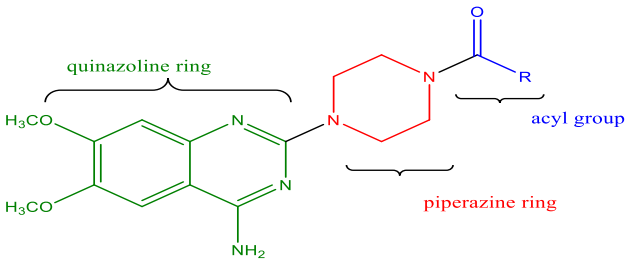
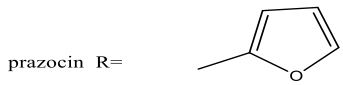
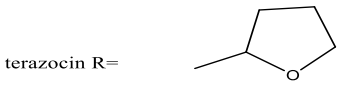
III. SELECTIVE α_1-BLOCKERS

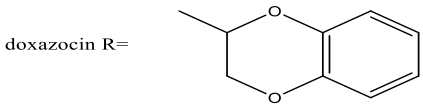
1. Prazosin (Minipress), terazosin (Hytrin), and doxazosin (Cardura

Structurally, these agents consist of three components: the quinazoline ring, the piperazine ring, and the acyl moiety. The 4-amino group on the quinazoline ring is very important for α_1-receptor affinity. Although they possess a piperazine moiety attached to the quinazoline ring, this group can be replaced with other heterocyclic moieties (e.g., piperidine moiety) without loss of affinity.









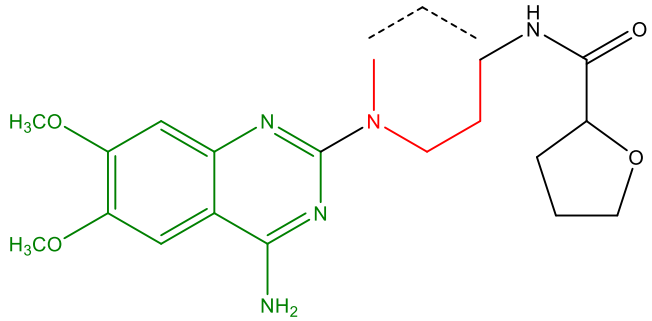
- They produce peripheral vasodilation without an increase in heart rate or cardiac output, thus use in treatment hypertension.
- Contraction of the smooth muscle of prostate gland, prostatic urethra, and bladder neck is also mediated by α_1- adrenoceptors, with **α_{1A}** being predominant, and blockade of these receptors **relaxes the tissue**. For this reason, these agents are also used in the treatment of BPH, where they help improve urination flow rates.
- The main adverse effect **is the first-dose phenomenon**, is sometimes severe. This is a dose-dependent effect characterized by marked excessive postural hypotension and syncope, and can be minimized by giving an initial low dose at bedtime.
- The main difference between prazosin, terazosin, and doxazosin lies in their pharmacokinetic properties. These differences are dictated by the nature of the acyl moiety attached to the piperazine ring. These drugs are metabolized extensively with the metabolites excreted in the bile.

2. Alfuzosin and Tamsulosin

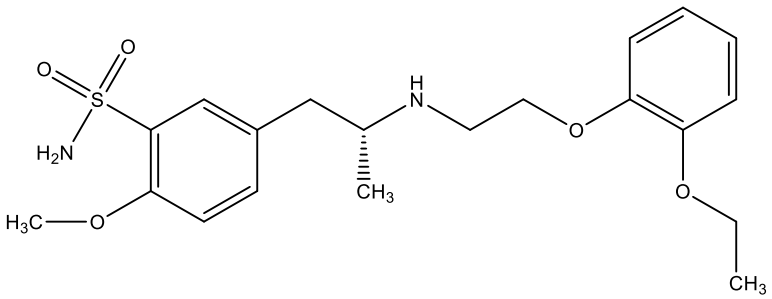
Is also a quinazoline α_{A1}-blocker but differs from terazosin in replacing the piperazine ring in terazosin with an open piperazine ring (a rotatable propylenediamine group).

Are uroselective α_{1A}-blockers and first-line drugs for treatment of BPH without utility in treating hypertension. The fact that a single α_{1A}-adrenoceptor subtype is found in the prostatic and urethral smooth muscle cells led to the design of drugs with uroselectivity for this receptor subtype.

Tamsulosin (Flomax), a nonquinazoline benzensulfonamide, is the first in the class of subtype selective α_{1A}blocker. It is many folds more selective for α_{1A} receptors than for the other α_1 receptors.



Alfazosin



Tamsulosin

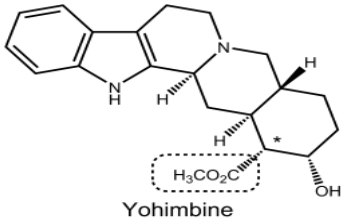
I. SELECTIVE α_2-BLOCKERS

1. Yohimbine

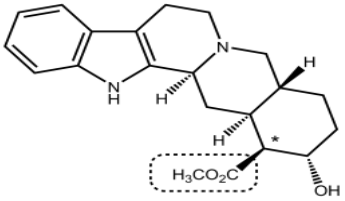
Is a competitive and selective α_2-blocker. The compound is an indolealkylamine alkaloid and is found in the bark of the tree *Pausinystalia yohimbe* and in *Rauwolfia* root.

- ✓ **selectivity toward the α_1- and α_2-receptors, depending on their stereochemistry.**

Yohimbine selective α_2-blocker, whereas corynanthine is a selective α_1-blocker. The only difference between these two compounds is the relative stereochemistry of the carbon containing the carbomethoxy substituent. In yohimbine, this group lies in the plane of the alkaloid ring system, whereas in corynanthine, it lies in an axial position and thus is out of the plane of the rings.



Yohimbine



Corynanthine

Uses

Yohimbine increases heart rate and blood pressure as a result of its blockade of α_2-receptors in the CNS. It has been used experimentally to treat male erectile impotence

Second: β-Blockers

Structure–Activity Relationships

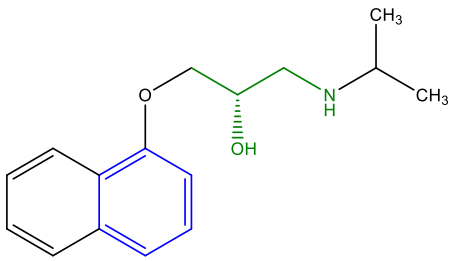
1. Most β-blockers drugs are known as aryloxypropanolamines. This term reflects the fact that an -OCH_2- group has been incorporated into the molecule between the aromatic ring and the ethylamino side chain.
2. The nature of the aromatic ring is also a determinant in their β_1-selectivity. One common structural feature of many cardioselective β-blockers is the presence of a para-substituent of sufficient size on the aromatic ring along with the absence of meta-substituents.
3. Like β-agonists, β-directing tert-butyl and isopropyl groups, are normally found on the amino function of the **aryloxypropanolamine β-blockers. It must be a secondary amine for optimal activity.**
4. For β-blockers, the β-OH-substituted carbon must be in the **S absolute configuration** for maximal β-blocking activity.

I. NONSELECTIVE β-BLOCKERS (FIRST GENERATION)

1. Propranolol

Is the prototypical and nonselective β-blocker. propranolol is approved for use in the United States for hypertension, cardiac arrhythmias, angina pectoris, postmyocardial infarction, hypertrophic cardiomyopathy, pheochromocytoma, migraine prophylaxis, and essential tremor. In addition, because of its high lipophilicity (log P =3.10) and thus its ability to penetrate the CNS, propranolol has found use in treating anxiety and is under investigation for the treatment of a variety of other conditions, including schizophrenia, alcohol withdrawal syndrome, and aggressive behavior.

Propranolol is well absorbed after oral administration, but it undergoes extensive first-pass metabolism before it reaches the systemic circulation.



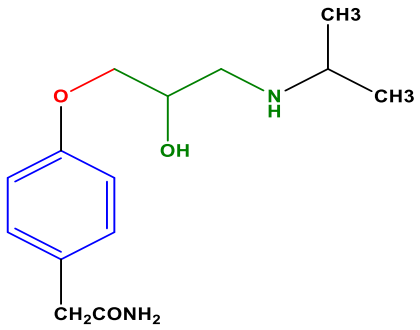
propranolol
a prototype of β bloker
high lipophilicity (log P =3.10)
well absorbed after oral administration
extensive first-pass metabolism

II. β_1-SELECTIVE BLOCKERS (SECOND GENERATION)

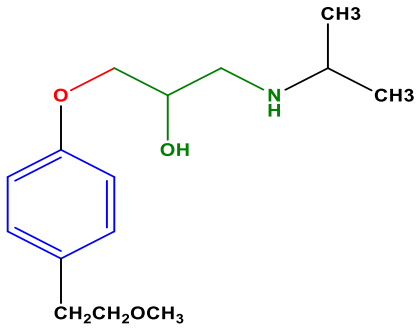
They are useful in the treatment of cardiovascular disease, such as hypertension. Cardioselective β_1-blockers are drugs that have a greater affinity for the β_1-receptors of the heart than for β_2-receptors in other tissues.

The first advantage should be the lack of a blocking effect on the β_2-receptors in the bronchi. Theoretically, this would make β_1-blockers safe for use in patients who have bronchitis or bronchial asthma. The second advantage 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. Unfortunately, cardioselectivity is usually observed with β_1-blockers at only relatively low doses. At normal therapeutic doses, much of the selectivity is lost.

1. **Atenolol and metoprolol** are also approved for use in treating angina pectoris and in therapy following myocardial infarction.

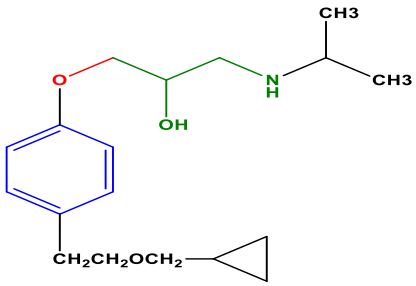


Atenolol
antihypertension



Metoprolol
antihypertension

2. **Betaxolol** is the only β_1-selective blocker indicated for the treatment of glaucoma.



Betaxolol
antihypertension & antiglaucoma

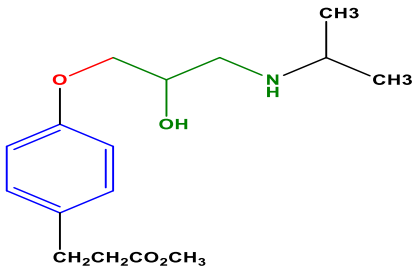
The half-life value of metoprolol is comparable to that seen with propranolol, and those of atenolol is about twice that of propranolol.

Betaxolol, with a half-life ranging between 14 and 22 hours, has the longest DOA of the β1-selective blockers.

Like propranolol, metoprolol has low bioavailability because of significant first-pass metabolism. Although the bioavailability of betaxolol is very high, it is metabolized extensively by the liver, with very little unchanged drug excreted in the urine.

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

3. **Esmolol** was designed specifically to possess a very short DOA; it has an elimination half-life of 9 minutes. Its effects disappear within 20 to 30 minutes after the infusion is discontinued.



Esmolol
short acting antihypertension

III. β-BLOCKERS WITH α_1-ANTAGONIST ACTIVITY (THIRD GENERATION)

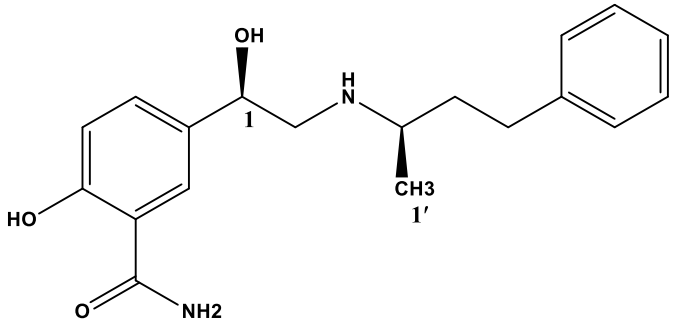
As in the case of dobutamine, the **arylalkyl group** with nearby **methyl group** in these molecules is responsible for its α_1-blocking activity. The bulky N-substituents and another substituted aromatic ring are responsible for its β-blocking activity.

1. Labetalol

phenylethanolamine derivative, is representative of a class of drugs that act as competitive blockers at α_1-, β_1-, and β_2-receptors. It is a more potent β-blocker than α-blocker.

Because it has two asymmetric carbon atoms (1 and 1′), it exists as a mixture of four isomers. It is this mixture that is used clinically in treating hypertension. The different isomers, however, possess different α- and β-blocking activities. The β-blocking activity resides solely in the (1R,1′ R) isomer, whereas the α_1-blocking activity is seen in the (1S,1′R) and (1S,1′S) isomers, with the (1S,1′R) isomer possessing the greater therapeutic activity.

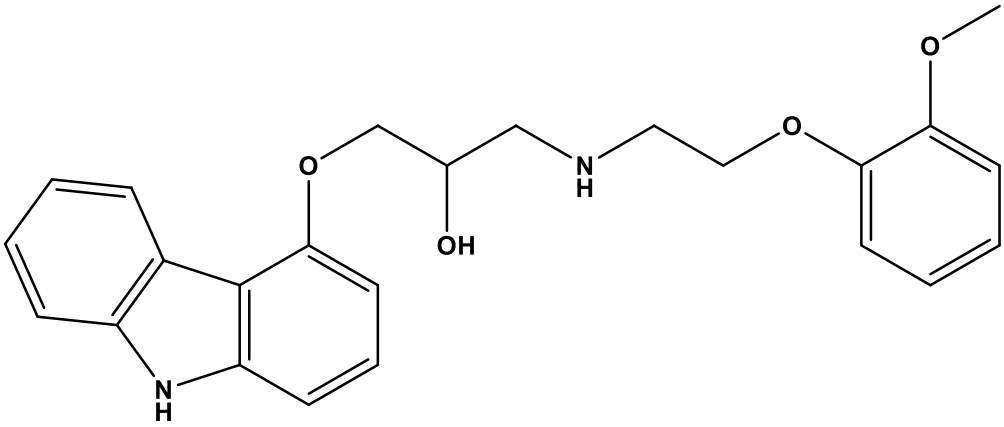
The rationale for its use in the management of hypertension is that its α-receptor–blocking effects produce vasodilation and its β-receptor–blocking effects prevent the reflex tachycardia usually associated with vasodilation. Although labetalol is very well absorbed, it undergoes extensive first-pass metabolism.



2. Carvedilol

It has two isomer, Only the (S) enantiomer possesses the β-blocking activity, although both enantiomers are blockers of the α_1-receptor.

This drug is also unique in that it possesses antioxidant activity and an antiproliferative effect on vascular smooth muscle cells. It thus has a neuroprotective effect and the ability to provide major cardiovascular organ protection. It is used in treating hypertension and congestive heart failure



Carvedilol