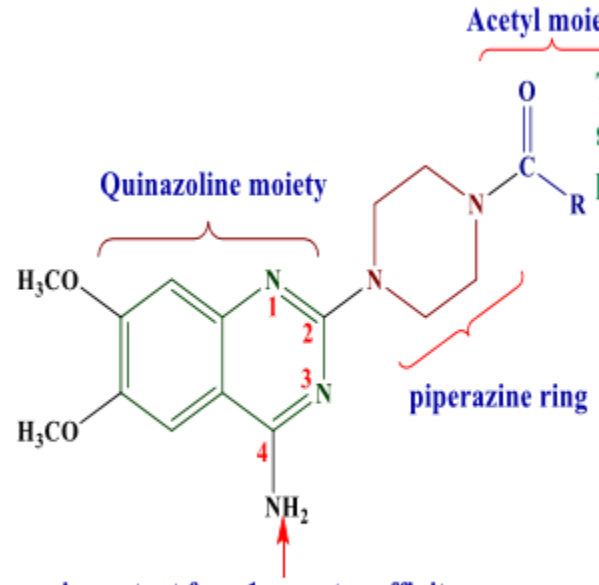
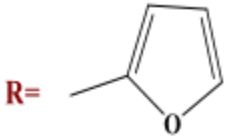
Selective α_1-blockers

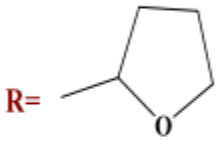
Quinazoline derivatives(α_1-blockers)



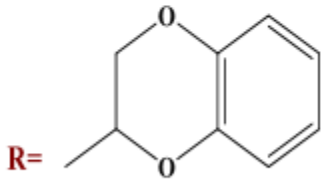
The nature of the acyl group has a significant effect on the pharmacokinetic properties



Prazosin

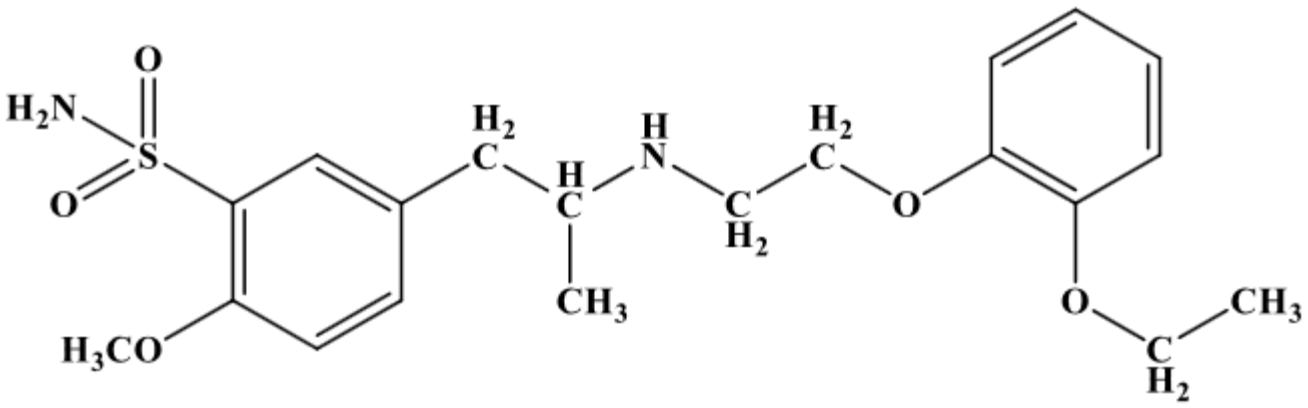


Terazosin



Doxazosin

they block α1 receptor selectively, without blocking α2 receptor
they produce peripherial vasodilation without increase in the heart rate.



Tamsulosin

nonquinazoline benzsulfonamide

more selective for α1A-receptors than for the other α1-receptors

blockade of α1A-receptors found in the prostate gland

over those found in vascular tissue.

treatment of BPH with little effect on blood pressure.

Orthostatic hypotension is not as great with this agent

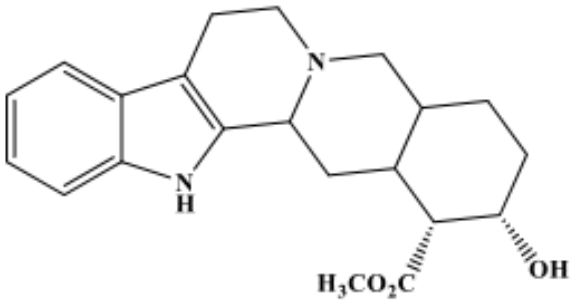
as with the nonselective quinazolines

Selective α2-blockers

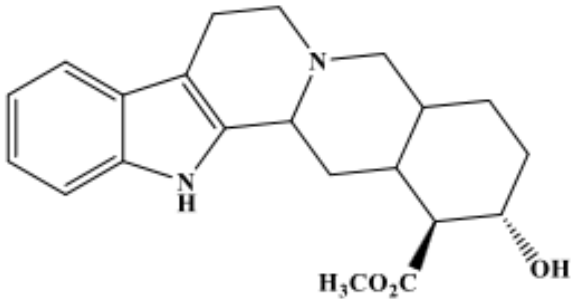
Example

•Indol alkaloide

These isomeric indol alkaloide known as yohimbine and corynanthine exhibited different degree of selectivity toward α1 and α2 receptors depending on the stereochemistry.



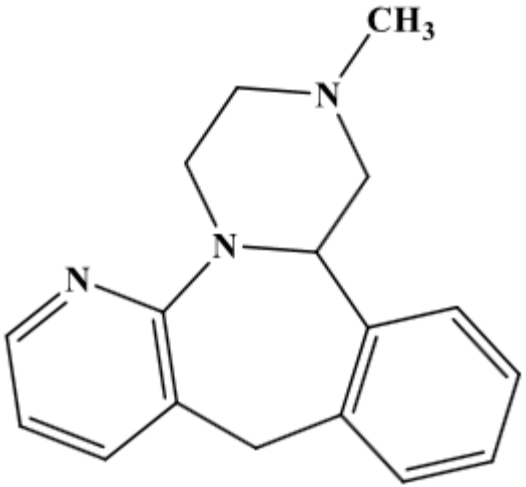
Yohimbine
selective α2-receptor
carbomethoxy in plan of alkaloid ring



Corynanthine
selective α1-receptor
carbomethoxy out of plan of alkaloid ring (axial)

increases heart rate and blood pressure as a result of its blockade of α2-receptors in the CNS.
It has been used experimentally to treat male erectile impotence.

2-Mirtazapine (Remeron)



selective α2-receptors versus α1-receptors

Blockade of central α2-receptors results in an increased release of NE and serotonin antidepressant.

This agent also has activity at nonadrenergic receptors.

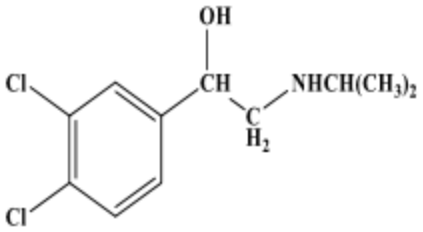
It is a potent blocker of 5-HT2 and 5-HT3 serotonin receptors and at histamine H1-receptors.

β-Blockers

Structure activity relationship

β-Blockers are among the most widely employed antihypertensives and are also considered the first-line treatment for glaucoma.

Most of β-blockers are in the chemical class of aryloxypropanolamines



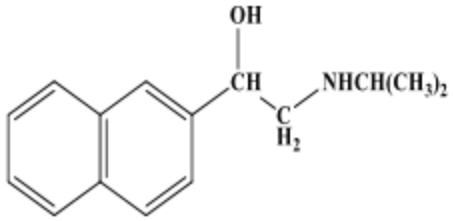
dichloroisoproterenol (DCI)

The first β-blocker, reported in 1958 by Powell and Slater

differs structurally from ISO in that the agonist directing

3',4'-di-OH groups have been replaced by two chloro groups

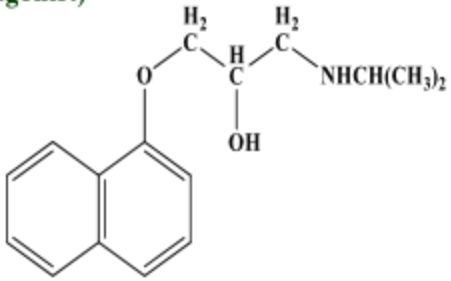
partial agonist (not pure antagonist)



Pronethalol

has much less intrinsic sympathomimetic activity (ISA) than DCI

cause tumor



propranolol

aryloxypropanolamines derivative

an -OCH_2- group has been incorporated into the molecule between

the aromatic ring and the ethylamino side chain

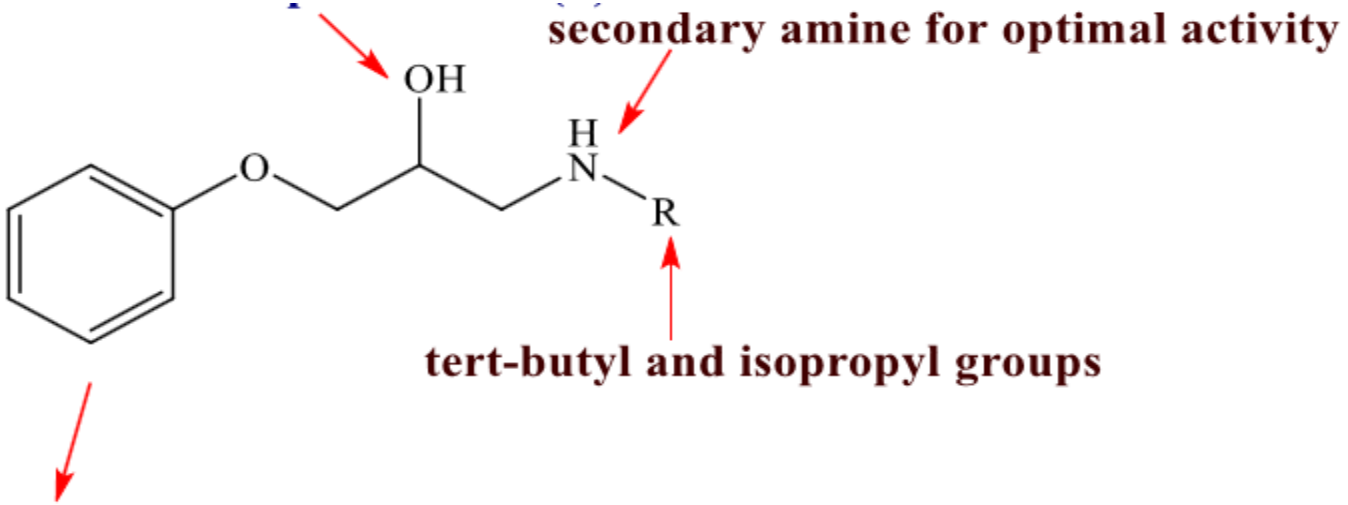
B-blocker (Aryloxypropanolamine)

SAR

presence of β-hydroxyl group

S-configuration

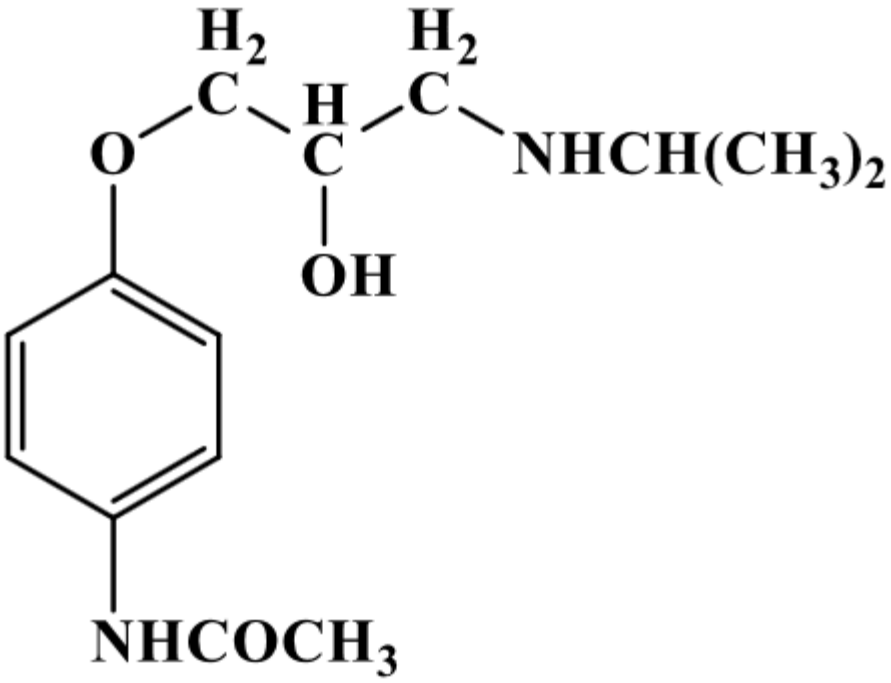
(R) isomer 100 times less potent than (S)isomer



The nature of the aromatic → β1-selectivity of the antagonist

presence of a para-substituent of sufficient size

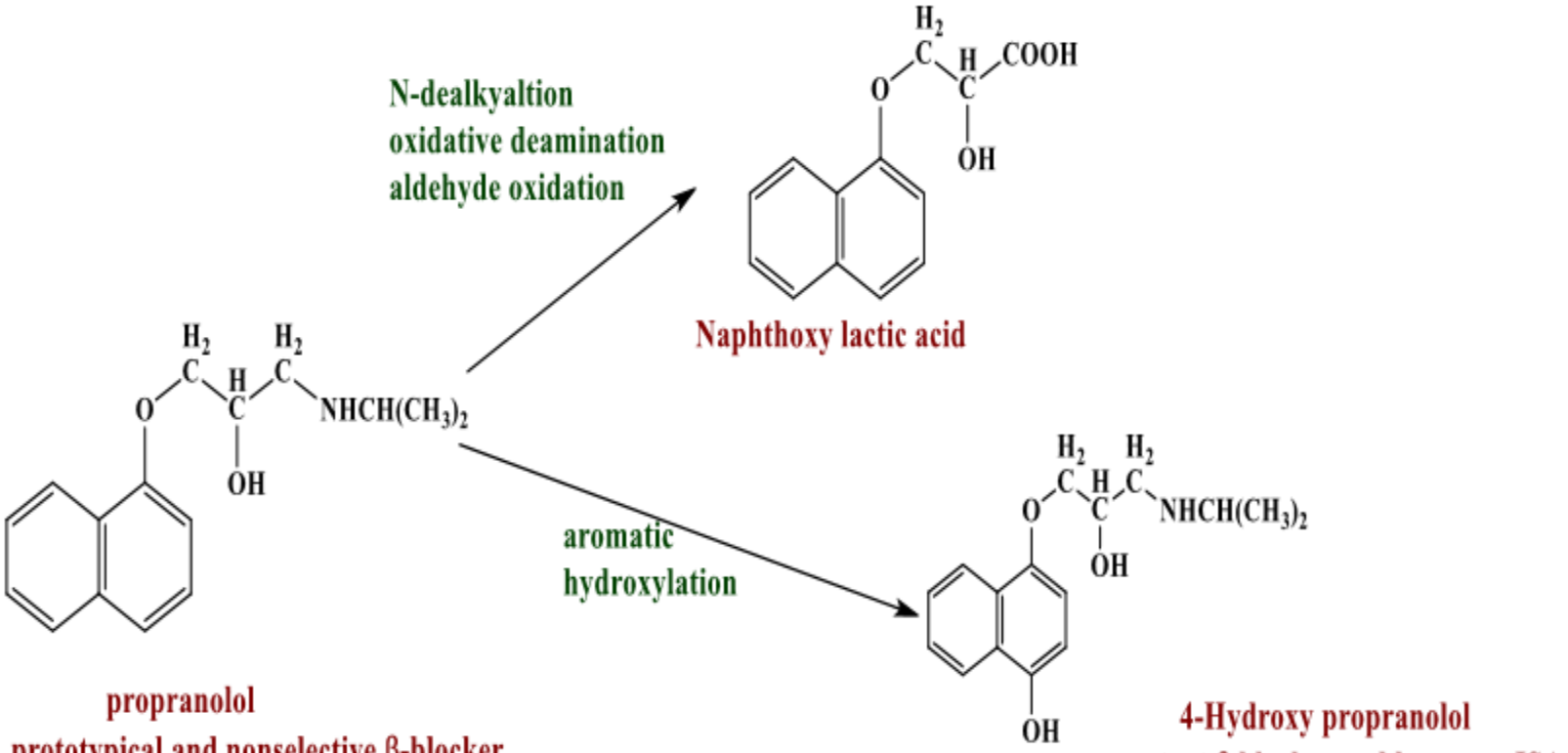
along with the absence of meta-substituents.



Practolol (a prototype of β1 blocker) cause several toxic effect so no longer use

NONSELECTIVE β-BLOCKERS (FIRST GENERATION)

•Propranolol (Inderal)



prototypical and nonselective β-blocker

(blocks theβ1- andβ2-receptors with equal affinity)

potent β blocker and has some ISA

Because it exhibits no selectivity for β1-receptors→ it is contraindicated in asthma and bronchitis.

lacks ISA, and does not block α-receptors

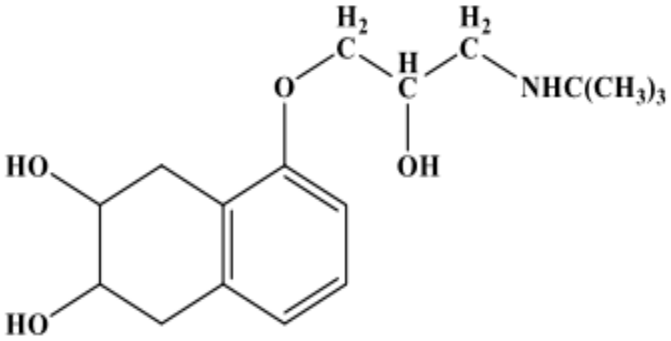
high lipophilicity (log P = 3.10) has ability to penetrate the CNS(use in treating anxiety)

competitive blocking agent

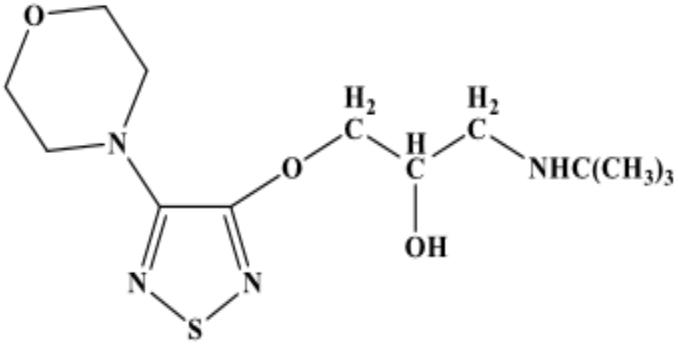
(receptor-blocking actions can be reversed with sufficient concentrations of β-agonists)

propranolol is approved for use in the United States for:-

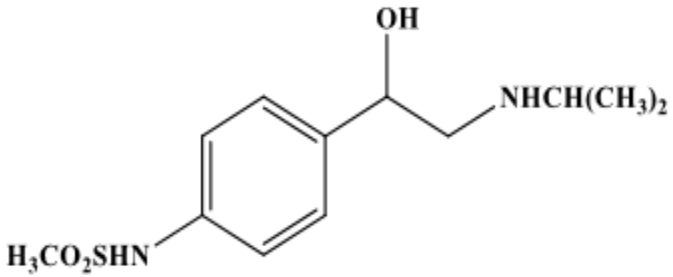
- **Hypertension.**
- **Cardiac arrhythmias.**
- **Angina pectoris.**
- **Post myocardial infarction.**
- **Hypertrophic cardiomyopathy.**
- **Pheochromocytoma.,**
- **Migraine prophylaxis.**
- **Essential tremor.**



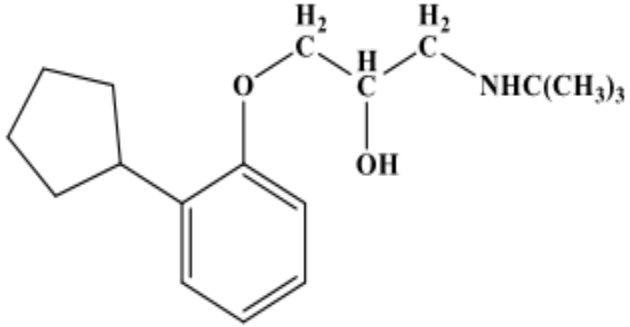
Nadolol
Antihypertensive
angina pectoris
longer DOA(20 hrs)



timolol
Antihypertensive
Antiglucoma
use in the prophylaxis migrain headach



Sotalol
Antiarrythmias
only phenyl ethyamine



Penbutolol
Antihypertensive
posses partial agonist activity→
cause less slowing of the resting heart rate
(brady cardia)

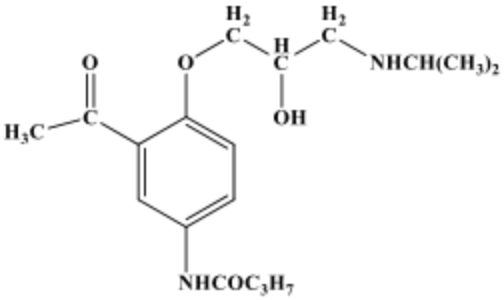
Selective β 1- blockers (Second generation(

β_1-blockers are drugs that have a greater affinity for the β -$_1$ receptors of the heart than for β_2-receptors in other tissues .

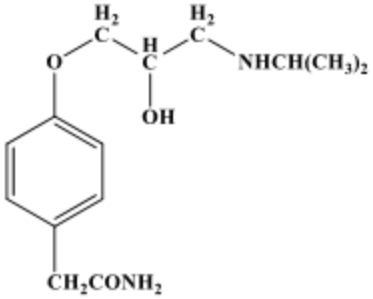
Such cardioselective agents should provide two important therapeutic advantages

- **Should be the lack of a blocking effect on the β_2-receptors in the bronchi (safe for use in patients who have bronchitis or bronchial asthma.(**
- **Should be the absence of blockade of the vascular β_2-receptors, which mediate vasodilation. This would be expected to reduce or eliminate the increase in peripheral resistance that sometimes occurs after the administration of nonselective β-blockers .**

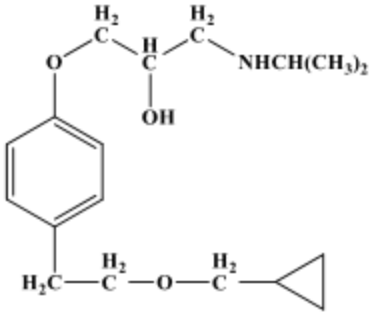
Note:- Unfortunately, cardioselectivity is usually observed with β_1-blockers at only relatively low doses. At normal therapeutic doses, much of the selectivity is lost.



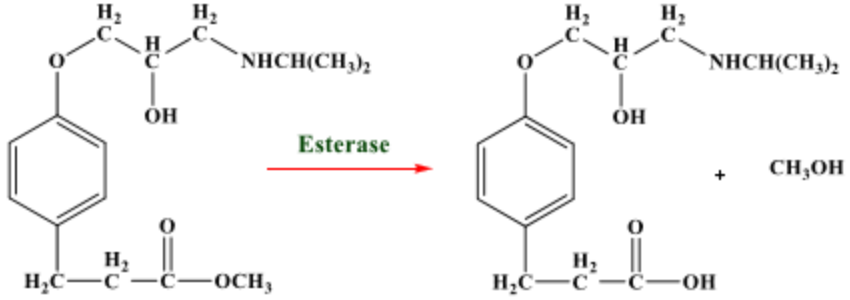
Acebutolol
Antihypertensive
cardiac arrythemias



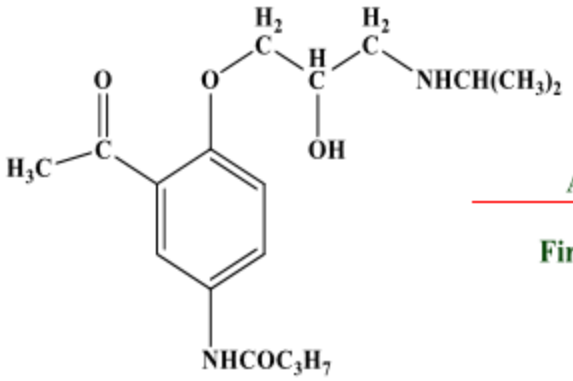
Atenolol
Antihypertensive
angina pectoris
Atenolol (log P = 0.10), →low lipid solubility →
does not readily cross the BBB.
It is absorbed incompletely from the gastrointestinal tract, the oral bioavailability being approximately 50%.



Betaxolol
Antihypertensive
antiglucoma
half-life 14-22hrs→ longer DOA

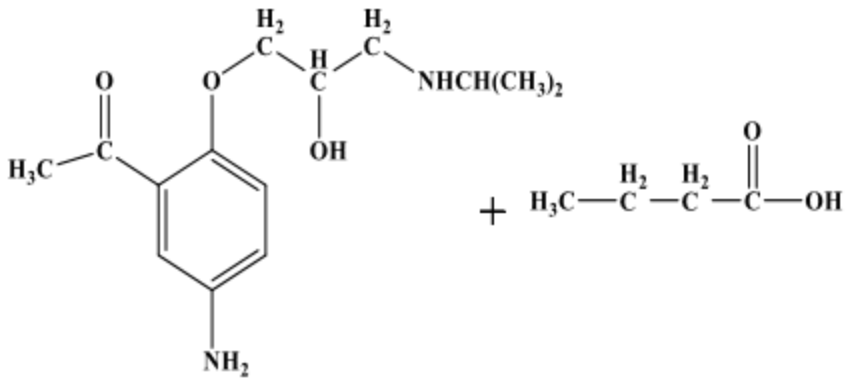


Esmolol
Antihypertensive and cardiac arrythemias
half-life 9 min→ short DOA→rapid hydrolysis by esterase
weak β-blockers and not exhibit clinically significant effects
administered by continous IV infusion for control ventricular rate in patient with atrial flutter , atrial fibrillation, or sinus tachycardia



Amidase

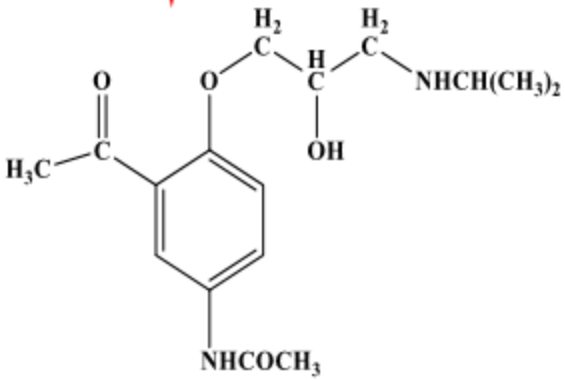
First pass efct



+

Acebutolol
absorbed well from the GIT,
but undergo extensive first pass metabolic conversion to diacetolol

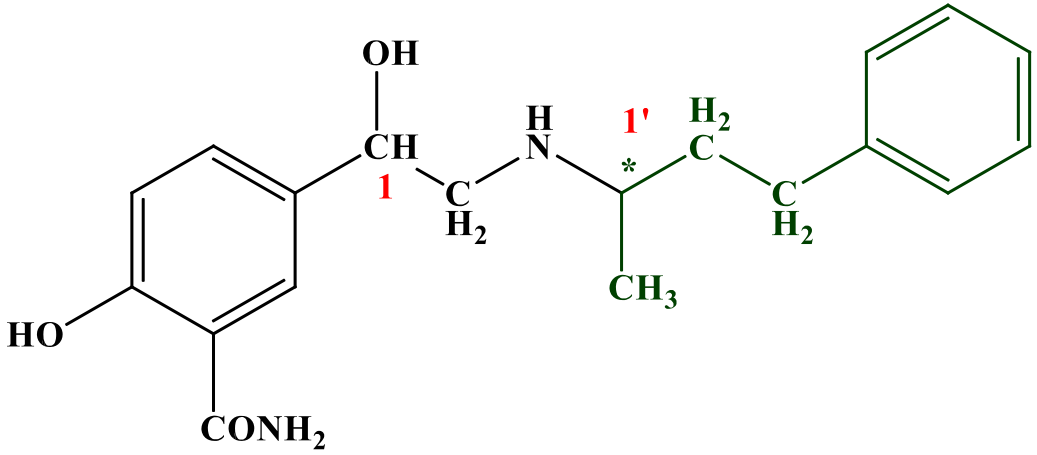
Acetylation
(cofactor, enzyme)?



Diacebutolol
a selective β1-blocker with partial agonistic activity
has a longer half-life (8-12 hours) than the parent drug
and is excreted by the kidneys

β-blockers with α_1-antagonist activity (third generation)

1- Labetalol



Labetalol

phenylethanolamine derivative

competitive blockers at α1-, β1-, and β2-receptors

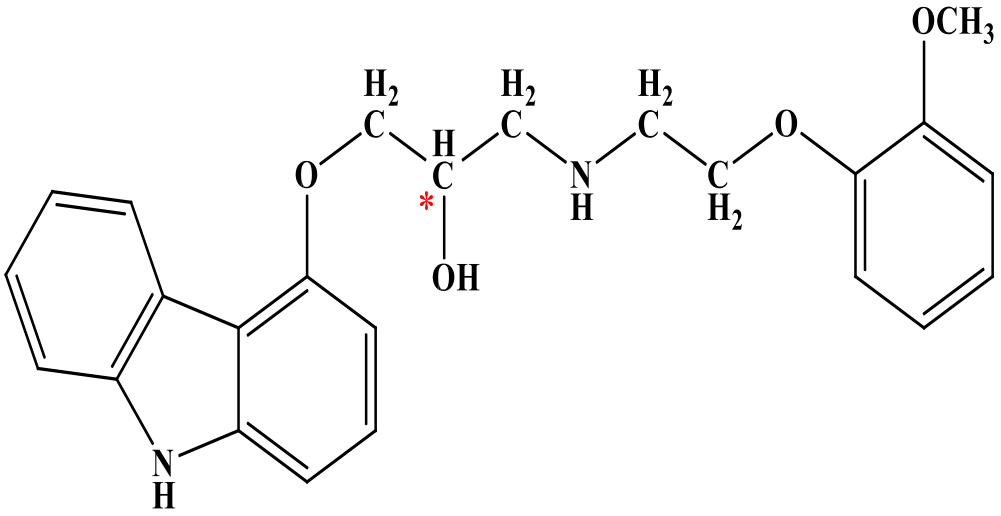
It is a more potent β-blocker than α-blocker

used as antihypertensive

Because it has two asymmetric carbon atoms (1 and 1'), it exists as a mixture of four isomers.

The different isomers, possess different β- and α-blocking activities

2- Carvedilol



Carvedilol*

β-blocker and α-blocker

Only the (S) enantiomer possesses theβ-blocking activity

both enantiomers are blockers of the α1-receptor

β-blocking activity is 10- to 100-fold of its α-blocking activity

possesses antioxidant activity and an antiproliferative effect on vascular smooth muscle cells

used in treating hypertension and congestive heart failure.