Kerbala University
College of Pharmacy
Dep. of Pharmaceutical Chemistry
Organic Pharmaceutical Chemistry II

By:

Zaid Al-Obaidi
Assistant Lecturer in Pharmaceutical Chemistry
MSc Pharmaceutical Analysis
Sheffield, UK

Sympathomimetic Agents

Continued ……

Methyldopa

- **Methyldopa** (L- α -methyldopa, Aldomet) differs structurally from L-DOPA only in the presence of α -methyl group.
- Methyldopa ultimately decreases the concentration of DA, NE, E, and serotonin in the CNS and periphery.
- Methyldopa is transported actively into CNS via an aromatic amino acid transporter, where it is decarboxylated

Dual α - And β -Agonists/Antagonists

Dobutamine

- It resembles DA structurally but possesses a bulky 1-(methyl)-3-(4-hydroxyphenyl) propyl group on the amino group.
- It possesses a centre of asymmetry, and both enantiomeric forms are present in the racemic mixture used clinically.
- The (-) isomer of dobutamine is a potent **α1-agonist**, which is capable of causing marked pressor responses.

Dobutamine

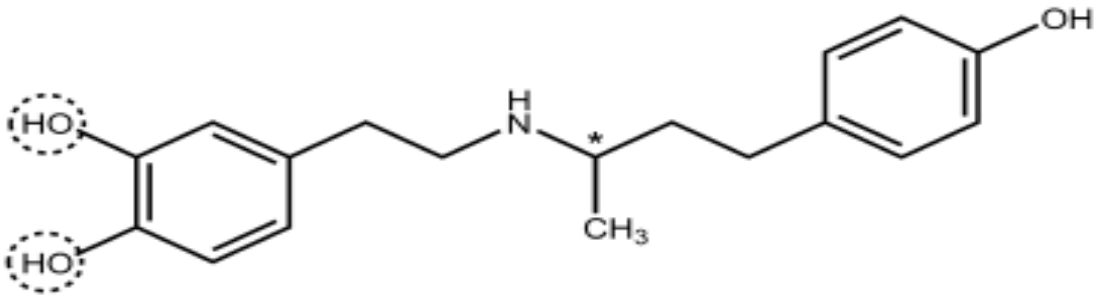
- In contrast, (+)-dobutamine is a potent α1-**antagonist**, which can block the effects of (-)-dobutamine.
- Importantly, *the effects of these two isomers are mediated via β1-receptors*.
- Both isomers appear to be full agonists, but the (+) isomer is a more potent β1-agonist than the (-) isomer (approximately tenfold).

Dobutamine

- Dobutamine contains a catechol group and is orally inactive and thus is given by intravenous infusion.
- Solutions of the drug can exhibit a slight pink color because of oxidation of the catechol function.
- It has a plasma half-life of about 2 minutes because it is metabolized by COMT and by conjugation, although not by MAO.

Dobutamine

- Dobutamine contains a catechol group and is orally inactive and thus is given by intravenous infusion.
- Solutions of the drug can exhibit a slight pink color because of oxidation of the catechol function.
- It has a plasma half-life of about 2 minutes because it is metabolized by COMT and by conjugation, but not by MAO.

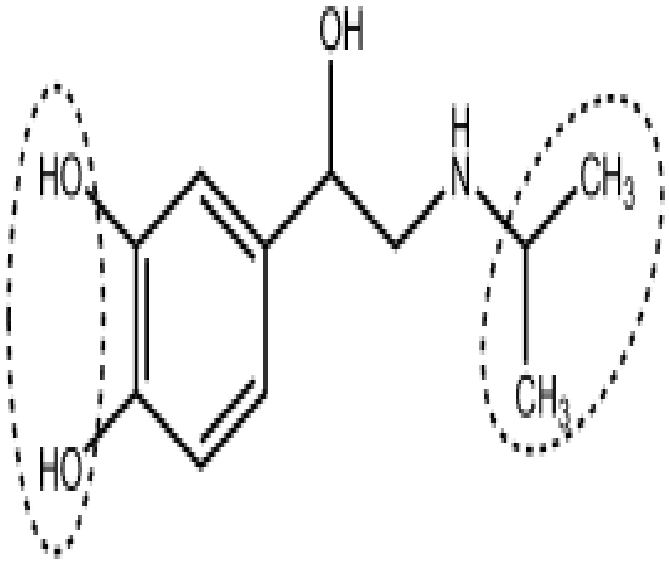


Dobutamine
oxidazed slightly by air
COMT metabolism and conjugation →
orally inactive and short DOA

β-Adrenergic Receptor Agonists

- Isoproterenol is a nonselective and prototypical β-agonist (β2/β1 =1).

Di-OH groups result in:
sensitive to air and light
metabolized by COMT, sulfate and glucuronide conjugation → poor absorption and short DOA



Isoproterenol

Isopropyl goup results in:
↑ β activity, virtually no α activity
resistant to MAO →

β3-Adrenergic Receptor Agonists

- ***Pharmacological effects:***
  - lipolysis, thermogenesis, and relaxation of the urinary bladder.

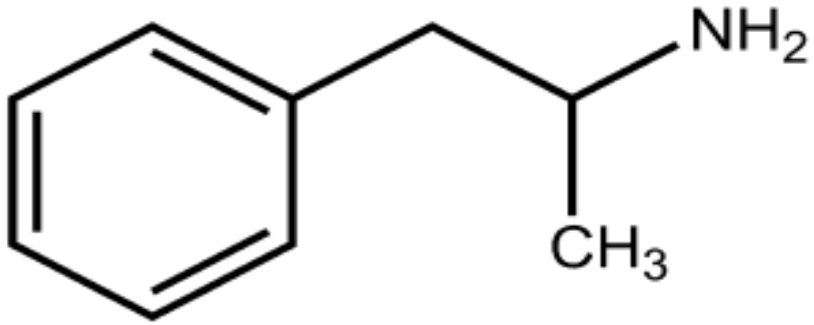
- Selective β3-agonists are recognized as an attractive target for drug discovery. Explain why?
- *Potential fields of utilization:*
- The treatment of obesity, type 2 diabetes mellitus, and frequent urination.

Indirect-Acting Sympathomimetics

- Indirect-acting sympathomimetics act by releasing endogenous NE.
- They also enter the nerve ending by way of the active-uptake process and displace NE from its storage granules.
- In contrast with the direct-acting agents, the presence of a β-hydroxyl group decreases, and an α-methyl group increases, the effectiveness of indirect-acting agents.
- The presence of nitrogen substituents decreases indirect activity, with substituents larger than methyl groups rendering the compound virtually inactive.

Indirect-Acting Sympathomimetics

- Given the foregoing structure–activity considerations, it is easy to understand why amphetamine and p-tyramine are often cited as prototypical indirect-acting sympathomimetics



Amphetamine

Sympathomimetics with a Mixed Mechanism of Action

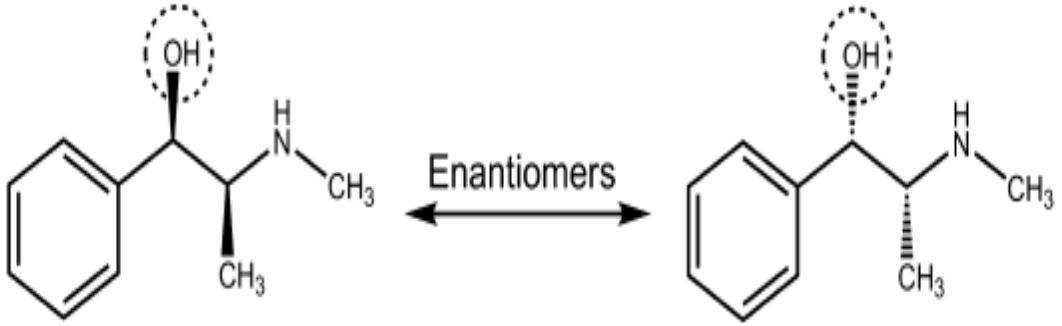
- ✓ Those phenylethylamines considered to have a mixed mechanism of action usually have no hydroxyls on the aromatic ring but do have a β-hydroxyl group.

D-(-)-Ephedrine

- The pharmacological activity of (1R, 2S)-D-(-)-ephedrine resembles that of E. The drug acts on both α- and β-receptors. Its ability to activate β-receptors probably accounted for its earlier use in asthma. It is the classic example of a sympathomimetic with a mixed mechanism of action.

correct (1R, 2S) configuration

Ephedrine = *erythro* racemate
cis
Mixed mechanism of action



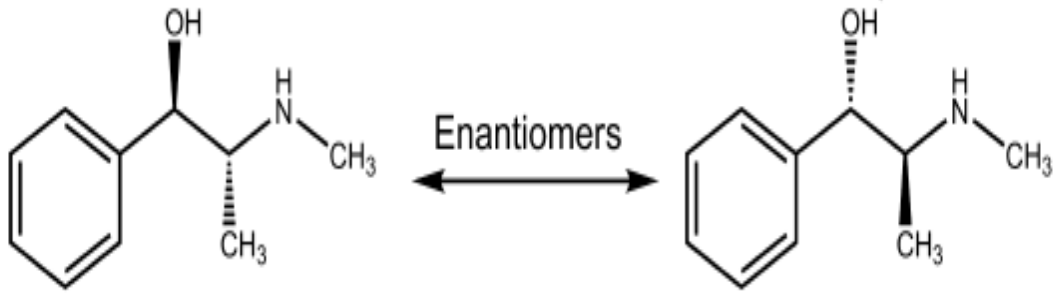
(1*R*,2*S*)-*D*-(-)-Ephedrine
Direct activity on α and β
Some indirect activity.
The most active of the four isomers as a pressor amine

(1*S*,2*R*)-*L*-(+)-Ephedrine
Mixed mechanism of action
but primarily indirect activity

Diastereomers

Diastereomers

Pseudoephedrine = *threo* racemate
trans
Principally, indirect-acting



(1*R*,2*R*)-*D*-(-)-Pseudoephedrine

(1*S*,2*S*)-*L*-(+)-Pseudoephedrine
Virtually no direct activity
Mostly indirect activity

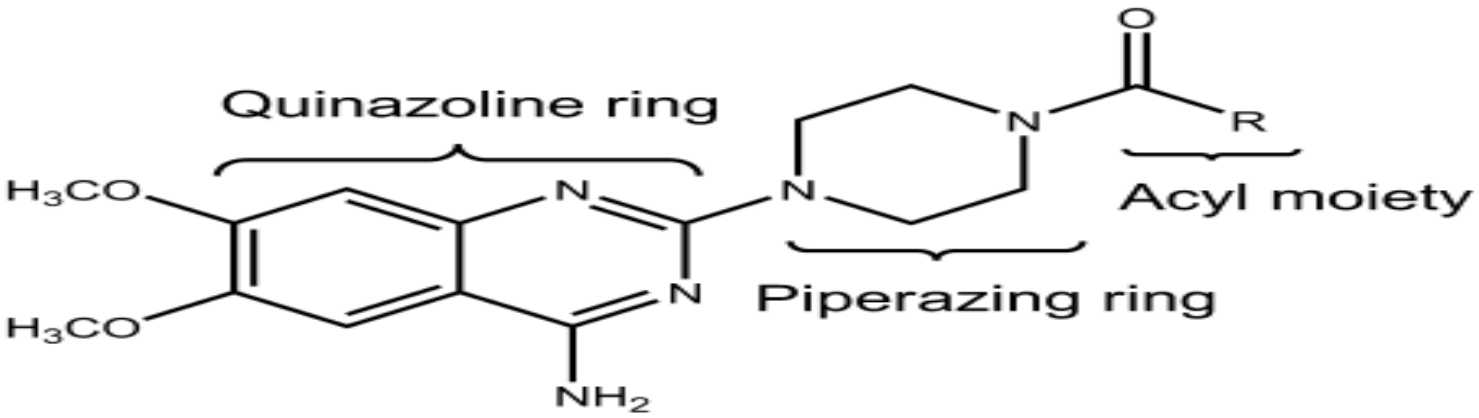
Adrenergic Receptor Antagonists (Blockers)

α-Blockers

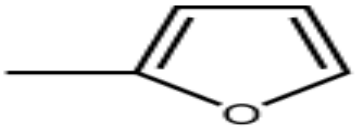
- α-blockers should be therapeutically used as antihypertensive agents.
- The β-blockers, which bear clear structural similarities to the adrenergic agonists NE, E, and ISO
- While, the α-blockers consist of several compounds of diverse chemical structure that bear little obvious resemblance to the α-agonists.

Selective α1-Blockers

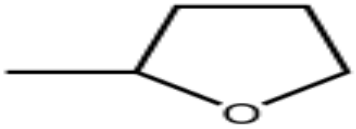
- Prazosin, terazosin, and doxazosin are quinazoline α1-blockers.
- Structurally, these agents consist of three components: the quinazoline ring, the piperazine ring, and the acyl moiety.



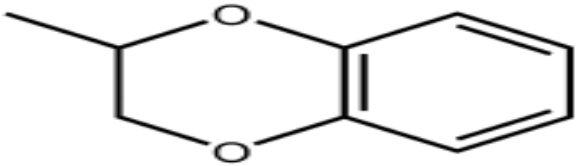
Prazosin: R =



Terazosin: R =

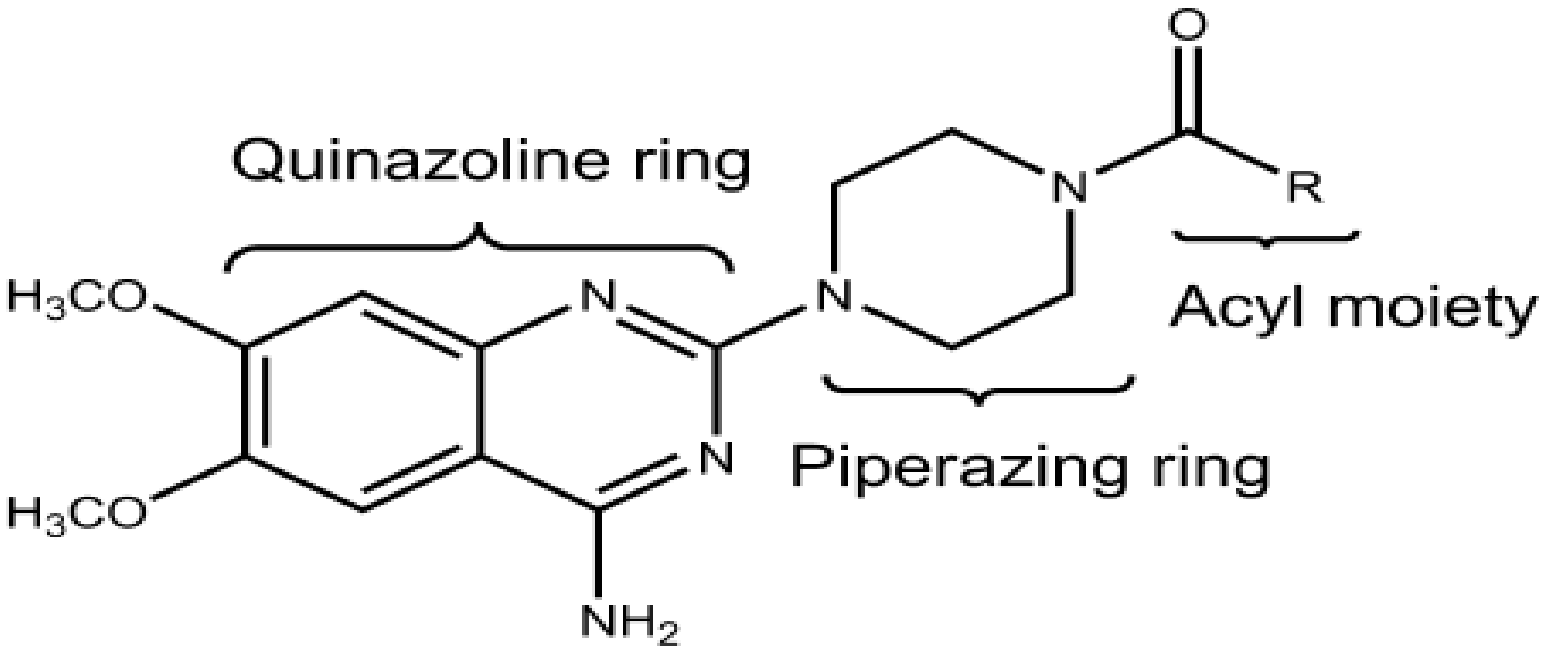


Doxazosin: R =



Selective α1-Blockers

- The 4-amino group on the quinazoline ring is very important for α1-receptor affinity.
- Piperazine moiety attached to the quinazoline ring, this group can be replaced with other heterocyclic moieties.
- The nature of the acyl group has a significant effect on the pharmacokinetic properties.

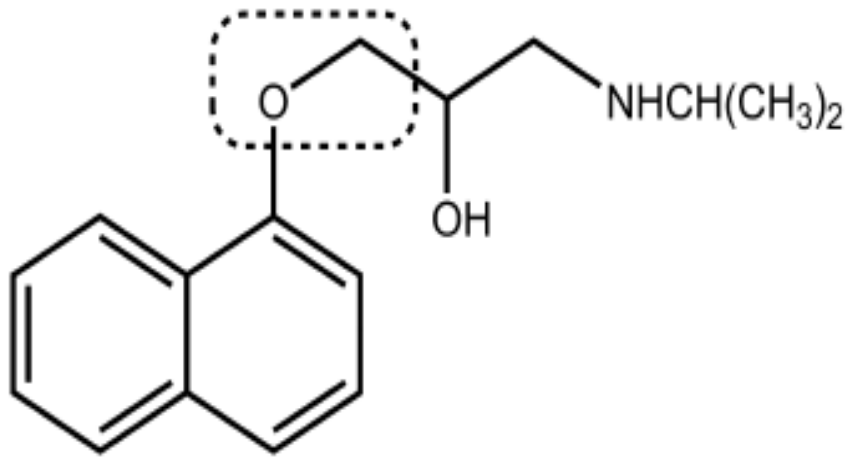


β-Blockers

Nonselective B-Blockers (First Generation)

Propranolol

- Propranolol (Inderal, others) is the prototypical and nonselective β-blocker. It blocks the β1- and β2-receptors with equal affinity, lacks ISA, and does not block α-receptors.



Propranolol (a prototype of β blockers)

β1-Selective Blockers

(Second Generation)

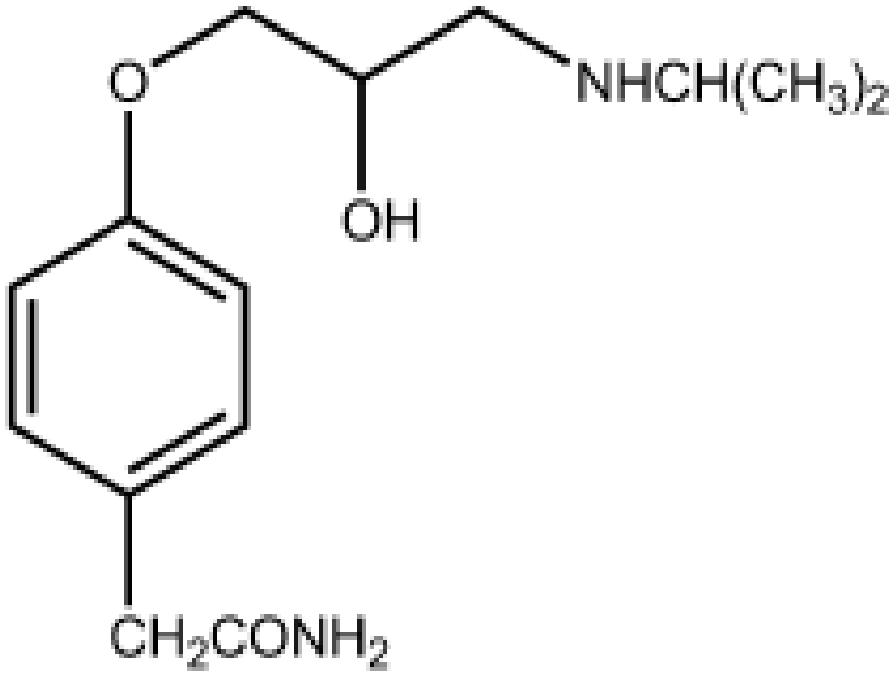
- Cardioselective β1-blockers are drugs that have a greater affinity for the β1-receptors of the heart than for β2-receptors in other tissues.

- Such cardioselective agents should provide two important therapeutic advantages:

  - The first advantage should be the lack of a blocking effect on the β2-receptors in the bronchi.

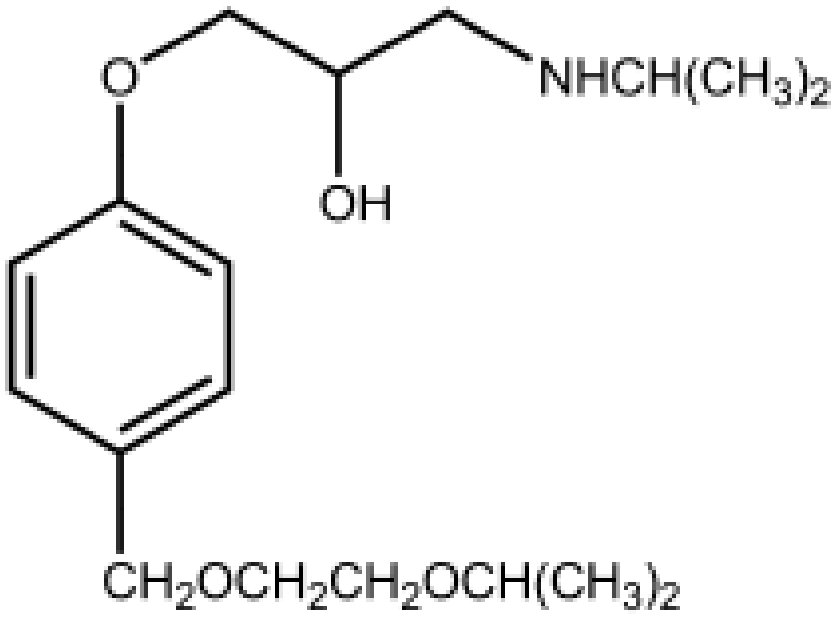
  - The second advantage should be the absence of blockade of the vascular β2-receptors, which mediate vasodilation.

Atenolol



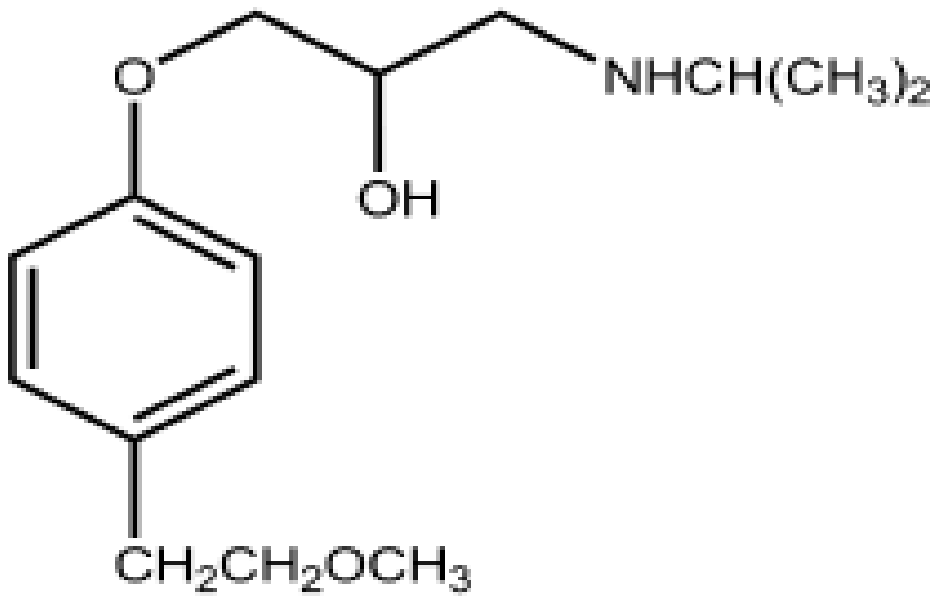
Atenolol: antihypertensive

Bisoprolol



Bisoprolol: antihypertensive

Metoprolol

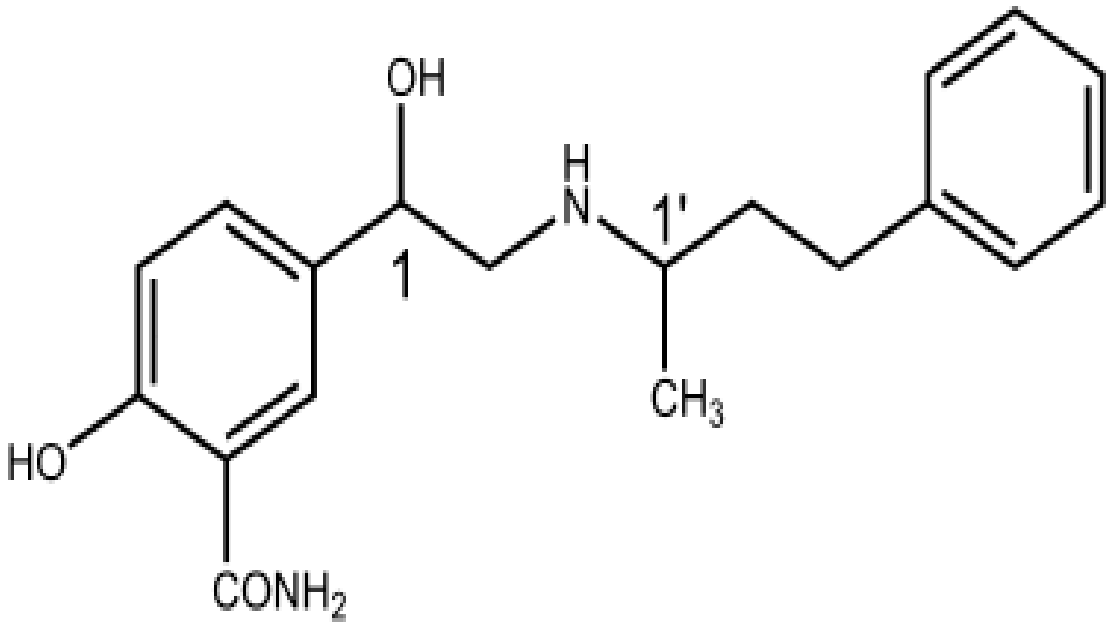


Metoprolol: antihypertensive

β-Blockers with α1-Antagonist Activity

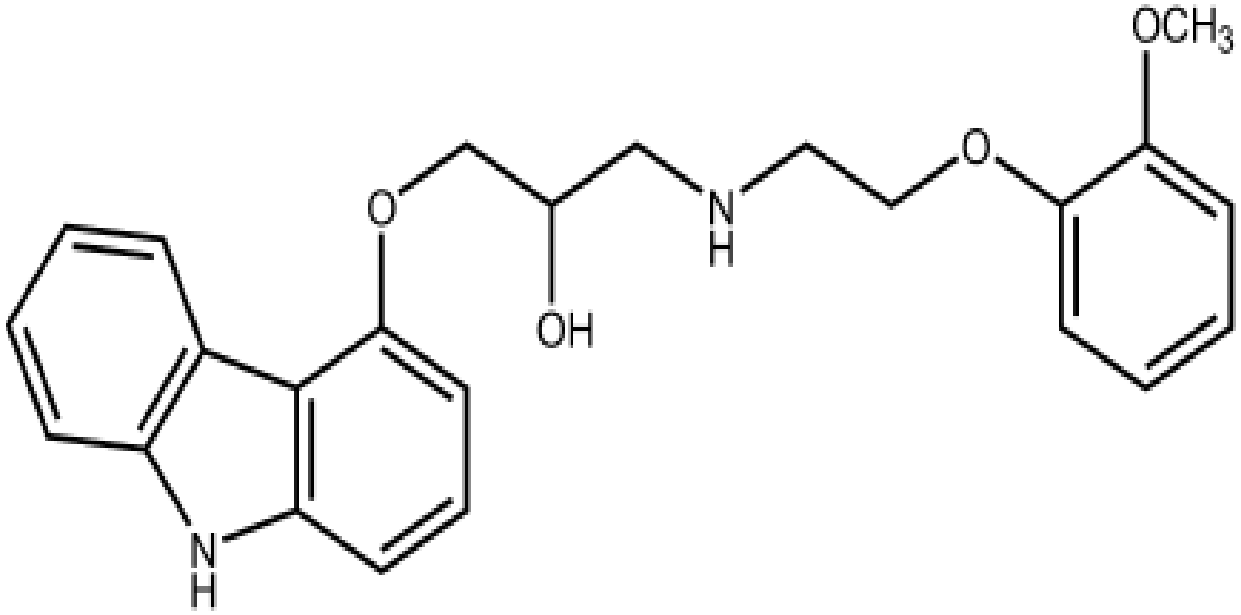
(Third Generation)

Labetalol



Labetalol

Carvedilol



Carvedilol

References:

- **Reference text**: Wilson and Gisvold Textbook of Organic Medicinal and Pharmaceutical Chemistry; Delgado JN, Remers WA, (Eds.); 12th ed., 2011.
- https://pubchem.ncbi.nlm.nih.gov/search/search.cgi