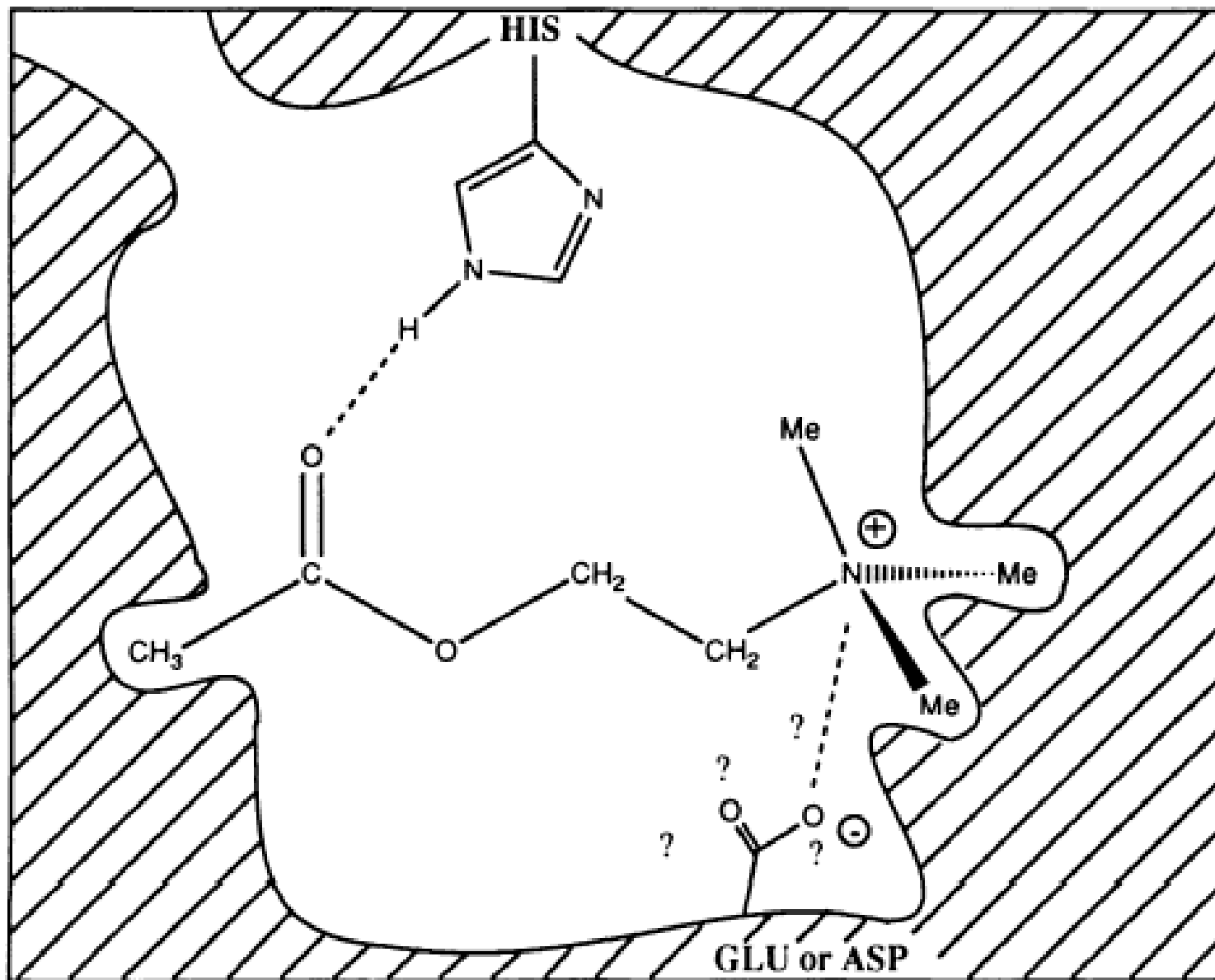
SAR ...

- The positively charged nitrogen atom is essential to activity.
 - Replacing it with a **neutral carbon** atom eliminates activity.
- The distance from the nitrogen to the ester group is important.
- The ester functional group is important.

- The overall size of the molecule cannot be altered greatly.
 - Bigger molecules have poorer activity.
- The ethylene bridge between the ester and the nitrogen atom cannot be extended.
- There must be two methyl groups on the nitrogen.
 - A larger, third alkyl group is tolerated, but more than one large alkyl group leads to loss of activity.

- Bigger ester groups lead to a loss of activity.
- **Conclusions:**
 - Clearly, there is a **tight fit** between acetylcholine and its binding site which leaves little scope for variation.
 - The above findings fit in with a receptor site as shown in figure below

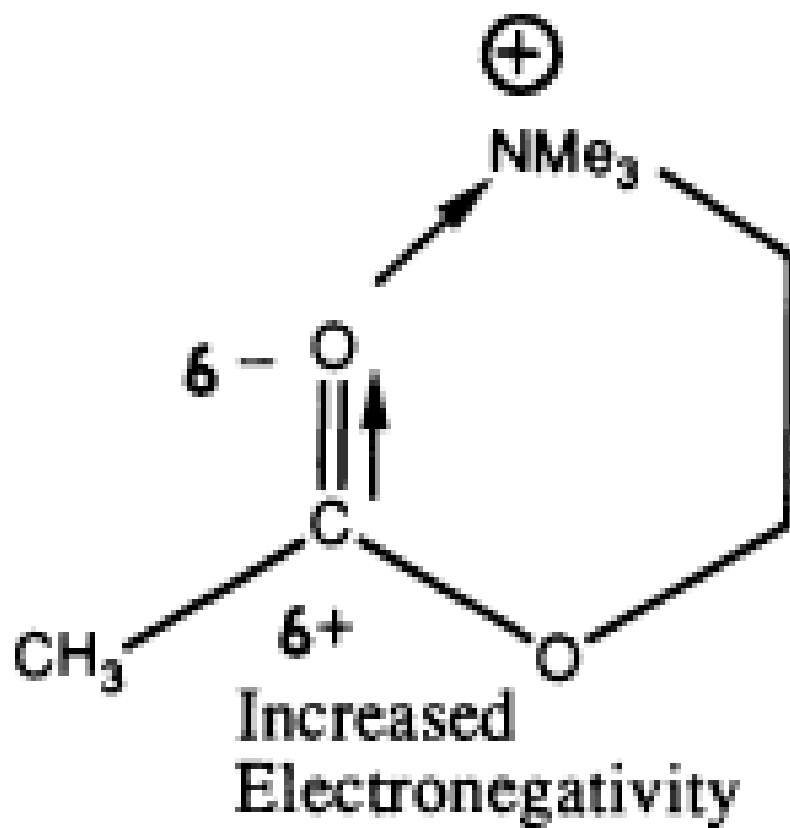
RECEPTOR SITE
(MUSCARINIC)



The instability of acetylcholine

- As described previously, acetylcholine is prone to hydrolysis.
- Why is this and how can the stability being improved?
 - The reason for acetylcholine's instability can be explained by considering one of the conformations that the molecule can adopt

Instability of Ach ...



- In this conformation, the positively charged nitrogen interacts with the carbonyl oxygen and has an electron withdrawing effect.
- To compensate for this, the oxygen atom pulls electrons towards it from the neighboring carbon atom and as a result makes that carbon atom **electron deficient** and more prone to nucleophilic attack.

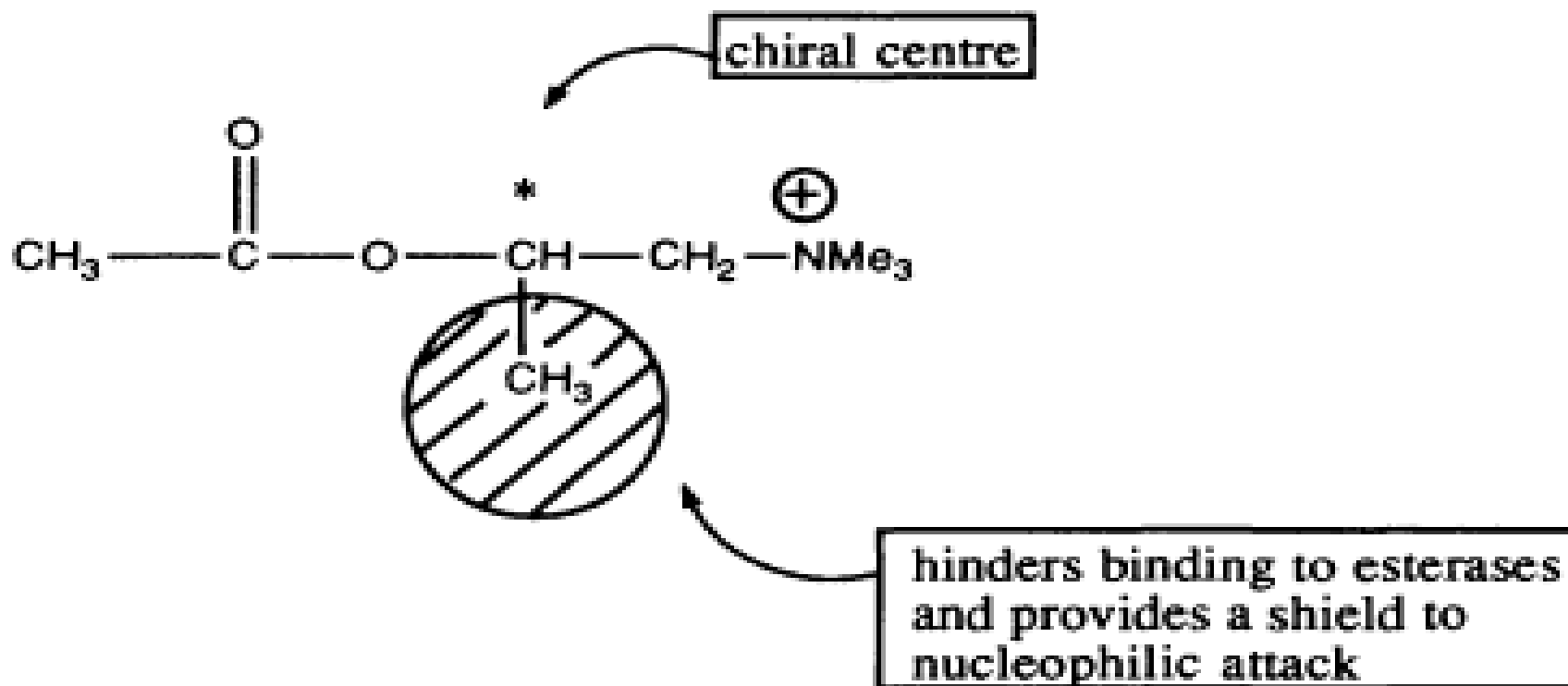
- Water is a poor nucleophile, but since the carbonyl group is now more electrophilic, hydrolysis takes place relatively easily.
- This influence of the nitrogen ion is known as neighbouring group participation or anchimeric assistance.

Design of acetylcholine analogues

- In order to tackle the inherent instability of acetylcholine, two approaches are possible:
 - Steric hindrance
 - Electronic stabilization

I. Steric hindrance

- The principle involved here can be demonstrated with methacholine



- This analogue of acetylcholine contains an extra methyl group on the ethylene bridge.
- The reasons for putting it there are twofold.
 - Firstly, it is to try and build in a shield for the carbonyl group.
 - The bulky methyl group should hinder the approach of any potential **nucleophile** and slow down the rate of hydrolysis.
 - It should also hinder binding to the **esterase enzymes**, thus slowing down enzymatic hydrolysis.

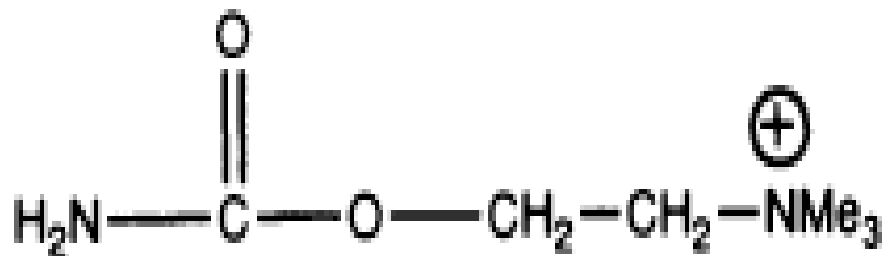
- The results were encouraging, with methacholine proving **three times more stable** to hydrolysis than acetylcholine.
- Why don't we put on a bigger alkyl group? Alternatively, why not put a bulky group on the acyl half of the molecule?

- In fact, these approaches were tried, but **failed**
- The fit between acetylcholine and its receptor is so tight that there is little scope for enlarging the molecule.
- The extra methyl group is as much as we can get away with.
- Larger substituents certainly cut down the chemical and enzymatic hydrolysis, but they also prevent the molecule binding to the cholinergic receptor.

- **In conclusion**, attempts to increase the steric shield beyond the methyl group certainly increase the stability of the molecule, but decrease its activity since it **cannot** fit the cholinergic receptor.
- One other very useful result was obtained from methacholine.
 - It was discovered that the introduction of the methyl group led to **significant muscarinic activity** and **very little nicotinic activity**.
- This result is perhaps more important than the gain in stability.

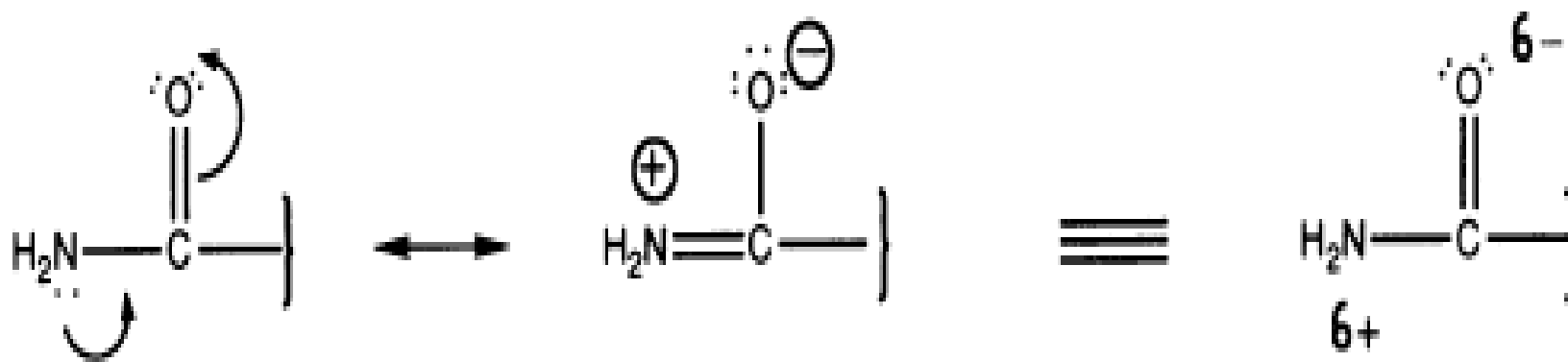
Electronic effects

- The best example of this approach is provided by **carbachol**, a long acting cholinergic agent which is resistant to hydrolysis.
- In carbachol, the acyl **methyl** group has been replaced by an **NH₂** group which is of comparable size and can therefore fit the receptor



- The resistance to hydrolysis is due to the electronic effect of the carbamate group.

- The resonance structures as shown in **Fig. below** demonstrate how the lone pair from the nitrogen atom is fed into the carbonyl group such that the group's electrophilic character is eliminated
- As a result, the carbonyl is no longer susceptible to nucleophilic attack.

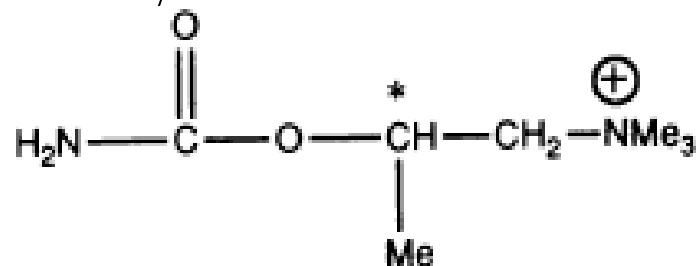


- **Carbachol** is certainly stable to hydrolysis and is the right size to fit the cholinergic receptor, but it is by no means a foregone conclusion that it will be active.
- After all, a hydrophobic methyl group has been replaced with a polar NH_2 group and this implies that a polar group has to fit into a hydrophobic pocket in the receptor.

- Fortunately, carbachol does fit and is active.
- Since the methyl group of acetylcholine has been replaced with an amino group without affecting the biological activity, we can call the amino group a '**bioisostere**' of the methyl group.
 - Therefore, the inclusion of an electron donating group such as the amino group has greatly increased the chemical and enzymatic stability of our cholinergic agonist.
- It is found that carbachol shows **very little selectivity** between the muscarinic and nicotinic sites.
- Carbachol is used clinically for the treatment of glaucoma.
 - The drug is applied locally and so selectivity is not a great problem.

Combining steric and electronic effects

- The compound obtained by combining the above two effects is **bethanechol** which is both stable to hydrolysis and selective in its action.



Bethanechol

- **Bethanechol** is used therapeutically in stimulating the gastrointestinal tract and urinary bladder after surgery.
 - Both these organs are '**shut down**' with drugs during surgery

Clinical uses of cholinergic agonists

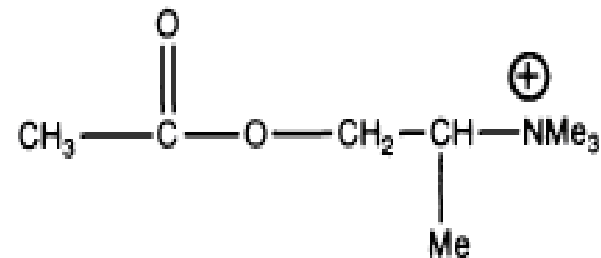
Muscarinic agonists:

- Treatment of glaucoma.
- 'Switching on' the GIT and urinary tract after surgery.
- Treatment of certain heart defects by decreasing heart muscle activity and heart rate.

Nicotinic agonists:

- Treatment of myasthenia gravis.
- An example of a selective nicotinic agonist is shown in Fig. below

- α -methyl group

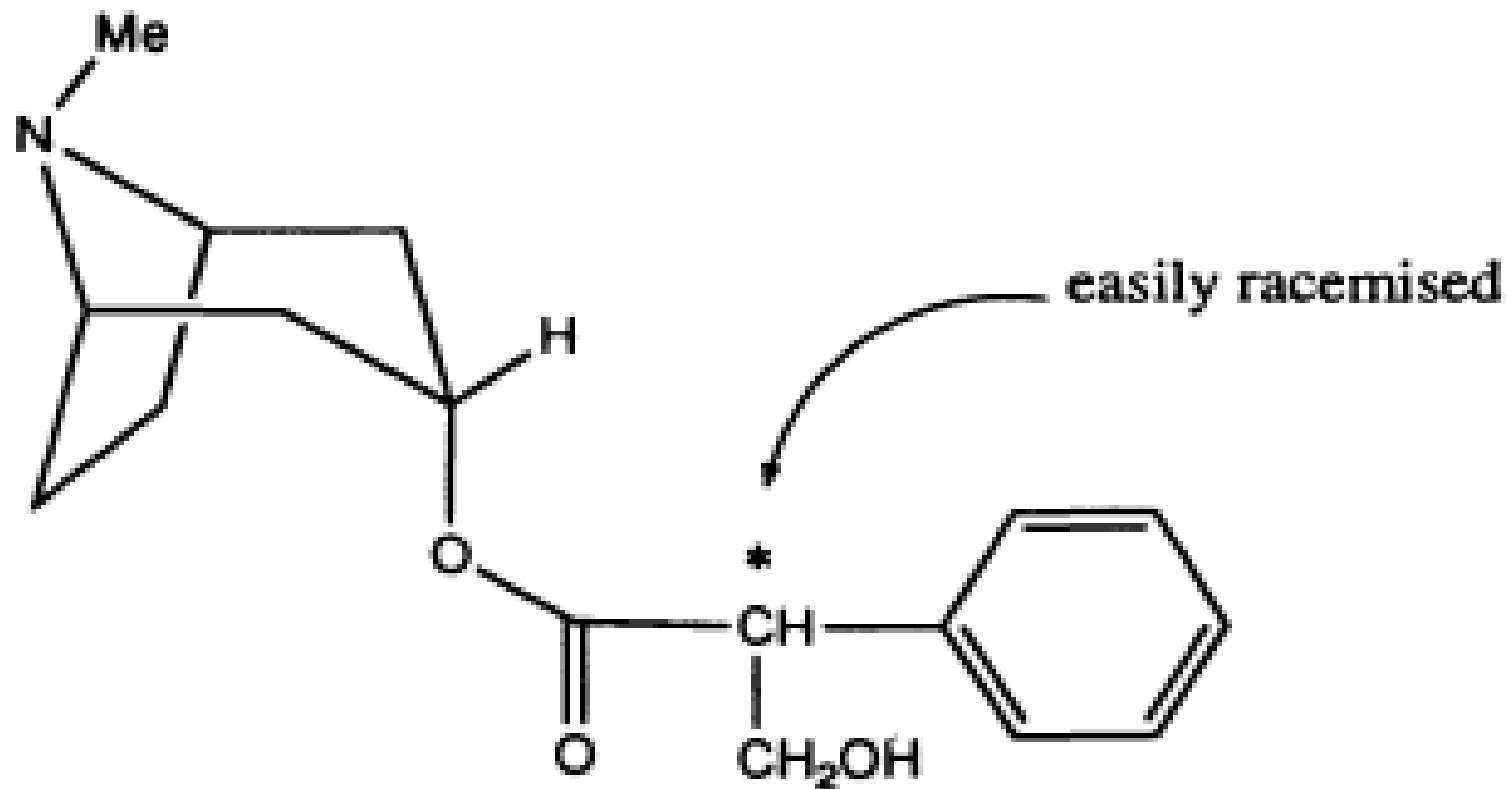


Muscarinic antagonists

- The first antagonists were natural products and in particular alkaloids.

Atropine

- Atropine was obtained from the roots of *Atropa belladonna* (deadly nightshade) in 1831.
- Atropine has a chiral centre (*) and therefore two enantiomers are possible.
- It is present in the plant species *Solanaceae* as a single enantiomer called **hyoscyamine**.

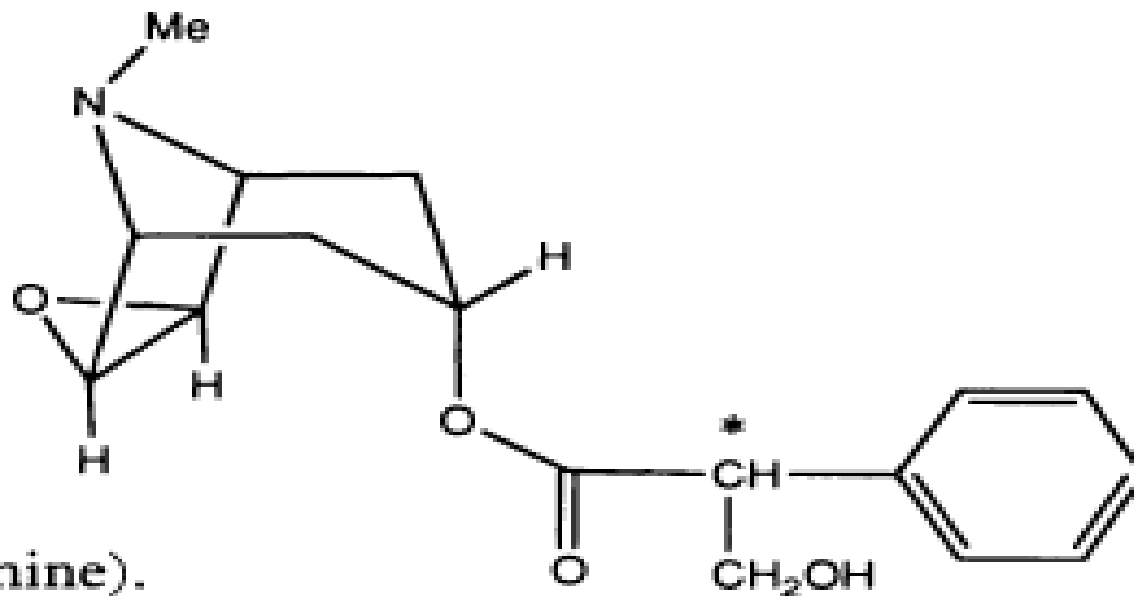


Atropine (hyoscyamine)

- However, as soon as the natural product is extracted into solution, the chiral centre racemizes such that atropine is obtained as a racemic mixture and not as a single enantiomer.
- The chiral centre in atropine is easily racemized since it is next to a **carbonyl group**.
- The proton attached to the chiral centre is **acidic** and as a result is easily replaced.

Hyoscine (1879-84)

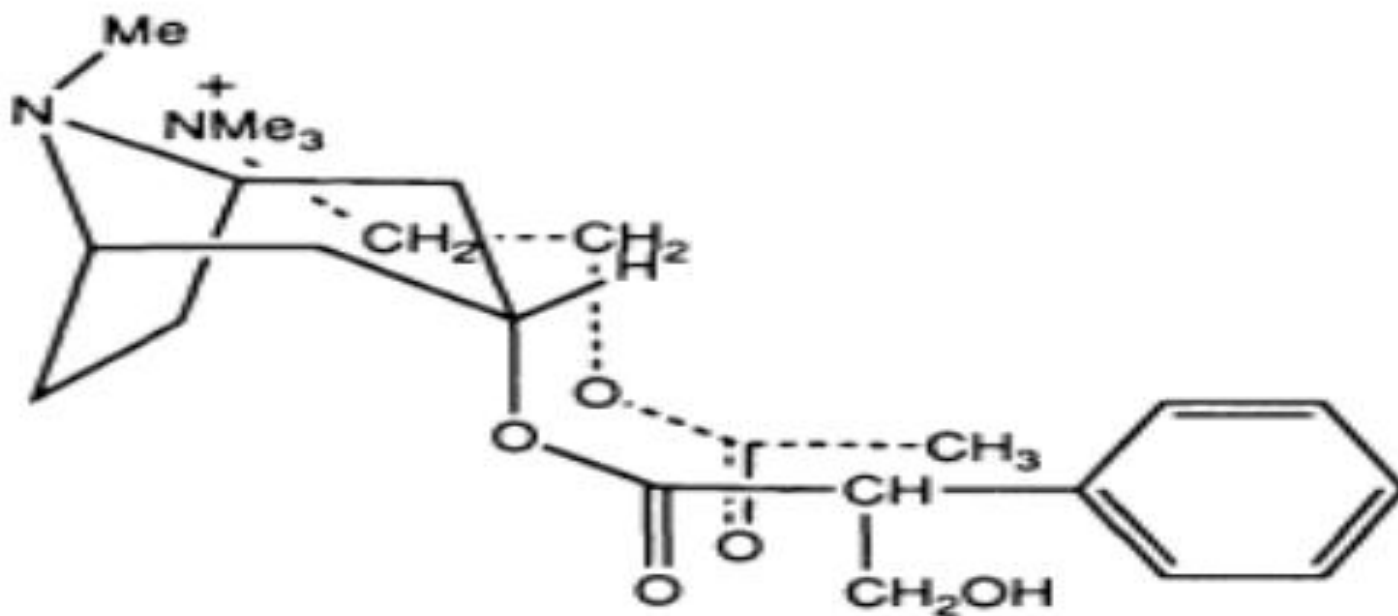
- Hyoscine (or scopolamine) is also obtained from solanaceous plants.
- In high doses, both hyoscine and atropine are hallucinogens



Hyoscine (scopolamine).

- These two compounds can bind to and block the cholinergic receptor.
- From their structure we can see that basic nitrogen and an ester group are present.

- If we superimpose the acetylcholine skeleton on to the atropine skeleton, the distance between the ester and the nitrogen groups are similar in both molecules

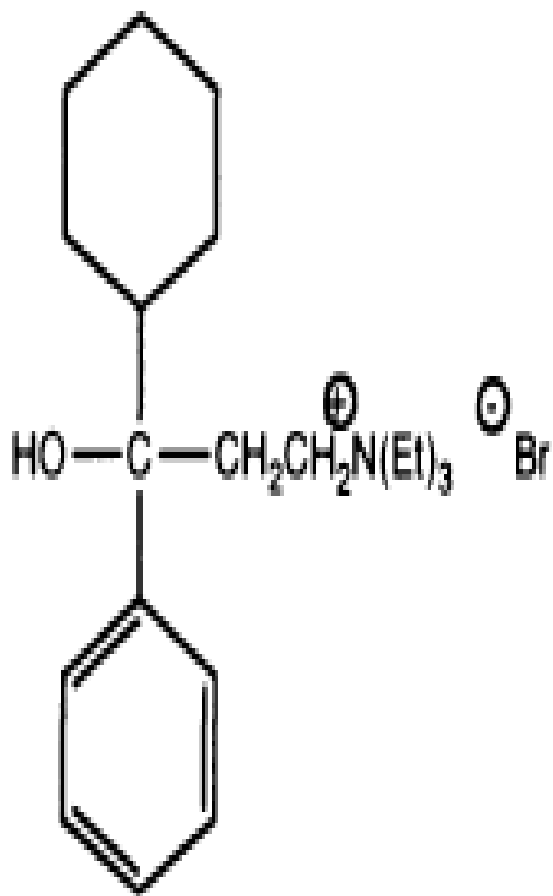


- The nitrogen atom in atropine is protonated when it binds to the cholinergic receptor.
- Atropine can be seen to have the two important binding features of acetylcholine
 - A charged nitrogen (when protonated) and
 - An ester group
- It is, therefore, able to **bind** to the receptor, but is unable to '**switch it on**'.

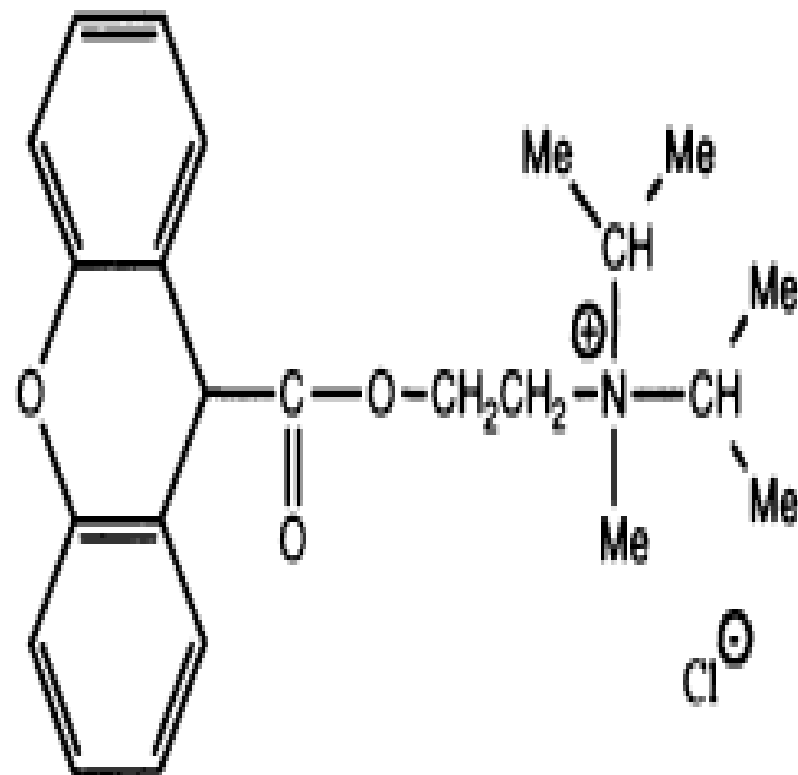
- Since atropine is a larger molecule than acetylcholine, it is capable of binding to other binding groups outside of the acetylcholine binding site.
- As a result, it interacts differently with the receptor, and does not induce the same conformational changes as acetylcholine.

Structural analogues based on atropine

- Analogues of atropine were synthesized to 'slim down' the structure to the essentials.
- This resulted in a large variety of active antagonists (e.g. tridihexethyl bromide and propantheline chloride).

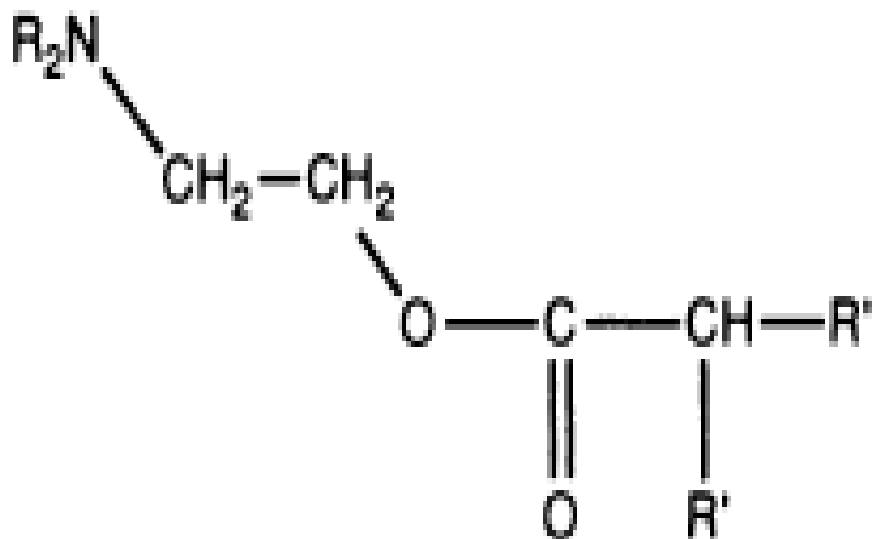


TRIDIHETHYL BROMIDE



PROPANTHELINE CHLORIDE

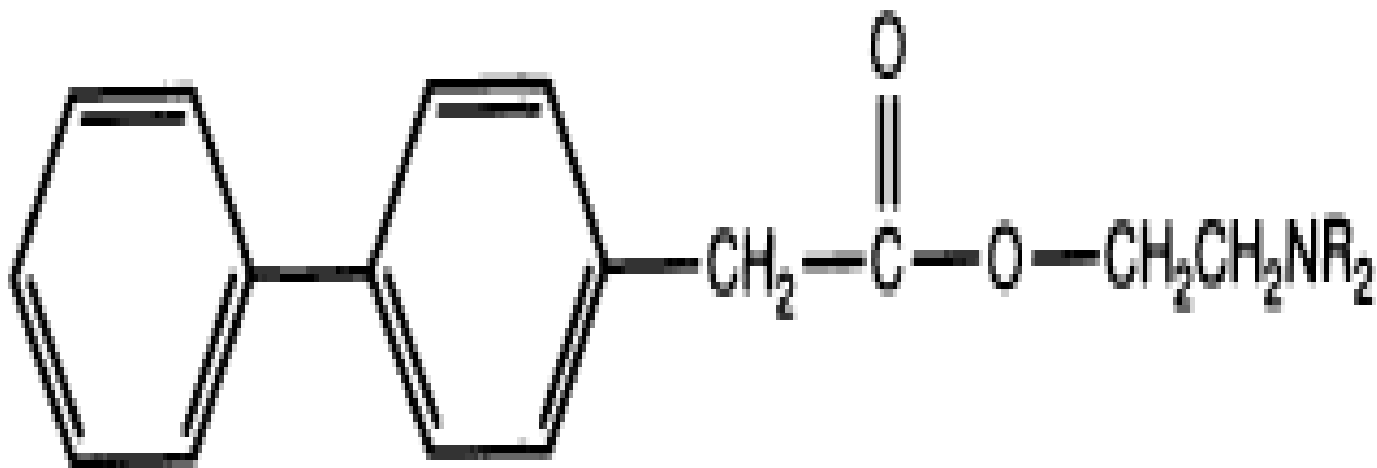
- SAR studies have come up with the following generalizations:



R' = Aromatic or
Heteroaromatic

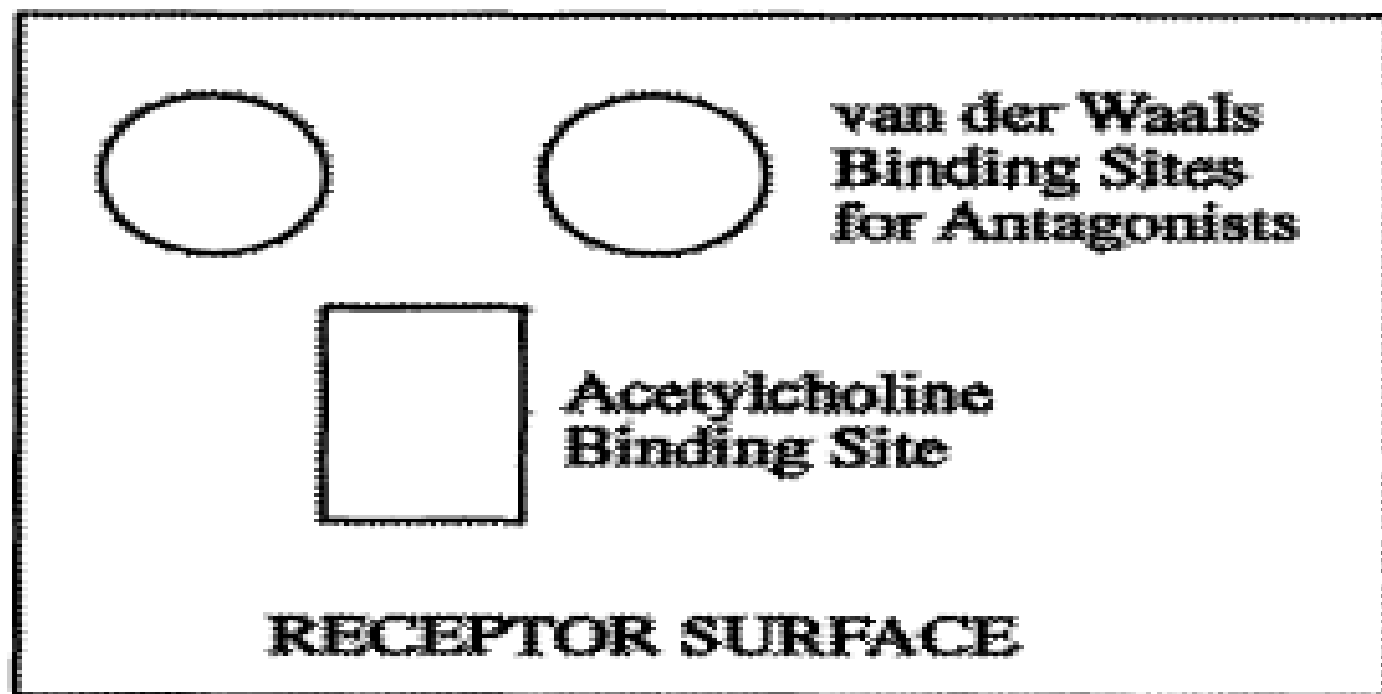
- The alkyl groups on nitrogen (R) can be larger than methyl (in contrast to agonists).
- The nitrogen can be tertiary or quaternary, whereas agonists must have quaternary nitrogen.
- Very large acyl groups are allowed ($R' =$ aromatic or heteroaromatic rings).
- This is in contrast with agonists where only the **acetyl** group is permitted.

- It is the last point which appears to be the most crucial in determining whether a compound will act as an antagonist or not.
- The acyl group has to be bulky, but it also has to have that bulk **arranged** in a certain manner (i.e. there must be some sort of branching in the acyl group).
- For example, the molecule shown in Fig. below has a large **unbranched acyl** group but is **not** an **antagonist**.

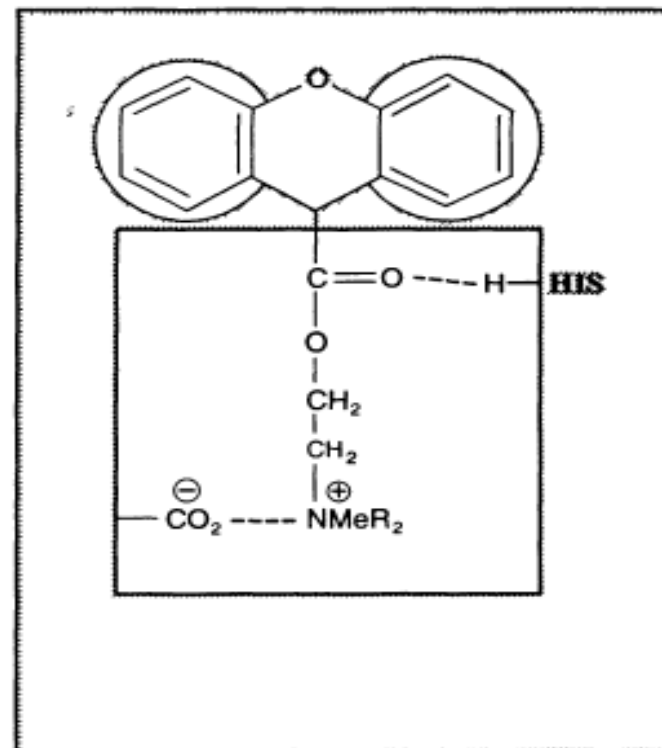
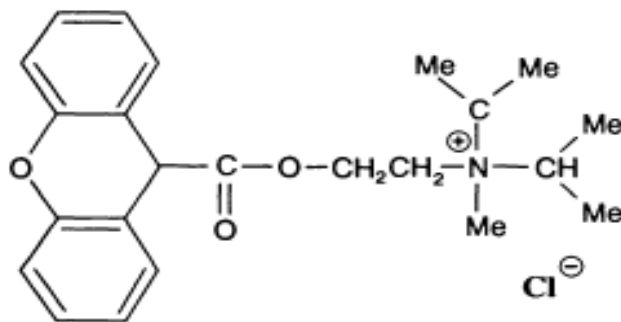


- There must be another binding site on the receptor surface next to the normal acetylcholine binding site.
- This area must be hydrophobic since most antagonists have aromatic rings.

- The overall shape of the acetylcholine binding site plus the extra binding site would have to be **T** or **Y-shaped** in order to explain the importance of branching in antagonists.

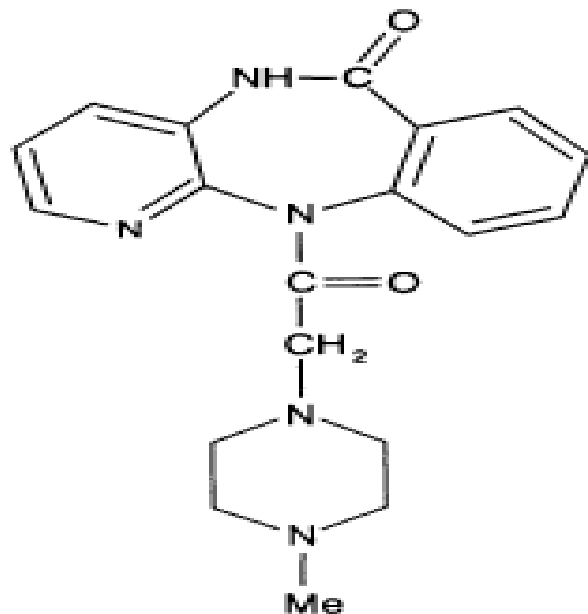


- A structure such as propantheline binds more strongly to the receptor than acetylcholine itself.



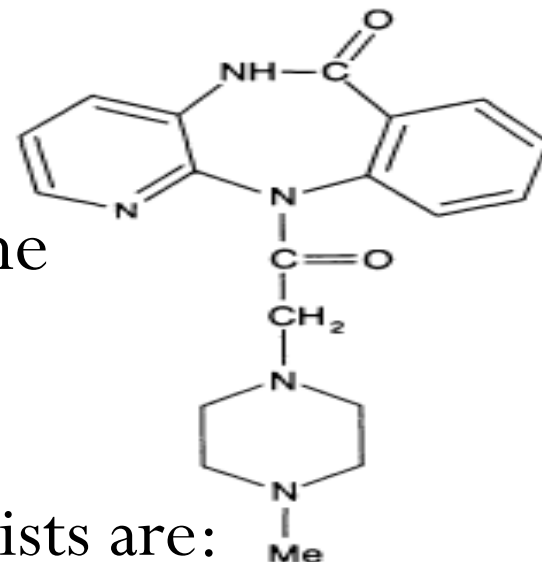
- The conformational changes induced in the receptor (if any are induced at all) will be different from those induced by acetylcholine.
- A large variety of antagonists have proved to be useful medicines, with many showing **selectivity for specific organs**.
- For example, some act at the intestine to relieve spasm, some act selectively to decrease gastric secretions, and are useful in ulcer therapy.

- This selectivity of action is due to the distribution properties of the drug than to receptor selectivity i.e.
- Compounds can reach one part of the body more easily than another
- However, the antagonist **pirenzepine**, which is used in the treatment of peptic ulcers, is a selective **M1 antagonist** with no activity against **M2** receptors.



- Since antagonists bind more strongly than agonists, they are better compounds to use for the labelling and identification of receptors on tissue preparations.

Pirenzepine



- The clinical uses of muscarinic antagonists are:
 - Shutting down the GIT and urinary tract during surgery;
 - Ophthalmic examinations;
 - Relief of peptic ulcers;
 - Treatment of Parkinson's disease;
 - Treatment of anticholinesterase poisoning;
 - Treatment of motion sickness

Antagonists of the nicotinic cholinergic receptor

Applications of nicotinic antagonists

- Nicotinic receptors are present in nerve synapses at ganglia, as well as at the neuromuscular synapse.

- Antagonists of ganglionic nicotinic receptor sites are not therapeutically useful since they **cannot distinguish** between the ganglia of the sympathetic nervous system and the ganglia of the parasympathetic nervous system (both use nicotinic receptors).
- But antagonists of the **neuromuscular junction** (NMJ) are therapeutically useful and are known as neuromuscular blocking agents.

Nicotinic antagonists

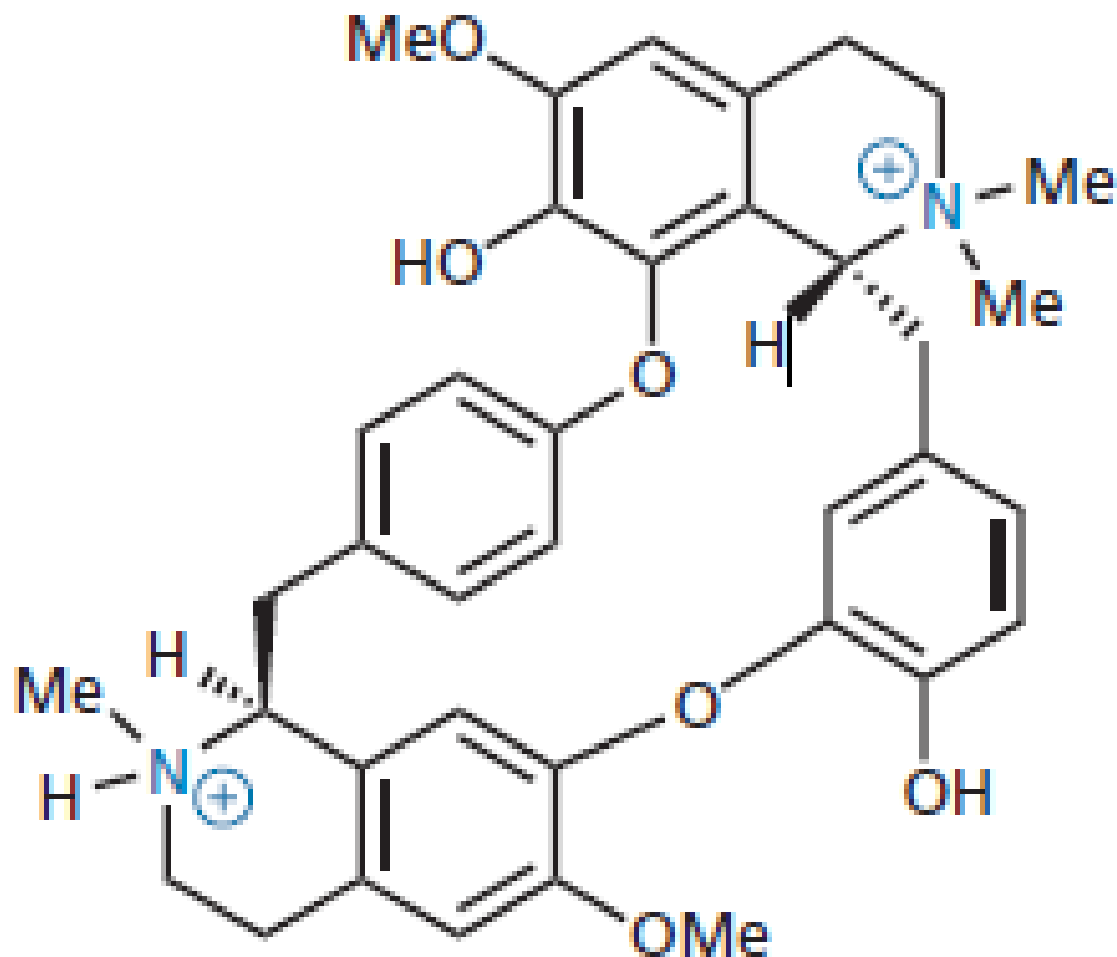
Curare (1516) and tubocurarine

- Curare was first identified when Spanish soldiers in South America found themselves the unwilling victims of poisoned arrows.
- It was discovered that the Indians were putting a poison on to the tips of their arrows.
- This poison was a crude, dried extract from a plant called *Chondrodendron tomentosum* and caused paralysis as well as stopping the heart.

- We now know that curare is a mixture of compounds.
- The active principle, however, is an antagonist of acetylcholine which blocks nerve transmissions from nerve to muscle.
- Can be used medically if they are taken at the right dose levels and under proper control.

- The main application is in the **relaxation** of abdominal muscles in preparation for surgery. (This allows the surgeon to use lower levels of general anesthetic)
- Curare, as mentioned above, is actually a mixture of compounds, and it was not until 1935 that the active principle (**Tubocurarine**) was isolated.

- The determination of the structure took even longer and was not established until 1970.



Important question to be raised here

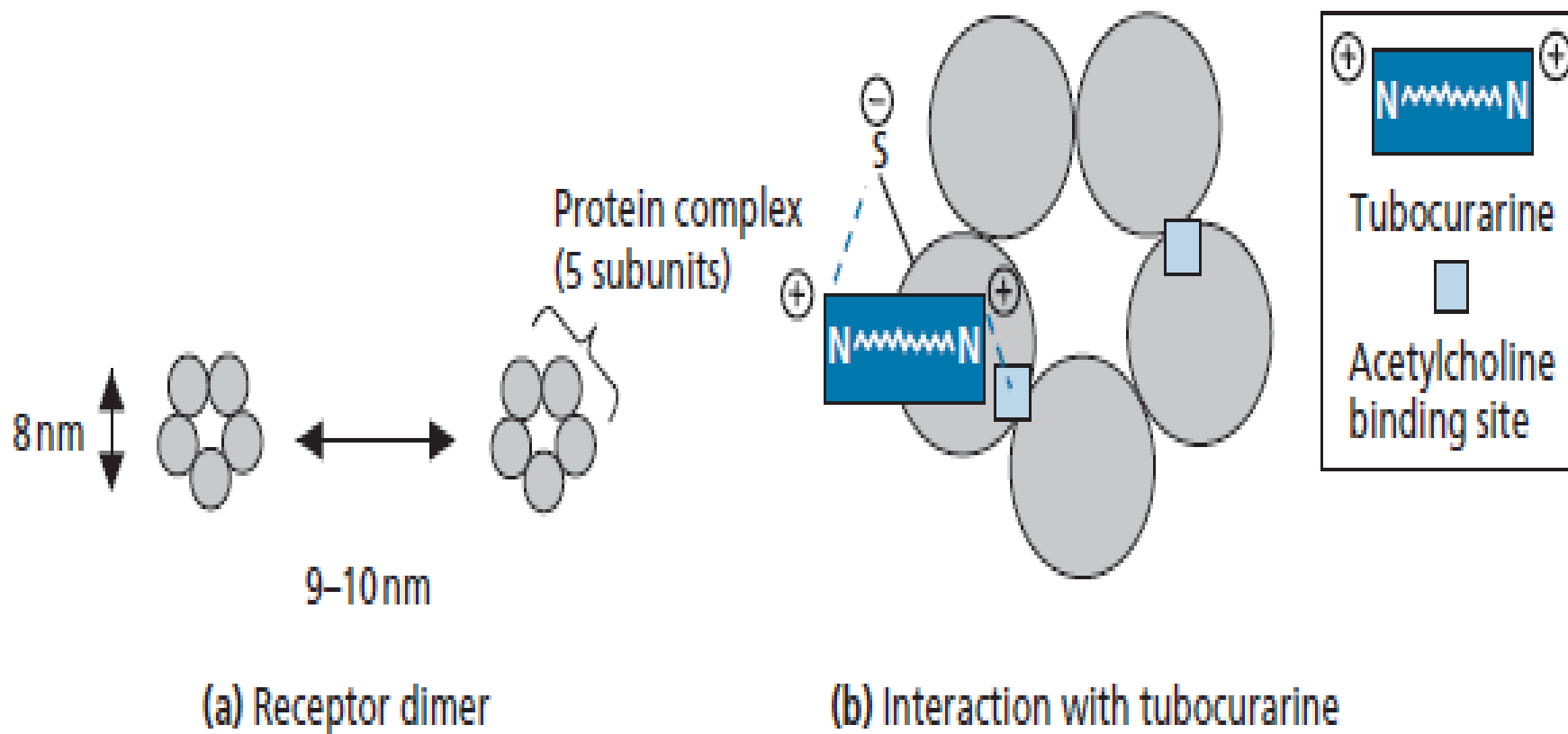
- Why should tubocurarine bind to and block the cholinergic receptor without having **ester** functional group?
- The answer lies in the fact that the molecule has *two positively charged nitrogen* atoms (one tertiary which is protonated, and one quaternary).

There are three assumptions

1. Tubocurarine forms a bridge between two adjacent cholinergic receptors.
 - But latter it was proved that the distance between the two receptor proteins dimer was larger than (9-10 nm) the distance between the two positively charged nitrogen centers (1.15nm).

2. The tubocurarine molecule bridges two acetylcholine binding sites within the one protein complex. Since there are two such sites within the complex, this appears an attractive alternative theory.
- However, the two sites are further apart than 1.15 nm and so this too seems unlikely.

3. One of the positively charged nitrogens on tubocurarine binds to the anionic binding site of the acetylcholine receptor in the protein complex, while the other nitrogen binds to a nearby cysteine residue 0.9-1.2 nm away.



- Anyways despite the above uncertainties, the interaction is **extremely strong** and would more than make up for the lack of the ester binding interaction.
- It is also clear that the distance between the two positively charged nitrogen atoms is crucial to activity.
 - ❖ Therefore, **analogues which retain this distance** should also be good antagonists.

Decamethonium and suxamethonium

- Decamethonium is a simple analogue of tubocurarine.
- It is a straight-chain molecule and as such is capable of a large number of conformations.
- The fully extended conformation would position the nitrogen centres **1.4 nm** apart
- but there are more folded conformations that position the nitrogen centres 1.14nm apart which compares well with the equivalent distance in tubocurarine (**1.15 nm**).

- The drug binds strongly to cholinergic receptors and has proved a useful clinical agent.
- *Disadvantages;*
 - Initially it acts as agonist- leads to a brief contraction of the muscle.



- It binds too strongly and as a result patients **take a long time** to recover from its effects.
- Not completely selective for the neuromuscular junction and has an effect on acetylcholine receptors at the **heart**. This leads to an **increased** heart rate.

- So to overcome such limitations the following approaches were tried;
- Introduction of instability to the molecule
 - Incorporating timer control whereby the molecule can be **switched off** quickly and become inactive.
- Success was first achieved by introducing ester groups into the chain while retaining the distance between the two charged nitrogens to give **suxamethonium**.

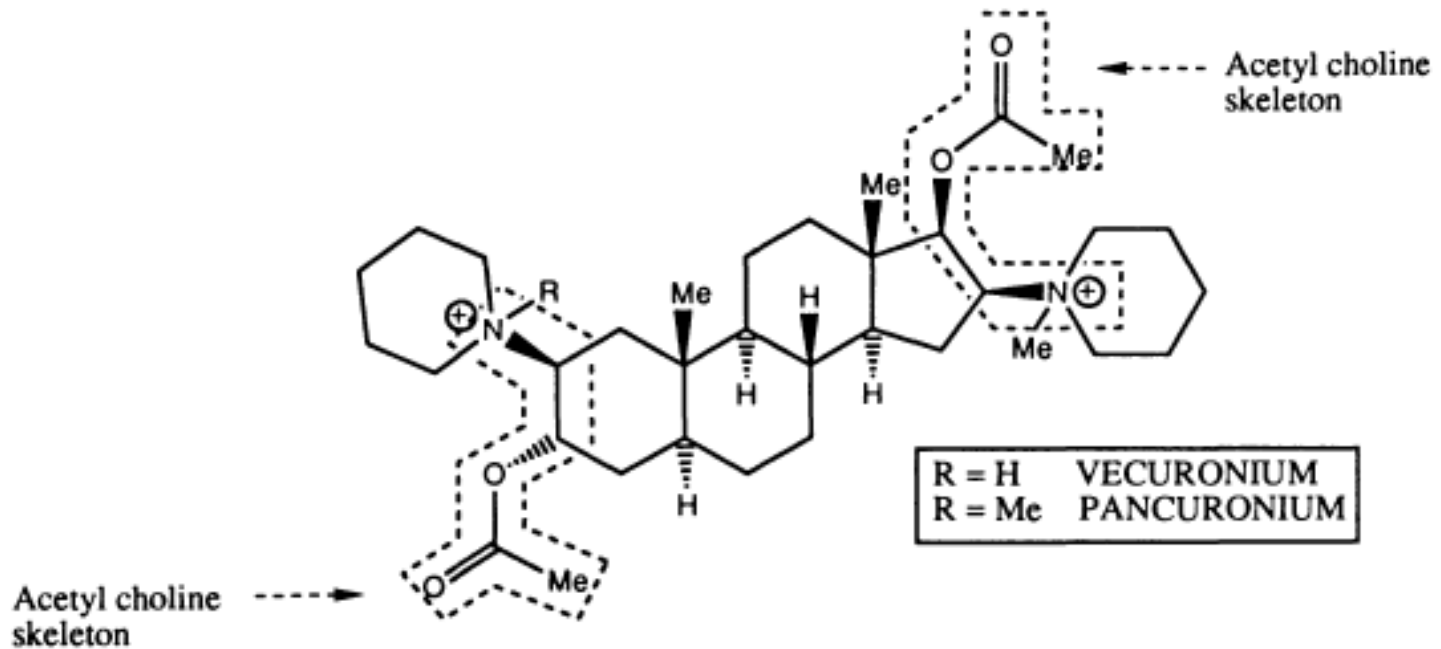


- The ester groups are susceptible to chemical and enzymatic hydrolysis.
- Suxamethonium has duration of action of five minutes, but suffers from other side-effects.(effect on autonomic ganglia)
- Furthermore, about one person in every two thousand lacks the enzyme which hydrolyses suxamethonium.

Pancuronium and vecuronium

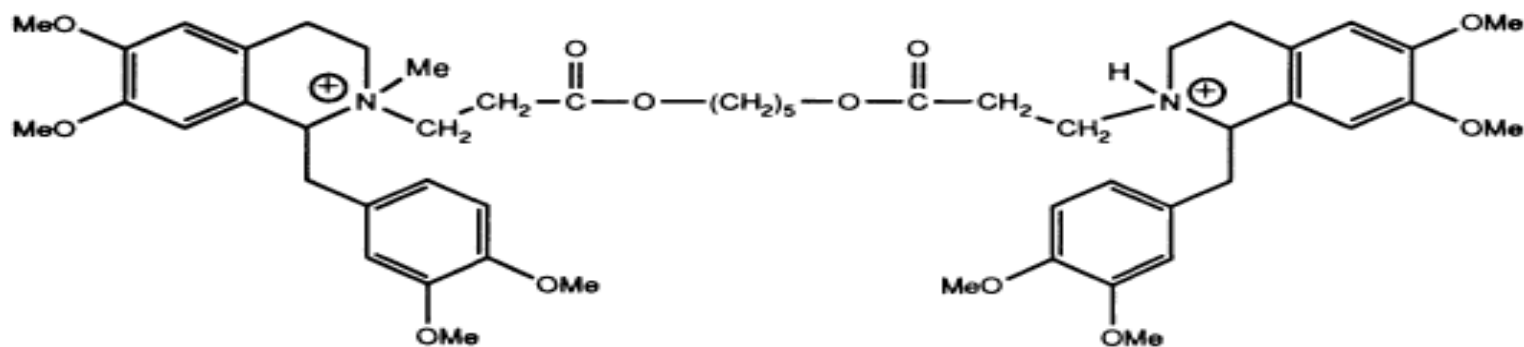
- Pancuronium and vecuronium were designed to act like tubocurarine, but with a steroid nucleus acting as the 'spacer'.
- The distance between the quaternary nitrogens is 1.1 nm as compared to 1.15 nm in tubocurarine.
- Acyl groups were also added to introduce two acetylcholine skeletons into the molecule in order to improve affinity for the receptor sites

- These compounds have a **rapid onset of action** and do not affect blood pressure. However, they are not as rapid in onset as suxamethonium and also last too long (45 minutes).



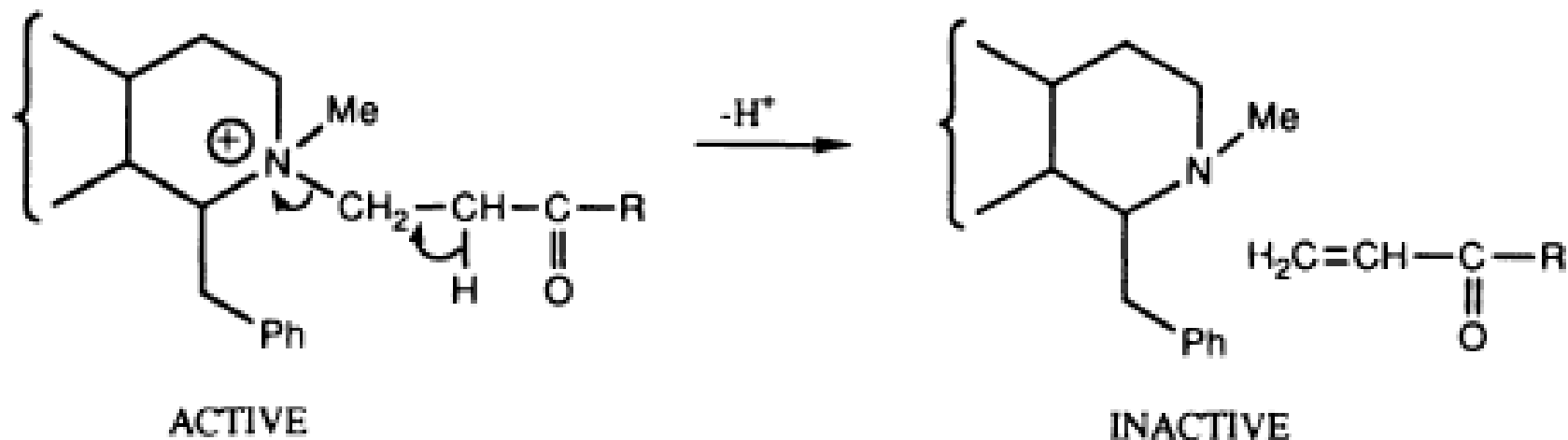
Atracurium

- The design of atracurium was based on the structures of tubocurarine and suxamethonium.
- It is superior to both since it **lacks cardiac side-effects** and is rapidly broken down in blood.



- The rapid breakdown was designed into the molecule by incorporating a **self destruct** mechanism.

- At blood pH (slightly alkaline at 7.4), the molecule can undergo a **Hofmann elimination**.



- Once this happens, the compound is inactivated since the positive charge on the nitrogen is lost.
- It is a particularly clever example of drug design in that the very element responsible for the molecule's biological activity promotes its deactivation.

The important features of atracurium are:

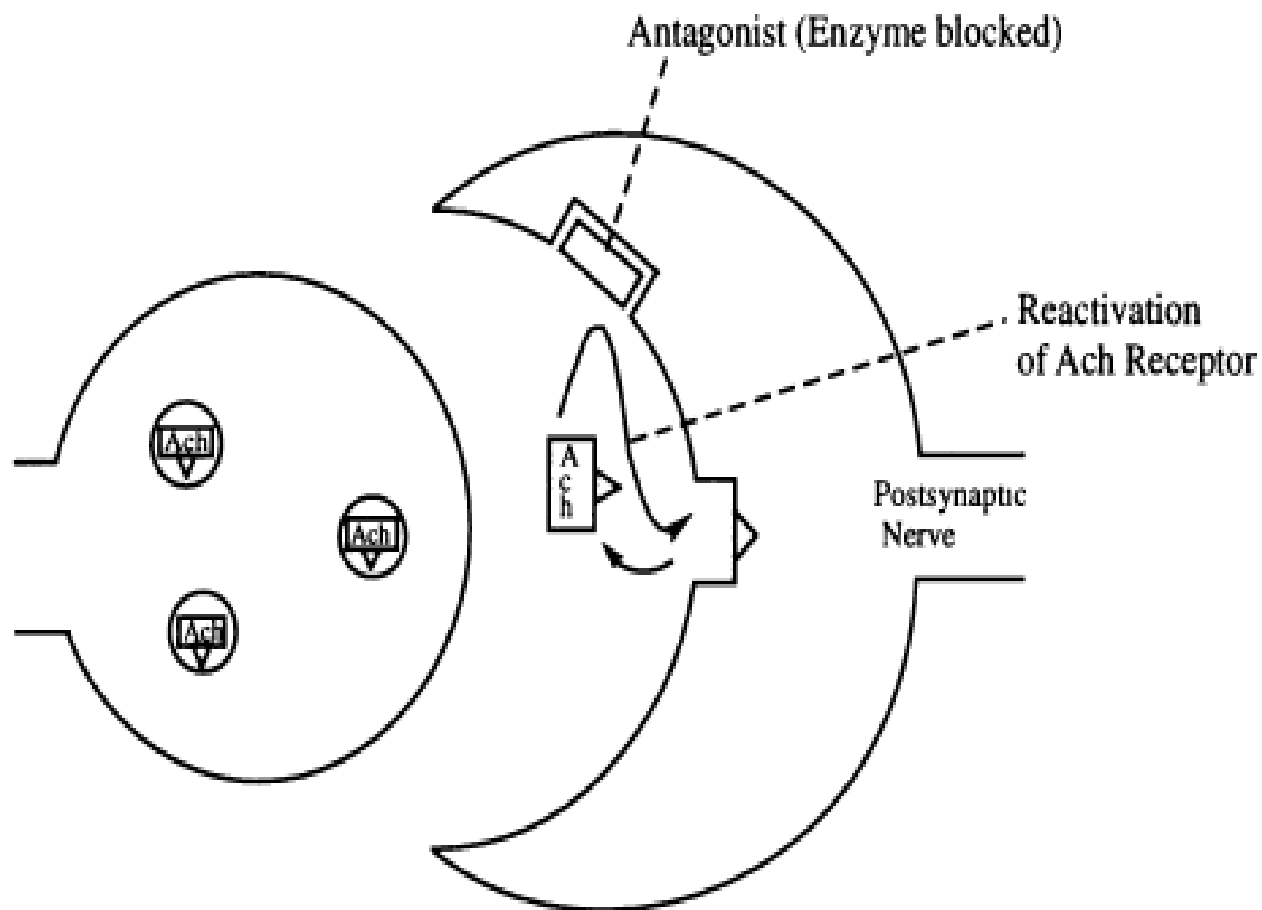
- The spacer.
 - This is the 13-atom connecting chain which connects the two quaternary centres and separates the two centres.
- The blocking units;
 - The cyclic structures at either end of the molecule block the receptor site from acetylcholine.
- The quaternary centres.
 - These are essential for receptor binding. If one is lost through Hofmann elimination, the binding interaction is too weak and the antagonist leaves the binding site.

Acetylcholinesterase inhibitors (indirectly acting cholinergic agonists)

Anticholinesterases and acetylcholinesterase

- **Acetylcholinesterase** is the enzyme which hydrolyses acetylcholine.
- Anticholinesterases are antagonists of this enzyme
- Antagonist at the acetylcholinesterase enzyme will have the same biological effect as an agonist at the cholinergic receptor.

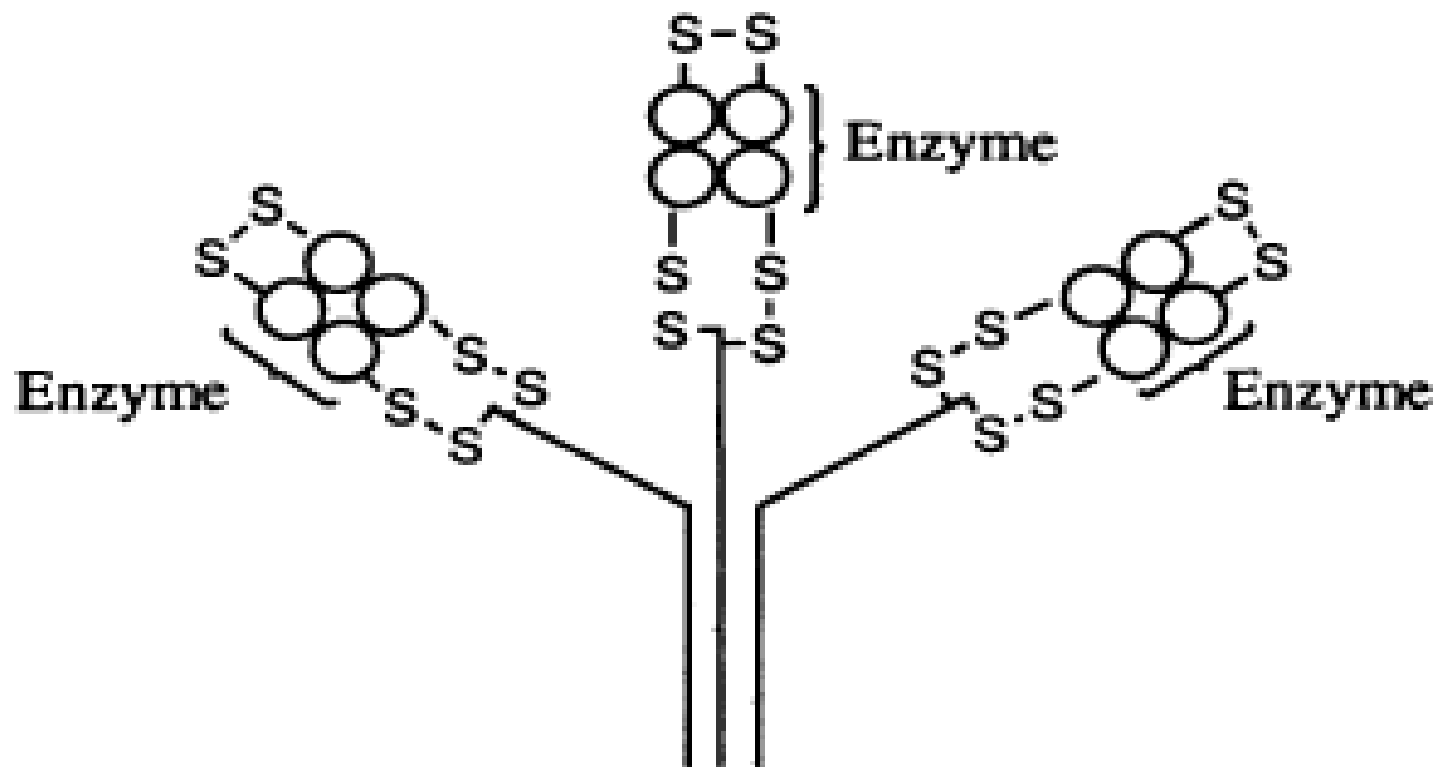
Anticholinesterases...



Structure of the acetylcholinesterase enzyme

- Has a fascinating tree-like structure
 - The trunk of the tree is a collagen molecule
 - There are three branches (disulfide bridges) leading off from the trunk
 - The enzyme itself is made up of four protein subunits, each of which has an active site

Structure of the...



Design of anticholinesterases

- The design of anticholinesterases depends on
 - The shape of the enzyme active site,
 - The binding interactions involved with acetylcholine, and
 - The mechanism of hydrolysis.

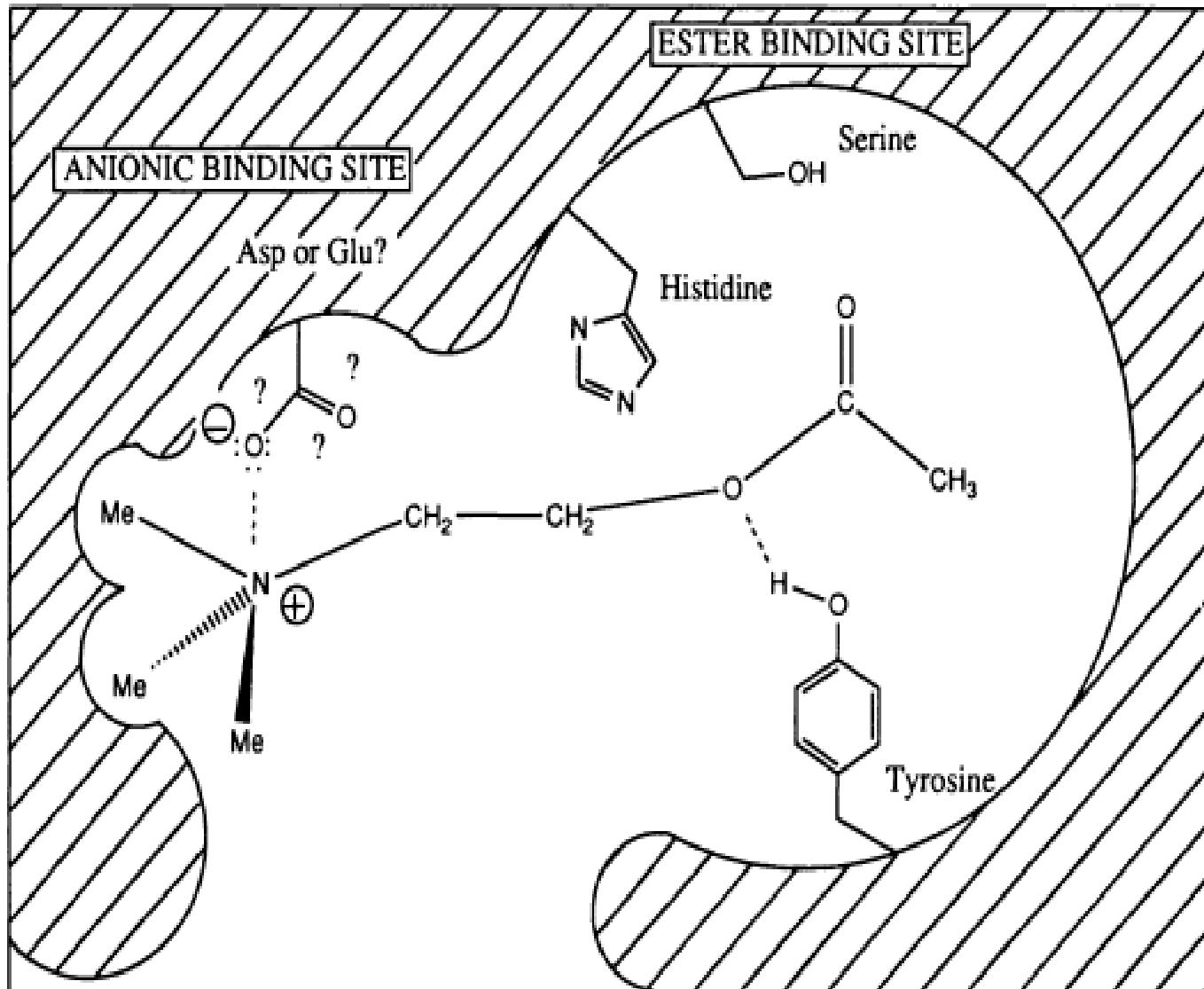
Binding interactions at the active site

- There are two important areas to be considered
 - The *anionic* binding site and the *ester* binding site
- Note that:

Acetylcholine binds to the cholinesterase enzyme by

- (a) Ionic bonding to an Asp or Glu residue,
- (b) Hydrogen bonding to a tyrosine residue

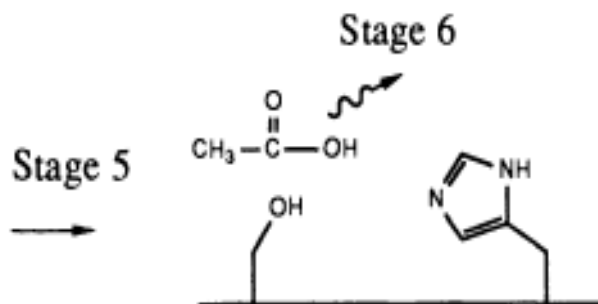
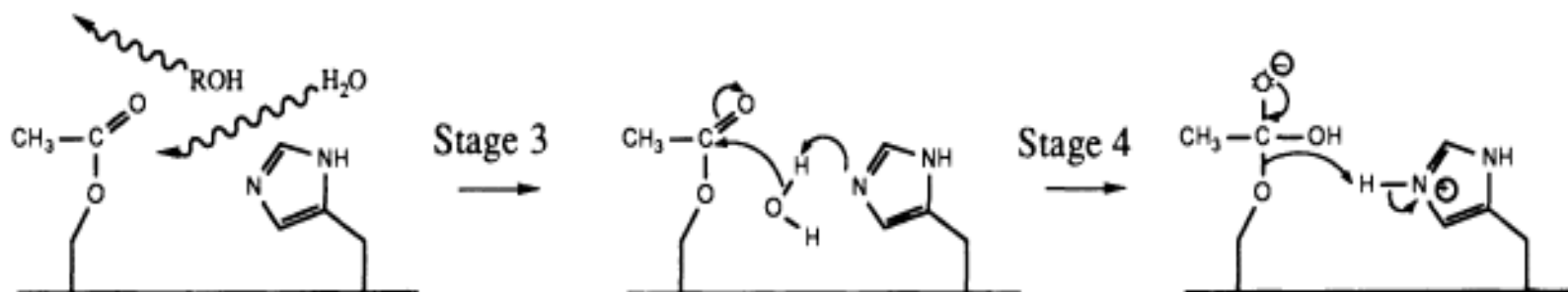
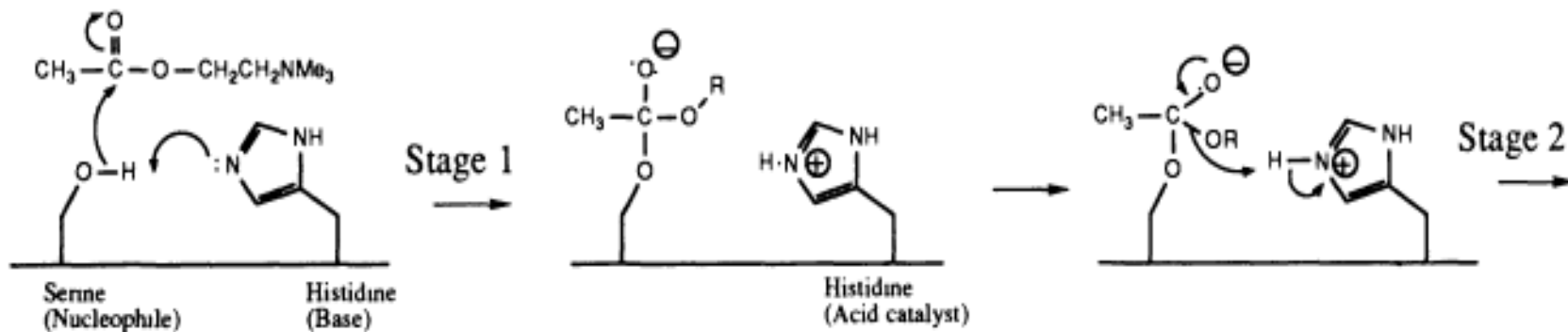
Binding interactions...



Mechanism of hydrolysis

- The histidine residue acts as an **acid/base catalyst** throughout the mechanism
- Serine plays the part of **a nucleophile** (but is poor nucleophile)

Stages to the mechanism



Stages to ...

- Enzymatic hydrolysis by cholinesterase is one hundred million times faster than chemical hydrolysis.
- The process is so efficient that acetylcholine is hydrolysed within a hundred microseconds of reaching the enzyme

Anticholinesterase drugs

- Anticholinesterase drugs stop the enzyme from hydrolysing acetylcholine
- This antagonism can be
 - reversible
 - Irreversible
- There are two main groups of acetylcholinesterases
 - i. Carbamates
 - ii. Organophosphorus agents

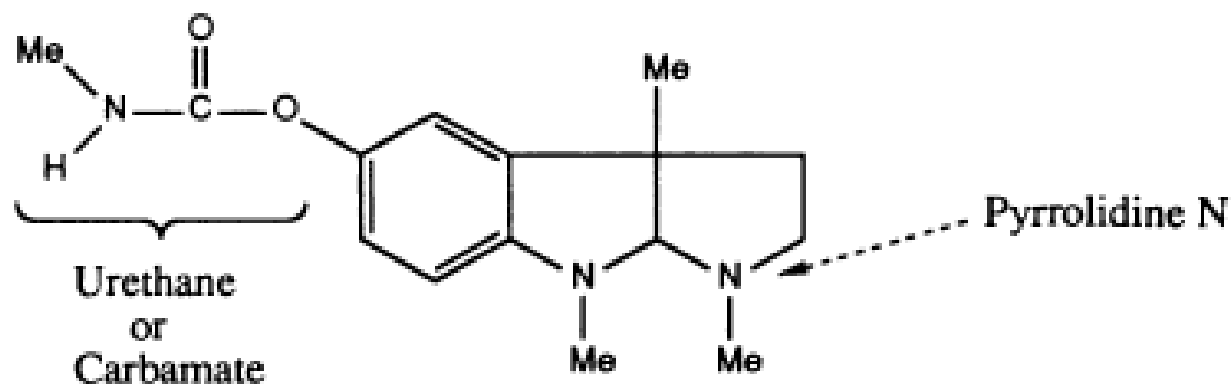
i. The carbamates

Physostigmine

- Is a natural product
- was discovered in 1864 as a product of the poisonous calabar beans from West Africa
- The structure was established in 1925

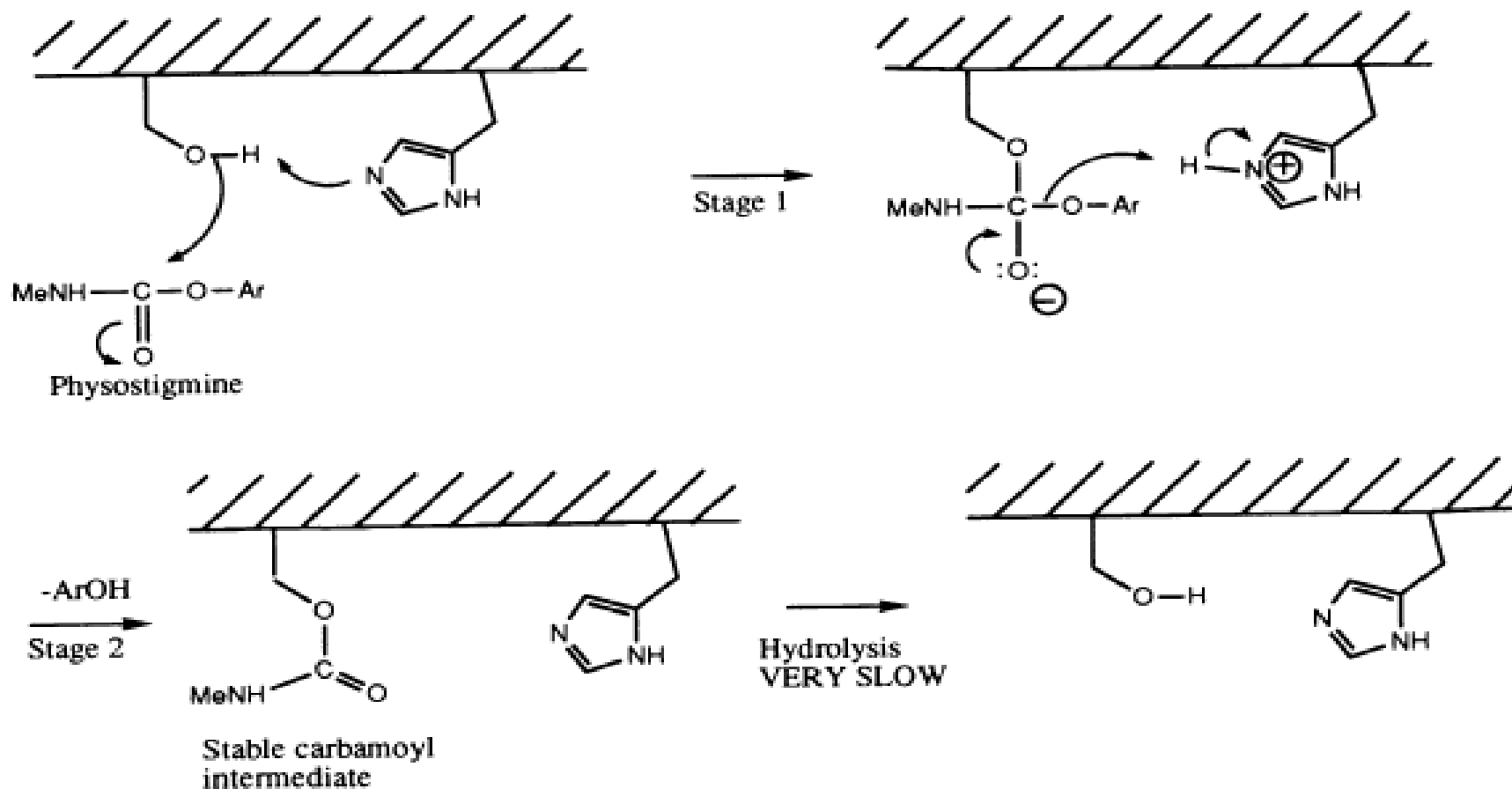
The carbamates...

Structure-activity relationships (SAR)



- The carbamate group is essential to activity
- The benzene ring is important
- The pyrrolidine nitrogen (which is ionized at blood pH) is important

Physostigmine's antagonistic properties

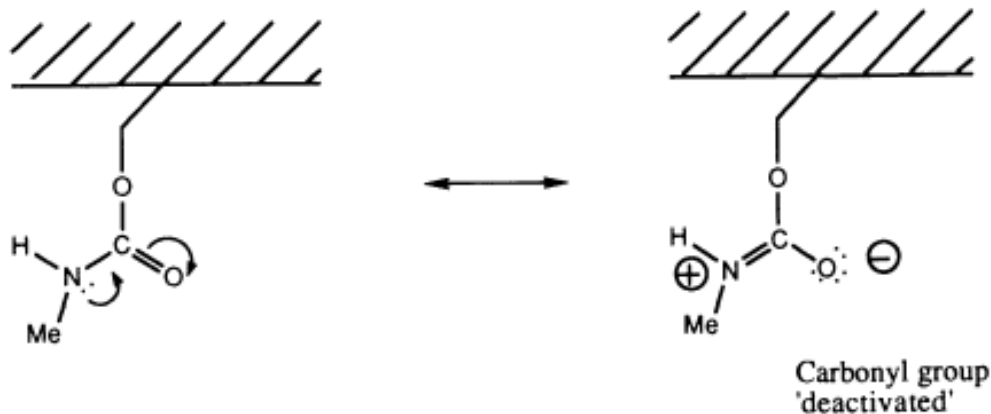


Physostigmine's antagonistic...

- The first three stages proceed as normal with the above steps that we have seen for acetylcholine. However; the next stage turns out to be extremely slow.

Why is this final stage so slow?

- The carbamoyl/enzyme intermediate is stabilized because the nitrogen can feed alone pair of electrons into the carbonyl group

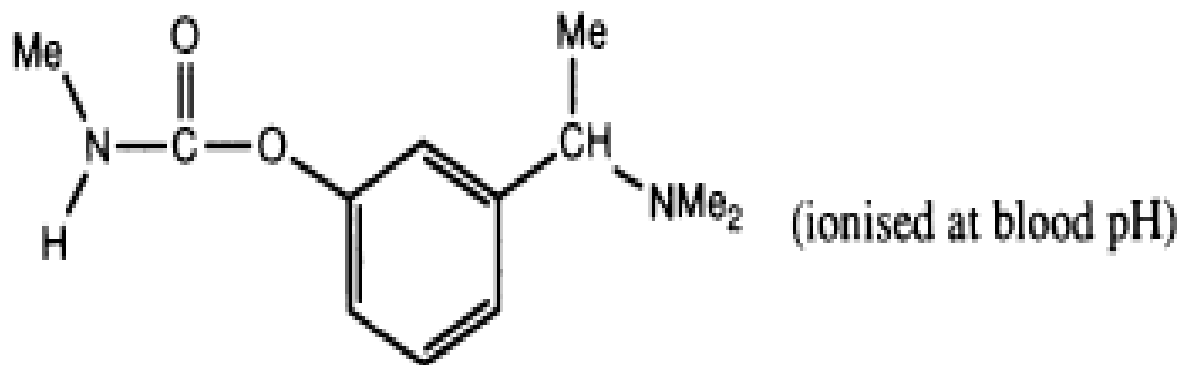


Analogues of physostigmine

- Physostigmine has limited medicinal use
 - only been used in the **treatment of glaucoma**
- Simpler analogues have been made and have been used in the treatment of **myasthenia gravis** and as an **antidote to curare**.

- They include

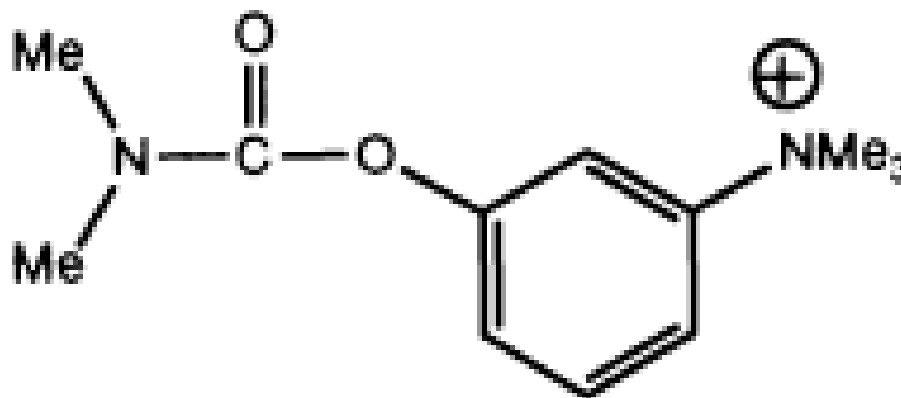
Miotine



Analogues of...

- Miotine suffers from the following disadvantages:
 - susceptible to chemical hydrolysis
 - CNS side effect

Neostigmine

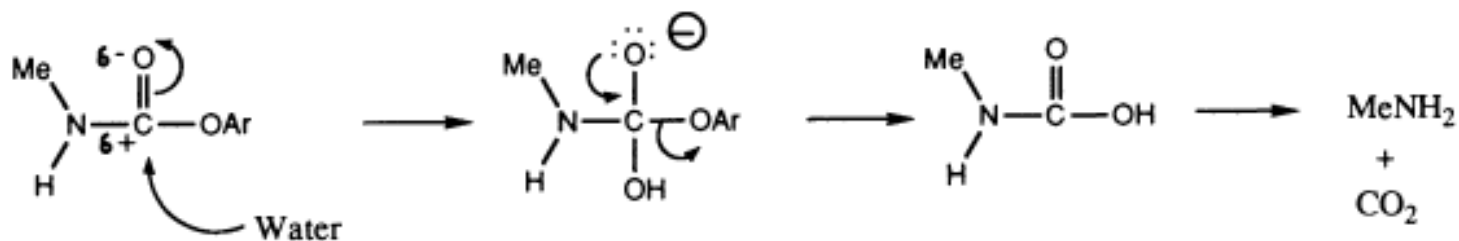


- ✓ Was designed to deal with both the problems described above.

Analogue of...

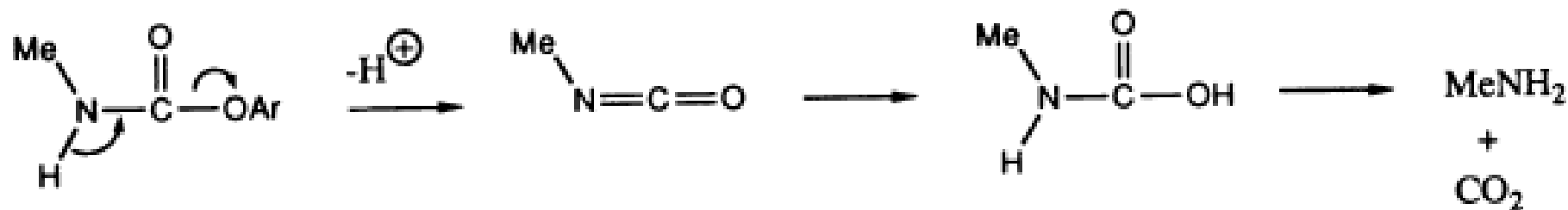
- Increased stability to hydrolysis is achieved by using a **dimethylcarbamate** group rather than a **methylcarbamate** group.
- There are two possible explanations for this, based on two possible hydrolysis mechanisms

Mechanism 1- nucleophilic substitution by a water

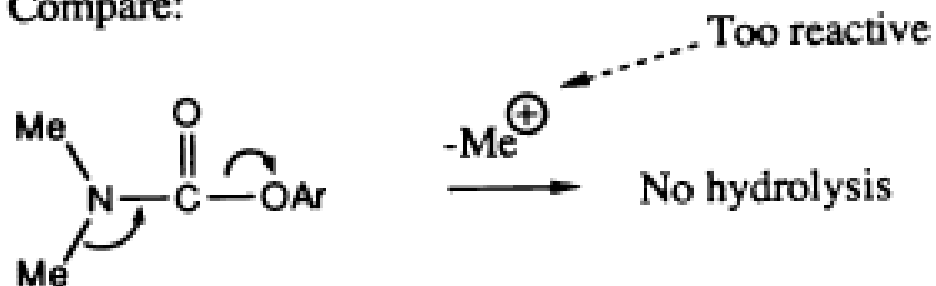


Analogues of...

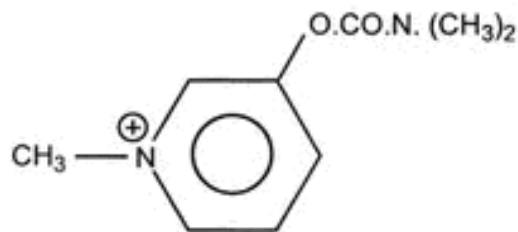
- **Mechanism 2**- a fragmentation whereby the phenolic group is lost before the nucleophile is added



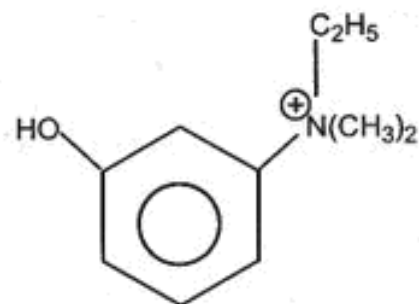
Compare:



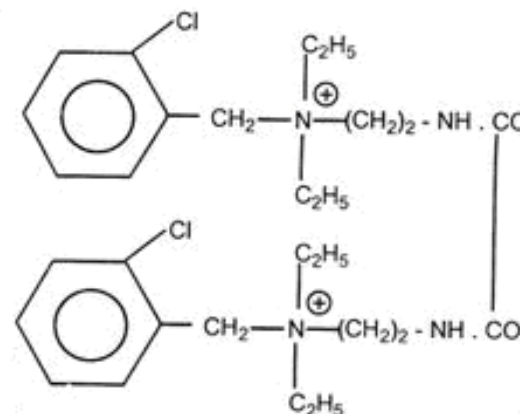
Other Reversible Cholinesterase Inhibitors



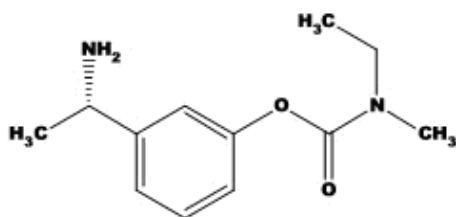
Pyridostigmine



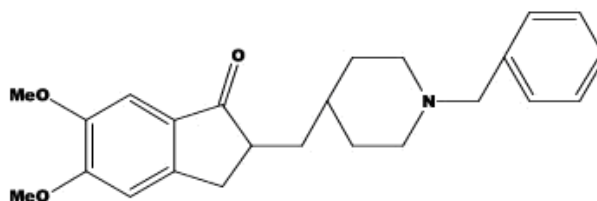
Edrophonium



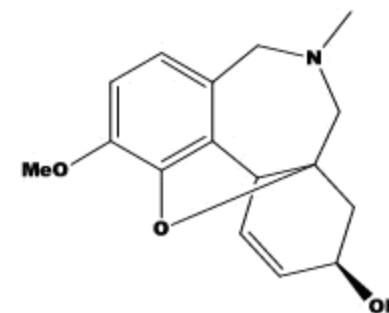
Ambenonium



Rivastigmine



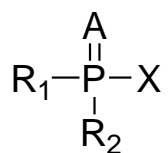
Donepezil



Galantamine

Irreversible Inhibitors of Acetylcholinesterase

- Both AChE and BuChE are inhibited irreversibly by a group of phosphate esters that are highly toxic.
- These chemicals are nerve poisons and have been used in warfare, in bioterrorism, and as agricultural insecticides.
- A general formula for such compounds



where R_1 = alkoxy

R_2 = alkoxy, alkyl, or tertiary amine

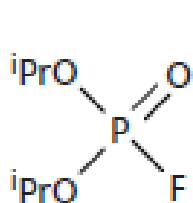
X = good leaving group (e.g., F, CN, thiomalate, *p*-nitrophenyl)

When A is sulfur, bioactivation is required before the compound becomes effective as an inhibitor of cholinesterase.

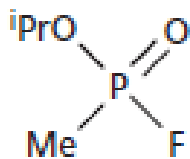
- Inhibition of AChE by organophosphorus compounds takes place in two steps
 - Association of enzyme and inhibitor and
 - **Phosphorylation** step, completely analogous to **acylation** by the substrate.
- Although insecticides and nerve gases are irreversible inhibitors of cholinesterases by forming a phosphorylated serine at the esteratic site of the enzyme, it is possible to **reactivate** the enzyme if action is taken soon after exposure to these poisons.
- Several compounds can provide a nucleophilic attack on the phosphorylated enzyme and cause regeneration of the free enzyme.

1. Nerve gas

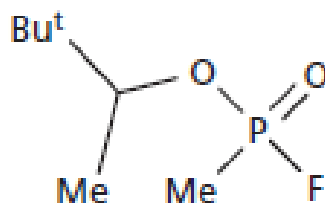
- The nerve gases **dyflos** and **sarin** were discovered and perfected long before their mode of action was known.
- Dyflos was developed as a nerve gas in the Second World War.
 - It inhibits AChE by irreversibly phosphorylating the serine residue at the active site.



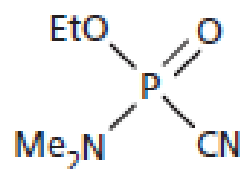
Dyflos
(Diisopropyl
fluorophosphonate)



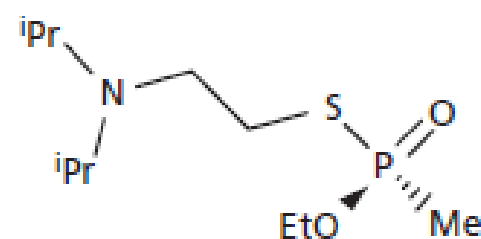
Sarin



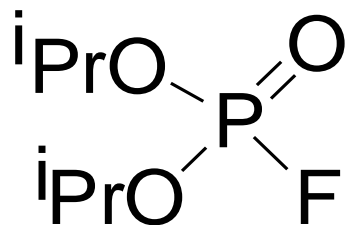
Soman



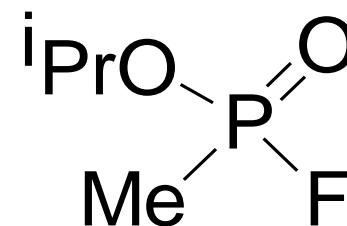
Tabun



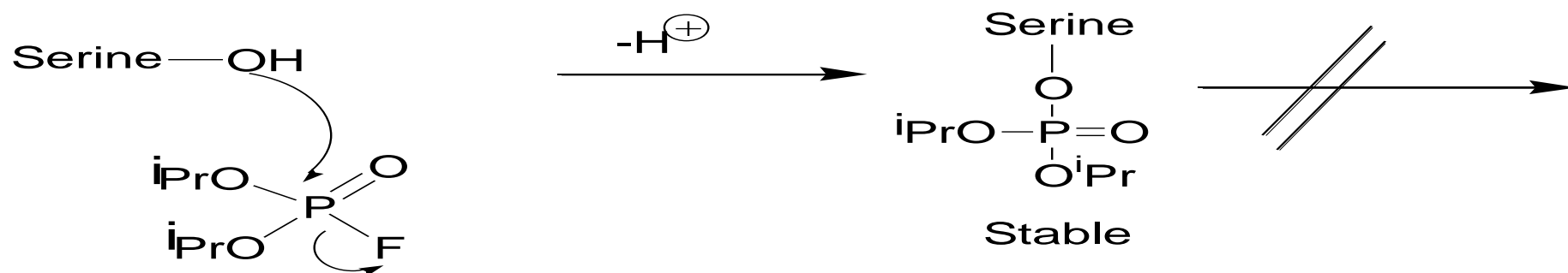
VX



DYFLOS (Diisopropyl fluorophosphate)



SARIN

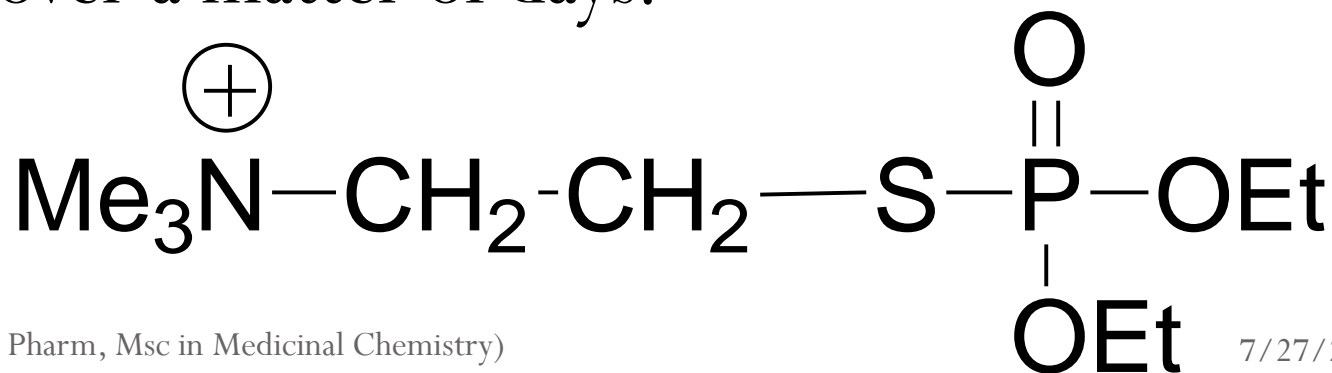


- Phosphorylated enzyme is extremely resistant to hydrolysis

2. Medicine

- **Echothiophate** were designed to fit the active site more accurately by including a quaternary amine to bind with the anionic region.

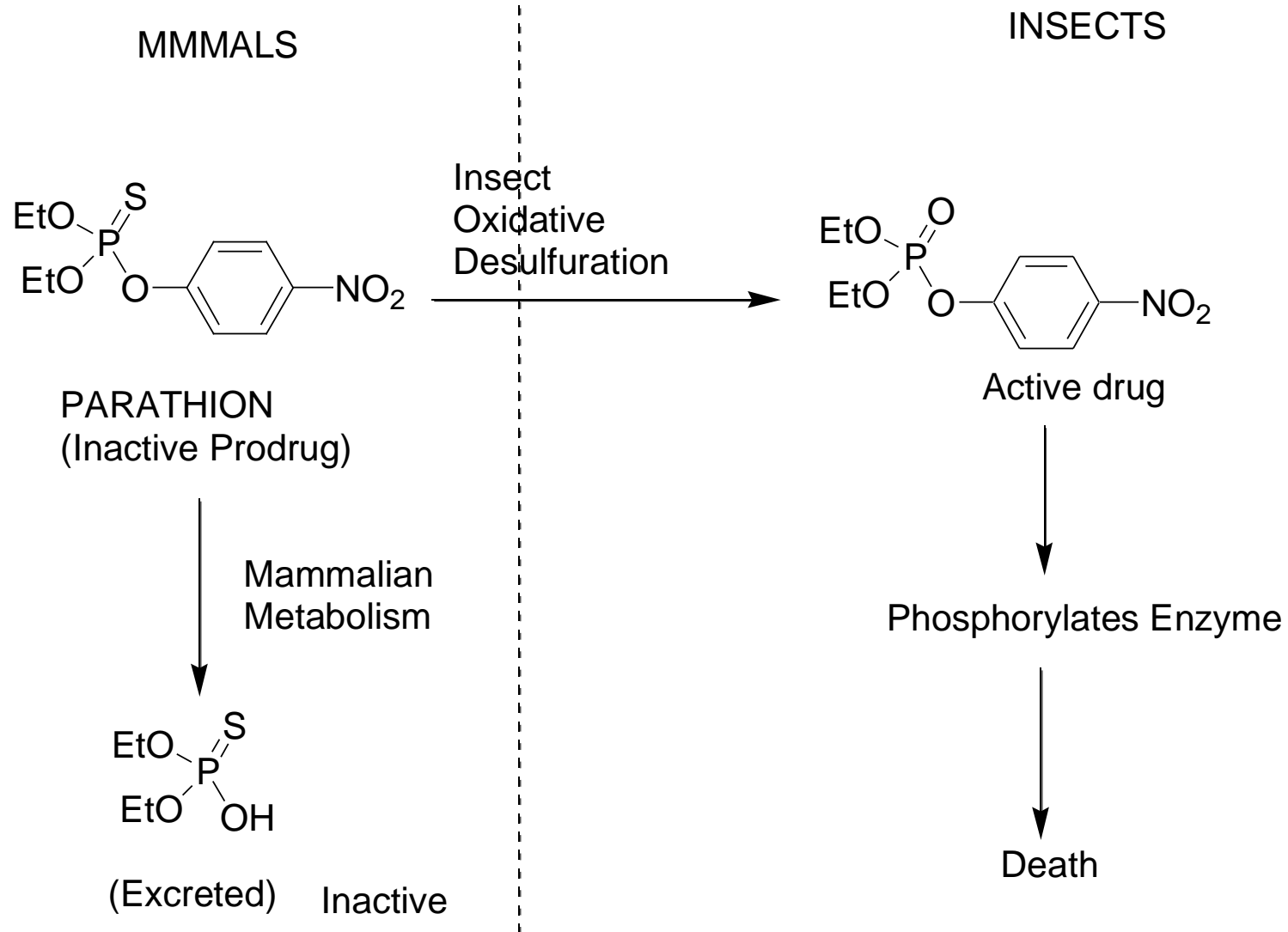
- This meant that lower doses would be more effective.
- Echothiopate is used medicinally in the form of eye drops for the treatment of **glaucoma** and has advantages over dyflos.
- Unlike dyflos, ecothiopate slowly hydrolyses from the enzyme over a matter of days.



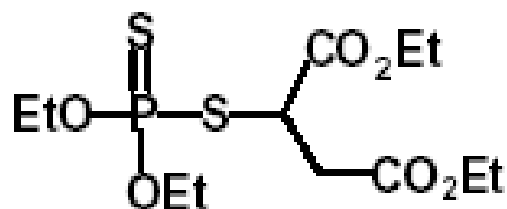
3. Insecticides

- Parathion and malathion are relatively non-toxic with respect to nerve gases.
- The phosphorus-sulfur double bond prevents these molecules from antagonizing the active site on the acetylcholinesterase enzyme.
- The equivalent compounds containing a phosphorus-oxygen double bond are, on the other hand, **lethal** compounds.

- There are no metabolic pathways in mammals, which can convert the phosphorus-sulfur double bond to a phosphorus-oxygen double bond.
 - Such pathway does, however, exist in insects
- In the latter species, parathion and malathion act as **prodrugs**.
- They are metabolized by oxidative desulfuration to give the anticholinesterases, which irreversibly bind to the insects' acetylcholinesterases enzymes and lead to death.
- In mammals, the same compounds are metabolized in a differently way to give inactive compounds which are then excreted.



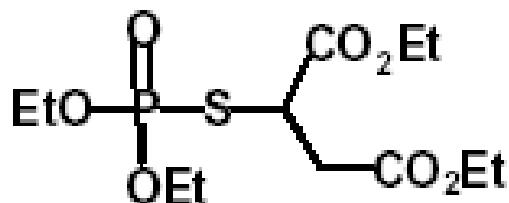
Metabolization of insecticides in mammals and insects



Malathion

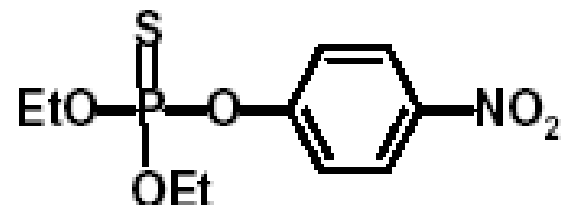
(Weah AChE inhibitor)

↓
**Microsomal
oxidation**



Malaoxon

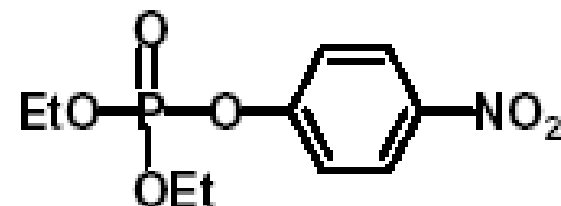
(10,000 times more active
AChE inhibitor)



Parathion

(Weah AChE inhibitor)

↓
**Microsomal
oxidation**



Parathion

(High AChE inhibitory
activity)

Mechanism of Action

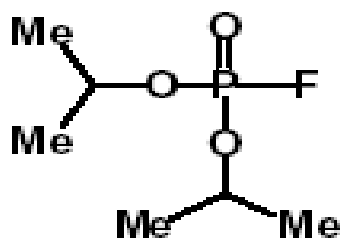
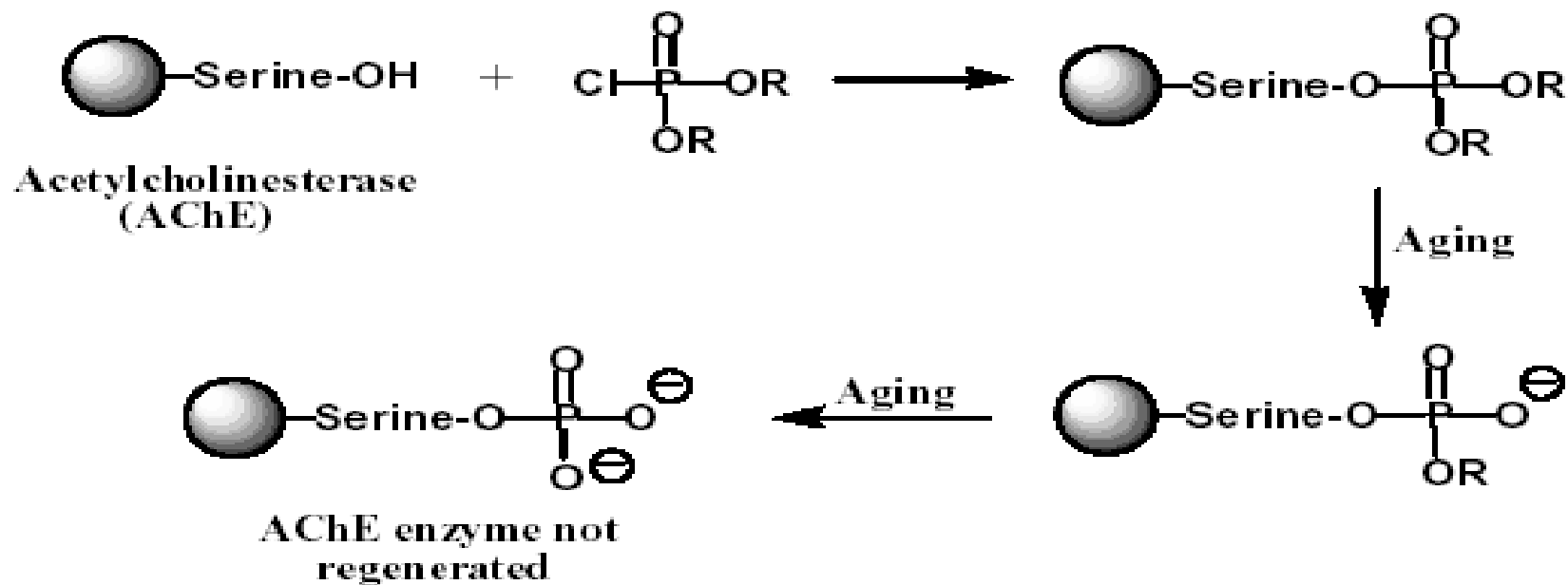
- The chemical logic involved in the development of effective AChEIs was to synthesize compounds that would be substrates for AChE and result in an acylated enzyme **more stable** to hydrolysis than a **carboxylate ester**.

- Phosphate esters are very stable to hydrolysis, being even more stable than many amides.
- Application of this chemical property to the design of AChEI compounds led to derivatives of **phosphoric**, **pyrophosphoric** and **phosphonic** acids that are effective inhibitors of AChE.
- These act as inhibitors by the same mechanism as the carbamate inhibitors except that they leave the enzyme esterified as the phosphate esters.

- The rate of hydrolytic regeneration of the phosphorylated enzyme is much slower than that of the carbamylated enzyme and its rate is measured in hours.
- Because duration of action of these compounds is much longer than that of the carbamate esters, they are referred to as **irreversible inhibitors** of AChE.

- An important difference between irreversibly phosphoester derived AChEIs and reversible AChEIs is that the phosphorylated AChE can undergo a process known **as aging**.
- Aging is the result of **cleavage** of one or more of the **phosphoester** bonds while the AChE is phosphorylated.
- This reaction affords an **anionic phosphate** that possesses a phosphorus atom which is much less electrophilic and therefore, much less likely to undergo hydrolytic regeneration than the original phosphoester.

- Thus, the aged phosphorylated enzyme does not undergo nucleophilic attack and regeneration by antidote for phosphate ester AChEIs.
- This aging process occurs over a period of time, which depends on the rate of the P-O bond cleavage reaction; during this time, the antidotes to phosphate ester poisoning may be effective.



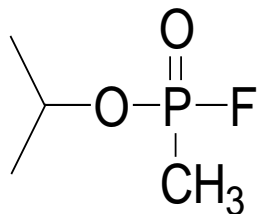
Diisopropylfluorophosphate



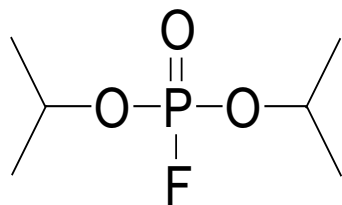
Ecothiophosphate

- Only those phosphorus-derived AChEIs that possess at least one phosphoester group undergo this aging process.
- Knowledge of the chemical mechanisms associated with irreversible inhibition of AChE and the aging process led to the development of deadly phosphorus-derived chemical warfare agents, one of which is **sarin**.

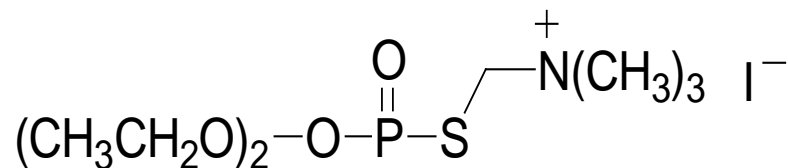
- When this compound phosphorylates AChE, only one aging reaction takes place, and then the enzyme becomes completely refractory to regeneration by the currently available antidotal agents.



Sarin



Diisopropylfluorophosphate
(DFP)



Echothiophate Iodide

Cholinesterase Activators (Antidote for Irreversible AChEIs)

- Water is a nucleophile capable of hydrolyzing acetylated AChE rapidly and regenerating the active enzyme.
- Phosphorylated AChE (irreversibly inhibited), however, was known to involve a phosphate ester of serine.

- The rate of hydrolysis is much slower for organic phosphate esters than carboxylate esters, and significantly **stronger nucleophile** than water would be required for efficient hydrolysis of phosphate esters.
- **Problem:** design of reagents capable of efficiently catalyzing phosphate ester hydrolysis and regenerating active ACh, while being **safe** enough for use as therapeutic agents.

- **Hydroxylamine** ($\text{NH}_2\text{-OH}$) is a strong nucleophilic compound that efficiently cleaves phosphate esters and increases significantly the rate of hydrolysis of phosphorylated AChE but only at toxic concentration.

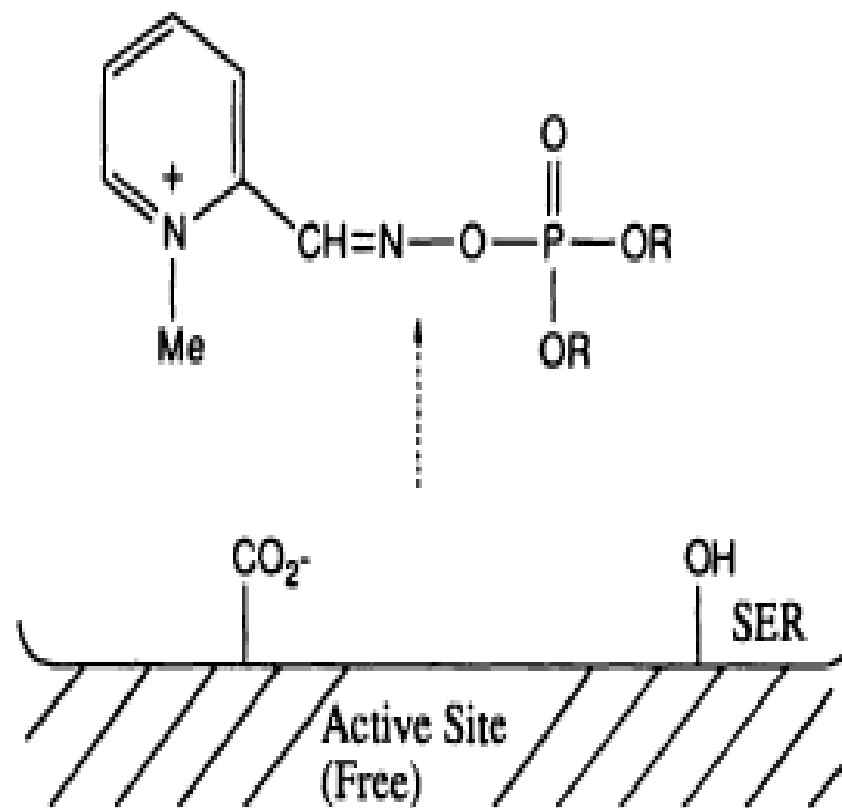
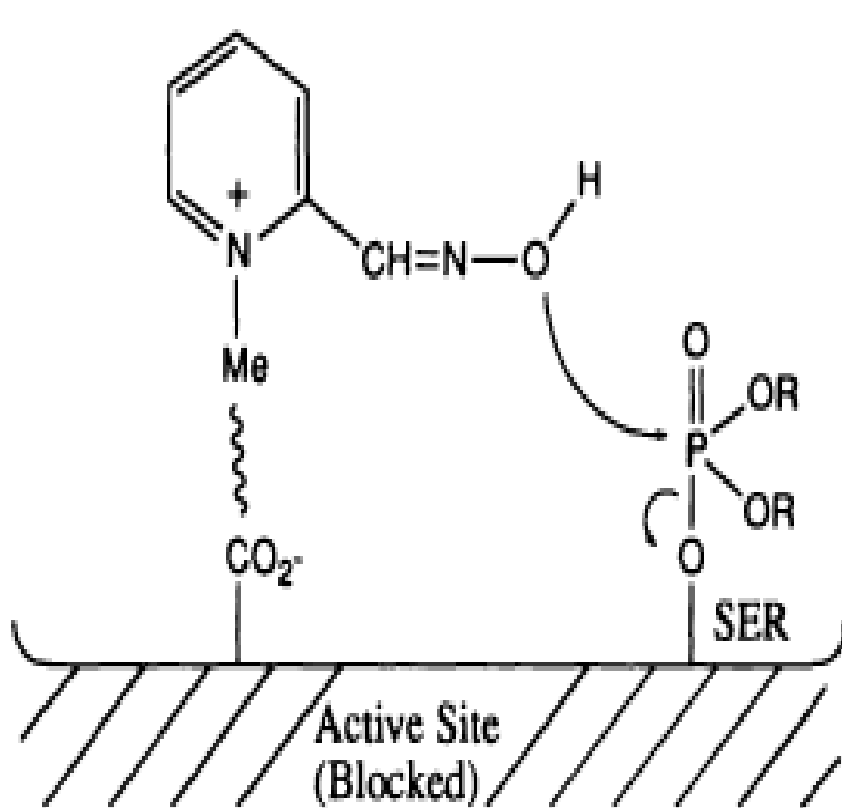
Development of structural analog of hydroxylamine without toxicity

- Logical approach is to design compound with (1) a high degree of **selectivity** and **strong binding affinity** for AChE and (2) carry a hydroxylamine-like nucleophile into close proximity to the phosphorylated serine residue.
- **Approach:** synthesis of hydroxylamine derivatives of organic compounds possessing a functional group bearing a positive charge.

- The reaction of hydroxylamine with aldehydes or ketones affords oximes, which possess the desired nucleophilic oxygen atom.
- **Pyridine ring is an attractive carrier for the oxime function** because such groups are common in a number of biochemical systems (e.g., NAD, NADP), indicating a possible lower order of toxicity.

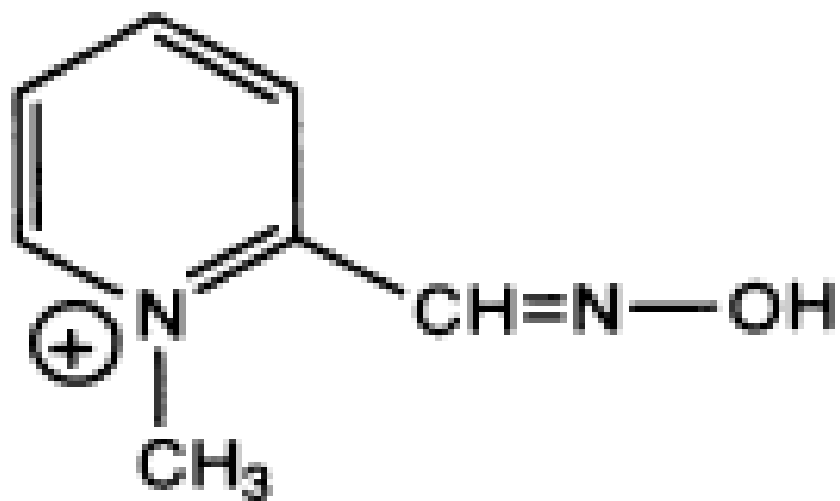
- There are three readily available positional isomers of pyridine aldehyde that can be converted easily to **oximes**.
- Finally, the nitrogen atom of the pyridine ring can be converted to a quaternary ammonium salt by treatment with **methyl iodide**.
- This cationic charge increases affinity of the compound for the “**anionic binding site**” of the phosphorylated AChE.

- Of the three isomeric pyridine aldoxime methiodides, the most effective is the isomer derived from 2-pyridinaldehyde (2-pyridine aldoxime methyl chloride (Pralidoxime, 2-PAM)).
- Proposed mechanism for regeneration of AChE
 - Binding of the quaternary ammonium nitrogen of 2-PAM to the “anionic binding site” of phosphorylated AChE, which places nucleophilic oxygen of 2-PAM in close proximity to the electrophilic phosphorus atom



- Nucleophilic attack of the oxime oxygen results in breaking of the ester bond between the serine oxygen atom and the phosphorus atom., resulting in regenerated active form of AChE and phosphorylated

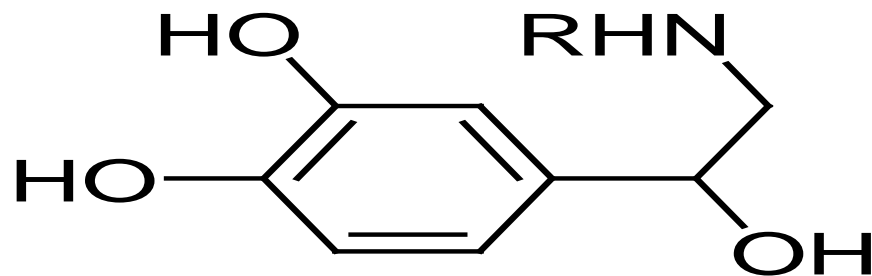
2-PAM



- Pralidoxime must be given within a short period of time, after enzyme phosphorylation generally a few hours, for it to be effective because of the aging process of the phosphorylated enzyme.
- After aging has occurred, 2-PAM will not regenerate the enzyme.

2- Adrenergic agents

- Adrenergic drugs act on effector cells through **adrenoceptors** that are normally activated by the neurotransmitter norepinephrin (noradrenaline), or they may act on neurons which release the neurotransmitter.
- Adrenergic neurons system and sympathetic neurons system used interchangeably.

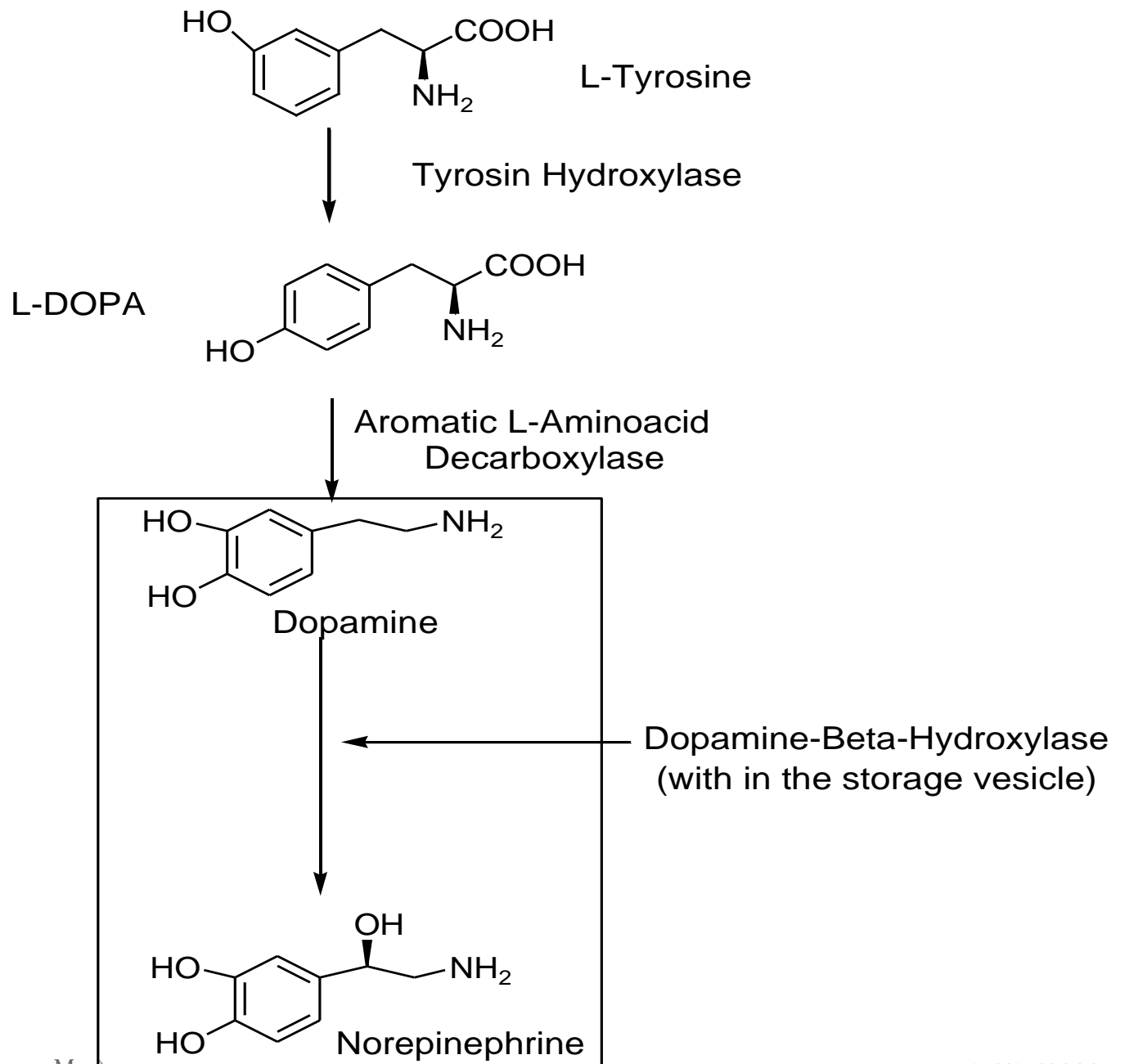


Norepinephrin, $R=H$
Epinephrin, $R=CH_3$

- Norepinephrin and epinephrine are members of a class of pharmacologically active substances known as **Caticholamines**.
- Because they contain with in their structures both an amine and ortho dihydroxy benzene (Catichol).

Biosynthesis, storage and release of norepinephrine

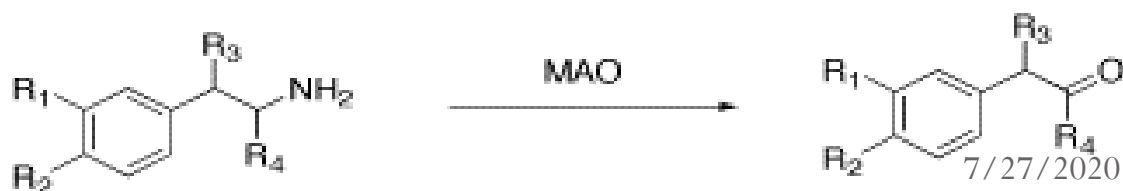
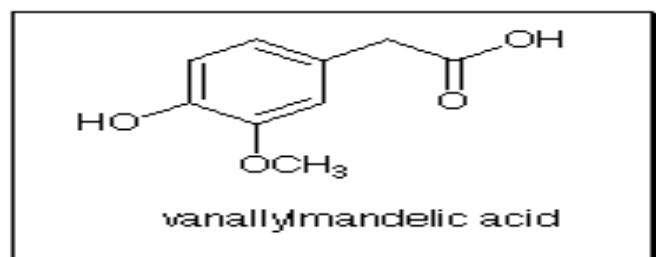
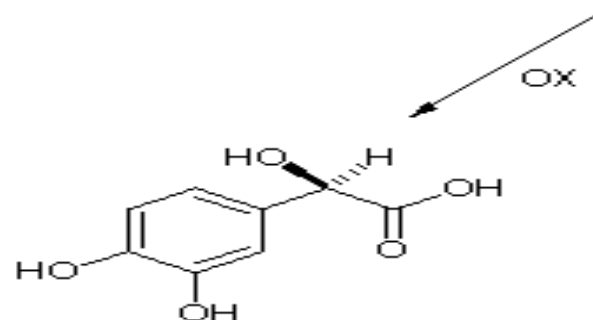
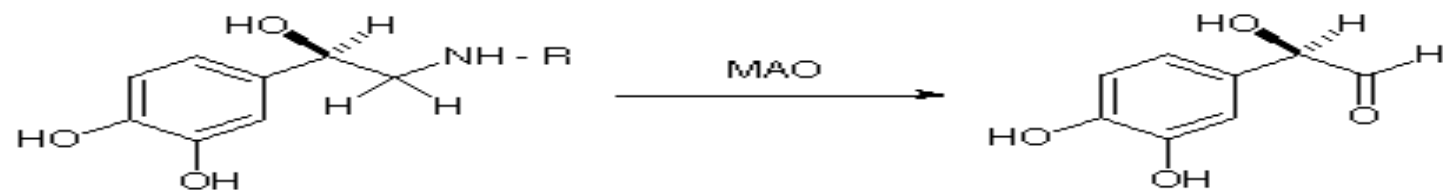
- Biosynthesis of norepinephrine takes place within adrenergic neurons near the terminus of the axon near the junction with the effector cell.
- The biosynthesis begins with the active transport of the amino acid **L-tyrosine** into the adrenergic neuron.



Reuptake and metabolism of norepinephrine following release

- Following its release, norepinephrine diffuses through the intracellular space to bind reversibly to **adrenoceptors (α, β)**, on the effector cells, triggering a biochemical cascade that results in physiologic response in effector cell.
- Once it has been released and is stimulating its various receptors, there must be a mechanism for removing the norepinephrine from the synapse and terminating the adrenergic impulse.
- Recycling through active transport uptake into the presynaptic neuron (uptake-1) up to 95 % of NE
- Less efficient processes (uptake -2) operates at only high concentration of NE.

- That portion of released NE which escapes uptake -1 diffuses out of the synapse and is metabolized in extraneous site by catichol-O-methyl transferase, **COMT**, which methylates the *meta* hydroxyl group.
- Norepinephrin is also metabolized to DOPAGAL by **MAO**
- This pathway is also important to drug which are catichol and subject to metabolism by COMT and drugs with unsubstituted aliphatic amino group are often substrates for MAO.



Adrenergic receptors

- α, β receptors subtypes are sufficiently well differentiated by their small molecule binding characteristics.
- The existence of two subtypes of adrenoceptors was first proposed by **Ahlquist** in 1948.
- According to his theory, the two types, which he termed **alpha** and **beta**, had different functions at their respective sites of action.
- Both of them are G-protein coupled receptors which consists of seven transmembrane (TM) helices.
- For each type of receptors there are various receptor subtypes which differ in structure and function.

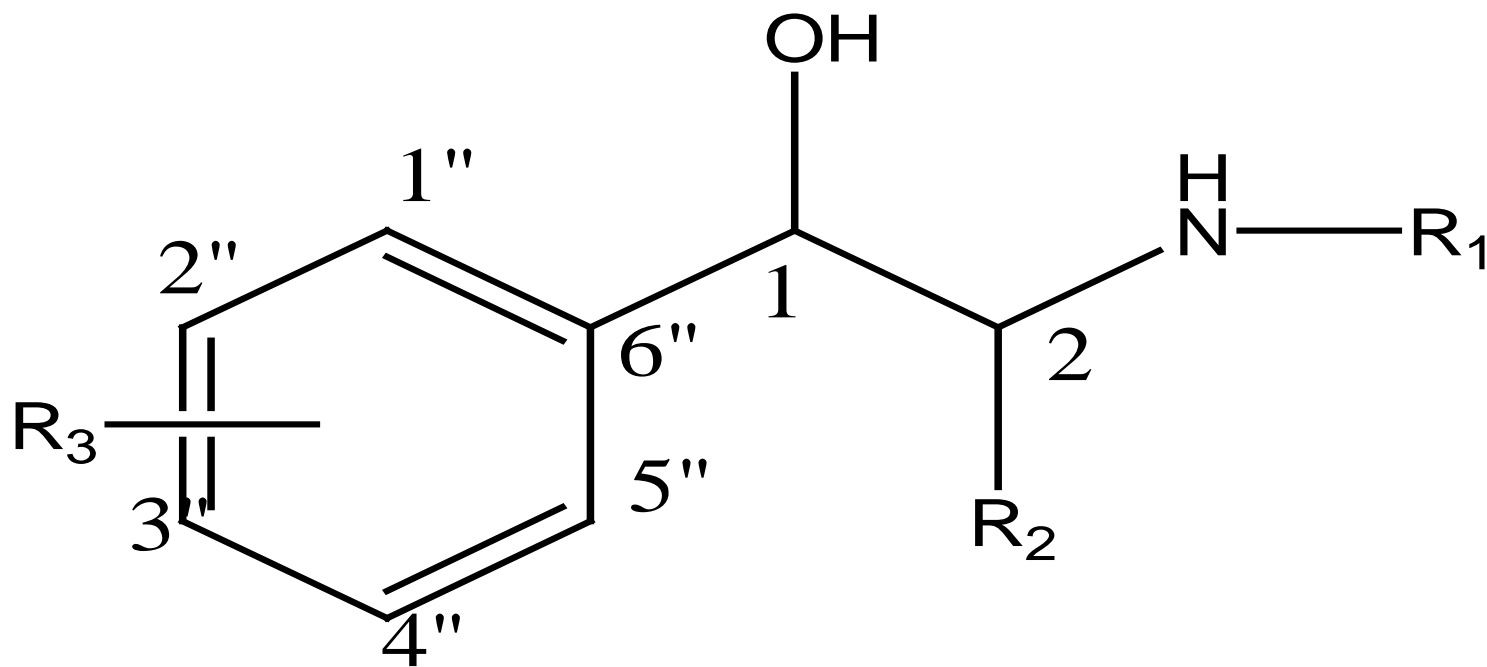
- The α -adrenoceptors consists of α_1 and α_2 – subtypes
 - Both these receptors have further sub categories
(α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , and α_{2C})
- Similarly there are three receptor subtypes for β receptors found on different parts of our body (β_1 , β_2 and β_3)

Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
Heart muscle	β_1	Muscle contraction	Increased heart rate and force
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways
	β_2	Smooth muscle relaxation	Dilates and opens airways
Arteriole smooth muscle (not supplying muscles)	α	Smooth muscle contraction	Constricts arterioles and increases blood pressure (hypertension)
Arteriole smooth muscle (supplying muscle)	β_2	Smooth muscle relaxation	Dilates arterioles and increases blood supply to muscles
Veins	α	Smooth muscle contraction	Constricts veins and increases blood pressure (hypertension)
	β_2	Smooth muscle relaxation	Dilates veins and decreases blood pressure (hypotension)

Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
Liver	α_1 and β_2	Activates enzymes which metabolize glycogen and deactivates enzymes which synthesize glycogen	Breakdown of glycogen to produce glucose
Gastrointestinal tract smooth muscle	α_1 , α_2 and β_2	Relaxation	'Shuts down' digestion
Kidney	β_2	Increases renin secretion	Increases blood pressure
Fat cells	β_3	Activates enzymes	Fat breakdown

Structure Activity relationship of Adrenergic agonists

- Phenyl Ethanolamine agonists



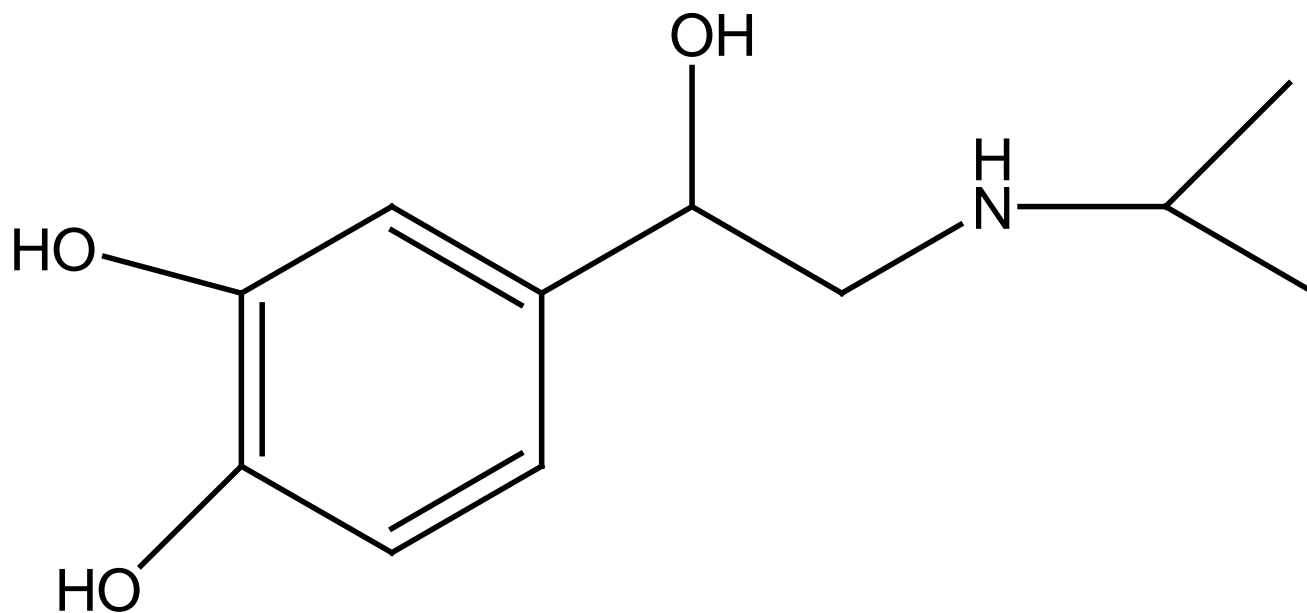
- Because of the basic amino groups, p^{ka} , range approximately 8.5 to 10 all of these agents are highly positively charged at physiologic p^H .
- Agents in this class have a hydroxyl group on C-1 of the side chain, β -to the amine.
- This hydroxyl substituted carbon must be in the **R** absolute configuration for maximal direct activity as in the natural neurotransmitter, although most drugs are currently sold as mixtures of both **(R)** and **(S)** stereoisomers at this position (racemates).
- The nature of the other substitutes determines receptor selectivity and duration of action.

R_1 substitution on the Amino Nitrogen

- Increase in size of R_1 from hydrogen in norepinephrine to methyl in epinephrine to isopropyl in isoproterenol,
 - Activity at α -receptors decrease and
 - Activity at β -receptors increases
- The activity at α and β -receptors is maximal when R_1 is methyl as in epinephrine, but α -agonist activity is dramatically decreased when R_1 is larger than the methyl and is negligible when R_1 is isopropyl, as in isoproterenol leaving only β -activity.

- Most likely, the β -receptor has a large **lipophilic-binding pocket** adjacent to the amine binding aspartic acid (COOH) residue, which is absent in the α receptor.
- As R_1 becomes larger than butyl, affinity for α_1 -receptor returns but **not intrinsic activity**, which means large lipophilic groups can afford compounds with **α_1 -blocking activity** e.g. Labetolol

- N- substituent can also provide selectivity for β -receptors.
 - E.g. T-butyl group \Rightarrow selectivity for β_2 –receptors
- Colterol ($R_1 =$ T-butyl) is a selective β_2 -agonist, whereas isoproterenol is a non-selective β -agonist.



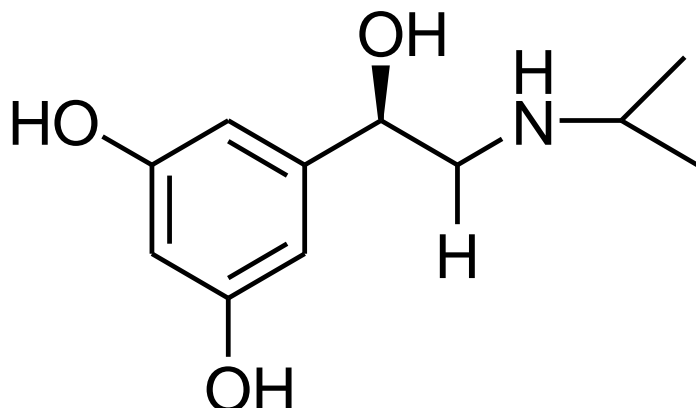
R₂-Substitution α - to basic Nitrogen, Carbon-2

- Substitution like methyl or ethyl group **slow metabolism by monoamine oxidase (MAO)** but has little overall effect on duration of action in catecholamine because they remain substrates for COMT.
- An ethyl group in this position diminishes α -activity far more than β -activity, affording compounds with β -selectivity such as ethylnorepinephrine.

R₃-substitution on the aromatic ring

- The natural 3',4'-dihydroxy substituted benzene ring present in norepinephrine provides excellent receptor activity for both α and β -sites.
- But such cathicol-containing compounds have poor oral activity because they are hydrophilic and rapidly metabolized by COMT.
- Alternative substitution have been found that retain good activity but are more resistant to COMT metabolism.

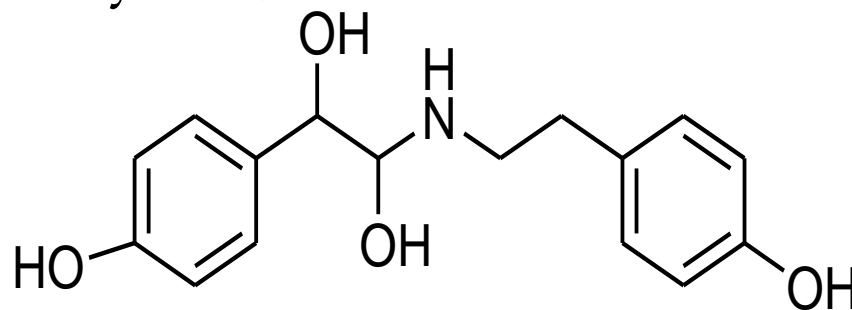
- 3',5'-dihydroxy compounds are not good substrates for COMT and in addition show **selectivity** for β_2 -receptors.



Metoproterinol

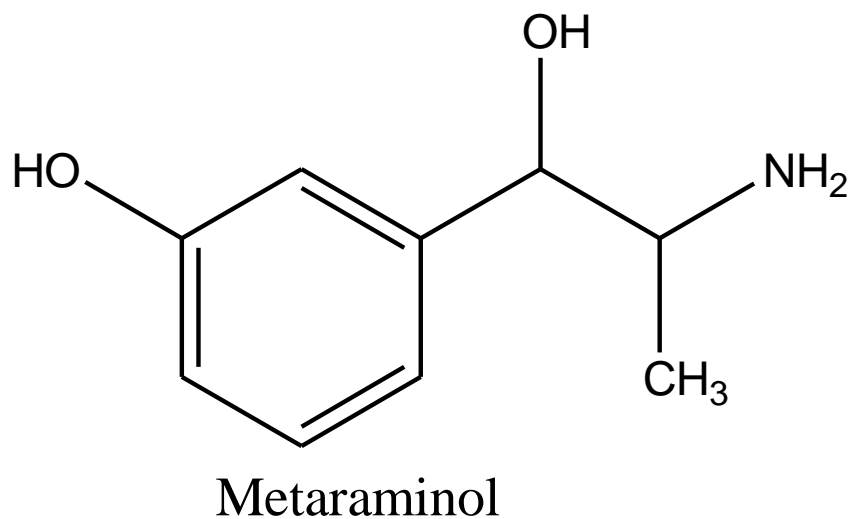
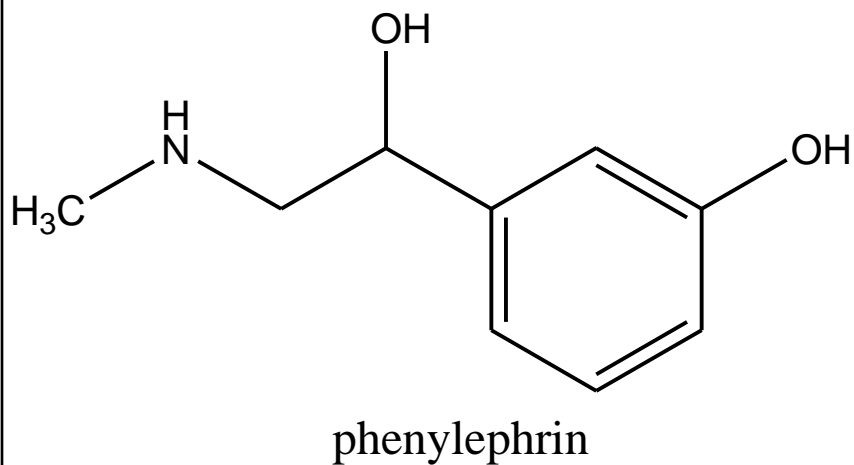
- Metoproterinol is orally active bronchodilator that have little of the cardiac stimulatory properties possessed by isoproternol.

- Other substitution are possible that enhance oral activity and provide selectivity, such as the 3'-hydroxymethyl, 4'-hydroxyl substitution pattern of albuterol, which is also resistant to COMT.
- At least one of the groups must be capable of forming hydrogen bonds and if there is only one; it should be at the 4'-position to retain β -activity.



Ritodrine

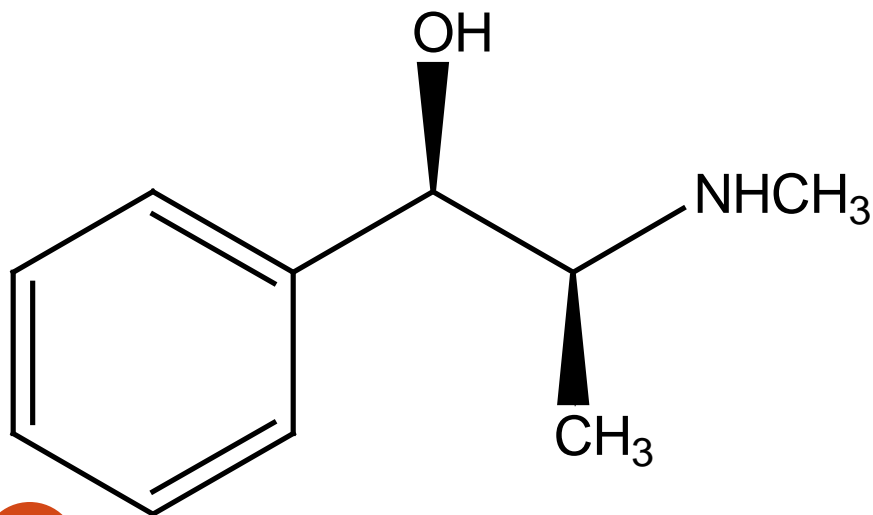
- If R_3 is only a 3'-OH, however, activity is reduced at α sites and almost eliminated at β sites, thus selective α -agonists such as phenylephrine and metaraminol.



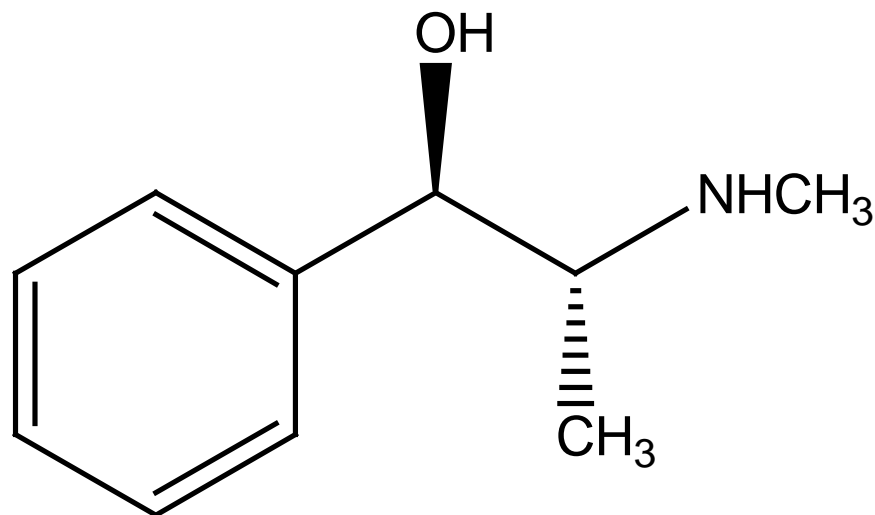
- When the phenyl ring has **no** phenolic substituents, i.e. $R_3=H$ these phenyl ethanolamines may have both direct and indirect activity.
- Direct activity (i.e. agonist) is the stimulation of adrenoceptor by the drug it self while
- Indirect activity is the result of the displacement of NE from its storage granules resulting in **non-selective** stimulation of the adrenoceptors by the displaced NE

- Since norepinephrine stimulates both α and β receptors, indirect activity cannot be selective.

EPHEDRIN



PSEUDOEPHEDRIN



Norepinephrine and adrenergic drugs

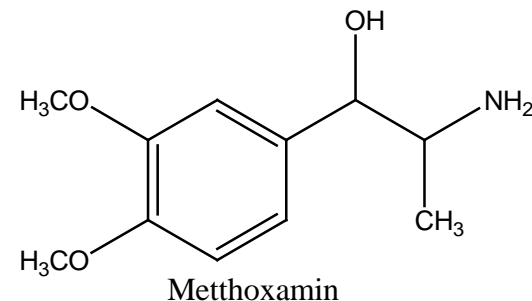
- NE has limited clinical application b/c
 - It is non-selective
 - Given only iv, because of metabolism by intestinal and liver COMT and MAO.
 - Low lipophilicity
 - Rapid metabolism limits its duration of action only 1 or 2 minutes given by infusion.

- Similar to norepinephrine, epinephrine is used to treat hypotensive crisis and because of its greater β -activity, it is used to stimulate the heart in cardiac arrest.
- Its activity on β_2
 - Administered iv and in inhalers to relieve bronchoconstriction in asthma and to application inhibiting uterine contractions.

α -Adrenergic agonists

α_1 -Agonists

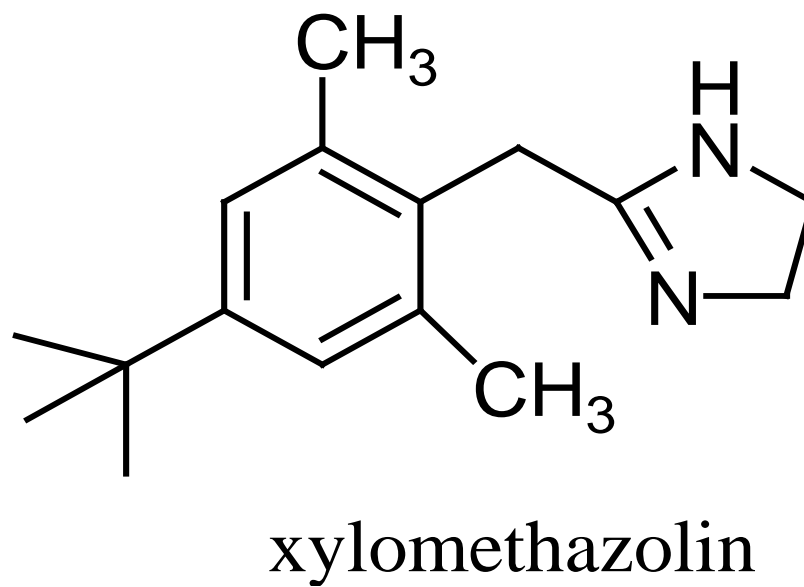
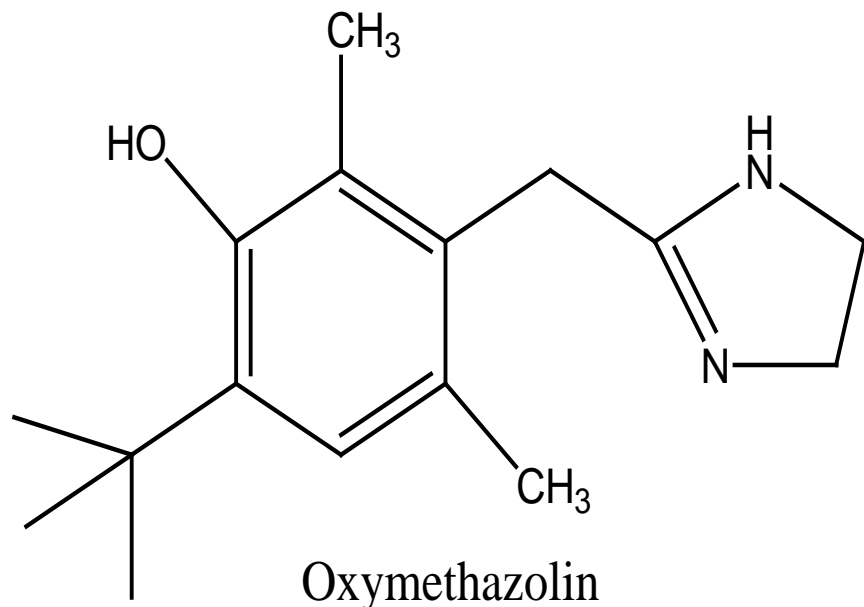
- Phenyl ethanol amines
 - Meteraminol, Methoxamine and phenylephrine
- Metaraminol and methoxamine are selective α_1 receptors and have little cardiac stimulatory properties.
- Because they are not substrates for COMT, their duration of action is significantly longer than norepinephrine.



2-Arylimidazoline α_1 -agonists

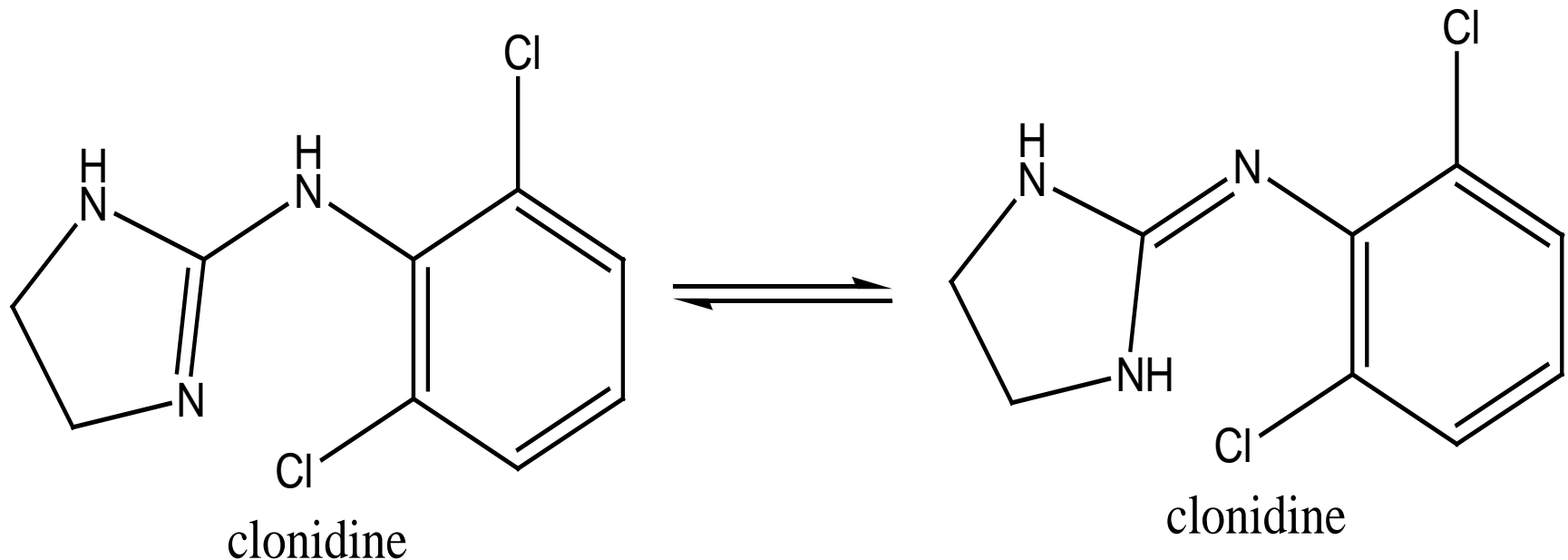
- Selective α_1 -agonists and therefore they are vasoconstrictors/ vasopressors.
- They all contain a one-carbon bridge between C₂ of imidazole ring and a phenyl substituent, and therefore
 - The general skeleton of phenyl ethylamine is contained within the structures.

- Lipophilic substitution on the phenyl ring ortho to the methyl bridge appears to be required for agonist at α_1 and α_2 receptors.
- The bulky lipophilic groups attached to the phenyl ring at the **meta** or **para**-positions
 - Provide selectivity for the α_1 -receptor by diminishing affinity for α_2 -receptors.



α_2 -Adrenergic Agonists

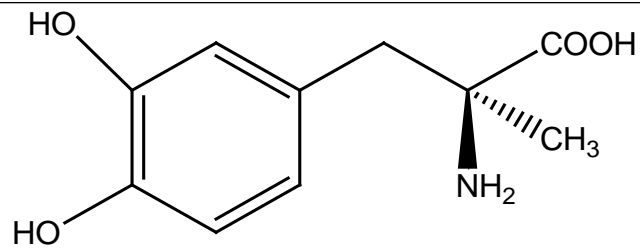
- **2-aminoimidazoline**
 - Closely related structurally to the imidazoline structure



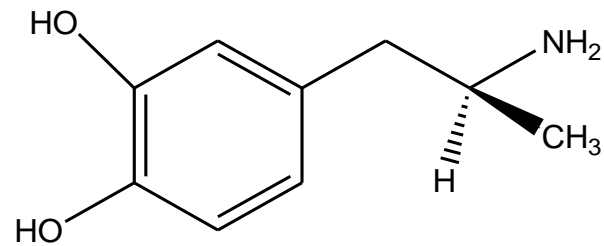
- Because of its peripheral activity on extra neuronal vascular postsynaptic α_1 -receptor,
- Initial doses of clonidine may produce a transient vasoconstriction and an increase in blood pressure that is soon overcome by vasodilatation
- Clonidine penetrates the **BBB** and interact with central nervous system α_2 -receptors.

Methyldopa

- Although it is structurally unrelated to the clonidine, it is antihypertensive.
- It is also a pro-drug and it is active metabolite.
 - α -Methyl norepinephrine
- Methyldopa is decarboxylated by aromatic L-amino acid decarboxylase to α -methyl dopamine, which is stereospecifically hydroxylated to **1R,2S - α -methyl norepinephrine**.

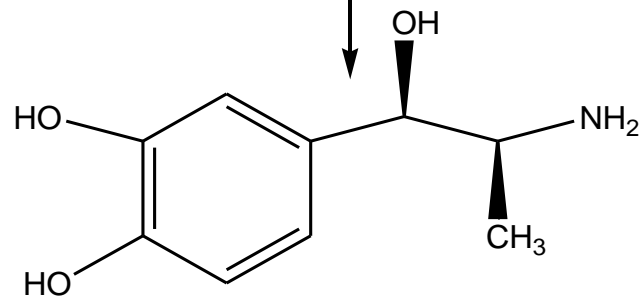


Aromatic L-aminodecarboxylase



α methyl dopamine

Dopamine-beta-hydroxylase



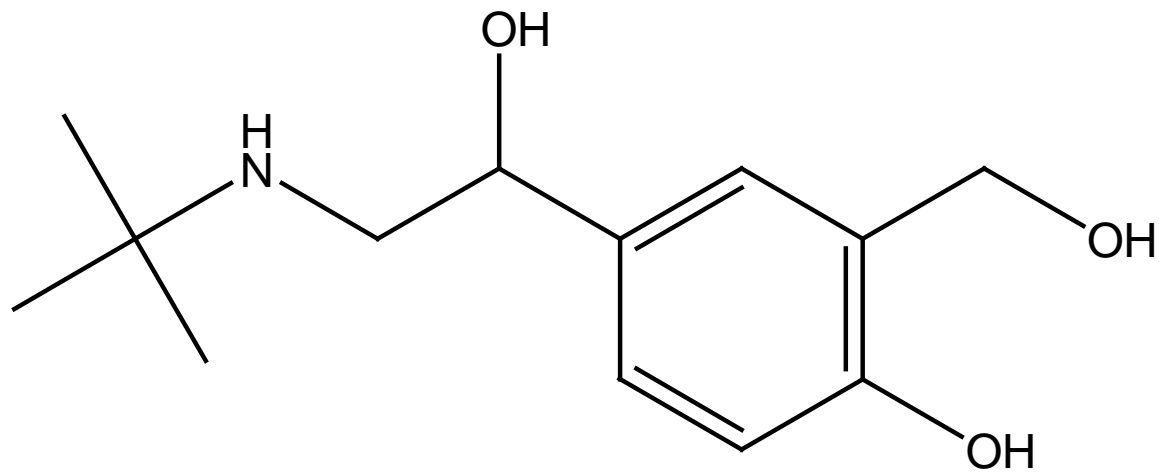
β -Adrenergic agonists

β_2 -selective agonists

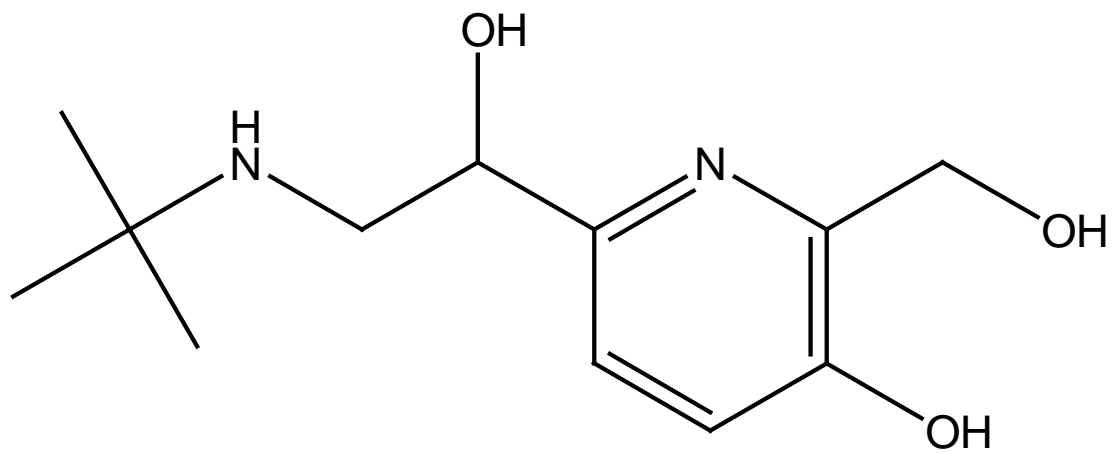
- Phenyl ethanolamines:
 - Most of β_2 selective adrenergic agonists are used primarily as bronchodilators in asthma and other constrictive pulmonary conditions.

Albuterol, Pirbuterol, Terbutaline

- Non-cathicol selective β_2 -agonists.
- Available in oral dosage forms.



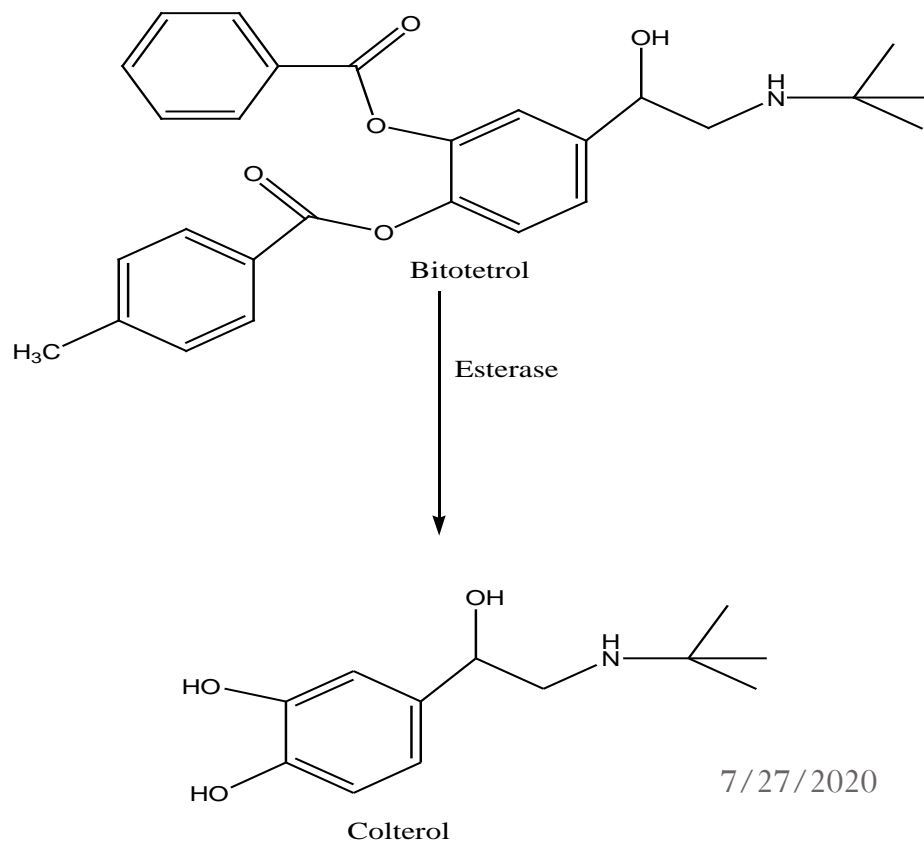
albuterol



Pirbuterol

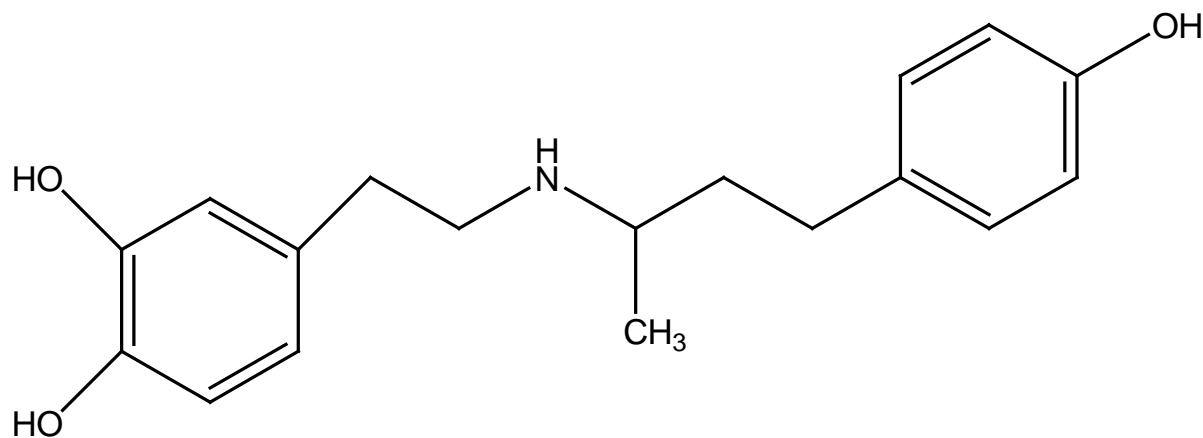
Bitolterol

- Is a prodrug form of colterol
- Has high lipophilicity and prolonged duration of action.
- The ester group is hydrolyzed by esterase to liberate the active drug, colterol.



β_1 -Adrenergic agonists:

- Dobutamine
 - Has no aliphatic β -hydroxy group.
 - Dopamine analogue with bulky arylalkyl group on the nitrogen and one chiral (asymmetric) center.

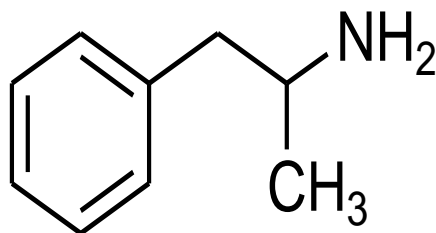


Mixed Acting Sympathomimethics

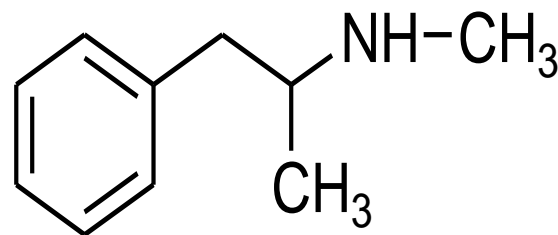
- Ephedrine
 - Ephedrine is a natural product isolated from several species of **ephedra** plants
 - Ephedrine does not have any phenolic substituents on the phenyl ring, giving it a mixed acting response and good oral activity because it is not substrate for **COMT**
 - Lacking hydrogen bonding phenolic substituents, ephedrine is less polar and can easily pass BBB

Amphetamine and Methamphetamine

- Methylsubstituted phenylethylamine (phenylisopropylamine), such as S(+) amphetamine and S(+)-Methamphetamine which lack both ring substituents and side chain hydroxyl group.
- Sufficiently lipophilic to cross the BBB & cause dramatic central nervous system stimulation, which gives them serious abuse potential



Amphetamin

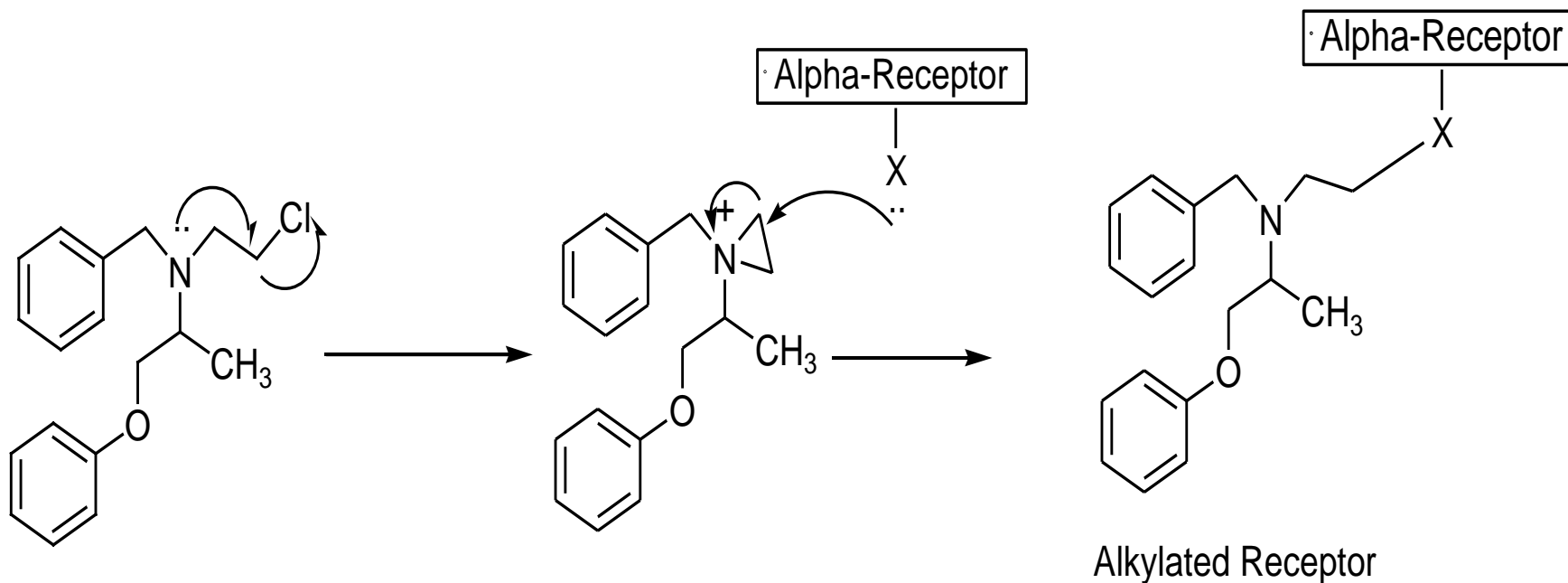


Methamphetamin

SAR of Adrenergic Antagonists

General α -antagonists

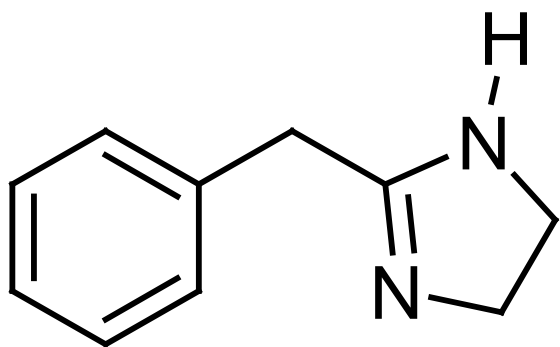
- Phenoxybenzamine
 - α -agonists cause vasoconstriction and raise blood pressure
 - α -antagonists to be therapeutically used as antihypertensive agents
- phenylbenzamine(dibenzylamine)
 - a β -haloalkylamine that alkylate α -receptors.



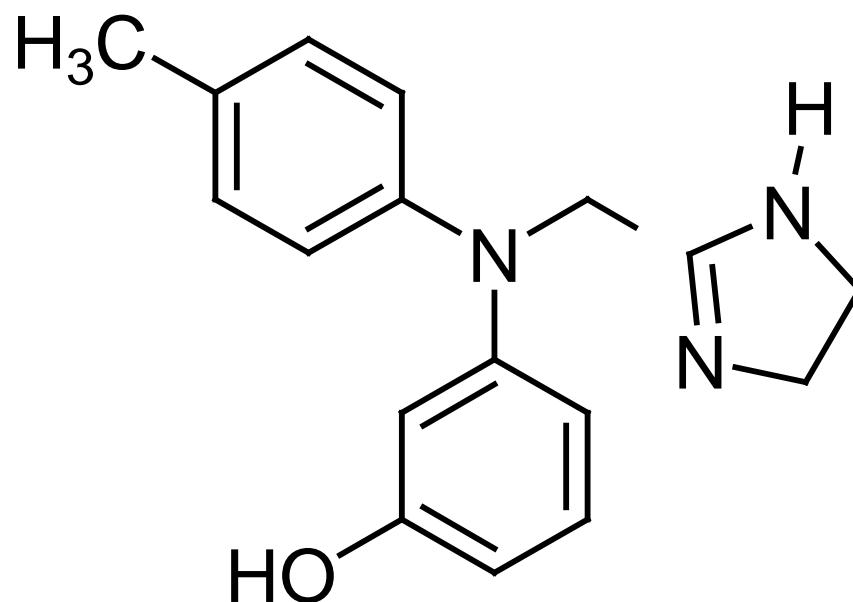
Phenylbenzoxamine

- Phenoxybenzamin alkylation of alpha receptors, X-is Nucleophile such as S,N,O (Part of amino acid)
- Unfortunately, other biomolecules besides the target α -receptors are also alkylated

- Tolazoline and Phentolamine



Tolazoline

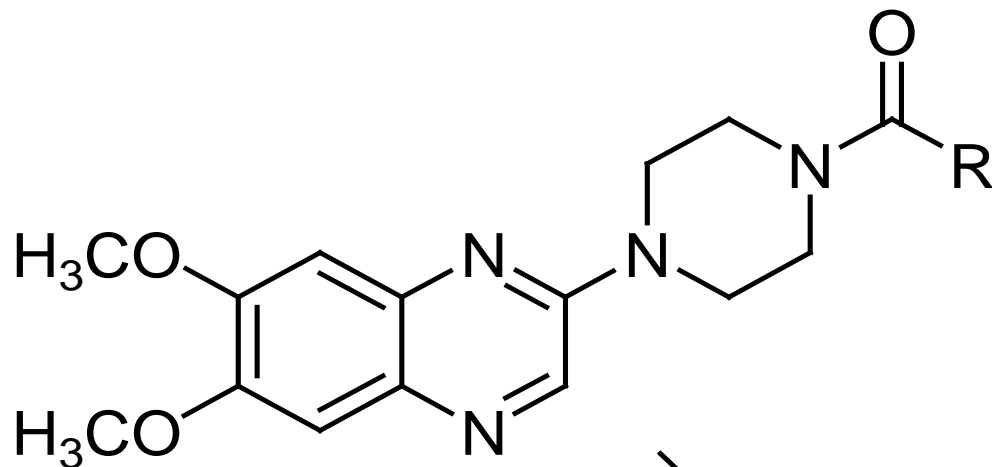


Phentolamine

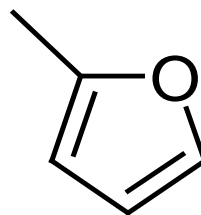
- Are two imidazoline α -antagonists that also have antihypertensive activity, although they have been replaced by far better agents

Selective α_1 -Antagonists

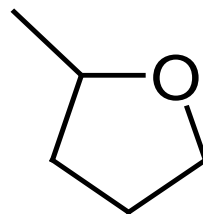
- Prazosin, doxazosin, terazosin and tamsulosine



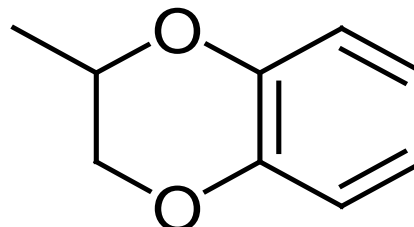
Prazosin:R =



Terazosin:R =



Doxazosin:R =



SAR of Quinazolines

- Prazocin, dexazocin and Terazosin contain 4-amino-6,7-dimethoxyquinazoline ring system attached to piperazin nitrogen
- The only structural difference is to the structure attached to the other nitrogen of the piperazin
- The difference in this groups afford dramatic difference in the pharmacokinetic properties of these drugs

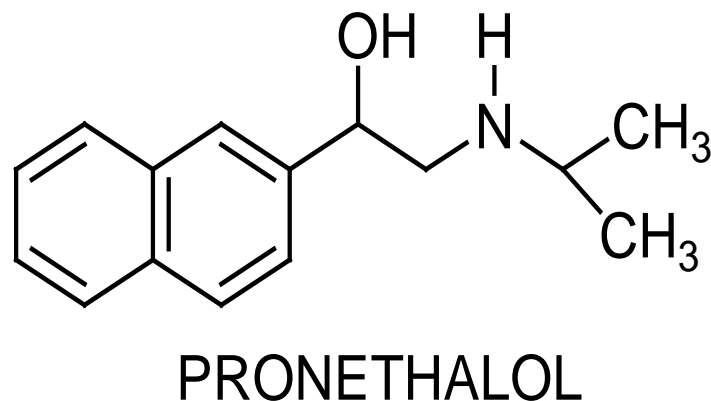
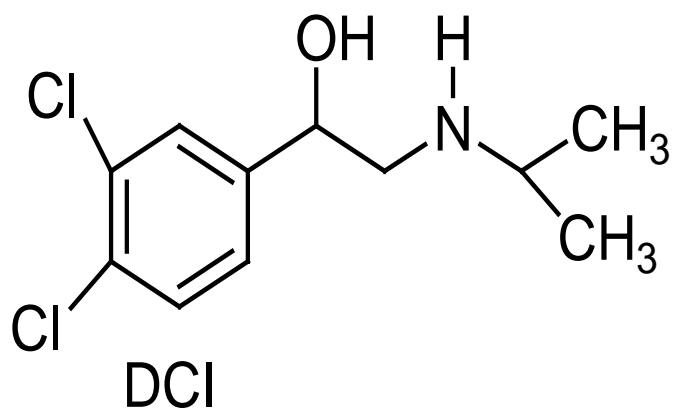
- When the furan ring of prazosin is reduced to form tetrahydrofuran ring of terazocin, the compound becomes significantly hydrophilic.

β -Adrenergic antagonists

- A derivative of **isoproterenol** in which the catichol hydroxyls had been replaced by chlorines, dichloroisoproterinol (DCI) was discovered to be

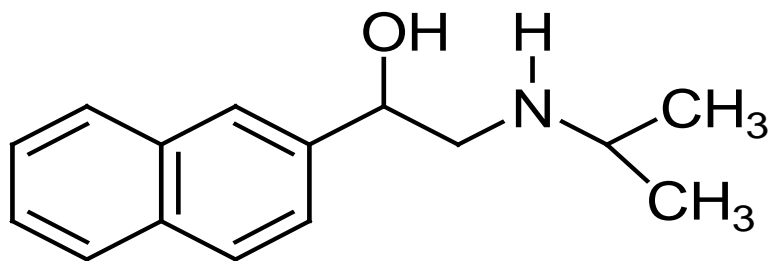
β -antagonist

- DCI- had no clinical utility, replacement of the 3,4-dichlorosubstituents with a carbon bridge to form a naphthalylethanolamine derivative did afford a clinical candidate, **Pronethalol**

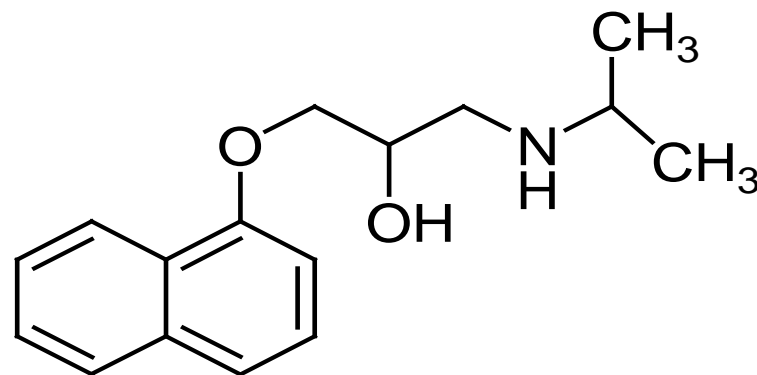


Structure Activity Relationship

- Introduction of **oxy methylene** bridge OCH_2 , into the aryl ethanolamine structure of pronethalol gives propranolol

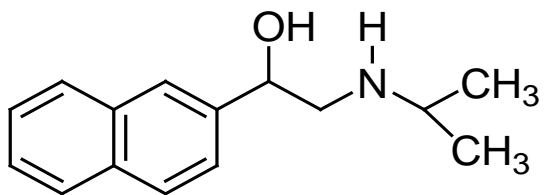


Pronethalol

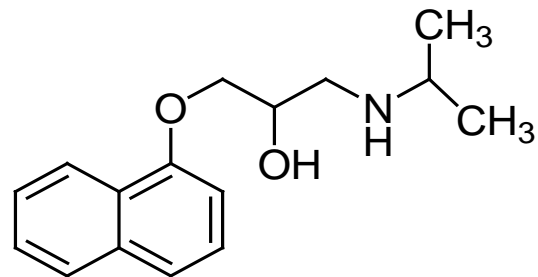


Propranolol

- In general, the **aryloxy propanolamines** are more potent β -blockers than the corresponding aryl ethanolamines and most of the β -blockers currently used clinically are **aryloxypropanolamines**
- Initially it might appear that lengthening the side chain would prevent appropriate binding of the required functional groups to the same receptor.
- But molecular modeling show that the side chains of aryloxypropanolamines can adopt a conformation that places the hydroxyl and amine groups into approximately the same position.

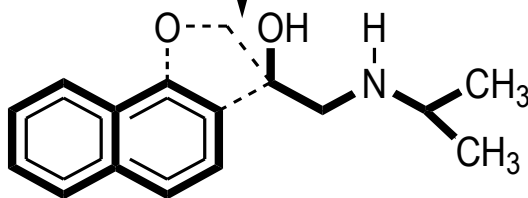


Arylethanolamine



Aryloxypropanolamine

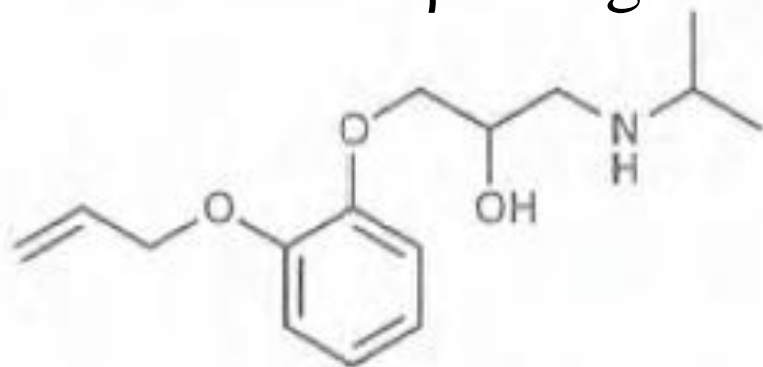
Superimposition



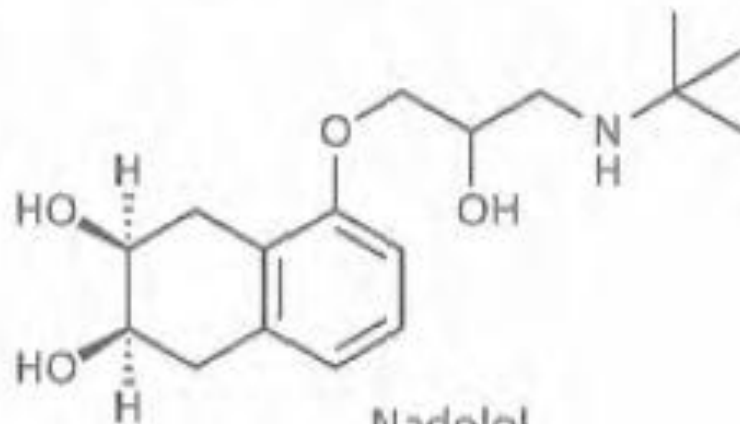
Propranolol

- Was originally discovered for the treatment of angina pectoris
- During clinical trial as antianginal, propranolol was discovered to have antihypertensive property
- A new series of 4-substituted phenyloxy- propanolamines emerged such as **practolol**, which selectively inhibited sympathetic cardiac stimulation(β_1 -selective).

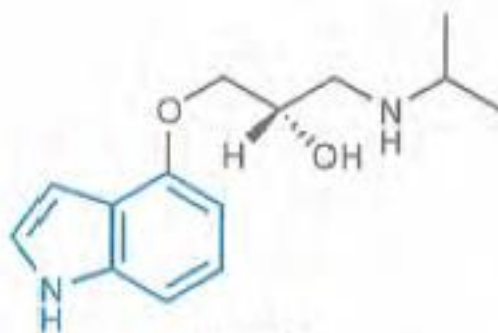
Non-selective β antagonists



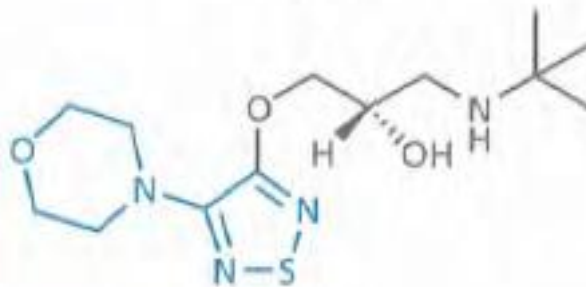
Oxprenolol



Nadolol

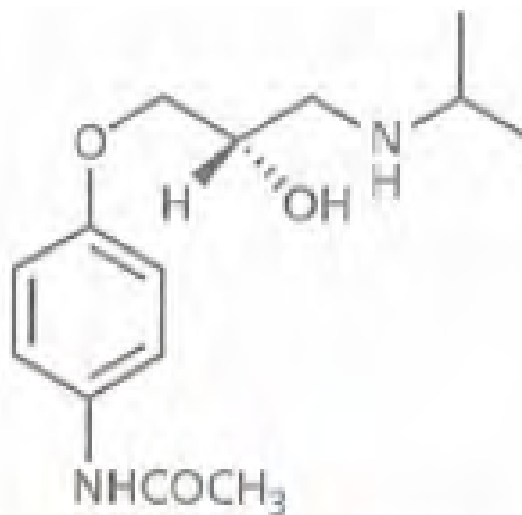


Pindolol

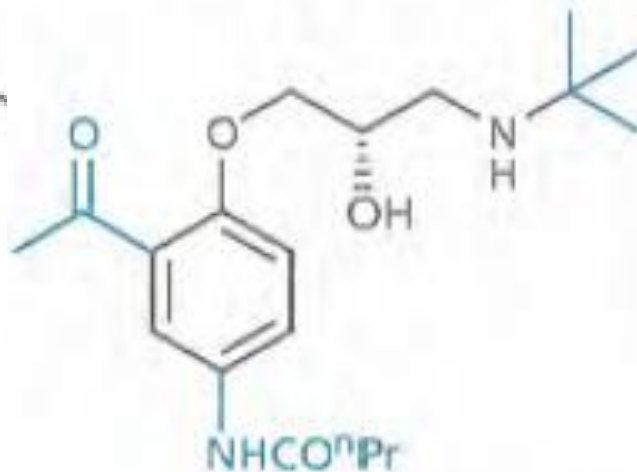


Timolol

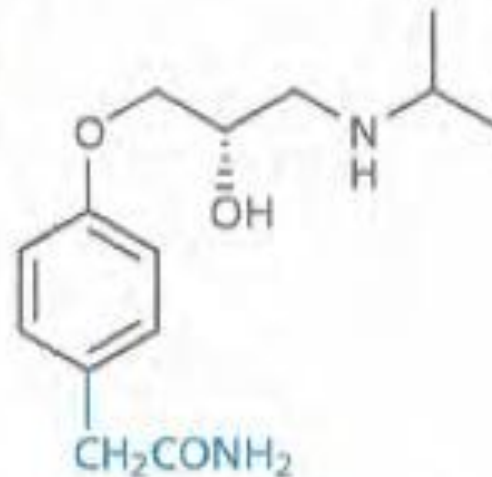
- Selective β_1 - blockers



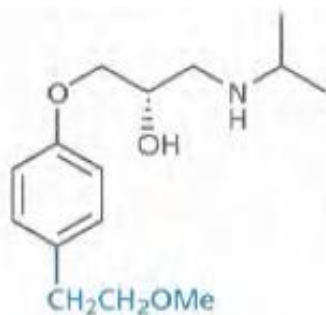
Practolol.



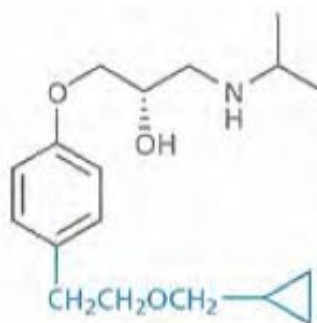
Acebutolol



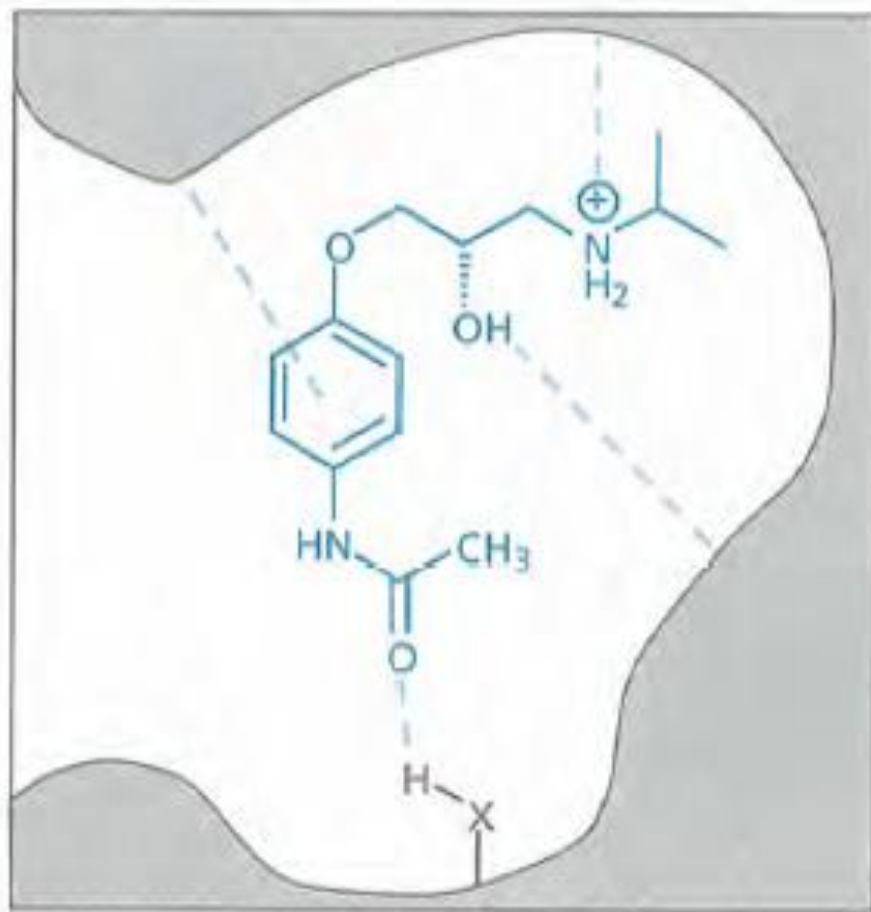
Atenolol



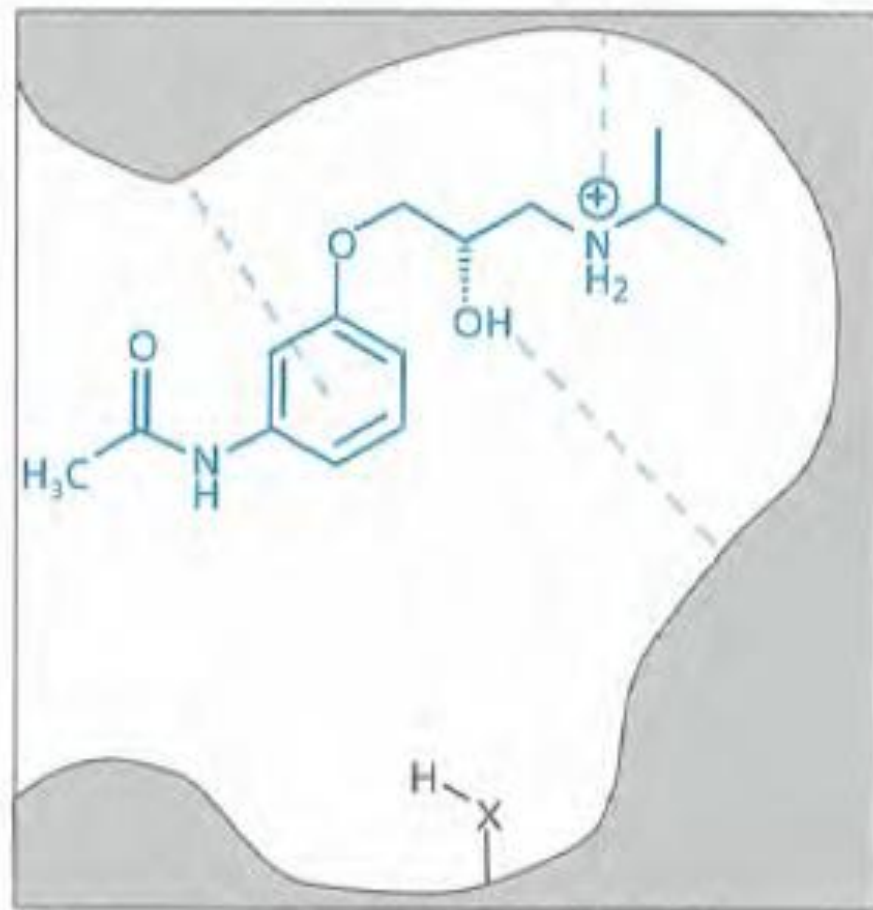
Metoprolol



Betaxolol

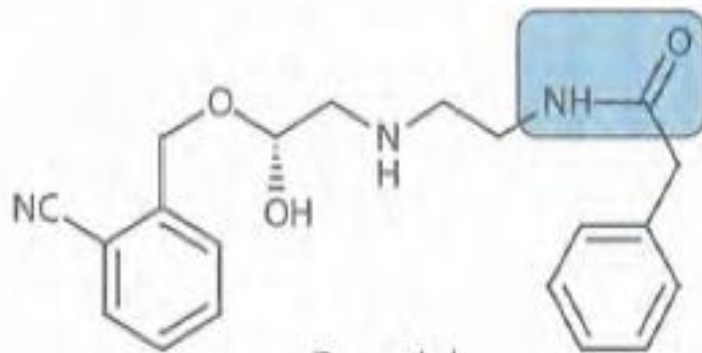


para substitution
Extra H-bonding interaction

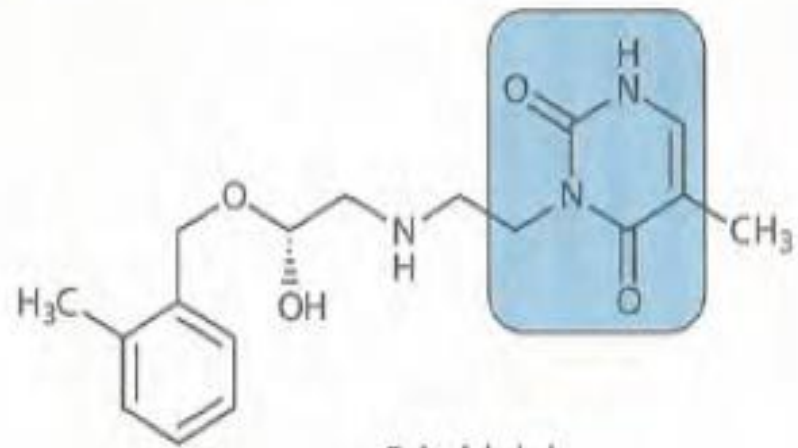


meta substitution

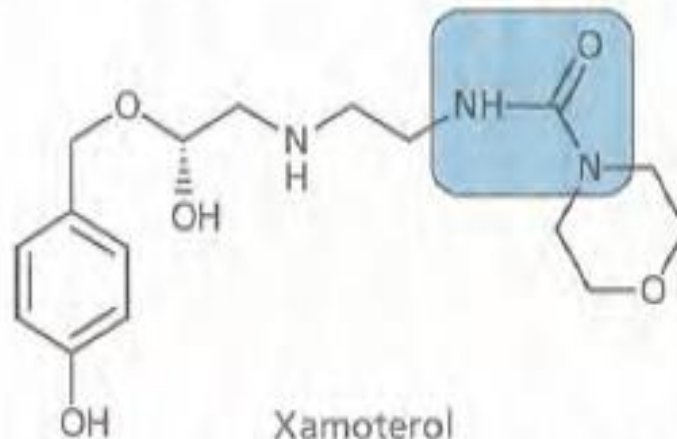
Third generation selective β_1 blockers



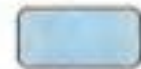
Epanolol



Primidolol



Xamoterol

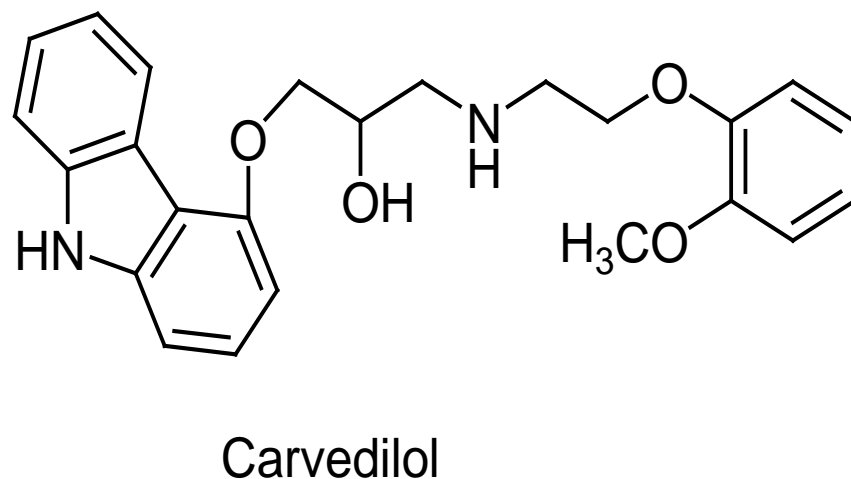
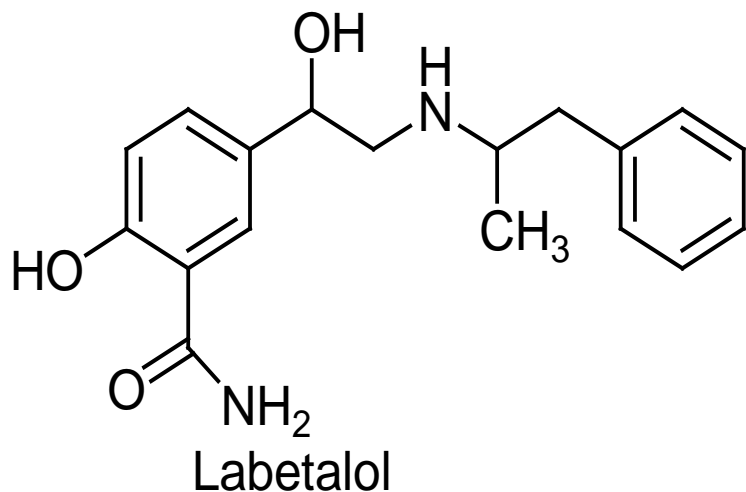


Groups involved
in additional
hydrogen bonding

Mixed α/β Adrenergic Antagonists

Labetalol and Carvedilol

- They have unusual activity in that they are antihypertensive with $\alpha_1, \beta_1, \beta_2$ blocking activity



- Groups such as isopropyl and t-butyl eliminated α -receptor activity, still larger groups could bring back α_1 -affinity but not intrinsic activity.
- Thus these two drugs have structural features permitting binding to both the α_1 and non-selectively to both β -receptors.

2. Adrenergic Drugs

Introduction

- Adrenergic agents (also known as sympathomimetics) are drugs that mimic or block the action of norepinephrine and epinephrine at postganglionic synapses of the sympathetic nervous system, and in the CNS.
- The endogenous neurotransmitters norepinephrine and epinephrine are neurotransmitters at postganglionic synapses of
 - Smooth muscle
 - Glands
 - Cardiac muscle

- Norepinephrine synthesis occurs in sympathetic nerve terminals, where it is stored in granules until it is released by depolarization of the neural membrane.
- Epinephrine synthesis occurs primarily in the adrenal medulla, and is secreted into the general circulation and transported to adrenergic receptor sites.

- The existence of two subtypes of adrenoreceptors was first proposed by Ahlquist in 1948.
- According to his theory, the two types, which he termed alpha and beta, had different functions at their respective sites of action.
- Both of them are G-protein coupled receptors
- For each type of receptors there are various receptor subtypes which differ in structure and function.

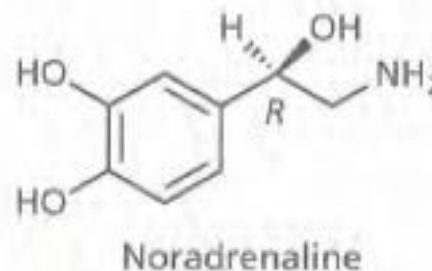
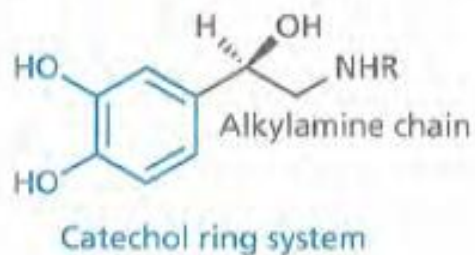
- The α -adrenoceptors consists of α_1 and α_2 – subtypes
 - Both these receptors have further sub categories (α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , and α_{2C})
- Similarly there are three receptor subtypes for β receptors found on different parts of our body (β_1 , β_2 and β_3)

Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
Heart muscle	β_1	Muscle contraction	Increased heart rate and force
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways
	β_2	Smooth muscle relaxation	Dilates and opens airways
Arteriole smooth muscle (not supplying muscles)	α	Smooth muscle contraction	Constricts arterioles and increases blood pressure (hypertension)
Arteriole smooth muscle (supplying muscle)	β_2	Smooth muscle relaxation	Dilates arterioles and increases blood supply to muscles
Veins	α	Smooth muscle contraction	Constricts veins and increases blood pressure (hypertension)
	β_2	Smooth muscle relaxation	Dilates veins and decreases blood pressure (hypotension)

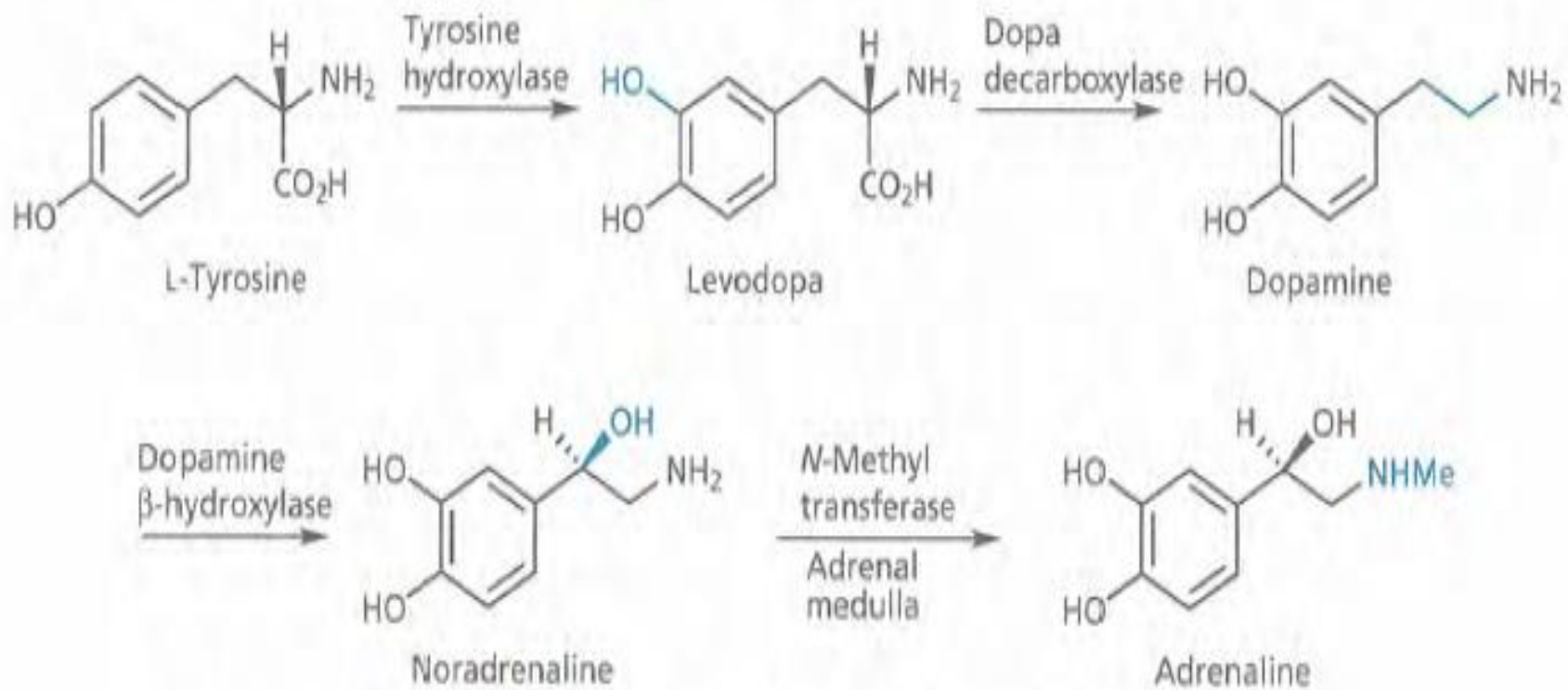
Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
Liver	α_1 and β_2	Activates enzymes which metabolize glycogen and deactivates enzymes which synthesize glycogen	Breakdown of glycogen to produce glucose
Gastrointestinal tract smooth muscle	α_1 , α_2 and β_2	Relaxation	'Shuts down' digestion
Kidney	β_2	Increases renin secretion	Increases blood pressure
Fat cells	β_3	Activates enzymes	Fat breakdown

Endogenous agonists for adrenergic receptors

- They belong to a group of compounds called catecholamines

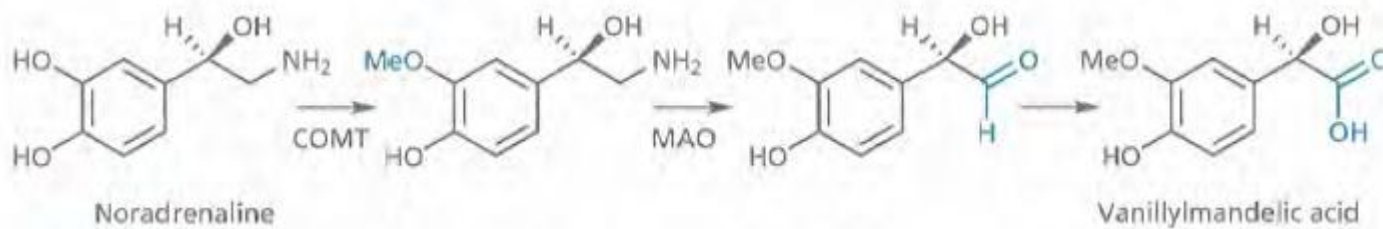
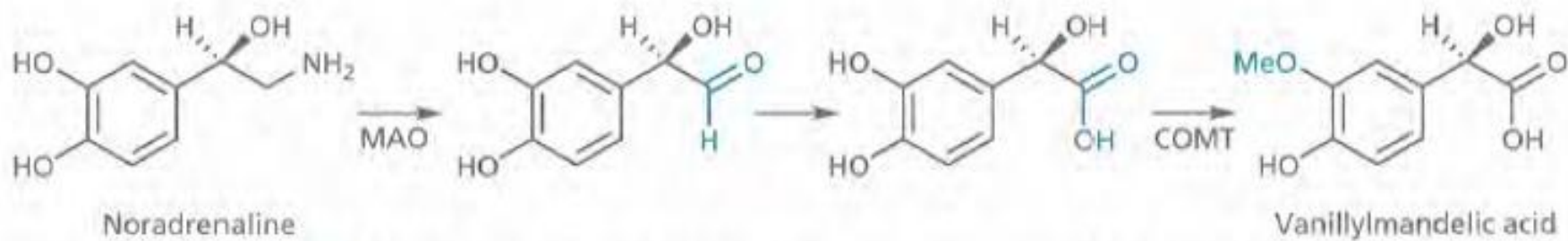


Biosynthesis of catecholamines

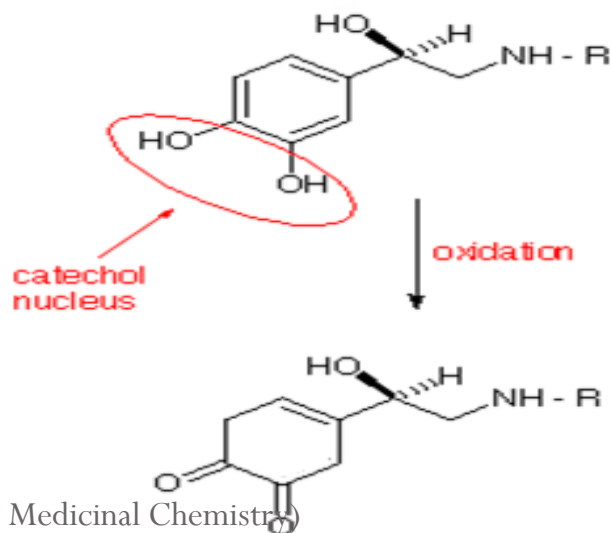


Metabolism

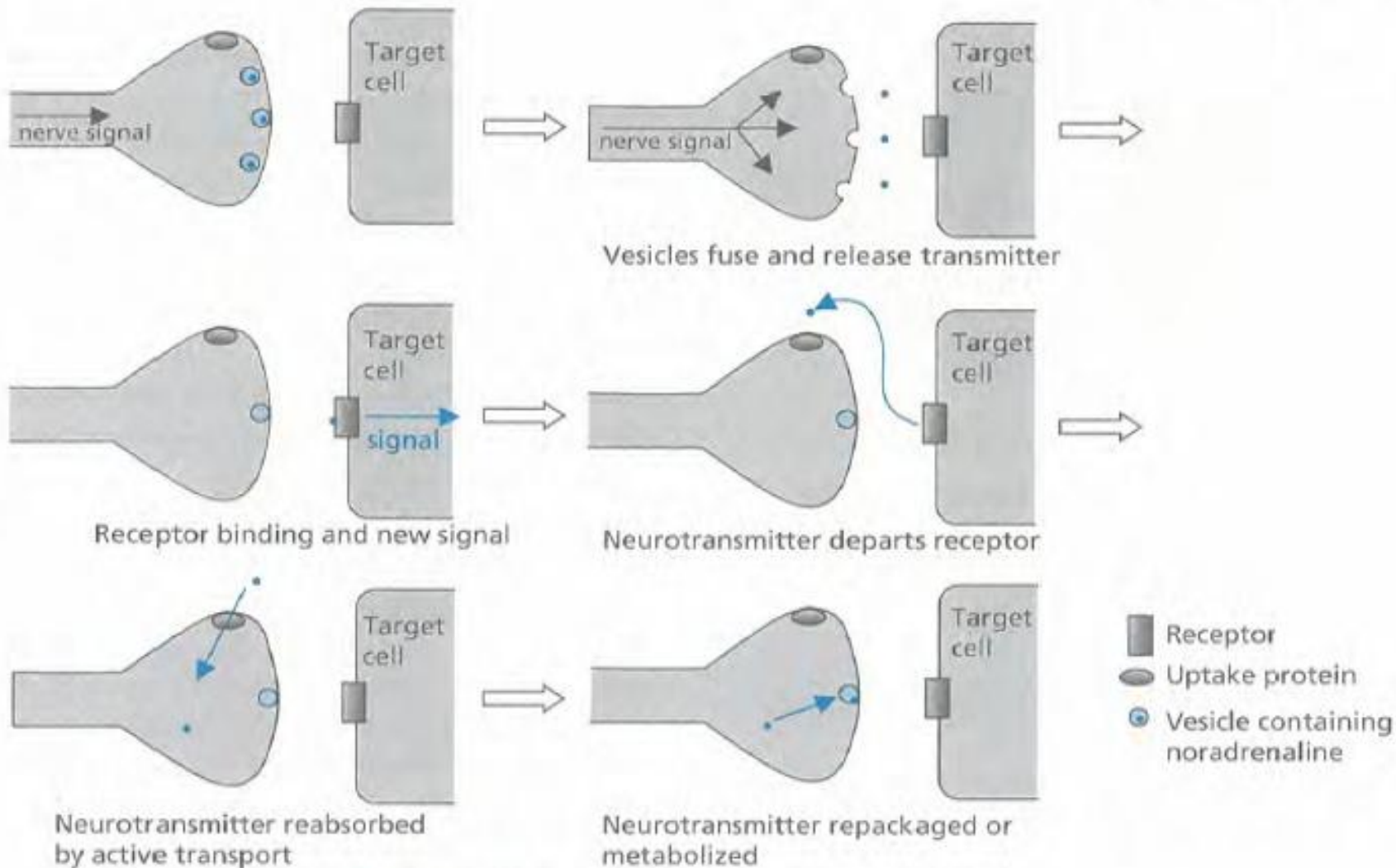
- Metabolism of catecholamines in the periphery takes place within cells and involves two enzymes
 - MAO (Mono Amine Oxidase)
 - COMT (Catecholamine O-Methyl Transferase)



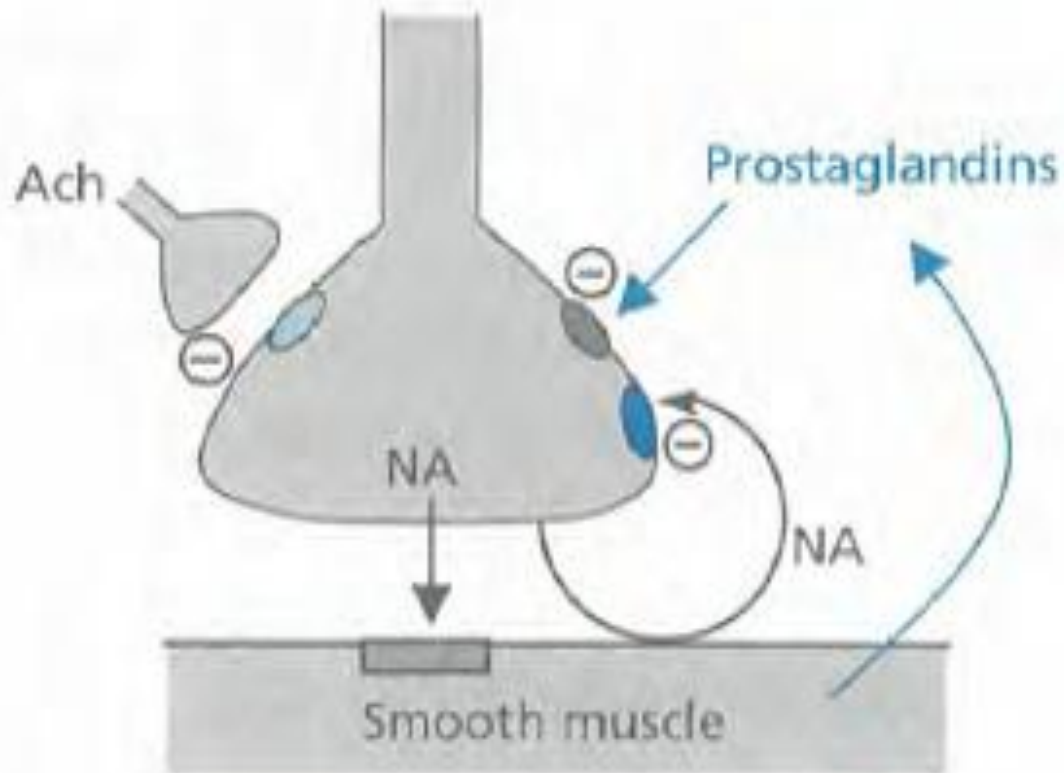
- Catechols are notoriously unstable, and catecholamines are no exception.
 - In the presence of air and light, they oxidize to form **quinones**, which have no adrenergic activity.
 - For this reason, solutions of catecholamines are kept at alkaline pH in sealed, brown glass containers.



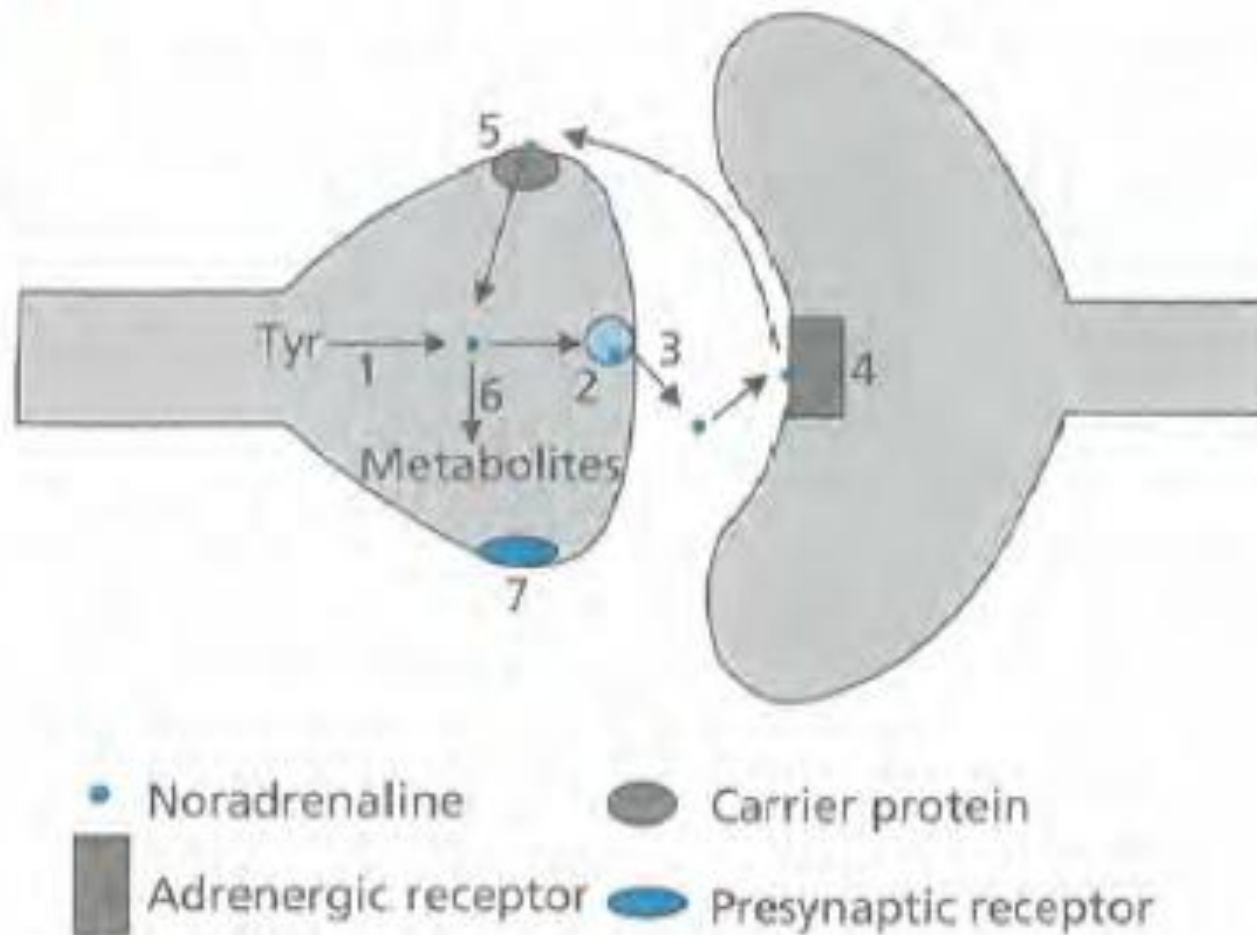
Neurotransmission



Pre-synaptic receptor and control

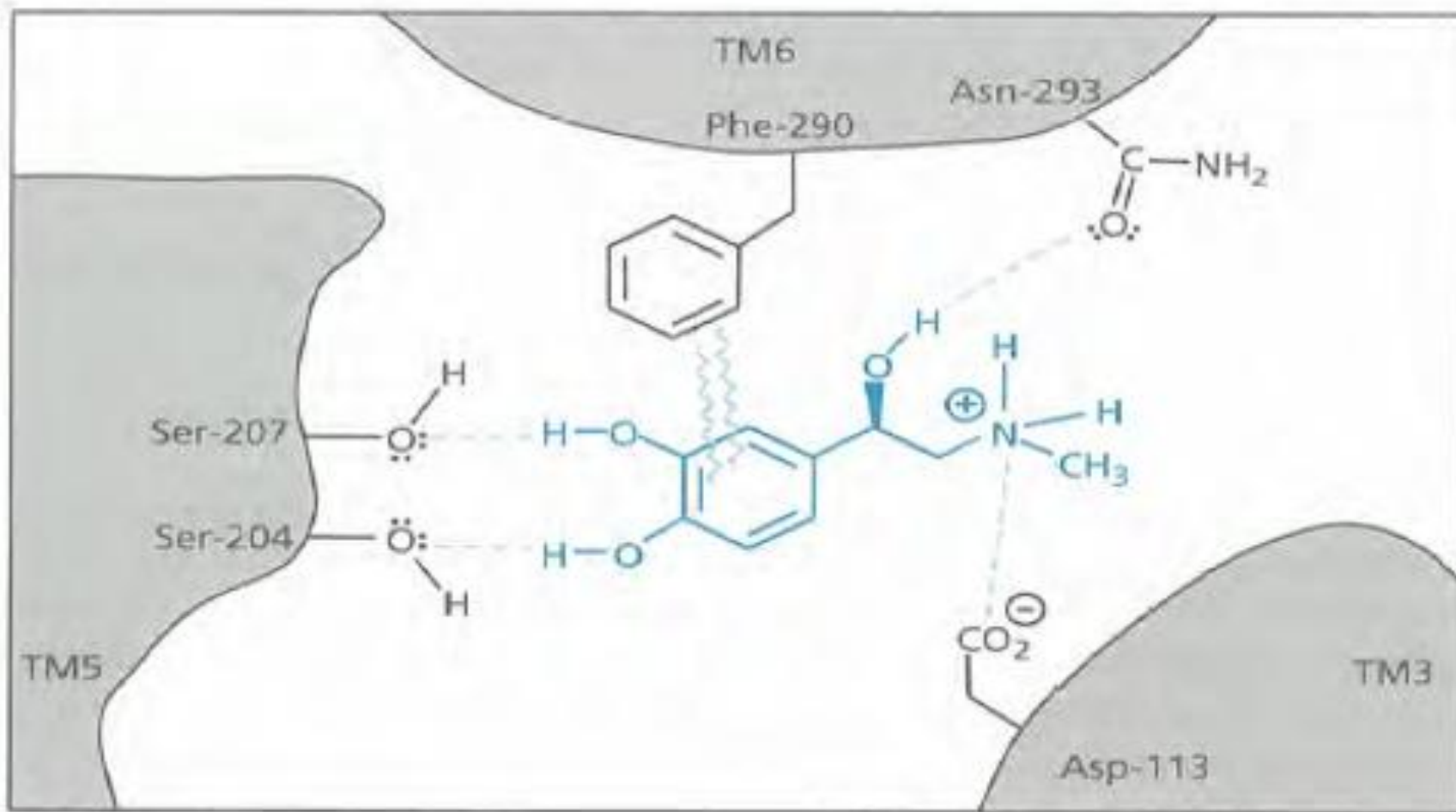


Possible drug targets

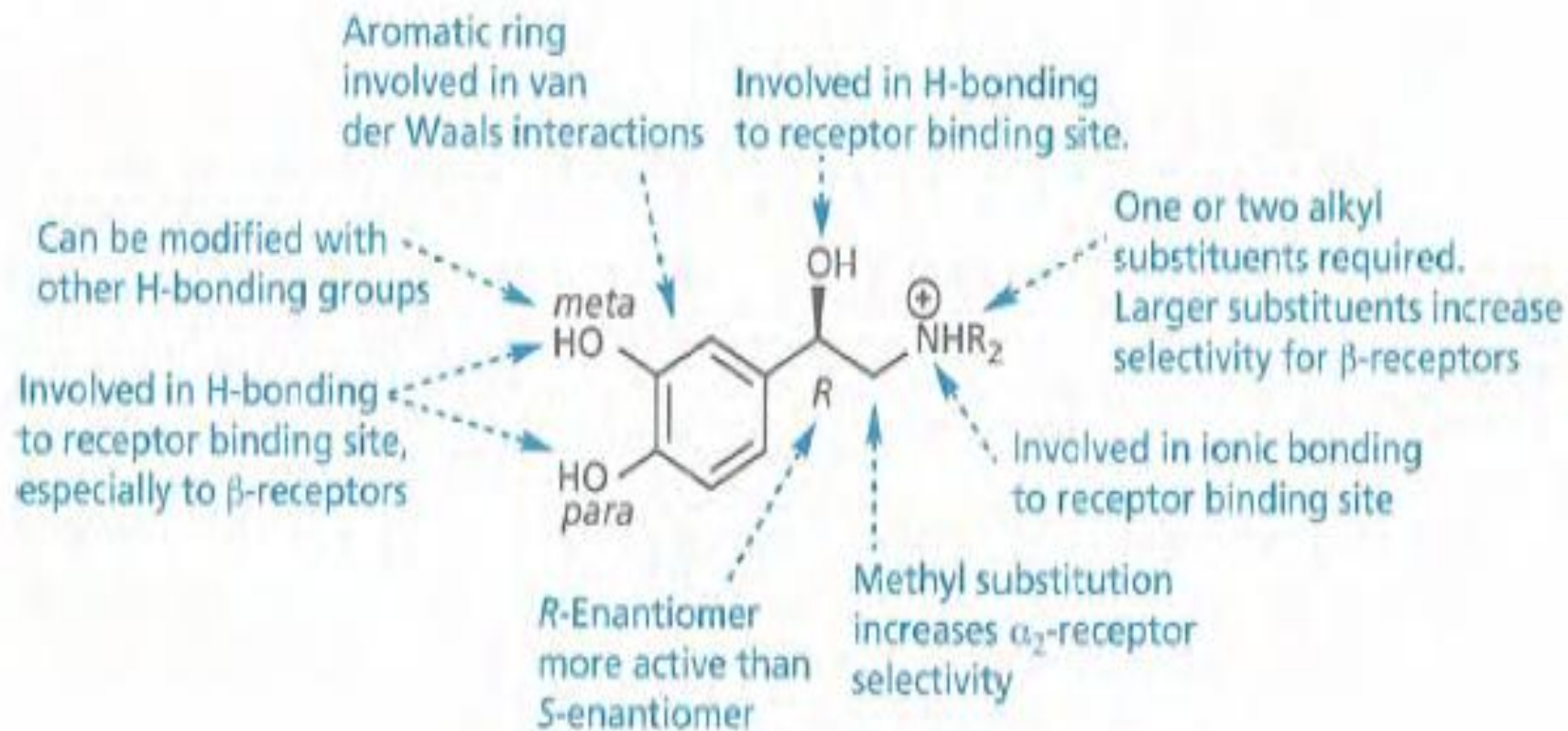


Adrenergic binding site

- The adrenergic receptors are G-protein coupled receptors which consists of seven transmembrane (TM) helices.
- From studies it has been proposed that TM3, TM5 and TM6 are important for binding interaction



SAR...

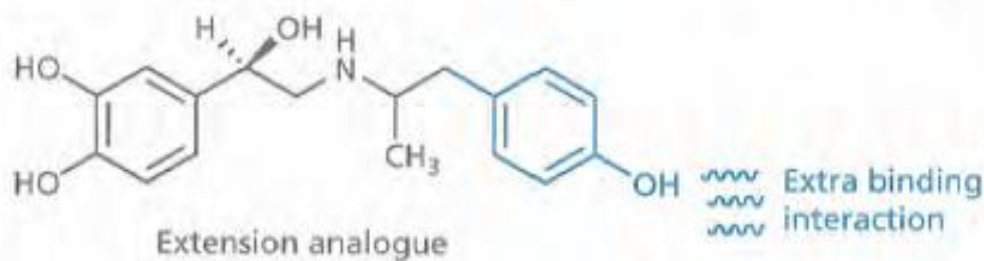
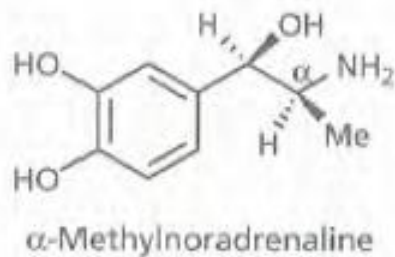


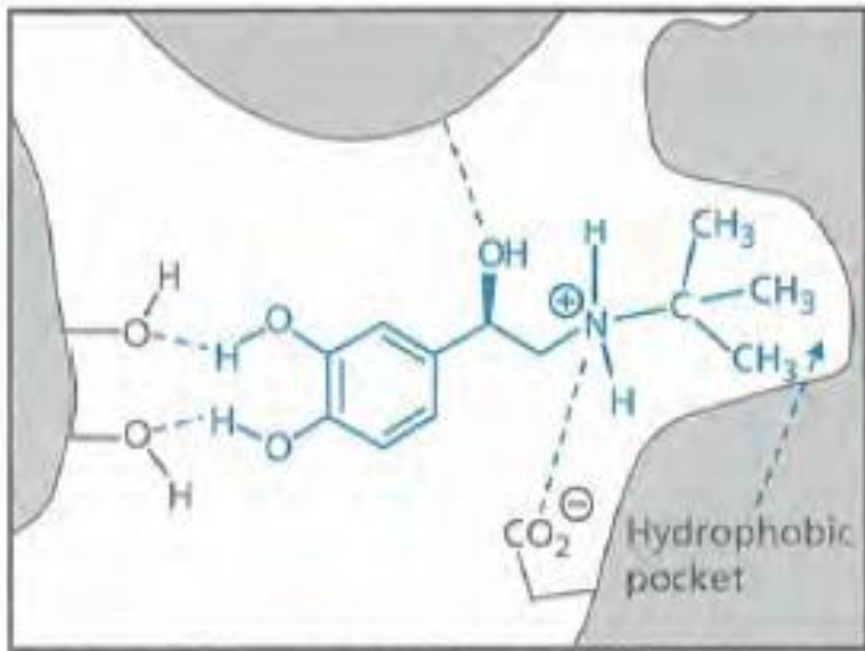
Selectivity for α - versus β - receptors

- Important features for selectivity
 - Large alkyl group on the terminal nitrogen – increases β selectivity
 - branched alkyl group – more β_2 selective

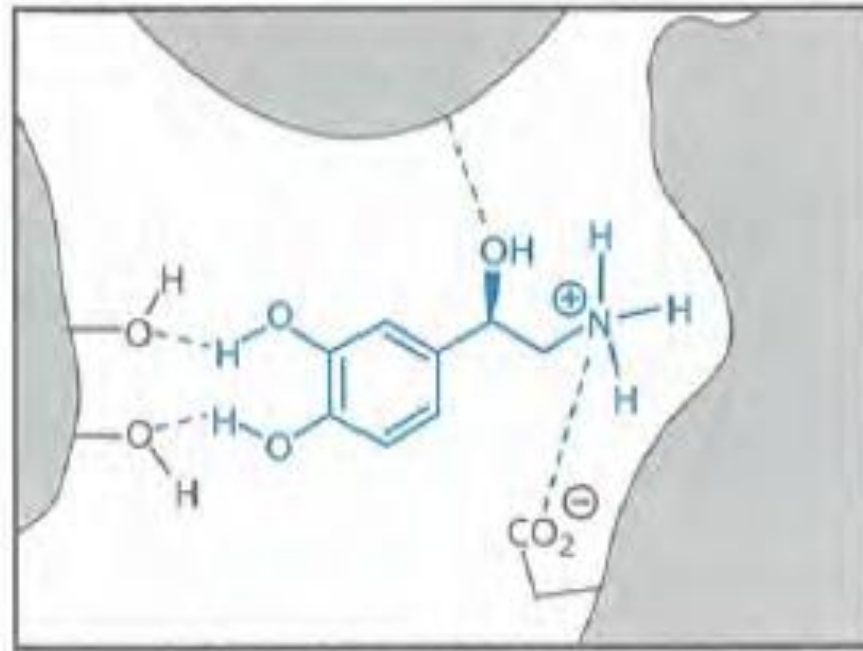


- Phenol group seems particularly important for β - receptors than α - receptors
- α - methyl substitution – addition of α - methyl group increase α_2 selectivity
- Extension





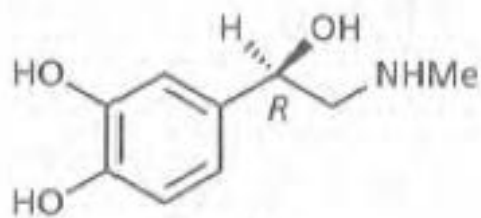
β -Adrenoceptor



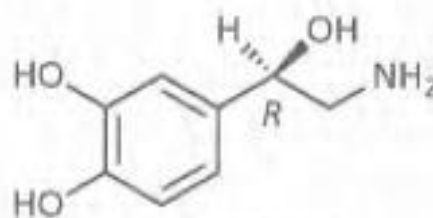
α -Adrenoceptor

Adrenergic agonists

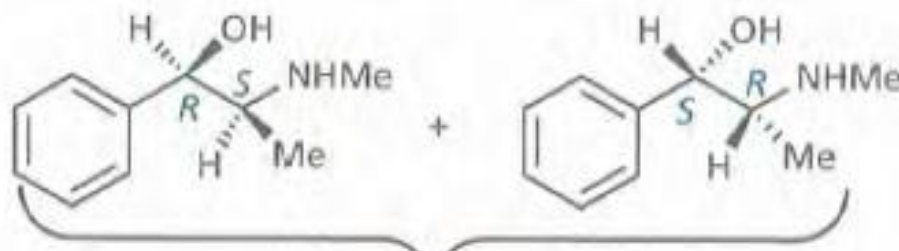
- General adrenergic agonists (α and β)
 - They are all natural products



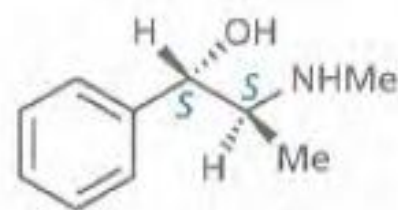
Adrenaline



Noradrenaline

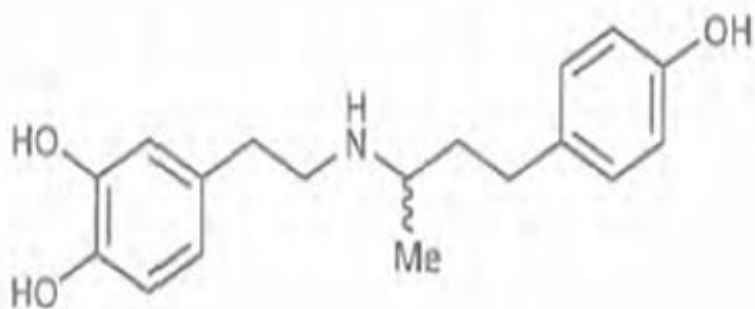


Ephedrine

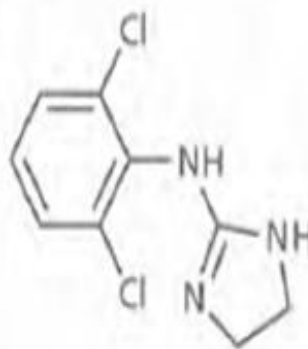


Pseudoephedrine

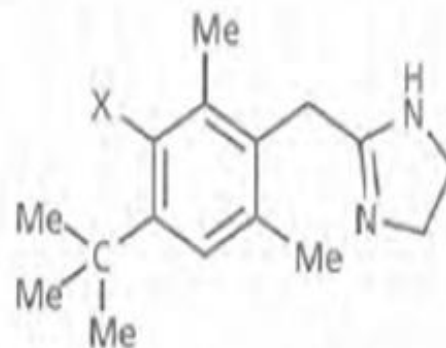
α_1, α_2 and β_1 agonists



Dobutamine

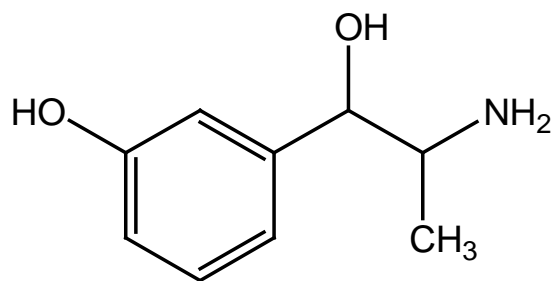


Clonidine

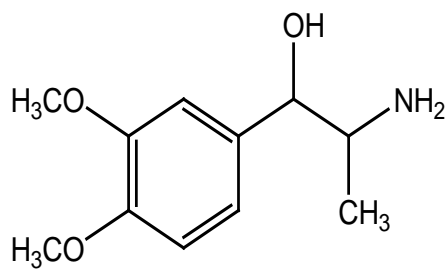


Oxymetazoline; X=OH
Xylometazoline; X=H

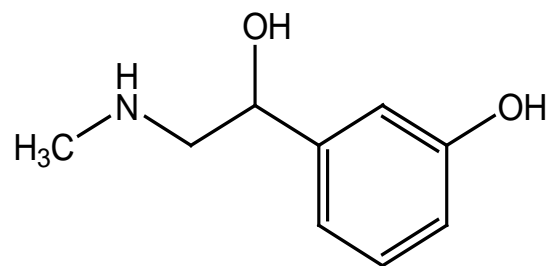
Other α_1 -agonists



meteraminol



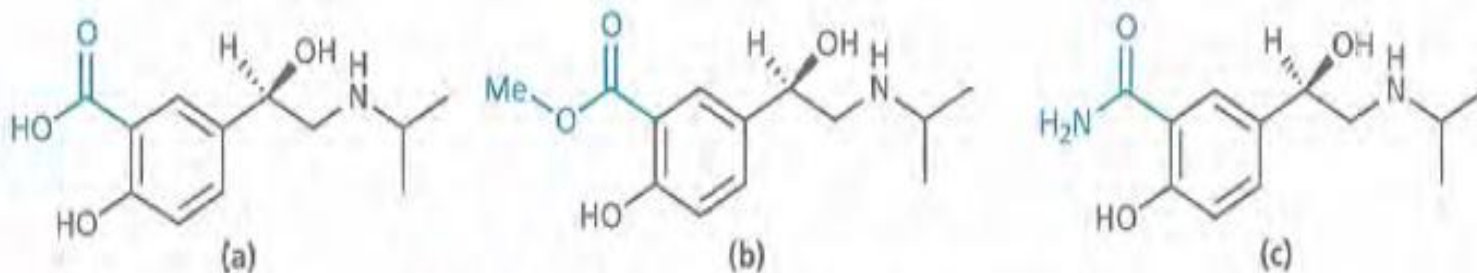
methoxamine



phenylephrine

β_2 -agonist and treatment of asthma

- Most of β_2 selective adrenergic agonists are used primarily as bronchodilators in asthma and other constrictive pulmonary conditions
- Early attempts (unsuccessful)



- Next successful attempts

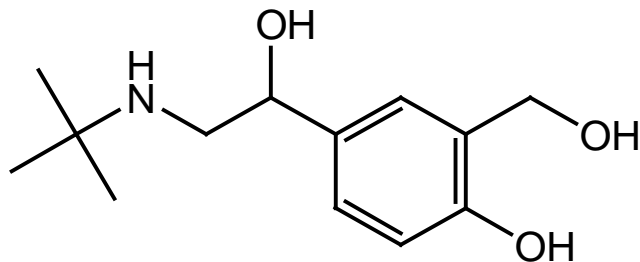


(the R enantiomer;
levalbuterol)

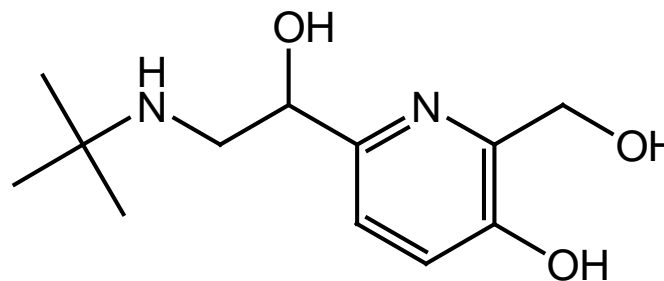
β_2 -agonist and...

Albuterol, Pirbuterol, Terbutaline

- Non-catechol selective β_2 -agonists.
- Available in oral dosage forms.



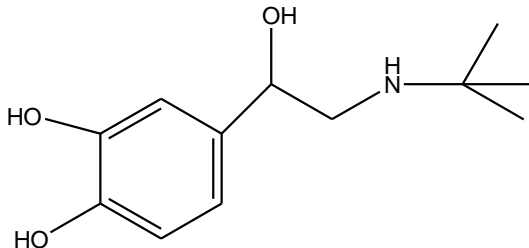
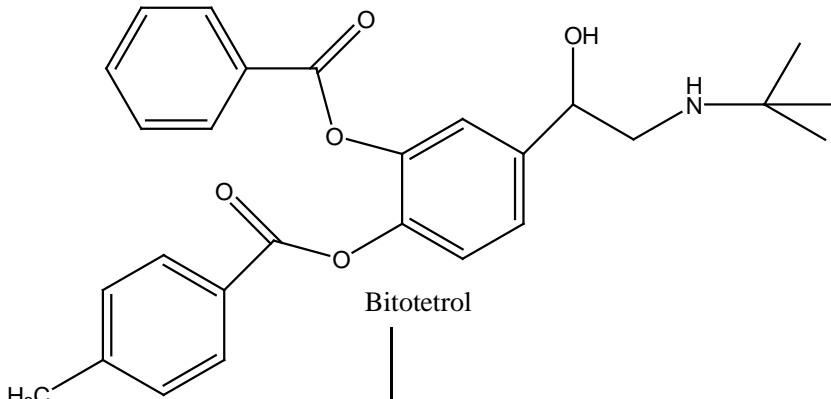
Albuterol (salbutamol)



pirbuterol

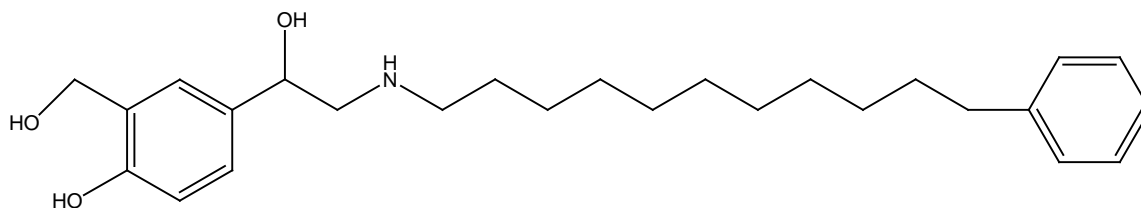
Bitoterol

- Is a prodrug form of colterol
- Has high lipophilicity and prolonged duration of action
- The ester group is hydrolyzed by esterase to liberate the active drug, colterol.



Salmetrol

- Has the same phenyl substitution R_3 as albutrol;
- Unusually long lipophilic group R' on the nitrogen.

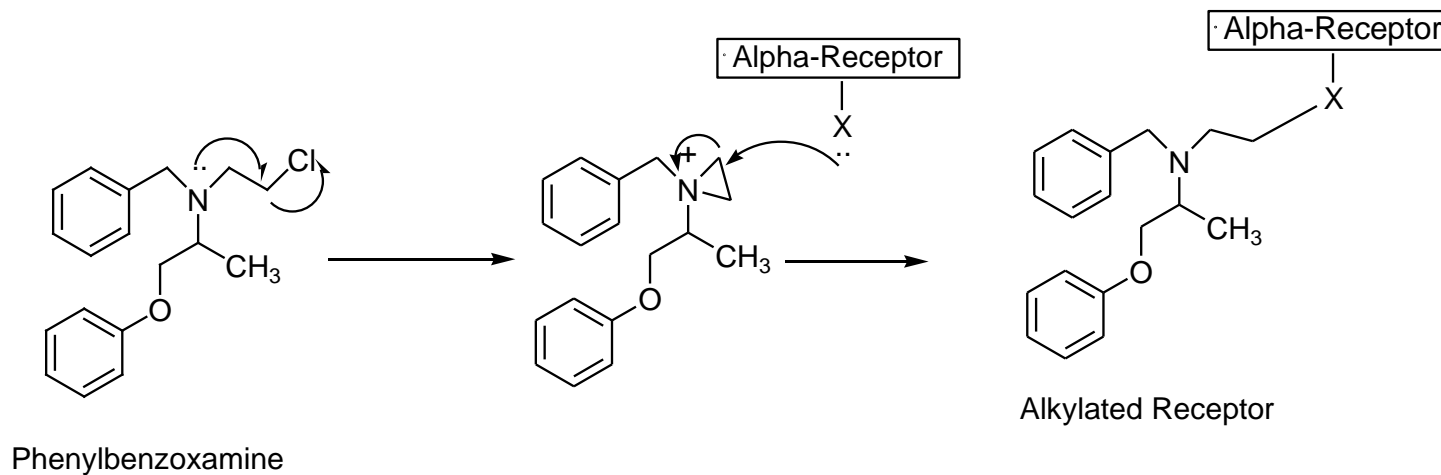


Salmeterol

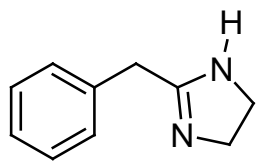
ADRENERGIC ANTAGONISTS

A. General α -antagonists

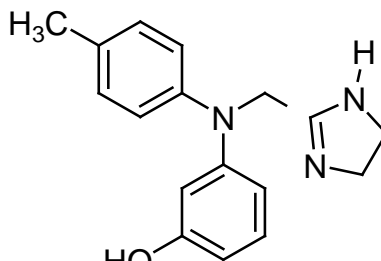
- α -antagonists to be therapeutically used as antihypertensive agents
- An old powerful drug in this class is phenylbenzamine(dibenzylamine) a β -haloalkylamine that alkylate α -receptors.



- Unfortunately, other biomolecules besides the target α -receptors are also alkylated.
- The other non selective alpha blockers are tolazoline and phentolamine
 - They are imidazoline α -antagonists that also have antihypertensive activity, although they have been replaced by far better agents



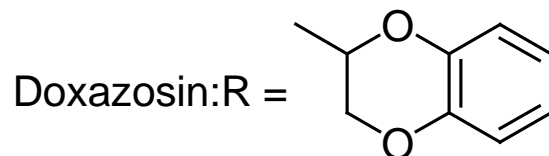
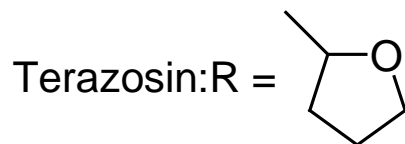
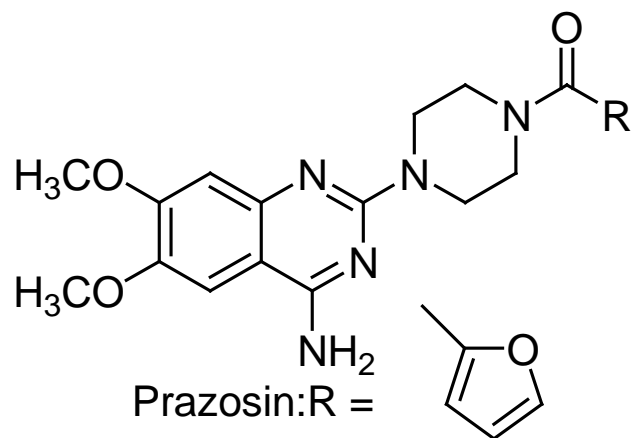
Tolazoline



Phentolamine

B. Selective α_1 -Antagonists

- Prazosin, doxazosin, and terazosin



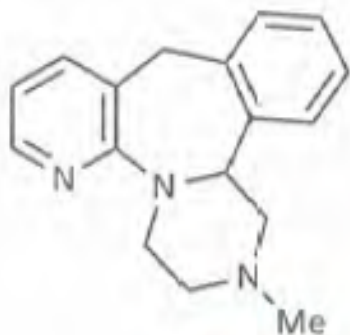
SAR –of Quinazolines

- Prazocin, dexazocin and Terazosin contain 4-Amino-6,7-Dimethoxyquinazoline ring system attached to piperazin nitrogen
- The only structural difference is to the structure attached to the other nitrogen of the piperazin.
- The difference in this groups afford dramatic difference in the pharmacokinetic properties of these drugs

Selective α_2 -antagonist

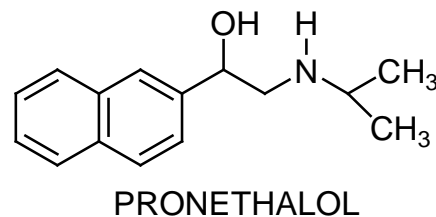
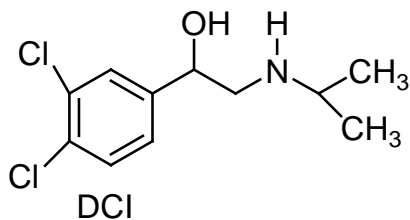
- Used clinically for treatment of depression (increasing the level of serotonin and adrenaline)

Example - Mirtazepine [antidepressant drug]

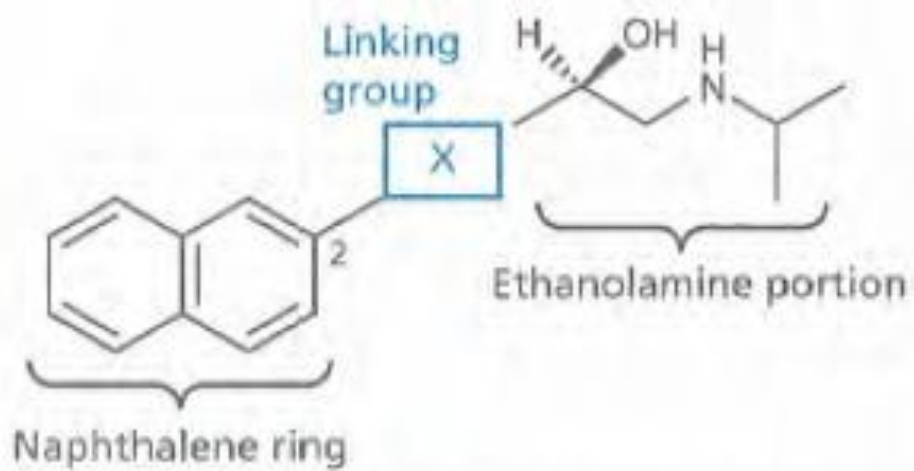


- **β -Adrenergic antagonists**

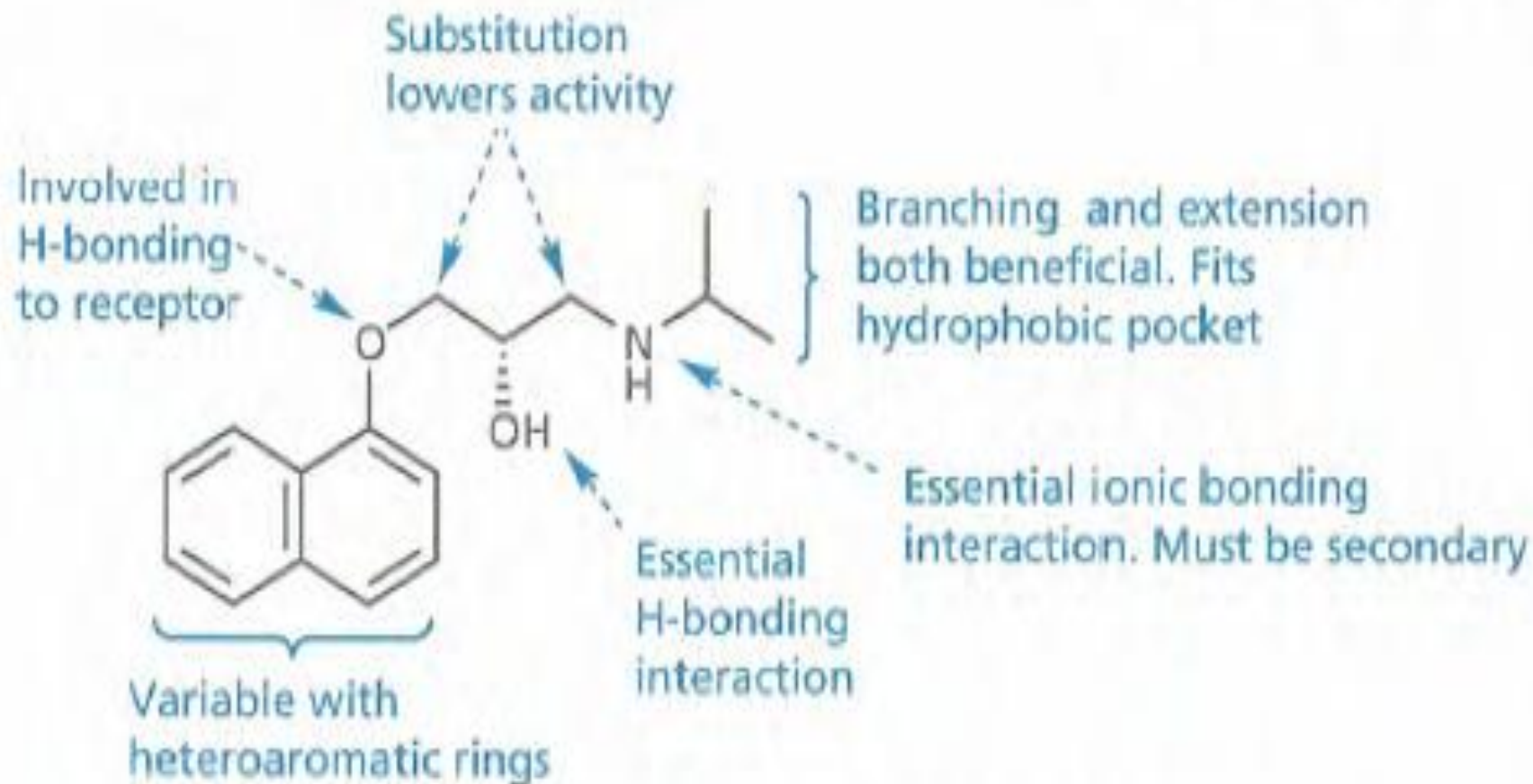
- A derivative of isoproterenol in which the catichol hydroxyls had been replaced by chlorine, dichloroisoproterenol (DCI) was discovered to be β -antagonist
- DCI- had no clinical utility, replacement of the 3,4-dichlorosubstituents with a carbon bridge to form a naphthayl ethanolamine derivative did afford a clinical candidate, **Pronethalol**



- Research was carried out to see what effect extending the length of the chain between the aromatic ring and the amine would have.
- This had led to the discovery of propranolol -a pure antagonist having 10-20X potency than Pronethalol
- The inventor James Black got a nobel prize in 1988

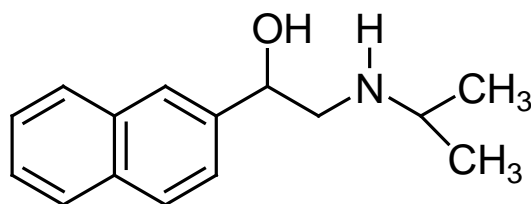


SAR of aryloxypropanol amine

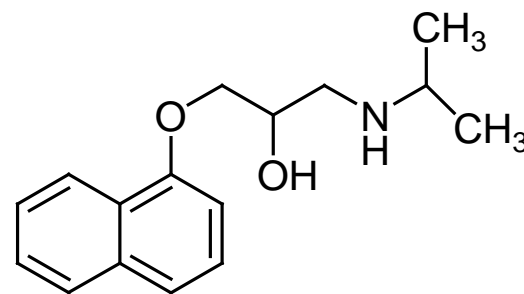


First generation β - blockers

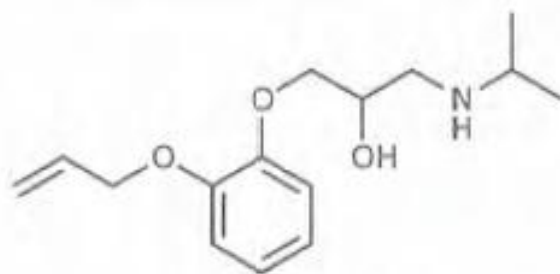
- Non selective blockers



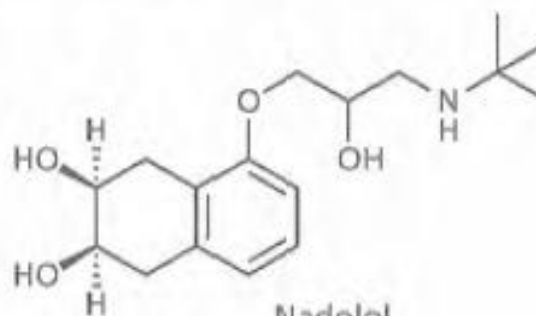
Pronethalol



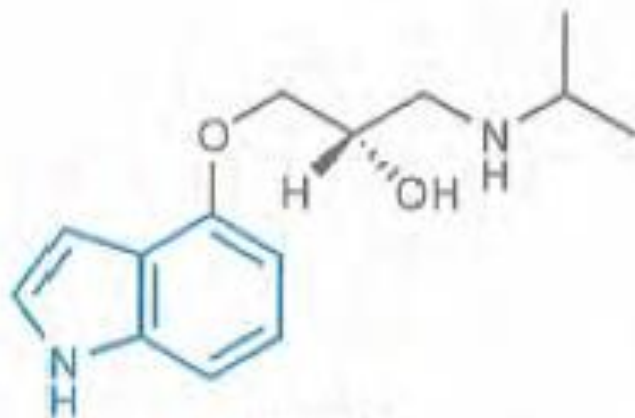
Propranolol



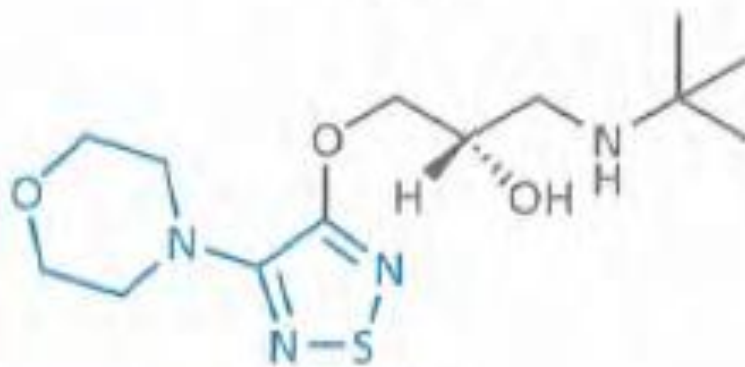
Oxprenolol



Nadolol



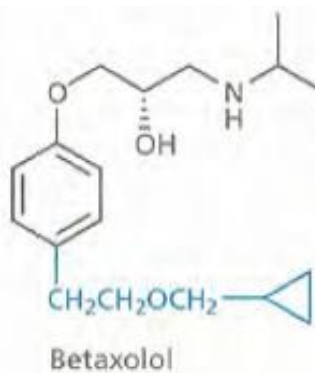
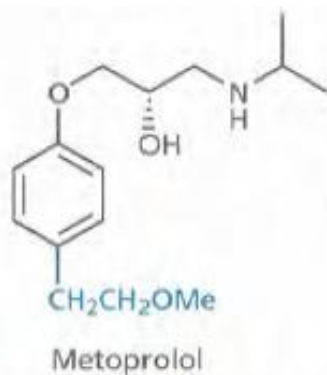
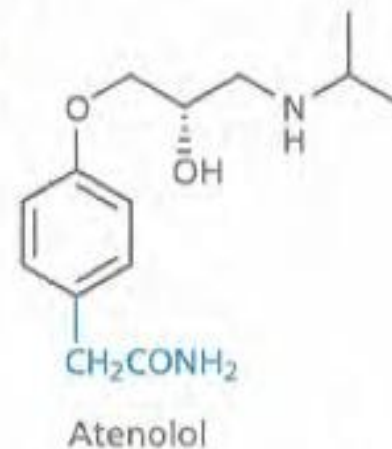
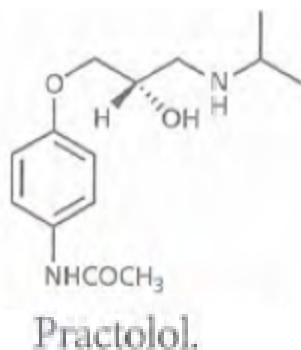
Pindolol

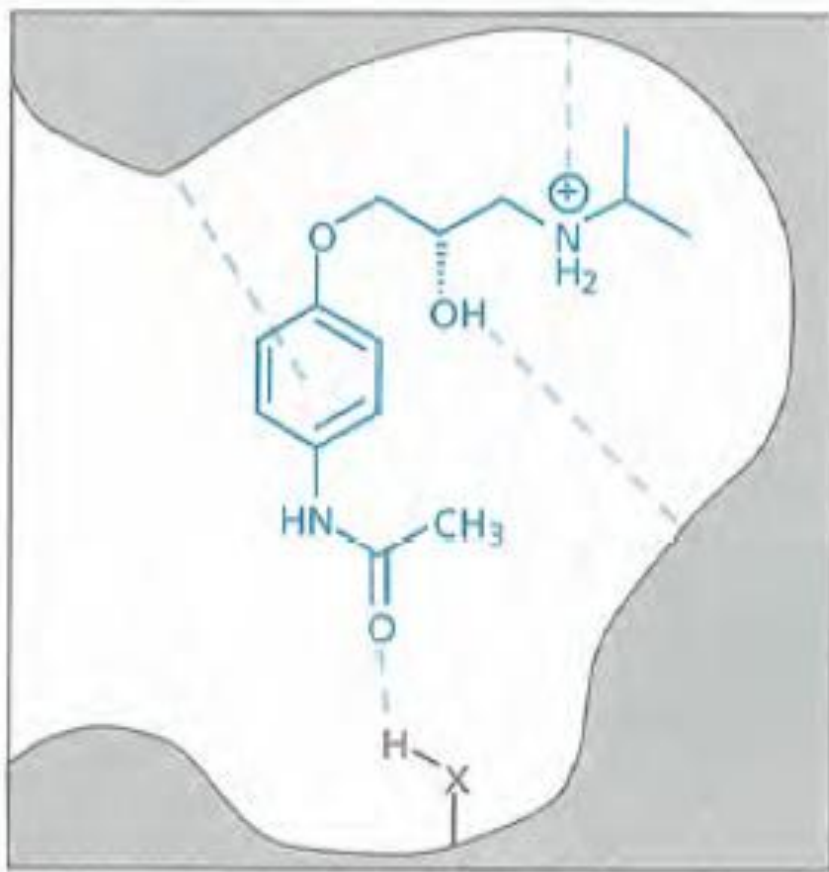


Timolol

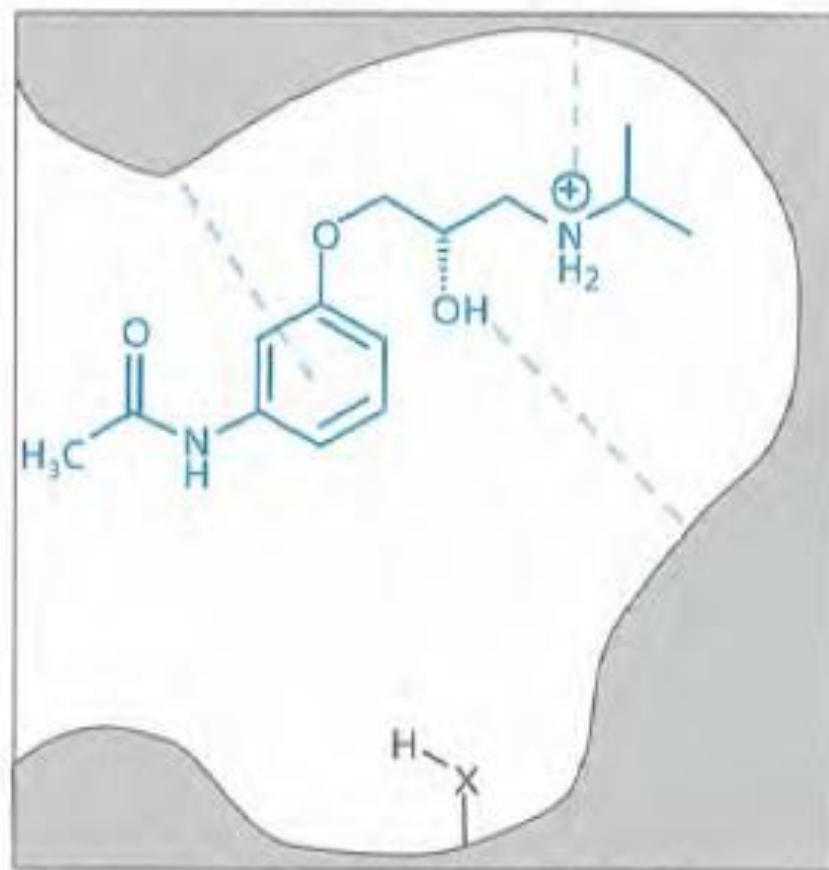
Second generation β - blockers

- Selective β_1 - blockers



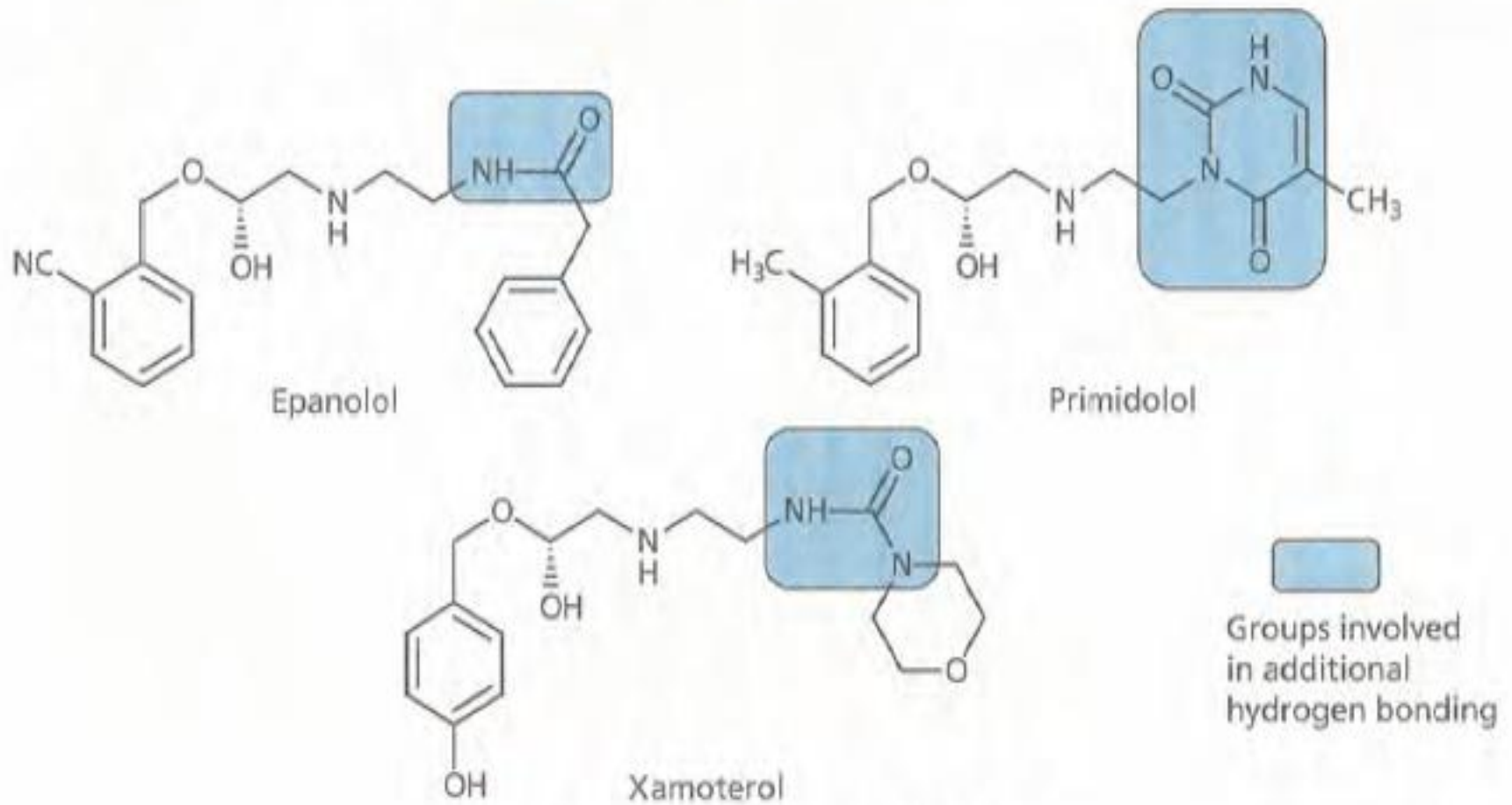


para substitution
Extra H-bonding interaction



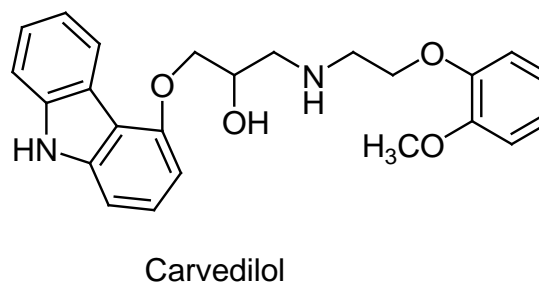
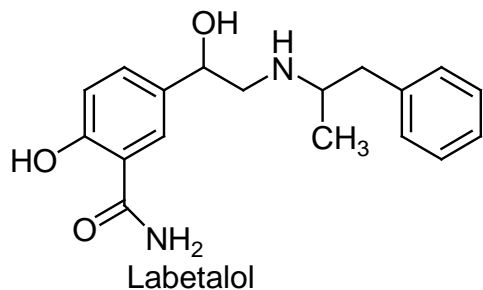
meta substitution

Third generation selective β_1 blockers



Mixed α/β Adrenergic Antagonists

- They have unusual activity in that they are antihypertensive with $\alpha_1, \beta_1, \beta_2$ blocking activity

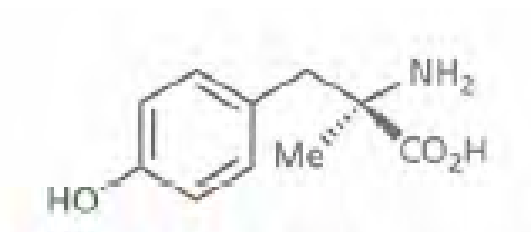


- These two drugs have structural features permitting binding to both the α_1 and non-selectively to both β -receptors.

Other drugs that affect adrenergic transmission

Drugs affecting biosynthesis of adrenergic neurotransmitters

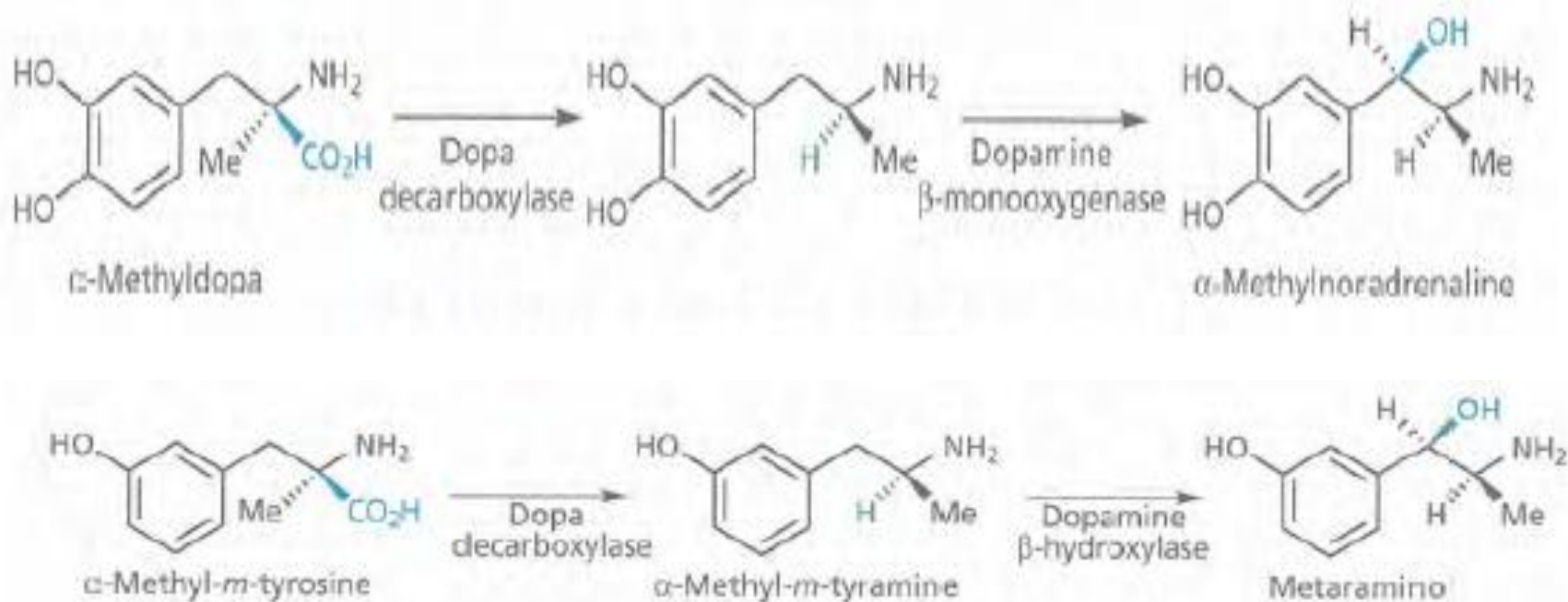
- Tyrosine hydroxylase inhibitor



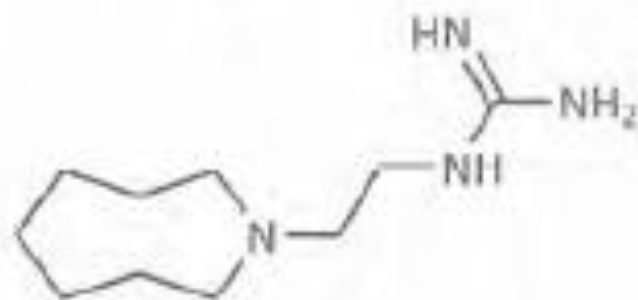
α-methyltyrosine

- To treat pheochromocytoma

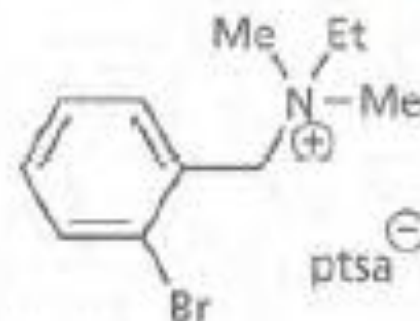
- **Methyldopa and α -methyl-m-tyrosine**
- **antihypertensive**



- Drugs that inhibit release of NA from vesicles
 - For treatment of HTN and arrhythmia



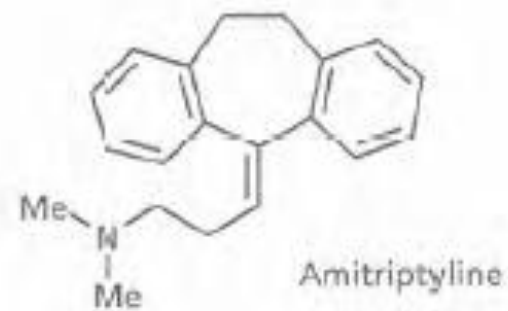
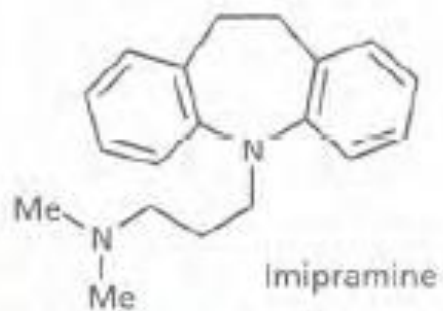
Guanethidine



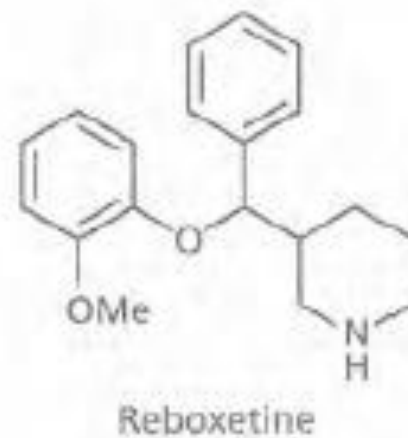
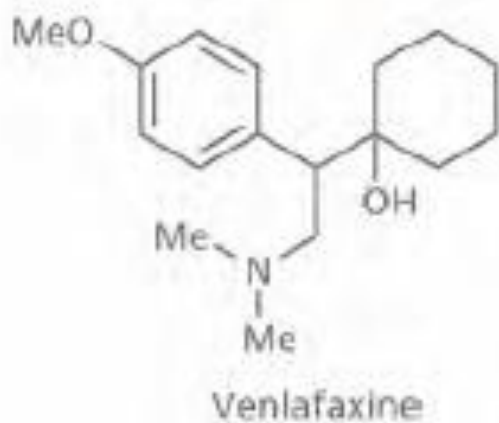
Bretylium

ptsa[⊖]

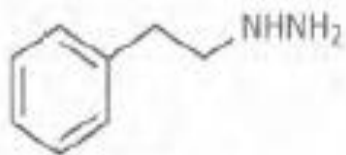
- Drugs that inhibit reuptake of NA
- For treatment of depression



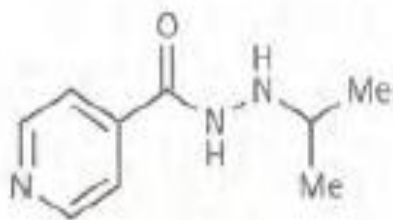
- SNRIs less toxic than TCAs



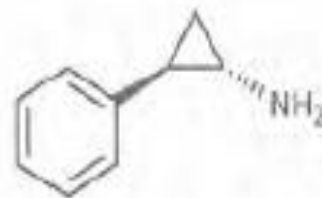
- MAO inhibitors
 - Used also as antidepressants



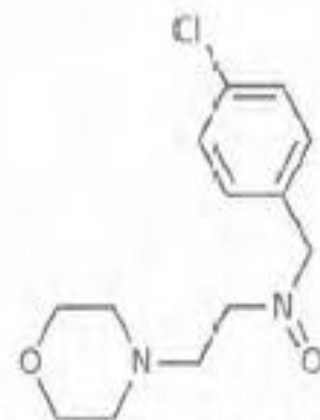
Phenelzine



Iproniazid



Tranylcypromine



Moclobemide

100Q