

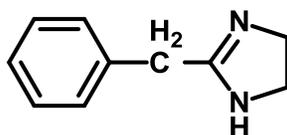
## Adrenergic Receptor Antagonist (Blockers)

### $\alpha$ -Blockers

Because  $\alpha$  -agonists cause vasoconstriction and raise blood pressure,  $\alpha$  -blockers should be therapeutically used as antihypertensive agents. Unlike the  $\beta$ -blockers, which bear clear structural similarities to the adrenergic agonists NE and E, the  $\alpha$  -blockers consist of several compounds of diverse chemical structure that have little resemblance to the  $\alpha$ -agonists.

### Nonselective $\alpha$ - Blockers

Tolazoline and phentolamine



Tolazolin

They are imidazolines. The structure of tolazoline is similar to the imidazoline  $\alpha_1$ -agonists, but does not have the lipophilic substituents required for agonist activity. The type of group attached to the imidazoline ring thus dictates whether an imidazoline is an agonist or a blocker.

Tolazoline is used in persistent pulmonary hypertension of the newborn when supportive measures are not successful.

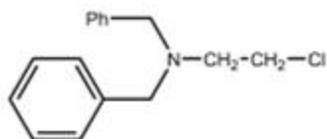
### Irreversible $\alpha$ – Blockers

The produce prolonged adrenergic blockade by long-lasting, irreversible  $\alpha$  -receptor blockade.

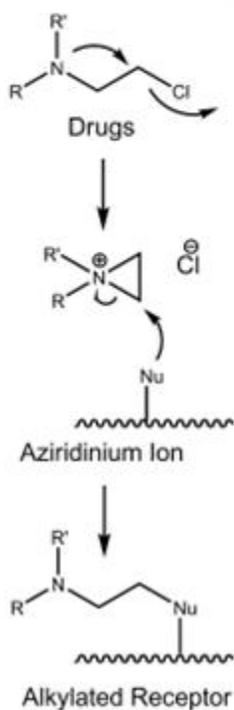
The initial step involves the formation of an intermediate aziridinium ion. The positively charged aziridinium ion electrophile then reacts with a

nucleophilic group on the  $\alpha$ -receptor resulting in the formation of a covalent bond between the drug and the receptor.

Unfortunately, these nonselective drugs alkylate not only  $\alpha$ -receptors but also other biomolecules, leading to their toxicity.



Dibenamine



The onset of action is slow, but the effects of a single dose of drug may last 3 to 4 days, because new receptors must be made to replace those that have been inhibited irreversibly.

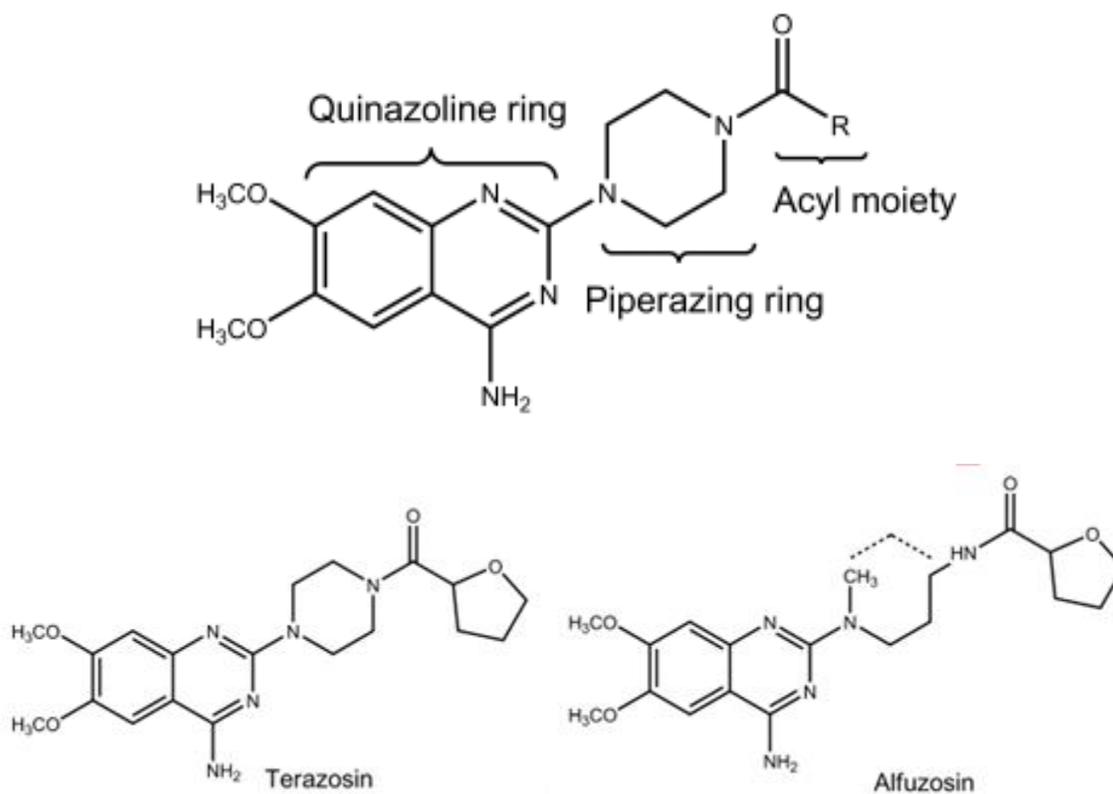
### Selective $\alpha_1$ - Blockers

Prazosin, **Alfuzosin**, terazosin, Tamsulosin and doxazosin

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  $\alpha_1$ -receptor affinity.
- The piperazine moiety attached to the quinazoline ring can be replaced with other heterocyclic moieties (e.g., piperidine moiety) without loss of affinity.
- The nature of the acyl group has a significant effect on the pharmacokinetic properties.

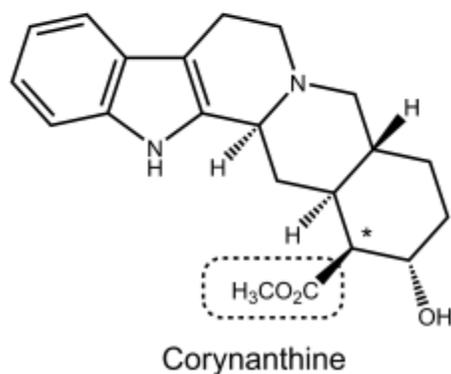
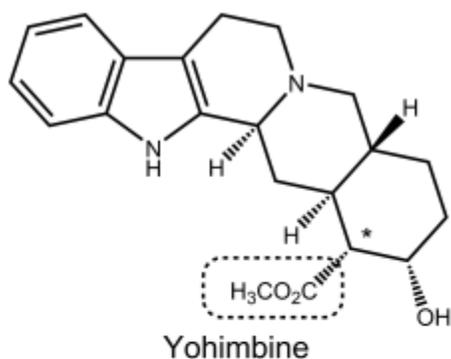
Clinically they are used as **antihypertensive** and for **BPH**.



### Selective $\alpha_2$ - Blockers

The isomeric alkaloids which are known as the yohimbanes exhibit different degrees of selectivity toward the  $\alpha_1$ - and  $\alpha_2$ -receptors, depending on their

stereochemistry. For example, yohimbine is a selective  $\alpha_2$ -blocker, whereas corynanthine is a selective  $\alpha_1$ -blocker.



## $\beta$ -Blockers

### Structure–Activity Relationships

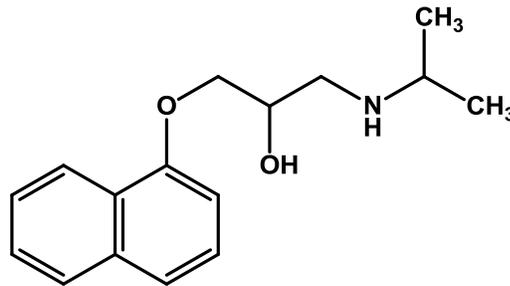
$\beta$ -Blockers are among the most widely employed antihypertensives and are also considered the first-line treatment for glaucoma.

- 1- Most of  $\beta$  -blockers are in the chemical class of aryloxypropanolamines.
- 2- The aryl group also affects the absorption, excretion, and metabolism of the  $\beta$  –blockers.
- 3- One common structural feature of many cardioselective  $\beta$  –blockers ( $\beta_1$  –blockers) is the presence of a para-substituent of sufficient size on the aromatic ring along with the absence of meta-substituents.

- 4- Like  $\beta$ -agonists,  $\beta$ -directing tert-butyl and isopropyl groups, are normally found on the amino function of the aryloxypropanolamine  $\beta$ -blockers. It must be a secondary amine for optimal activity.
- 5- The  $\beta$ -OH-substituted carbon must be in the **S** absolute configuration for maximal  $\beta$ -blocking activity.

### Nonselective $\beta$ . Blockers (First Generation)

Because they exhibit no selectivity for  $\beta_1$ -receptors, they are contraindicated in the presence of conditions such as asthma and bronchitis.



Propranolol

### $\beta_1$ - Selective Blockers (Second Generation)

Cardioselective  $\beta_1$ -blockers are drugs that have a greater affinity for the  $\beta_1$ -receptors of the heart than for  $\beta_2$ -receptors in other tissues. Such cardioselective agents should provide two important therapeutic advantages.

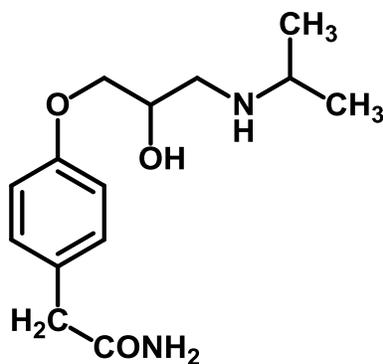
The first advantage should be the lack of a blocking effect on the  $\beta_2$ -receptors in the bronchi. Theoretically, this would make  $\beta_1$ -blockers safe for use in patients who have bronchitis or bronchial asthma.

The second advantage should be the absence of blockade of the vascular  $\beta_2$ -receptors. This would be expected to reduce or eliminate the increase in peripheral resistance that sometimes occurs after the administration of nonselective  $\beta$ -blockers.

Unfortunately, cardioselectivity is usually observed with  $\beta_1$ -blockers at only relatively low doses. At normal therapeutic doses, much of the selectivity is lost.

All of these agents except esmolol are indicated for the treatment of hypertension.

Atenolol and metoprolol are also approved for use in treating angina pectoris and in therapy following myocardial infarction. Betaxolol is the only  $\beta_1$ -selective blocker indicated for the treatment of glaucoma. Only acebutolol possesses ISA.



**Atenolol**

### **$\beta$ - Blockers With $\alpha_1$ -Antagonist Activity (Third Generation)**

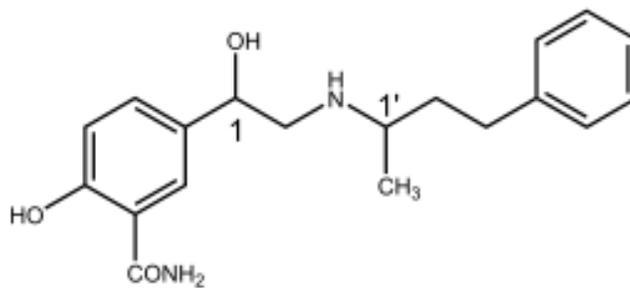
#### **Labetalol**

A phenylethanolamine derivative, is representative of a class of drugs that act as competitive blockers at  $\alpha_1$ -,  $\beta_1$ -, and  $\beta_2$ -receptors. It is a more potent  $\alpha$ -blocker than  $\beta$ -blocker. It is used clinically in treating hypertension.

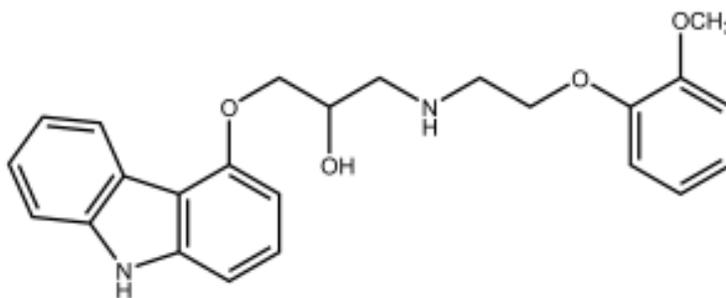
The rationale for its use in the management of hypertension is that its  $\alpha$ -receptor-blocking effects produce vasodilation and its  $\beta$ -receptor-blocking effects prevent the reflex tachycardia usually associated with vasodilation.

#### **Carvedilol**

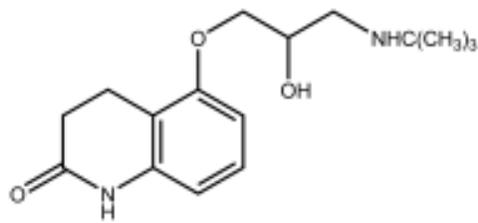
It is a  $\beta$ -blocker that possesses  $\alpha_1$ -blocking activity. Only the (S) enantiomer possesses the  $\beta$ -blocking activity, although both enantiomers are blockers of the  $\alpha_1$ -receptor. Its  $\beta$ -blocking activity is more than its  $\alpha$ -blocking activity. It is used in treating hypertension and congestive heart failure.



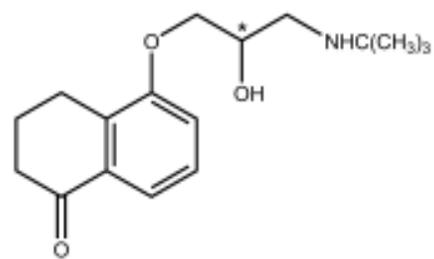
Labetalol



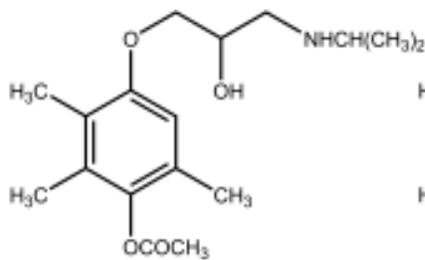
Carvedilol



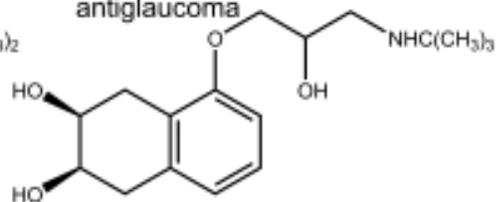
Carteolol: antihypertensive & antiglaucoma



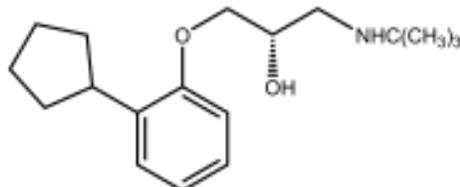
Bunolol  
Levobunolol, S(-) isomer of bunolol  
antiglaucoma



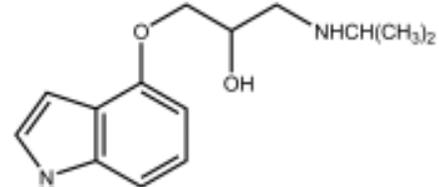
Metipranolol: antiglaucoma



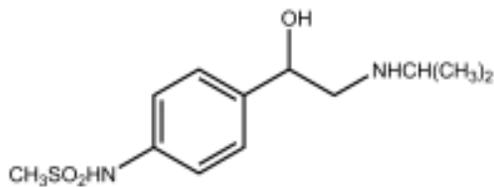
Nadolol: antihypertensive



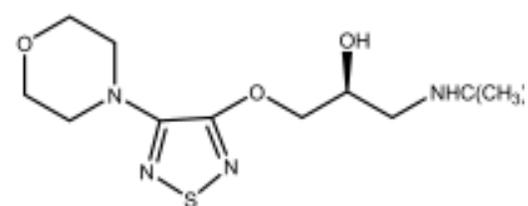
Penbutolol: antihypertensive



Pindolol: antihypertensive

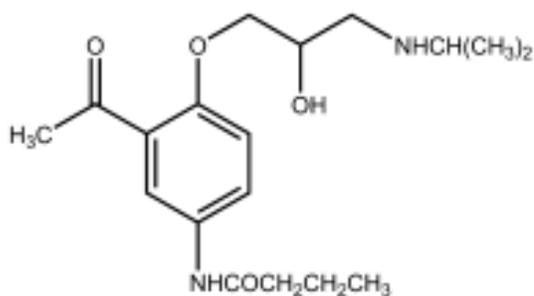


Sotalol: antiarrhythmias & only phenylethylamine

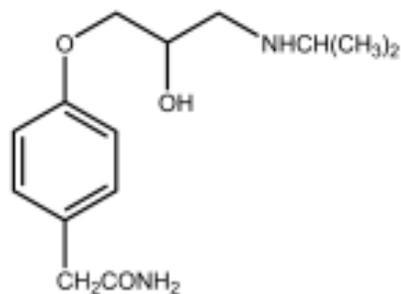


Timolol: antihypertensive & antiglaucoma

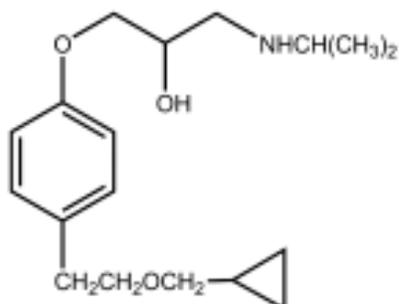
Figure 16.15 • Nonselective  $\beta$ -blockers.



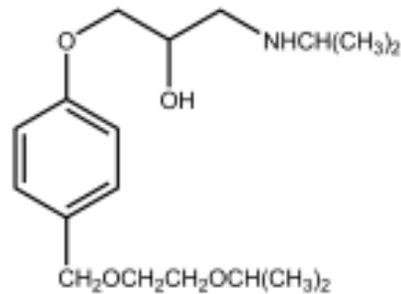
Acebutolol: antihypertensive



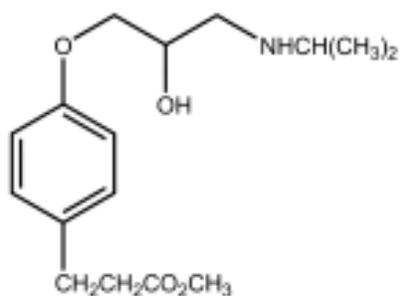
Atenolol: antihypertensive



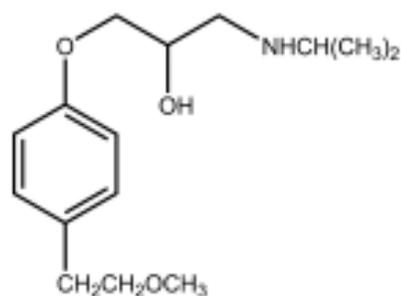
Betaxolol: antihypertensive & antiglaucoma



Bisoprolol: antihypertensive



Esmolol: short-acting antihypertensive



Metoprolol: antihypertensive

Figure 16.16 •  $\beta_1$ -Selective blockers.